Pharmacologic Treatment of First-Episode Schizophrenia: Early Intervention Is Key to Outcome

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The early recognition and management of a first episode of schizophrenic illness is a difficult task, with identification complicated by a broad differential diagnosis, lack of definitive data on the prognostic implications of premorbid/prodromal symptoms, and, until recently, treatment limited to pharmacologic agents with severe adverse effects. The first psychotic episode in patients with schizophrenia is the most responsive to treatment in terms of both rate and degree. However, first-episode patients are also more likely to develop motor side effects, even at lower medication doses, than multiepisode patients. Considerable evidence supports the assertion that early treatment can improve outcome and possibly prevent the development of full-blown illness in high-risk individuals. There is evidence that atypical antipsychotic medications are effective in the treatment of first-episode schizophrenia and are well tolerated. The improved tolerability associated with the newer antipsychotic medications, including a lower risk for motor side effects and possible lower risk for development of tardive dyskinesia, has swung the risk-benefit balance in favor of early and aggressive treatment. By intervening early and providing long-term maintenance treatment, the course of schizophrenic illness may be altered in the coming years with overall decreased deterioration and chronicity and overall improved functioning resulting in lower societal costs.

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The onset of first-episode psychosis in young adults causes considerable difficulty to patients, families, and clinicians. Patients and families often deny the severity of dysfunction and attempt to normalize behavior or see it as temporary, thereby leading to delay in seeking treatment. Furthermore, because patients may be secretive about symptoms and geographically removed from familial supports, obtaining accurate information regarding baseline level of functioning (premorbid ability) and timing and course of earliest signs of illness (prodromal symptoms) is difficult. Many somatic diseases and psychiatric illnesses may present with psychosis as the initial manifestation of abnormality, mandating a broad differential diagnosis and the need for thorough medical/neurologic evaluation to rule out reversible causes. Once diagnosed, first-episode schizophrenia offers the psychiatrist an opportunity to intervene pharmacologically and psychosocially and thereby potentially influence dramatically the course of illness. Patients at this early stage of the illness are more responsive to pharmacologic treatment as well as more susceptible to side effects.[1] By initiating such treatment early and aggressively, long-term outcome may be markedly improved, since it has been shown repeatedly that delay in initial treatment is associated with slower, less complete symptom response and overall poorer outcome.[2] By involving patients and their support network in a collaborative treatment relationship, and providing ongoing psychoeducation regarding schizophrenia and its treatment, and helping to improve communication skills and problem solving ability, a pattern of long-term treatment compliance can be established that will go a long way toward preventing future episodes. The atypical antipsychotic medications, with their clear efficacy and improved side effect profiles, are easier for patients to take than conventional agents and tip the risk-benefit balance toward early and prolonged treatment. These newer drugs should positively impact outcome by improving adherence to treatment and thereby decreasing the risk of future episodes of psychosis.

This paper will address first-episode schizophrenia from the perspectives of differential diagnosis, evaluation,

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treatment, strategies for early recognition, and implications of delay in pharmacologic intervention. The underlying assumption/hypothesis for this discussion is that episodes of psychosis in schizophrenia—whether neurodevelopmental, environmentally determined, or both—are not benign and if left unchecked result in clinical deterioration with likely progressive neuroanatomic changes and overall poorer outcome. The discussion begins with a case report that emphasizes many of the important issues that must be addressed in first-episode schizophrenia.

CASE HISTORY

Mr. A is a 21-year-old man with a history of insulin-dependent diabetes mellitus (IDDM) who presented with a chief complaint of worsened depressed mood in the preceding months; he also noted a low-level depressed mood since age 13. Mood disturbance was associated with mood swings, decreased hedonic capacity, low energy, tearfulness, poor sleep, impaired concentration, diminished academic performance, and suicidal ideation with a suicide attempt in the week before admission. Vegetative impairment was recent when compared with duration of depressed mood. The patient also noted auditory hallucinations that were critical in content and consisted of voices talking about him in the third person and commenting on his actions; these had been present for several months. Mr. A also reported visual hallucinations, paranoid ideation, thought insertion, feeling as though "something great was going to happen," subjectively disorganized thoughts, and social withdrawal. He had a history of regular cannabis use; the last use was 2 days prior to admission. He had no prior history of psychiatric treatment. Medical history was notable only for IDDM the past 5 years, and his only medication was insulin. Family history was positive for depression, negative for schizophrenia. The patient was described by his mother as "a loner, shy," and "hard on himself." He was single, without children, and lived in a co-op apartment while attending school; he had been an excellent student majoring in accounting. Mental status examination was remarkable for inappropriate smiling and monotonous idiosyncratic speech with overall poverty of content owing to circumstantiality and mild loosening of associations. No significant cognitive abnormalities were present on bedside testing of the patient.

Physical and neurologic examinations were normal, laboratory assessment was unremarkable, and urine toxicology was negative. Magnetic resonance imaging (MRI) scan of the brain was normal. Neuropsychological testing demonstrated a Full Scale I.Q. of 118 with no significant cognitive deficits noted. After observation on the unit for 48 hours, the patient's depressed mood improved but psychotic symptoms, affect abnormality, and thought disorder persisted; the pretreatment Brief Psychiatric Rating Scale (BPRS) score was 53. A diagnosis of schizophreniform disorder was rendered and treatment with olanzapine 10 mg p.o. h.s. begun. Mr. A experienced a rapid improvement in psychotic symptoms, mood, and socialization, and he was discharged to outpatient follow-up after 7 days. At follow-up, 4 weeks after initiation of treatment, the BPRS score was 37, and Mr. A had returned to school and was doing well. The only side effects noted were mild sedation and light-headedness early in the course of treatment with olanzapine; no extrapyramidal side effects (EPS), akathisia, or dystonia emerged.

Table 1. Differential Diagnosis of First-Episode Psychosis*

Schizophrenia
Schizophreniform disorder
Psychotic mania
Substance-induced psychosis
Psychosis with secondary gain
Schizoaffective disorder
Brief psychotic disorder
Major depression with psychotic features
Psychosis secondary to medical condition

*Adapted from DSM-IV.

DIFFERENTIAL DIAGNOSIS AND EVALUATION

The above case highlights many of the difficulties in the process of reaching a working diagnosis for patients with first-episode psychosis. Owing to the short history of psychopathology and problems with accuracy of recall of historical information by patients and family, the most important aspects of the history, in terms of differential diagnosis, are largely unavailable. Additionally, substance abuse, comorbid somatic illness, and psychosocial factors can cloud the picture. Table 1 provides a list of the most common psychiatric diagnoses to be considered in the differential diagnosis of first-episode psychosis.

As with any psychiatric evaluation, assessment begins with a detailed history, gathering data from all available sources. Obtaining information—after receiving informed consent from the patient—from employers, teachers, roommates, and prior school records can be invaluable.[3,4] These sources can help to fill in gaps and overcome some of the above-noted difficulties in obtaining data from patients and family. Documenting all current medications, including over-the-counter and herbal preparations, is vital. A complete physical and neurologic examination and laboratory assessment are crucial first steps in identifying comorbid disease that can produce psychotic symptoms or potentially complicate pharmacologic treatment. Laboratory assessment, as recommended by the American Psychiatric Association Practice Guidelines[5] and the Expert Consensus Guideline Series,[6] includes electrolytes, BUN, creatinine, glucose, liver function profile, thyroid function studies, syphilis serology, serum pregnancy test, urinalysis, and urine toxicology, as well as other studies as clinically indicated (e.g., antinuclear antibodies, sedimentation

rate). An ECG is recommended, particularly in patients with a personal or family history of cardiac disease and if other known risk factors exist.

The need for neuroimaging studies in first-episode patients is controversial, and the use of such costly studies is being increasingly restricted by managed health care organizations. Both sets of schizophrenia guidelines[5,6] recommend neuroimaging studies as secondary assessments, particularly in the absence of neurologic signs and symptoms. The debate is fueled in large part by retrospective studies investigating the results of screening computed axial tomography (CT) or MRI scans in unselected general psychiatric populations, some of which have demonstrated a relatively low yield of identification of etiologically relevant neuropathology.[7,8] However, when studies are restricted to samples of patients with schizophrenia, the rate of identifying significant CNS abnormalities is much higher. Lieberman et al.[9] studied 45 first-episode patients with schizophrenia and found abnormal brain morphology on MRI in 52%. MRI abnormalities, particularly lateral ventricular enlargement, were significantly correlated with slower treatment response, and there was a trend for association with greater negative symptoms and EPS. Falkai[10] reported that 6% to 10% of patients with schizophrenia demonstrate unsuspected brain lesions. He notes that this finding is particularly relevant because psychopathology is not clearly helpful in distinguishing primary from secondary schizophrenia. Gerwitz et al.[11] studied a mixed population of 168 patients with first-episode psychosis and found that 40% had cortical atrophy and 6.6% demonstrated other specific CT scan abnormalities. The authors concluded that their findings suggest that the onset of psychosis is an indication for a CT scan.

Medical Work-Up

As seen in the case presented in this paper, patients who have psychotic symptoms are not immune to development of serious somatic disease that, if not identified and treated, can have serious consequences not only in the resolution of psychosis, but also in overall morbidity and mortality. Symptomatic response to pharmacologic treatment does not assure that serious somatic disease or substance abuse is not producing the psychotic symptoms.[12] Johnstone et al.[13] found significant, etiologically relevant organic pathology, including seizure disorder, syphilis, substance abuse, sarcoidosis, lung cancer, thyrotoxicosis, and head trauma, in 5.6% of 268 patients with first-episode schizophrenia. Davidson[14] reported multiple medical/neurologic causes of schizophrenia-like psychosis, including seizure disorder, CNS trauma, encephalitis, degenerative CNS diseases, and brain tumors. As noted above, psychoses due to organic disease are phenomenologically indistinguishable from primary schizophrenia (phenocopies); clues to their presence include the absence of genetic risk for schizophrenia and atypical age at presentation. Furthermore, these secondary psychoses must have their underlying etiologies addressed, although they often have their own momentum and pursue a course independent of the cerebral disorder; thus, psychopharmacologic intervention will be necessary despite successful treatment of somatic disease.

TREATMENT

Beginning treatment with a patient who has first-episode schizophrenia offers the psychiatrist the opportunity to set the stage for long-term management, which is important since schizophrenia is a lifelong illness. It is crucial to engage the patient and the support network in a collaborative treatment relationship. Providing clear information about the diagnosis, beginning the process of explaining the known facts about the clinical manifestations, course, etiology and prognosis of schizophrenia, and laying out treatment options from which the patient (if competent) can choose establishes a team-oriented approach to treatment. Such a treatment-planning philosophy can serve to empower the patient and communicate to him/her that there are solutions to address what seems to be an overwhelming situation. It must be repeatedly emphasized to the patient during the course of treatment that being aggressive with treatment and preventing recurrence of psychosis are keys to better overall outcome.

In addition to beginning the process of psychoeducation and laying the groundwork for a collaborative therapeutic alliance, completion of several other tasks is indicated to round out the framework for treatment and enhance patient supports. Obtaining informed consent from the patient for pharmacologic treatment reinforces the patient's active role in treatment planning. This is an ongoing process that is readdressed at virtually every follow-up appointment. Education of patients and family about target symptoms and side effects of antipsychotic treatment is clearly part of the informed consent process. Informing patients of side effects will prompt them to raise these issues with their psychiatrist at follow-up appointments. By addressing and managing side effects, medication noncompliance will be minimized. Often overlooked problems associated with antipsychotic medications are impaired sexual functioning and endocrinologic side effects,[15] including diminished libido, impotence, menstrual irregularities, breast enlargement/engorgement, and galactorrhea. These problems are, in large part, due to the prolactin-elevating effects of virtually all antipsychotics. As quality-of-life issues are clearly important outcome measures for the treatment of patients who have schizophrenia, attention to all aspects of patient functioning, including sexual functioning, is needed.

Assisting the patient and family in linking with community resources is important to the provision of optimal

treatment. Education about available financial resources; community supports, such as National Alliance for the Mentally Ill and clubhouse programs; and resources available in times of crisis is helpful in case-management, which often is performed by the patient and family in conjunction with the psychiatrist. Assessing patient and family understanding of the illness and outcome expectations is important to further the process of psychoeducation. As part of this process, assessing communication patterns and problem-solving/coping skills is vital to minimize relapse risk and maximize patient functioning. It has been repeatedly demonstrated that adverse communication style in the families of patients with schizophrenia is associated with an increased risk of relapse despite optimal compliance with medication.[16]

Pharmacologic Intervention

Once the diagnosis of schizophrenia has been made, it is important to expedite the initiation of pharmacologic treatment. As discussed below, there is evidence that the longer the initial psychotic episode, the poorer the overall outcome. Once antipsychotic medication has been initiated, it must be emphasized that patience is essential, since it may take 2 or more weeks to see antipsychotic effects independent of sedative effects. Remaining patient may be particularly difficult with inpatients, given the current trends in medical economics. However, using the lowest effective dose of antipsychotic medication will minimize side effects leading to improved compliance, decreased relapse risk and need for readmission, and will thereby reduce the overall cost of care. Should lack of sleep and agitation complicate the clinical picture and fail to improve with initial doses of antipsychotic medication, short-term treatment with a high-potency benzodiazepine is recommended. Pretreatment and regular psychopathology ratings with structured instruments, such as the BPRS,[17] quantify severity of illness and response to pharmacologic intervention and help to plot the course of illness, identify early signs of relapse, and clarify areas of residual psychopathology. Likewise, regular structured ratings for medication side effects, such as the Simpson-Angus Scale[18] for extrapyramidal side effects and the Abnormal Involuntary Movement Scale (AIMS),[19] are recommended to focus the clinician's attention on these potential sources of treatment noncompliance and facilitate the ongoing informed consent process.

Initial pharmacologic treatment can include a high-potency conventional antipsychotic agent, such as haloperidol 6 to 10 mg/day, or one of the available atypical antipsychotic medications, such as olanzapine 10 to 20 mg/day or risperidone 4 to 8 mg/day. Either of these strategies is recommended as first-line therapy for patients with schizophrenia early in the course of illness.[5] Evidence for the efficacy of each approach, as well as potential drawbacks, is discussed below.

Conventional antipsychotics. Schizophrenia is associated with multiple dimensions of psychopathology, with positive symptoms (hallucinations, delusions, formal thought disorder) and negative symptoms (affective flattening, asociality, anhedonia, amotivation) receiving the greatest attention.[20] Since the introduction of chlorpromazine in the early 1950s, it has been clear that conventional antipsychotic medications (neuroleptics) are beneficial in reducing the positive symptoms of schizophrenia. However, a significant minority of patients (30%–40%) respond incompletely to conventional antipsychotics, and these medications do not improve primary negative (deficit) or mood symptoms; they also introduce a significant side effect burden, including extrapyramidal side effects (EPS), sedation, and dizziness. Several studies have demonstrated that conventional antipsychotic medications are effective in patients with first-episode schizophrenia. In a particularly noteworthy investigation, Lieberman et al.[21] studied 70 rigorously screened patients with first-episode schizophrenia or schizoaffective disorder, as defined by the Research Diagnostic Criteria, to assess response to algorithmically defined treatment with conventional antipsychotic medication. Treatment progressed from fluphenazine to haloperidol and finally to molindone—all administered at moderate to high doses—before a patient was defined as nonresponsive and considered for clozapine treatment. Response (remission) was defined as, at most, mild positive symptoms on the Schedule for Affective Disorders and Schizophrenia,[22] severity of mild or better on the Clinical Global Impressions (CGI) scale,[23] and a CGI improvement rating of much or very much improved, a level of improvement that must have persisted for 8 weeks. The mean time to remission was 36 weeks, median 11 weeks; 83% of the patients responded by 1 year. Eighty-one percent of the patients responded to fluphenazine (mean dose = 20 mg/day), 10% responded after being switched to haloperidol (mean dose = 28 mg/day), and 9% responded after being switched to molindone (mean dose = 225 mg/day).

Although this group of medications is effective against the most overt symptoms of schizophrenia, the occurrence of side effects—particularly motor side effects—makes it difficult to maintain patients on these agents over prolonged periods of treatment. Furthermore, the clear relationship between conventional antipsychotics and tardive dyskinesia, and with the risk increasing with time of medication exposure,[24] makes physicians reluctant to institute them in equivocal cases of early psychotic illness. These potential adverse effects make patients reluctant to start therapy, thereby increasing the period of untreated psychosis and increasing the risk for self-discontinuation of medication and relapse, both of which are associated with poorer long-term outcome. The introduction of atypical antipsychotic agents with improved side effect profiles and possible decreased risk for tardive dyskinesia[25] is

helping to overcome these limitations of conventional antipsychotics. The improved tolerability of the newer agents has swung the risk-benefit balance in the direction of early aggressive treatment, decreasing the duration of psychotic episodes and, thereby, possibly limiting disease progression and deterioration. Improved tolerability also increases the likelihood that patients will be maintained on medication over prolonged periods, thus decreasing relapse risk.

Risperidone. The first atypical agent with a risk-benefit profile that allowed use in first-line treatment of psychosis was risperidone. It was demonstrated to be at least as effective as haloperidol in decreasing positive symptoms and global psychopathology, and, in the recommended dose range, has a much lower risk for motor side effects.[26] The most common side effects reported with risperidone use include EPS, akathisia, somnolence, dizziness, and headache. Kopala et al.[27] treated by open label 22 neuroleptic-naive, first-episode patients with a mean illness duration of 246 weeks using a mean dose of risperidone of 4.7 mg/day for 7 weeks; the mean baseline Positive and Negative Syndrome Scale (PANSS) score was 113. During the trial, PANSS total score decreased 31.3%; the positive symptom score decreased 46.1% and the negative symptom score decreased 21.5%. Only 2 of 22 patients required anticholinergic medication at study endpoint; thus, the risk of EPS appeared to be low.

McCreadie[28] described a double-blind, multicenter, parallel group trial involving 183 first-episode psychotic patients comparing haloperidol (mean = 5.6 mg/day) and risperidone (mean = 6.1 mg/day). Responders were defined as those patients demonstrating a 50% reduction in PANSS total score. Given these criteria, 63% responded to risperidone and 56% responded to haloperidol; this difference was not significant. Six percent of risperidone-treated patients versus 18% of haloperidol-treated patients dropped out due to adverse effects ($p < .02$). Risperidone was found to be associated with a significantly lower risk of EPS and decreased requirement for antiparkinsonian medication.

Olanzapine. In a series of controlled trials, olanzapine has been shown to be at least as, and possibly more, effective as conventional antipsychotic medication, with a markedly decreased risk of motor side effects.[29,30] The most common side effects experienced by olanzapine-treated patients included sedation, dizziness, constipation, hypertonia, and weight gain. In addition to efficacy against positive symptoms, olanzapine was shown to significantly reduce overall ratings of negative symptoms—although not necessarily primary negative symptoms—global psychopathology, and depressive symptoms in those individuals with at least a moderate degree of depression. At some doses, these clinical improvements were significantly greater than those seen with haloperidol treatment.[30] As with risperidone, clear efficacy and a decreased side effect burden, as well as broader symptom efficacy, render olanzapine a first-line agent.

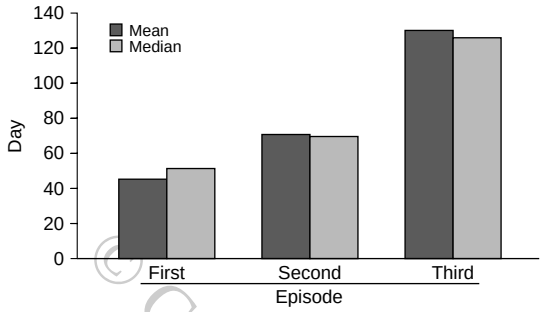
Olanzapine has been investigated in patients with first-episode schizophrenia by Tollefson et al.[31] They examined 83 first-episode patients participating in a 6-week, acute treatment, double-blind, randomized, multicenter trial involving a total of 1996 patients. These patients had no prior psychotic episodes, had been ill for less than 5 years, and were less than 45 years of age; the mean duration of illness was 390 days and 29% were neuroleptic-naive. Fifty-nine patients (mean age = 29) received olanzapine and 24 patients (mean age = 27) received haloperidol; the mean modal doses were olanzapine 12.7 mg/day and haloperidol 11 mg/day. Response was defined as greater than 40% reduction in pretreatment BPRS total score. Olanzapine resulted in significantly greater improvement in measures of global psychopathology and positive and overall negative symptom scores than haloperidol. A significantly greater percentage of olanzapine-treated patients were defined as responders than haloperidol-treated patients ($p < .003$). Haloperidol was also associated with significantly greater EPS and akathisia ratings ($p < .005$) and significantly more patient withdrawals due to adverse events than olanzapine ($p < .03$).

ECT. As noted above, the presentation of first-episode psychosis is variable and the certainty with which one can render a diagnosis limited until the longitudinal course is examined. As a result, the differential diagnosis is broad, with the distinction between first-episode schizophrenia and psychotic mood disorder being particularly difficult. Thus, Kellner[32] opined that ECT may be the treatment of choice in first-break psychosis patients. ECT has been shown to be effective in treating psychotic mood disorders, schizophreniform disorder, and early schizophrenia.[33,34] Use of ECT as initial treatment for first-episode psychosis renders establishment of the precise diagnosis prior to initiation of treatment less of a stumbling block; it does not delay definitive treatment while efforts to confirm a given diagnosis are made and may spare patients exposure to potentially neurotoxic antipsychotic medication. At this point, however, ECT is not a first-line treatment for early psychotic illness—despite clear evidence of its safety and efficacy—but should be considered in the choice of treatments available. Future studies should be conducted to clarify the role of ECT in treating this group of patients.

TREATMENT RESPONSE

Patients in their first-episode of schizophrenic psychosis present not only a challenge in terms of diagnosis and initiation of treatment but also the opportunity to influence the lifetime course of the illness. By initiating treatment early, maintaining patients on medication, and, thereby, preventing long and/or repeated exposure to psychosis, deterioration may be greatly limited or prevented and overall

Figure 1. Time to Remission Increases With Successive Psychotic Episodes in Schizophrenia*



*From reference 36, with permission.

outcome dramatically improved. Several lines of research come to bear on this issue and will be addressed individually below.

First-episode patients respond symptomatically to a greater degree and more rapidly than multiepisode patients. Early studies investigating the efficacy of antipsychotic medications found greater response in nonchronically ill individuals as compared to those who had long courses of illness.[1] In a more recent investigation, Lieberman et al.[21] reported that 83% of first-episode patients responded to rigorous systematic treatment with conventional antipsychotic medication. This rate of response is contrasted with response rates of approximately 70% reported in studies of more chronically ill patients.[35] These authors concluded that patients in their first episode of illness respond to antipsychotic treatment better than chronically ill patients.

The above studies were limited to examining the use of conventional antipsychotic agents in treating patients with schizophrenia. In the study by Tollefson et al.[31] discussed above, first-episode patients were extracted and analyzed separately from multiepisode patients, all of whom were involved in a large trial comparing response to olanzapine and haloperidol. First-episode patients treated with olanzapine were reported to respond to a greater degree than multiepisode patients so treated—approximately 65% versus 45%, respectively.

Not only does it appear that first-episode patients respond to treatment to a greater degree than chronically ill patients, they also respond more rapidly. Lieberman et al.[36] reported on a subgroup of first-episode patients who had remitted; these patients were followed and treated after a second (N = 27) and third (N = 10) psychotic episode. As seen in Figure 1, the time to remission increased progressively with subsequent episodes.

Prolonged psychosis prior to first treatment is associated with less complete and slower response to antipsychotic medication. Studies to directly address the question of random assignment of first-episode patients to antipsychotic medication and placebo cannot currently be ethically conducted owing to the established efficacy of antipsychotic medication and the suffering experienced by patients in the throes of a psychotic episode. However, the issue can be addressed indirectly by (1) assessing the relationship between outcome and duration of symptoms before treatment is initiated, (2) examining studies investigating the efficacy of antipsychotic medication shortly after their introduction when placebo treatment was acceptable, and (3) assessing relative outcome of patient samples before and after effective somatic therapies became available (mirror image studies).

Loebel et al.[2] studied 70 rigorously screened patients with first-episode schizophrenia or schizoaffective disorder involved in a protocol of algorithmically defined treatment with conventional antipsychotic medication. Treatment progressed from fluphenazine to haloperidol and, finally, to molindone—all at moderate to high doses—before a patient was defined as nonresponsive. Response (remission) was defined conservatively. Duration of untreated illness was defined both as the time from first behavioral change to admission and as the time from first psychotic symptoms to admission. The mean age at onset of psychotic symptoms was 23 years. The mean duration of illness based on behavioral change was 151 weeks; based on psychotic symptoms, it was 52 weeks. A longer duration of illness from the time at onset of psychosis was associated with a significantly longer time to treatment response ($p < .03$); the duration of illness, defined by either behavioral changes or psychotic symptoms, was associated with poorer levels of response ($p < .01$). Mode of onset was not associated with time to remission. Several other studies investigating pharmacologic treatment of first-episode patients[37–40] have reported similar results—i.e., poorer outcome when the period of initial untreated illness is greater than 6–12 months. These findings suggest that active psychosis is a morbid process that results in lasting morbidity if not ameliorated by antipsychotic medication.

May et al.[41,42] studied the hospital course and 5-year outcome (measured by number of days in hospital) in 228 patients with schizophrenia who were hospitalized for the first time. Patients were randomly assigned to one of five treatment groups: milieu therapy, psychotherapy, antipsychotic medication, psychotherapy plus medication, or ECT. Only treatment during the index hospitalization was controlled. Patients receiving medication or ECT spent considerably less time in hospital at index admission and demonstrated a significant outcome advantage over patients not receiving somatic treatment during initial hospitalization. Data from this patient sample was recently reexamined[43]; the results demonstrated that patients treated with antipsychotic medication at index admission required fewer days of rehospitalization in the second year after discharge. Patients initially treated pharmacologically were also functioning at a significantly higher level 6 to 7

years after index admission than patients initially receiving nonsomatic therapies ($p < .04$). Early initial somatic treatment appears to confer a long-lasting prognostic advantage as compared with delay of such treatment—independent of subsequent treatment or compliance.

Wyatt[44] reexamined data from 22 investigations (19 studies involved primarily first-episode patients) of patients with schizophrenia, comparing those who received antipsychotic medication during the study versus those who did not. In the majority of these studies, patients were only treated during index hospitalization since maintenance treatment was not the standard of care at the time the original studies were conducted. Despite this fact, the sum of the data suggests that first-episode patients who were treated early with antipsychotic medication and other somatic therapies had a significant advantage in outcome compared with those in whom this treatment was withheld or unavailable. The author suggested that unchecked psychosis may be biologically toxic, resulting in progressive neuroanatomical changes as well as psychopathologic and cognitive deterioration.

Deterioration may occur in the prepsychotic and early years of illness, setting the stage for long-term deficit/disability. The studies by May et al.[41,42] and Wyatt and colleagues[43,44] suggest strongly that delay in the pharmacologic treatment of first-episode schizophrenia results in significantly poorer outcome regardless of subsequent treatment. This notion is further supported by recent investigations of duration of untreated illness that demonstrate significantly poorer treatment outcome (slower and less complete response) when initiation of antipsychotic medication is delayed.[2] Clinical progression is also suggested by the increasing time of response to treatment during subsequent psychotic episodes[36] and increase in the prevalence of negative symptoms in chronically ill patients when compared with patients early in the course of illness.[45] Clinical progression of active illness is consistent with the assertion that untreated psychosis is a morbid process that results in disease progression unless ameliorated by treatment with antipsychotic medication. Moreover, clinical progression may be associated with changes in neuroanatomy and cognitive functioning.

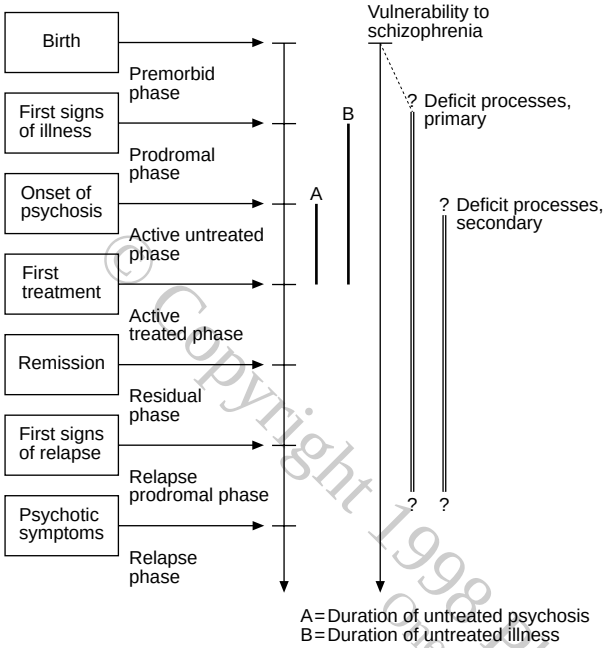
The evidence for progressive brain changes in schizophrenia is mixed and controversial, with older studies that relied on area-based global indices of neuroanatomy (such as ventricle-brain ratio) reporting both positive[46,47] and negative[48,49] findings of progressive lateral ventricle enlargement. Recent studies using volumetric indices have found evidence for changes in ventricle size and volume of other structures over time.[50,51] Findings of functional neuroanatomical differences between first-episode and chronically ill patients with schizophrenia also are consistent with disease progression over time.[52] Neuropsychologic deficits in schizophrenia are clearly demonstrated in both first-episode and chronically ill individuals. As with neuroanatomical evidence for progression, the neuropsychologic reports on worsening deficits over time are mixed.[53,54] However, the finding of cognitive decline during the course of illness is consistent with progression of illness severity (deterioration) over time.[55]

Early recognition and treatment of high-risk and prepsychotic individuals may result in a lower incidence of schizophrenia. At the time an individual is diagnosed in the first psychotic episode of schizophrenia, signs and symptoms representing premorbid and prodromal features of the illness have likely been present for many months or years. Premorbid features that are associated with later schizophrenia include teacher ratings of behavioral abnormalities (distractibility, lability, withdrawal),[3] affect abnormalities,[56] and early motor abnormalities.[57] Prodromal signs have most often been evaluated in patients undergoing relapse of an established illness rather than in first-episode patients. Frequently described symptoms include blocking of thought/speech,[58] impaired concentration/attention, decreased drive/motivation, depressed mood, disturbed sleep, anxiety, social withdrawal, suspiciousness, and irritability.[59] There is no consensus in the literature on the clinical features of the prodrome of schizophrenic psychosis. Furthermore, not all occurrences of prodromal symptoms lead to a full-blown psychosis.

In an effort to assess the impact of early treatment of individuals manifesting prodromal symptoms of psychosis, Faloon et al.[60] reported the results of a community-based project involving primary care physicians. The doctors were trained by and worked closely with a team of mental health professionals including psychiatrists, social workers, and nurses. The goal was to facilitate the earliest possible recognition of impending psychosis and intervene aggressively to prevent full-blown psychotic episodes and, thus, schizophrenia. Interventions included psychiatric evaluation and follow-up, provision of psychoeducation to the patient and family, enhancement of community supports, instruction in stress-reduction and problem-solving skills, and time-limited antipsychotic treatment; much of the treatment was provided in the home. The authors concluded that their early recognition and treatment strategy resulted in a substantial decrease in the incidence of diagnosed schizophrenia in the catchment area involved.

A model of the early life history of an individual with schizophrenia was described recently[61] and is presented in Figure 2. The diagram defines important concepts relevant to the early treatment of schizophrenia. Recommendation of early treatment intervention in first-episode psychosis—and possibly in episodes of relapse—initiated as close to the start of Phase A as possible is the primary thrust of this paper; treat early and aggressively, and the period of active psychosis and associated deterioration will be minimized and outcome enhanced. Community-based interventions aimed at recognizing prepsychotic in-

Figure 2. Conceptualization of the Early Course of Schizophrenia*



*From reference 61. ? = indefinite timing of onset and offset of schizophrenic process. - - - = primary deficit process may start with vulnerability to schizophrenia.

dicators (premorbid features, prodromal symptoms/signs) and providing multifaceted interventions are initiated as close to the beginning of Phase B as possible and are geared toward preventing full-blown psychosis and possible primary deterioration associated with the earliest period of schizophrenic illness.

CONCLUSION

The management of first-episode psychosis in young patients presents many difficulties, including problems in differential diagnosis, choice of treatment, and duration of follow-up. Patients must be quickly evaluated and pharmacologic treatment and patient education initiated as early as possible. Untreated psychosis has severe consequences for patients such as suboptimal treatment response, progressive deterioration for a portion of patients, and, ultimately, impaired functioning and increased need for treatment resources. Early and consistent treatment with antipsychotic medication appears to mute the actively morbid aspects of unchecked psychosis. The widespread implementation of a program of identification and treatment of incipient psychosis is limited by lack of rigorous study of the long-term prognostic implications of early pharmacologic treatment and clear evidence of its safety. By improving our ability to identify first-episode schizophrenic patients and treating them early with newer better-tolerated antipsychotic medications, it is possible that noncompliance will be decreased, duration of psychosis limited, and the natural history of the disorder improved. This line of thought also has tremendous implications for the financing of psychiatric treatment and societal costs related to schizophrenia given its tendency to strike early in an individual's life and markedly impair social and occupational functioning thereafter.

Drug names: chlorpromazine (Thorazine and others), clozapine (Clozaril), fluphenazine (Prolixin and others), haloperidol (Haldol and others), molindone (Moban), olanzapine (Zyprexa), risperidone (Risperdal).

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Disclosure of Off-Label Usage

The author of this article has determined that, to the best of his clinical estimation, no investigational or off-label information about pharmaceutical agents has been presented that is outside Food and Drug Administration–approved labeling.