The Evaluation and Treatment of First-Episode Psychosis

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Abstract

A first episode of psychosis is a traumatic experience for patients and families. At the time of initial evaluation, the differential diagnosis should include a broad range of neurological, general medical, and psychiatric conditions. Methodological advances in operationally defining illness onset, "offset," and remission have allowed more careful studies of treatment response in first-episode patients. These studies strongly support the efficacy of antipsychotic medication as both acute and maintenance treatment for patients with a first episode of psychosis. The optimal duration of maintenance treatment, however, has not been determined, and patients at low risk for relapse following medication withdrawal cannot be identified with specificity. First-episode psychotic patients typically experience 12 to 24 months of psychosis before receiving treatment, and a long duration of untreated psychosis may be associated with a poorer treatment response. Early intervention may improve outcome in first-episode psychosis, and the use of novel antipsychotics with improved efficacy and fewer side effects may improve medication compliance and reduce morbidity associated with repeated relapses.


Compared with the substantial data available from the study of chronic multiepisode patients, there is a paucity of research describing the phenomenology and treatment of first-episode psychotic patients. Keshavan and Schooler (1992) identified 53 first-episode schizophrenia or psychosis studies; two-thirds of which focused on biological phenomena, most often neuroimaging. They described differences in clinical assessment methods and inconsistent reporting of key variables that have limited our ability to generalize from these investigations. Greater attention to carefully defining patient populations and illness characteristics has consistently been recommended to increase comparability across first-episode studies (Kirch et al. 1992; Lieberman et al. 1992; Maurer and Häfner 1995). In this article, we review the differential diagnosis of a first episode of psychosis, discuss selected methodological issues that must be considered in order to interpret available empirical studies, and comprehensively review the results of acute and maintenance treatment studies of first-episode psychotic, predominantly schizophrenia patients.

Differential Diagnosis

Evaluating a patient with a first episode of psychosis requires consideration of a broad differential diagnosis. Psychosis is not pathognomonic for schizophrenia, but rather a symptom of a wide array of psychiatric, neurological, and general medical disorders. The absence of a family history of major mental illness, an acute illness onset, an age at onset beyond the middle 30s, and psychosis in a patient undergoing treatment in an emergency, general medical, or intensive care unit will heighten concern that psychotic symptoms are secondary to a nonpsychiatric illness. Even if the index of suspicion is low, the prudent evaluating psychiatrist will consider a first episode of psychosis to be the result of a neurological or medical condition until completing a thorough evaluation.

Medical and Neurological Conditions. All first-episode psychotic patients should have a thorough medical evaluation, including a review of systems and a physical exam that includes a neurological evaluation. In addition, a complete blood count, electrolytes, serum creatinine, blood urea nitrogen, thyroid function tests, venereal disease tests, urinalysis, and a toxicology screen should...
Psychiatric Disorders.

Affective illness. When patients with a first episode of psychosis also demonstrate manic or depressive symptoms, differentiating a primary psychotic disorder from a mood disorder with psychotic symptoms is problematic. In order to make this determination, many classification systems require a retrospective assessment of the temporal relationship between the onset of mood symptoms and psychosis, which is often difficult to determine. In addition, many patients have depressive or manic symptoms, but do not meet the full syndromal criteria for an affective disorder. Because differentiating the two syndromes may have treatment and prognostic implications, a careful history that includes interviews with family members and other informants should be obtained. In a sample of first-episode psychotic patients for whom treatment was not controlled, Tohen et al. (1992) reported that patients diagnosed with affective psychotic disorders had shorter hospitalizations and a higher level of functional recovery than patients diagnosed with schizophrenia spectrum disorders. In an open treatment trial using a standardized medication algorithm, Koreen et al. (1993) reported that the depressive symptoms of the vast majority of acutely psychotic patients diagnosed with schizophrenia and schizoaffective disorder were resolved when psychotic symptoms had remitted.

Substance Abuse. A significant proportion of first-episode psychotic patients report current or past substance abuse (Bromet et al. 1992). The hallucinogens LSD and PCP—as well as cocaine, marijuana, and alcohol—may induce psychotic symptoms. Illicit substance abuse often presents a diagnostic challenge (e.g., the patient whose last use of cocaine is more than 3 days past, but who remains psychotic and agitated and requires antipsychotic medication). Strict adherence to DSM-IV (American Psychiatric Association 1994) requires that the psychotic symptoms persist for at least 1 month to exclude a diagnosis of substance-induced psychotic disorder. The effects of substance abuse on the onset, treatment response, course, and outcome of psychotic illnesses are not well understood, although most (DeQuardo et al. 1994; Chouljian et al. 1995; Gupta et al. 1996), but not all (Dixon et al. 1991) evidence suggests a deleterious effect on treatment response and outcome.

Brief psychosis. Extremely transient psychotic episodes, lasting minutes to hours, can sometimes occur in individuals with borderline or schizotypal personality disorder. In contrast, the diagnosis of brief psychotic disorder applies to psychosis that lasts at least 1 day, but less than 1 month. The episode is often characterized by florid symptoms, confusion, and emotional turmoil in the context of an environmental stressor (Frances et al. 1995). In a prospective study of 221 first-admission patients with psychosis, Susser et al. (1995) noted that 20 (9%) patients had a brief psychosis (defined as full remission of symptoms at 6-month followup). For patients with acute (as opposed to gradual) onset, brief psychosis appeared to be a distinctive and stable subgroup. Most patients with brief psychosis were women, and none of the patients' disorders had evolved into chronic schizophrenia or affective disorders by 24 months.

Prospective longitudinal observation over a period of 6 months or more may be required to clarify diagnosis in patients presenting with a first episode of psychosis.

Methodological Considerations

Illness Onset. Definitions of the beginning of a first psychotic episode must account for the likelihood that many dimensions of behavioral and cognitive functioning can be impaired with the time of onset of each symptom differing. Prodromal symptoms may appear many years before the onset of a frank psychosis (Carpenter and Kirkpatrick 1988; Häfner and Nowotny 1995; Yung and McGorry 1996), and patients often do not present for admission to a hospital for a first episode of psychosis until a significant amount of time after the onset of psychotic symptoms, that is, 12–24 months (Gift et al. 1981; Fenton 1997). Keshavan and Schooler (1992) have listed...
six distinct clinical events that need to be examined in identifying the onset of a first episode of psychosis: decline in social functioning, onset of general behavioral symptoms, onset of positive symptoms, onset of negative symptoms, first treatment, and first hospital admission.

**Response Criteria (Illness “Offset”).** In treatment and outcome studies where the end of the first episode and number of subsequent episodes are used as measures of illness course, a clear definition of the end of the episode or episode “offset” is required. Multiple dimensions of psychopathology in schizophrenia make the definition of response complex, with the potential for a wide disparity in response rates depending on the operational criteria used. Response rates based on the resolution of positive symptoms will be considerably higher than those based primarily on negative symptom resolution. Social and vocational disability may extend for a considerable period beyond that required for symptom resolution. Sole reliance on a percentage decrease in rating scale scores from a pretreatment baseline may result in inflated response rates, since most patients—particularly first-episode patients—would be expected to have at least some response to antipsychotic medication. Since managed care has supplanted clinicians’ judgment, the duration of initial hospitalization is likely to be of limited validity as a measure of treatment response.

The characterization of patients who develop non-schizophrenic symptoms following the remission of psychosis and those who admit to ongoing residual delusions can affect the response and relapse rates reported. A relatively common example of the former is the appearance of a postschizophrenic depression (McGilhlan and Carpenter 1976; Siris 1991). The concept and significance of a residual delusion (defined as a delusion about a past event that persists even though the patient no longer believes it is occurring at the present time and the patient’s behavior is not affected by it) has received little formal attention. An example is the patient who claims that her phones were tapped 1 year ago but not at present and is able to maintain work and social functioning despite the residual delusion.

**Treatment Studies**

Because of the difficulty in enumerating cases and obtaining patient consent, there have been relatively few studies of the efficacy of standardized treatment administered to first-episode psychotic patients. Treatment studies are to be differentiated from outcome studies (May et al. 1981), which assess illness course without controlling treatment. Acute treatment studies of the first episode of psychosis, primarily patients diagnosed with schizophrenia (May et al. 1976a, 1976b; Scottish Schizophrenia Research Group 1987a, 1987b; Lieberman et al. 1993a, 1993b; Szamuely et al. 1994; Kopala et al. 1996), and maintenance studies of remitted first-episode patients (Kane et al. 1982; Crow et al. 1986; Johnstone et al. 1986; Scottish Schizophrenia Research Group 1989; Nuechterlein et al. 1992, 1994) are reviewed here.

**Acute Treatment Studies.** May et al. (1976a, 1976b) conducted the first treatment study of first-episode schizophrenia. In this study, 228 patients were randomly assigned to one of five treatment arms: individual psychotherapy, trifluoperazine, psychotherapy plus trifluoperazine, electroconvulsive therapy (ECT), or milieu therapy alone. Patients with “no significant prior treatment” were selected on a “triage” basis from consecutive first-admission schizophrenia patients to a State hospital between 1959 and 1962. The authors attempted to select the middle third of schizophrenia patients by excluding those they believed would be unlikely to be discharged and those who had remitted during the 18-day evaluation period. The treatment continued until the patient was released or 6–12 months of treatment was determined unsuccessful. The response rates at the time of discharge were as follows: psychotherapy plus drugs (95%); drugs alone (96%); ECT (79%); psychotherapy (65%); milieu therapy alone (58%). Although this study has methodological limitations from today’s perspective, considering when it was conducted it stands as a remarkable achievement in clinical research. The results demonstrated the indisputable superiority of antipsychotic medication over psychotherapy in the treatment of patients with a first episode of schizophrenic psychopathology. At followup 3 to 5 years after treatment (May et al. 1981), patients in the groups that had received drugs or ECT had the best outcome, and those treated with psychotherapy alone had the poorest outcome. Treatment over the followup period, however, was not controlled.

The Scottish Schizophrenia Research Group (1987a) described a randomized, double-blind, 5-week treatment trial of pimozide versus flupenthixol for 49 first-episode schizophrenia patients. The dose of each neuroleptic began at 10 mg/day and could be titrated up to 40 mg for pimozide and 50 mg for flupenthixol. Approximately half of the eligible patients from four centers consented to participate. Criteria for study entry was a clinician’s International Classification of Diseases—Ninth Revision (ICD–9; World Health Organization 1978) diagnosis of a first episode of schizophrenia. The Present State Exam (PSE; Wing et al. 1974) administered during the first week of admission was used to confirm clinical diagnosis.
patients were also evaluated with Research Diagnostic Criteria (RDC; Spitzer et al. 1978a) and Feighner criteria (Feighner et al. 1972). Using the RDC classification system, there were 33 definite and 9 probable cases of schizophrenia; because of the requirement for 6 months of illness, Feighner criteria diagnosed only 15 cases of definite or probable schizophrenia. Sixty-three percent were classified as "responders" to antipsychotic medication, with similar results for each medication. Nonresponders tended to be male, and they had more neurological signs, cognitive deficits, and negative symptoms. Twenty percent of the patient sample was noted to have a history of possible neurological dysfunction. Response criteria were not operationally defined.

In a prospective study of the psychobiology of psychosis, Lieberman et al. (1993a, 1993b) reported the results of an open trial of standardized antipsychotic treatment for 70 RDC-diagnosed schizophrenia (n = 54) and schizoaffective (n = 16) first-episode patients. The inclusion-exclusion criteria were no prior psychotic episodes, a diagnosis of definite or probable schizophrenia or schizoaffective disorder (mainly schizophrenia) by RDC, age 16 to 40, and no history of neurological or general medical illness that could influence the diagnosis or the biological variables that were to be assessed. Of 416 patient admissions screened, 219 met inclusion criteria, but 127 either refused to participate or were excluded for clinical or administrative reasons. Of the 92 patients who entered the study, 19 were later withdrawn based on information that became available subsequent to the baseline assessments.

Patients were administered structured assessments—Schedule for Affective Disorders and Schizophrenia—Change Version (Spitzer et al. 1978b); Scale for the Assessment of Negative Symptoms (Andreasen and Olsen 1982); Clinical Global Impressions scale (CGI; Guy 1976); Simpson-Angus Neurological Rating Scale (Simpson and Angus 1970); Simpson Dyskinesia Scale (Simpson et al. 1979)—at baseline and biweekly and were treated within an open standardized algorithm of sequential trials of fluphenazine (20 mg for 6 weeks, then 40 mg for 4 weeks), haloperidol (20 mg for 6 weeks, then 40 mg for 4 weeks), molindone hydrochloride (up to 300 mg/day), and finally clozapine (up to 900 mg/day). Patients proceeded through the algorithm until response criteria were met. Based on positive and negative symptoms and CGI scores, operational response criteria were used to define full or partial remission. Illness onset was described both as the age at which the patient exhibited behavioral symptoms that, in retrospect, appear to have been related to and were contiguous to the current illness and as the age at first psychotic symptoms. The median durations of general behavioral symptoms and of psychotic symptoms before study entry were 151 ± 176 weeks and 52 ± 82 weeks, respectively.

Using a survival analysis, the proportion of patients remitting by 1 year was 83 percent, with the median and mean time to remission 11 and 35.7 weeks, respectively. Within the treatment algorithm, 62 percent of patients developed at least one form of extrapyramidal side effects (EPS) (Chakos et al. 1992). Brain pathomorphology and abnormal basal growth hormone secretion significantly predicted time to remission (Lieberman et al. 1993a). The length of time a patient had been psychotic before study entry (i.e., duration of untreated psychosis) was associated with both a longer time to remission and a lower level of remission among these first-episode patients (Loebel et al. 1992). In a followup to the Lieberman et al. (1993a) study, Szymanski et al. (1994) reported on the efficacy of open clozapine treatment among 10 first-episode patients who failed to respond to typical neuroleptic treatment in the standardized treatment protocol. The patients had been psychotic before clozapine treatment for a median time of 131 weeks. Brief Psychiatric Rating Scale (BPRS; Overall and Gorham 1962) scores were obtained after a 2-week drug washout and biweekly for 12 weeks after beginning clozapine treatment. Clozapine was titrated to 500 mg over 2 weeks and then adjusted as "clinically indicated." The mean maximum dose of clozapine was 687.5 mg/day (standard deviation [SD] = 214.8) with a range of 300–900 mg/day. Response criteria were a 20-percent reduction from a summed baseline BPRS score and a CGI severity of illness score less than or equal to 3 (mildly ill). Three of 10 patients met these criteria (2 at 6 weeks and 1 at 12 weeks), although none fully remitted. This 30-percent response rate was comparable to the rate reported by Kane et al. (1988) in treatment-resistant schizophrenia, suggesting that patients who are refractory to treatment in their first episode of illness may be among the most severely ill patients with schizophrenia.

Kopala et al. (1996) described the efficacy of open risperidone treatment among 22 (17 male) consecutively admitted, neuroleptic-naive patients hospitalized for the first time who met DSM-IV criteria for schizophrenia. Substance abuse, previous head injury, other "organic pathology," uncertain diagnosis, or inadequate collateral history were exclusion criteria; 11 patients were excluded based on these criteria. Patients had a mean duration of "illness" before treatment of 245.7 weeks (SD = 217.8). Psychopathology was assessed using the Positive and Negative Syndrome Scale (PANSS; Kay et al. 1987), with the authors reporting interrater reliability scores of 0.90. Response was defined as a 20 percent or greater reduction in the total PANSS score. Risperidone was initiated at
1 mg twice daily and increased to 2–8 mg/day; mean dose was 4.7 mg/day (SD = 1.5). The mean duration of treatment was 7.1 weeks (SD = 3.2; range, 1.8–14.1). The authors reported that 59 percent of patients met response criteria.

**Maintenance Treatment Studies.** Kane et al. (1982) were the first to report on the efficacy of prophylactic antipsychotic medication in a study of 28 (14 female) patients screened from referrals to an aftercare clinic who had achieved a stable remission following treatment for a first episode of schizophrenia. Inclusion criteria were one schizophrenic episode, no important psychopathology or mental health contact for a period of 3 months before hospitalization, a stable level of remission for at least 4 weeks (maximum, 1 year) following hospital admission, no evidence of substance abuse or important medical illnesses, and willingness to provide informed consent. When rediagnosed by RDC, only 19 of these 28 patients were diagnosed with schizophrenia. Subjects received oral fluphenazine (5–20 mg/day), fluphenazine decanoate (12.5–50 mg every 2 weeks), or placebo. Only subjects judged likely to be noncompliant were randomized to fluphenazine or placebo injections, and randomization was changed to favor placebo 2:1. Relapse was defined as substantial clinical deterioration, with a potential for marked social impairment. Of 28 patients enrolled, 7 relapsed and 8 others completed the 1 year of treatment. Of the RDC schizophrenia patients who received fluphenazine (n = 6), none relapsed; 4 left the study before 1 year, and 2 subjects completed; of the 13 RDC schizophrenic patients treated with placebo, 6 relapsed, 6 dropped out, and only 1 completed. Overall, 7 of the 17 patients who received a placebo, but none of the 11 drug-treated patients relapsed over 1 year. Despite methodological limitations, this study provided evidence of the efficacy of maintenance antipsychotic medication in reducing the risk of relapse among first-episode patients.

Crow et al. (1986) described a randomized, placebo-controlled trial of maintenance neuroleptics for 120 patients discharged following a first episode of schizophrenia. As part of the Northwick Park Study of first-episode schizophrenia, patients were recruited from several medical centers within 35 miles of Harrow, England. Inclusion criteria were age 15–70 years; a first psychotic episode (no past psychosis, possible psychosis, or previous inpatient care exceeding 3 days); admission to inpatient or day-patient care for at least 1 week; clinical diagnosis of schizophrenia, categories C, O, or P on the PSE (Wing et al. 1974); and absence of organic disease of definite or probable etiological significance. Of the 462 cases referred, 209 were excluded and 253 agreed to participate in the initial assessments. Of these, 120 (74 male) agreed to participate in the maintenance neuroleptic medication trial. Onset of illness was defined as the beginning of psychotic symptoms; response, as discharge from the hospital for 30 days or more; and relapse, as readmission to psychiatric care for any reason. Participating patients had been psychotic for a median of 2.8 months (range, 1–101 months) before index admission. Patients were assigned to one of five antipsychotics or to placebo. The minimum medication dosages were flupenthixol intramuscular 40 mg/month, chlorpromazine 200 mg, haloperidol 3 mg, pimozide 4 mg, and trifluoperazine 5 mg per day. Fifty-four patients (35 male) who received medication and 66 (37 male) who received placebo were treated up to 2 years or until study termination. Among 107 patients who completed the study, 62 percent of those on placebo and 46 percent of those on active medication relapsed. The duration of illness before beginning neuroleptic medication was the most important determinant of relapse, suggesting either that extended duration of untreated symptoms is more likely to be present in illnesses with a poor prognosis or that susceptibility to relapse is reduced by early treatment.

The Scottish Schizophrenia Research Group (1989) reported the results of a trial of maintenance treatment in a subgroup of patients (n = 15) from the Scottish First-Episode Schizophrenia Study who responded to drug treatment during their index episode and were entered into a double-blind study of either once-weekly pimozide or intramuscular flupenthixol decanoate for 1 year. After providing consent, these patients, none of whom relapsed during the first year, were then entered into a double-blind study of active medication (once-weekly pimozide or intramuscular flupenthixol decanoate) or placebo. Relapse was defined as a deterioration in schizophrenic symptoms or behavior sufficient to warrant the patient's withdrawal from the study. None of the eight patients who received active medication, but four of seven who received placebo, were readmitted in the second year of treatment.

As part of a longitudinal study of first-episode psychosis, Nuechterlein et al. (1994) described the relationship between life events and illness exacerbation during a first year of standardized outpatient antipsychotic treatment and a subsequent 24-week double-blind, drug-placebo crossover period. Patients (n = 106, 87 male) were recruited from admissions to four public hospitals and the outpatient service of a university medical center. Inclusion criteria were recent onset of a psychotic disorder with symptoms lasting at least 2 weeks and a first psychotic episode starting not more than 2 years before project entry; age 18 to 45 years; an RDC diagnosis of schizophrenia or schizoaffective disorder (mainly schizophrenia); and Anglo-American, Native American, or
acculturated Hispanic or Asian background. Exclusion criteria were a known neurological disorder; recent (less than 6 months) significant and habitual substance abuse; mental retardation (IQ < 70); and African-American descent (these patients were excluded due to differences in electrodermal conductivity from other groups, a biological variable that was also being studied). Two-thirds of the patients were neuroleptic naive before enrolling in the study. Assessments included BPRS and Psychiatric Assessment Scale (PAS; Krawieka et al. 1977), administered weekly; life-event interviews, monthly; and Strauss/Carpenter social and work outcome scale (Strauss and Carpenter 1972) and the UCLA social attainment scale (Goldstein 1978), quarterly. Operational criteria were used to define psychotic exacerbation, psychotic relapse, and nonpsychotic relapse. Phase 1 of the study was undertaken after 2 to 3 months of clinical stabilization following inpatient discharge. Patients then received 12.5 mg of fluphenazine decanoate every 2 weeks for 12 months. During this period, 11 patients needed their dose lowered due to side effects, and 6 patients were prescribed antidepressants. Phase 2 of the study recruited those patients who showed sufficient remission of psychotic symptoms over the first year. These patients received fluphenazine or placebo for 3 months and were then crossed over to the other treatment. Patients maintaining stability during this crossover period were invited to participate in an open, drug-free treatment period. During phase 1, independent life events and caregiver expressed emotion were associated with an elevated risk of relapse. Although the results from phase 2 are preliminary at this time, life events appeared to play a lesser role in the prediction of relapse during a medication-free period.

Conclusions

The limited number of available treatment studies of first-episode psychotic patients, most of whom were diagnosed with schizophrenia, strongly support the efficacy of antipsychotic medication, both in the acute phase of the illness and in relapse prevention in the first 2 years following stabilization. Compared to patients with long-established illnesses, a greater percentage of first-episode patients appear to respond to pharmacological treatment (Lieberman et al. 1996), even though 10 to 20 percent of patients may be resistant to conventional antipsychotic medication at the time of first treatment. Consistent with enhanced efficacy in reducing psychotic symptoms, first-episode patients also appear more vulnerable to side effects than chronic multiphase patients.

Many investigators note that patients typically experience active psychosis for 12 to 24 months before obtaining treatment (Fenton 1997). Although data are not definitive, the association between the duration of untreated psychosis and time to and quality of remission (Loebel et al. 1992) suggests that an active morbidity process may be operative in the early stages of schizophrenia (Wyatt 1991, 1995). In a prospective study of treatment response in first-episode and chronic patients, Szymanski et al. (1996) found that a longer duration of untreated illness was associated with diminished reduction in positive symptoms over 6-month and 2-year followup in both patient groups. In the Nottingham study of predictors of long-term outcome among first-hospitalized patients (Harrison et al. 1996), longer duration of untreated illness predicted poorer outcome at 13 years in the domains of disability, psychopathology, and social functioning. Waddington et al. (1995) found that muteness was the primary clinical correlate of initial duration of untreated psychosis in a group of older chronically ill schizophrenia patients. This symptom was viewed as the end stage in increasing severity of the negative symptom of poverty of speech; patients with a longer duration of untreated psychosis were more likely to progress to this end stage. It is possible that early identification and treatment of patients at or before a first episode of psychosis may limit the accrual of morbidity or alter the natural history of the illness (Wyatt 1995; McGlashan and Johannessen 1996).

Although antipsychotic treatment is clearly indicated for an acute psychosis and reduces the vulnerability to relapse over the year or two following a first episode, the important question of how long to continue prophylactic maintenance treatment is unclear. Many patients with schizophrenia will ask to stop their medication as soon as possible after they have recovered from an initial acute episode. Despite a reduction in relapse rates with maintenance treatment, data from maintenance studies that have followed patients for up to 2 years indicate that a significant (38% in the Crow et al. 1986 study) proportion of patients will not relapse during this period. A reasonable clinical approach must balance the possibility of the accrual of morbidity through relapses with the desire of most patients to discontinue medication. Maintenance treatment for 1 to 2 years, followed by a very slow medication taper (20% per month) in conjunction with psychosocial treatment that emphasizes psychoeducation for the patient and family, is likely the optimal recommendation (Frances et al. 1996). During medication reduction, both the patient and his or her family should be encouraged to contact the psychiatrist about even a remote suspicion that the patient may be experiencing such prodromal symptoms of relapse as difficulty sleeping, withdrawal, suspiciousness, or ideas of reference. In addition, the clinicians should see the patients with sufficient frequency to
detect signs of relapse, especially those patients who are unable to identify such symptoms themselves. The risks and benefits of medication continuation and withdrawal should be fully discussed with patients and family members before initiating medication withdrawal, and informed consent should be obtained.

In our opinion, the novel antipsychotics currently available (risperidone and olanzapine) and others soon to be marketed (sertindole, quetiapine, and ziprasidone) should be seriously considered as a first-line therapy for a first-episode of psychosis. Enhanced efficacy in the treatment of negative symptoms and a more favorable side-effect profile, particularly less EPS, have been demonstrated in chronic patient samples (Marder and Meibach 1994; Beasley et al. 1996) and might be expected to improve medication compliance, allowing longer periods of maintenance treatment in patients at the beginning of their illness (Lieberman 1993a).

Unfortunately, clozapine’s potential for hematologic toxicity, along with the need for indefinite white blood cell count monitoring, make this medication a less likely first-line agent.

Further research is needed to clarify a variety of clinical questions concerning first-episode psychosis for which insufficient data are available. Among these are the following:

1. What is the natural history of disease before the usual time of presentation to the hospital? That is, when and how does the illness actually begin, and how can prodromal symptoms be reliably distinguished from normal behavioral vicissitudes?
2. Do psychotic symptoms develop gradually, intermittently, or persistently?
3. What medication, at what dosage, over what duration of treatment is the best intervention in first-episode psychosis?
4. Can reliable clinical or biological indicators of outcome following drug discontinuation be identified?
5. What effect does early treatment have on long-term course and outcome?

Carefully designed early-intervention and first-episode treatment studies should inform these clinical questions and provide a broadened empirical basis for reducing the morbidity associated with psychotic illnesses.

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