

Treatment and Outcomes in Adolescents With Schizophrenia

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The pharmacologic treatment and assessment of outcomes in adolescents with schizophrenia have been inadequately addressed. Structural brain imaging and brain function studies both point to a continuity between adolescent and adult stages of schizophrenia. Because the teenage population seems to be less tolerant of physical side effects, the advent of atypical antipsychotic medications may offer increased safety and efficacy. Studies support the notion that adolescent illness is associated with a more severe form of schizophrenia and that length of illness before treatment is correlated with long-term outcome. As a consequence, the authors recommend assertive pharmacologic intervention in adolescents with schizophrenia and future research focused on the issues of treatment and outcome in teenagers suffering a psychotic disorder. *(J Clin Psychiatry 1998;59[suppl 1]:50-54)*

The pharmacologic treatment of teenagers who suffer from schizophrenia and schizophrenia spectrum disorders has not been adequately addressed by the literature. In addition, the assessment of outcomes of schizophrenia when its onset has occurred during teenage years has not been well studied. This shortage of investigation may be secondary to the view of psychiatrists and other clinicians who have historically perceived psychosis in teenagers as a reaction to stress rather than as the early stage of the generally lifelong illness, schizophrenia. Research on schizophrenia has focused more on childhood schizophrenia, which is a rare disorder, leading to the misperception/generalization that pre-adult psychosis is rare. Indeed, Loranger et al.¹ indicated that 39% of men and 23% of women have onset of schizophrenia before 19 years of age.

Recently, the research group at Case Western Reserve University has investigated teenagers with schizophrenia and bipolar illness to address the issue of neuropsychiatric parameters at this early phase of the illness. Other groups, such as the Child Psychiatry Branch of the National Institute of Mental Health (NIMH), have also pursued brain imaging and psychopharmacology studies in this previ-

ously ignored age group. Therefore, there is a growing interest in neuropsychiatric research in patients who are under 18 years old. The purpose of this paper is to describe the research indicating a continuity between adolescent and adult stages of schizophrenia, to review the psychopharmacologic strategies reported in the literature, to examine issues of outcome in teenagers, and lastly to speculate on the future work needed to improve treatment and outcome for teenagers suffering a psychotic disorder.

NEUROPSYCHIATRIC CONTINUITY: ADOLESCENCE TO ADULTHOOD

Early psychiatric diagnostic criteria described schizophrenia as a psychosis in a clear sensorium. The concept that schizophrenia was an illness without brain abnormality pervaded the American literature until the advent of noninvasive brain imaging research. Even though there are over a hundred brain imaging studies addressing various aspects of schizophrenia (see Elkis et al.² for a review and meta-analysis), little work has been performed during the adolescent phase of schizophrenia. Our group has recently reviewed this literature³ noting that of the few studies published, most report that adolescents have both brain imaging and neuropsychological test "abnormalities." Most, but not all, of the early computed tomography studies indicated findings in teenagers similar to those seen in adults. For example, Schulz et al.⁴ found enlarged ventricles in teenagers with schizophrenia or schizophreniform disorder when compared to teenagers in film library controls.

With the advent of MRI, our group⁵ has made a preliminary report indicating that teenagers with schizophrenia have a smaller brain size than community controls. This

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finding of small brain volume is consistent with a recently conducted meta-analysis that shows small brain volume to be a characteristic of schizophrenia.⁶ The NIMH Child Psychiatry Branch, having utilized MRI, has reported smaller temporal lobe area as well as smaller brain size in severely ill childhood-onset schizophrenic patients assessed during adolescence.^{7,8} Taken together, these studies indicate support for the view that adolescent schizophrenia is on a continuum with the adult stage of the illness. Further studies designed to follow young patients over time are needed to understand whether these are morphometric changes over time in the early onset group.

Brain function, as assessed by neuropsychological testing, also points to a continuum between adolescents with schizophrenia and adults with the disorder. Early reports noted differences between teenagers and other psychiatric patients³ as well as differences between verbal and performance IQ within patients.⁹ These preliminary studies pointed the way to possible functional difficulties in this young patient group and to the need for more extensive neuropsychological assessments of teenage patients. Again, in a preliminary report Kenny et al.¹⁰ have indicated that stabilized adolescent schizophrenic patients have diminished neuropsychological function, especially in the area of attention and short-term memory. Our group's findings in adolescents are not identical with nor as severe as the findings of treatment-refractory schizophrenic patients¹¹ and may indicate that functional disturbances could be progressive. However, ideas about progression need to be balanced with issues of sampling when comparing adolescent to adult studies.

The research in the exploration of continuity between adolescent and adult schizophrenic patients is also consistent with the neurodevelopmental hypothesis of schizophrenia. Many recently conducted studies have demonstrated difficulties in neuropsychological or neuromotor characteristics of young people who later became schizophrenic.¹² Brain imaging work showing smaller brain volume is consistent with the finding by McNeil et al.¹³ of decreased head size in newborns who later developed schizophrenia compared to newborns who did not. Looking at different measures—imaging and neuropsychology—as well as strategies such as those of McNeil et al.,¹³ we conclude there is ample evidence for continuity between adolescent and adult schizophrenia.

The significance of the work studying continuity between adolescent and adult stages of schizophrenia can be related to treatment strategies as well as more fundamental research. If schizophrenia during teenage years is an early stage of schizophrenia, then assertive treatment strategies, especially utilizing psychopharmacology, are indicated. Further support for an assertive approach to the pharmacologic treatment of adolescents comes from research in first-episode patients indicating a relationship between the length of time youngsters are ill to their long-term out-

come. This point will be discussed at greater length in the section on pharmacologic treatment. Therefore, in addressing treatment and outcome in adolescents with schizophrenia, our group feels that it is important to consider the evidence that adolescent schizophrenia is a stage of the overall disease.

ACUTE OUTCOME: PHARMACOLOGIC INTERVENTION

As noted in a recent review by Findling et al.,¹⁴ there are few psychopharmacology studies utilizing objective rating criteria to address the impact of medications on adolescents with schizophrenia.

Our group found two trials addressing the impact of antipsychotic medications on children who suffer from schizophrenia. One study demonstrated symptom reduction with both fluphenazine and haloperidol.¹⁵ It is an interesting historical note to see the relatively high doses used in this study. Also, an assessment of the paper reveals that some patients may have suffered from autism, thus not addressing only schizophrenia. A more recent study with DSM-III-R diagnosis by Spencer et al.¹⁶ utilized a placebo control, thus allowing for more certain conclusions about treatment effect of the active medication group. In this work, haloperidol was statistically more effective than placebo, especially in the area of positive symptoms. The study notes the sedating and movement disorder side effects of haloperidol treatment in adolescents.

Prior to this year, there were only two controlled trials in adolescents of antipsychotic medications utilizing objective rating scales. The first by Pool et al.,¹⁷ performed 20 years ago, compared loxapine, haloperidol, and placebo during a 4-week trial. Both of the antipsychotic medications were better than placebo with only minor differences between the two active treatments. The authors note that the most severely ill patients had the greatest effect of antipsychotic medication. Even though 75% of patients had extrapyramidal side effects (EPS), the authors indicated that side effects were not severe. In actuality, this is the only placebo-controlled trial of adolescents with schizophrenia in the refereed literature.

In describing the response of adolescents to the two antipsychotic medications tested, thiothixene and thioridazine, Realmuto and colleagues¹⁸ noted their clinical impression of a long prodrome prior to initial treatment for their patients. In some contrast to Pool et al.,¹⁷ Realmuto et al.¹⁸ were less impressed with the effect of the two drugs tested, even though there was significant reduction in Brief Psychiatric Rating Scale (BPRS) scores. The authors note that 9 of 21 patients were in the "slight improvement," "unchanged," or "worse" category of the Clinical Global Impressions (CGI). Another concern was the relationship of efficacy to side effects. The investigators indicated that many patients could not tolerate the most effica-

cious doses—mostly because of sedation. This problem was felt “to produce an ominous prognosis.”¹⁸ If this turns out to be a valid impression, it could be part of the reason many clinicians feel adolescent onset schizophrenia is a more severe form of the illness. The main outcome of the study was the finding that BPRS scores were reduced quickly and the reductions were sustained. It is of interest to note that there was no comment on “acceptability” of antipsychotic medications, an important concern which is different from an assessment of side effects.

In previous years, Schulz and Koller¹⁹ indicated the appropriateness of assertive psychopharmacology treatment based on the idea of continuity between the adult and adolescent forms of the illness. In earlier years, the only pharmacologic intervention for schizophrenia was the group of typical antipsychotic medications. There are difficulties with these medications which deserve some attention at this point. First is the general clinical impression that teenagers are much more sensitive to administration of typical antipsychotics than adult patients. Frequently, teenagers suffer from dystonic reactions, and some groups²⁰ have described the use of prophylactic anticholinergic medications for this age group. In addition, young patients appear to have other movement disorder side effects such as parkinsonism more frequently than adults. As these side effects occur during a period of development in which patients may be less tolerant of physical side effects, the therapeutic alliance and medication compliance may be markedly affected by the use of the typical antipsychotic medications. In addition, we have noted that many families are exceedingly distressed when these movement disorder side effects occur in their children. When these medications were all that was available for somatic treatment, the risk/benefit ratio was clearly on the side of initiating treatment; however, currently, there are alternatives to the typical antipsychotics for the treatment of teenage schizophrenic patients. The emerging literature concerning atypical antipsychotic medications will be discussed in the next section.

Outcome With Atypical Antipsychotic Medication

Clozapine was the first atypical antipsychotic medication available in the United States; however, its availability was limited to patients nonresponsive to typical antipsychotics or those suffering from severe tardive dyskinesia or neuroleptic intolerance.²¹ Our group’s impression is that psychiatrists treating teenagers with schizophrenia are reluctant to utilize clozapine in their young patients. However, there are case reports²² indicating the safety and efficacy of clozapine in treatment-refractory teenagers. At the NIMH, there are reports^{23,24} of the benefits of clozapine in neuroleptic-resistant childhood-onset schizophrenic patients treated during adolescence. In the latter controlled trial, clozapine was found to be statistically superior to haloperidol, thus indicating its usefulness in treatment-refractory patients. However, caution must be noted as the

study indicated a substantial sensitivity of the young patient group in the area of seizures and neutropenia.

As tardive dyskinesia can occur in teenagers suffering from schizophrenia and as there is evidence that clozapine can be useful for tardive dyskinesia, it is important to note that case reports²⁵ indicate the efficacy and safety of clozapine in teenage patients suffering from this movement disorder.

Risperidone was the first atypical antipsychotic available for frontline treatment of schizophrenia.²⁶ As with clozapine, there first appeared case reports of risperidone in the schizophrenic population under age 18. Simeon et al.²⁷ indicated that risperidone could be a useful antipsychotic agent in adolescent patients with a broad range of psychotic disorders who had previously failed to respond to typical antipsychotic medications. The research group at the University of Pittsburgh also published a case report series indicating the usefulness of the new agent risperidone in children and adolescents.²⁵

In an open-label assessment of risperidone in a large group of teenagers (N = 16) shortly after risperidone was made available, Grcevich et al.²⁸ showed that the medication was not only effective in decreasing symptoms, but was well accepted by the teenagers. It should be noted that the final doses used in this early study (approximately 6 mg/day) are higher than our group currently uses or recommends.

New atypical antipsychotic medications have just been made available such as olanzapine; and others, such as sertindole, ziprasidone, and quetiapine, may be available in the near future. We believe the newer medications may offer a better start for teenagers suffering from schizophrenia in that there will be fewer side effects and possibly fewer secondary negative symptoms. If this supposition is true, teenagers may be able to begin treatment with a better therapeutic alliance and also not be handicapped by negative symptoms during an important stage of psychological development.

LONG-TERM FOLLOW-UP

Many studies have explored the hypothesis that early onset schizophrenia is associated with poor outcome²⁹ with mixed results. However, most of these studies are retrospective analyses of age-at-onset in a clinical population. An early follow-up study of adolescent psychiatric inpatients (N = 77) had a portion who received the diagnosis of schizophrenia.³⁰ Of importance was the use of objective diagnostic criteria to reassess charts from the baseline period and for follow-up diagnosis. Of the 77 patients, 13 (17%) had schizophrenia and 2 of these 13 patients had died by suicide during the follow-up. By the authors’ assessment, all 13 had poor work history or had not worked, and their social adjustment was poor or nonexistent. One of the few long-term outcome studies performed prospec-

tively to examine the outcome of adolescents with schizophrenia was performed in Europe by Krauss and Muller-Thomsen,³¹ who addressed global function and handicap in 61 adolescent patients. The follow-up periods were 5 and 11 years—a considerably longer period than most studies of schizophrenia. Given that the initial treatment and the subsequent therapy were performed in a different health care system than the United States, it is of interest to note that a substantial number of adolescents remained in hospital care and suffered from schizophrenic symptoms at follow-up. At the 5-year assessment, 51% of the patients had a chronic course and 21% were in hospital. The inpatient percentage was 20% at 11 years. More women than men improved from the 5-year to the 11-year assessment. In this sample, 45% of patients had suicidal ideation, and 9 (15%) of 61 were deceased, 8 of the 9 by suicide. Also of note is the finding of the persistence of anxiety symptoms at follow-up. In fact, anxiety was the most prevalent symptom. The authors note the morbidity and mortality of these issues which are rarely addressed in U.S. follow-up studies. As noted repeatedly in this paper, the study supports the notion of adolescent illness being associated with a more severe form of schizophrenia. It must be noted that as valuable as these outcome studies are, neither described the intervening pharmacologic treatment. As researchers and clinicians aim to assess and improve outcome, the design of follow-up studies will need careful attention.

Length of Illness and Relationship to Outcome

For many years, the focus of psychopharmacologic research was the assessment of improvement of symptoms over a short period of time, and there was a tacit assumption that symptoms were stable without treatment. The assertion by Davis et al.³² that antipsychotic medications prevented progression of schizophrenia has often been ignored. Work by Johnstone et al.,³³ now 10 years ago, refocused attention on the possibility that there was a relationship between the length of time of symptoms prior to treatment and outcome. In their study of first-episode patients, the length of illness prior to treatment was correlated with outcome following discharge. This led to a re-examination of previous large studies such as that of May et al.³⁴ in which the patients assigned to treatment that did not include pharmacotherapy had poorer long-term outcome over the 3-year follow-up. A well-known first-episode study reported an association between length of psychosis and length of prodrome with the period of time needed to bring about a remission.³⁵ These data from different types of studies indicate that early intervention in the treatment of psychosis may have great importance for long-term outcome. Our clinical impression from assessing teenagers involved in our brain imaging study is that a number of our patients have had years of symptoms prior to the initiation of treatment. As a public health measure, it

is important for clinicians involved in treating the adolescent population to increase the awareness of the recognition of psychosis in this age group.

CONCLUSIONS

In summary, our group has explored the issues related to outcomes in adolescents suffering from schizophrenia. Studies of structural brain imaging and neuropsychology have been reviewed and point to the continuity between adolescent and adult stages of schizophrenia. Next, the efficacy and safety of both the typical and atypical antipsychotic medications have been summarized. In this article, our group has emphasized the hopefulness for increased safety and efficacy of the atypical antipsychotic medications. The long-term outcome of adolescent psychosis and the related issue of length of illness prior to initiation of pharmacologic treatment have been discussed. Taken all together, the research leads our group to recommend assertive pharmacologic intervention in adolescents with schizophrenia and to encourage the clinicians to interact with their communities to increase recognition of schizophrenia.

Drug names: clozapine (Clozaril), fluphenazine (Prolixin and others), haloperidol (Haldol and others), loxapine (Loxitane), olanzapine (Zyprexa), risperidone (Risperdal), thioridazine (Mellaril and others), thiothixene (Navane).

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