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PSYCHIATRY

Outcome of first-episode schizophrenia and the new antipsychotics

A literature review

Robin Emsley

This article reviews the English literature over the past 10 years with regard to treatment outcome in first-episode schizophrenia. Particular attention is paid to factors associated with poor outcome and predictors of relapse, and the use of the new antipsychotic agents.

Since the mid-1950s, conventional antipsychotic agents have consistently proved to be the most effective compounds in the treatment of schizophrenia.[1] Considerable variation in individual patient outcome is observed, with approximately 70% of patients showing substantial reduction of symptoms in the short term. Although a multitude of clinical trials has been conducted, no convincing data indicate that any one of these drugs, or a particular class of drugs, is more effective than any other.[1] While the short-term efficacy of antipsychotics is well established, earlier trials generally failed to appreciate that measurement of symptom reduction alone — often after only 6 or 8 weeks of treatment — did not provide an accurate indication of actual treatment outcome. A more comprehensive assessment of outcome is necessary, incorporating multiple outcome criteria such as level of occupational and social functioning, cognitive function, feeling of well-being, severity of side-effects, compliance, frequency of relapses and duration of hospitalisation.[2,3]

When outcome is considered in these terms, an entirely different picture emerges. In fact, the overall outcome for schizophrenia is anything but satisfactory.[4,5] Most patients require numerous hospitalisations for recurrence of psychotic symptoms, have impairment of functioning due to persistent negative symptoms and side-effects, are alienated from society, have impairment of cognitive functions (particularly attention, memory and executive functions),[6,7] and display frequent and protracted periods of depression.[8] About 10% of patients with schizophrenia eventually commit suicide.[9]

Major limitations of the conventional antipsychotic agents include the following:

1. Negative symptoms respond poorly.[10] Persistence of negative features such as akinesia and poverty of speech results in impairment of social and occupational functioning. The degree of impairment is often severe, so that the majority of patients with schizophrenia are unemployed and socially isolated.

2. Lack of responsiveness to treatment, even with high dosages.[11] Treatment refractoriness, if severe, usually results in chronic institutionalisation and severe impairment of function.

Department of Psychiatry, University of Stellenbosch, Tygerberg, W. Cape

Robin Emsley, M.B. CH.B., M.MED. (PSYCH.), M.D.

3. High incidences of extrapyramidal symptoms (EPS). These side-effects are seen in approximately 75% of patients treated with conventional antipsychotic agents. EPS, particularly akathisia, cause great distress and discomfort, and are the single most important factor contributing to poor compliance.[12] Poor compliance in turn leads to recurrence of psychotic episodes, readmissions to hospital, and increased morbidity.[13]

A new and important development in schizophrenia research has been to focus studies on first-episode schizophrenia (FES).[14] In this way, possible confounding variables such as the effects of medication and the development of chronic or secondary symptoms are eliminated. New information regarding the pathophysiology, psychopathology, course of illness and response to treatment has emerged. Several methodologically sound longitudinal studies have been conducted, and important findings reported.

With regard to treatment, it has been shown that the clinical response is *better* in FES than in patients with recurrent episodes, and fewer FES patients are refractory to treatment.[4,5,15,16] Also, medication is effective at a *lower* dosage, and FES patients appear more sensitive to EPS.[5,17] Very importantly, it has been found that the time between the first appearance of psychotic symptoms and initiation of treatment is the best predictor of *long-term* outcome. Patients with a recent onset of psychotic symptoms fare better in follow-up studies than do these with symptoms of longer duration. Crow *et al.*[18] reported that among 120 FES patients followed up for 2 years, relapse subsequent to initial hospital discharge was substantially more frequent in those whose pretreatment illness lasted more than 12 months. Loebel *et al.*[19] followed up 70 FES patients for 3 years. Patients received standardised treatment and uniform assessments. Outcome was measured in terms of time to remission as well as degree of symptom remission. Duration of illness before treatment was found to be associated to a significant extent with time to remission as well as level of remission.

Earlier studies also provide evidence for a relationship between early treatment and favourable outcome. Angrist and Schulz[20] reported poorer response to antipsychotics in chronic patients, Lo and Lo[21] found that a shorter duration of psychosis before treatment was significantly associated with a favourable outcome, and Rabiner *et al.*[22] found in a group of 64 FES patients that the longer the duration of illness, the poorer the outcome. Also, after each subsequent relapse there is a drop-off in response to treatment.[23] It has been suggested that the acute psychotic symptoms could reflect an active morbid process which, if not ameliorated by antipsychotic drug treatment, may result in lasting morbidity.[24] Otherwise put, it is possible that an extended period of dopaminergic neural dysfunction may result in a more severe, or less readily reversible, pathophysiological condition. Whatever the mechanism, it is apparent that there is an evolution of resistance to treatment in the progression of the illness.

For this reason, prompt and effective intervention in the early stage of schizophrenia is critical to the outcome. Particular attention should be given to the initial diagnosis and treatment plan. Care needs to be taken in choosing a drug at a dosage that is going to be effective and at the same time well tolerated. According to Lieberman,[25] if we

can reduce the duration of the acute psychotic phase of the illness, we can reduce the lasting impairment that schizophrenic individuals may sustain.

Another strategy to limit the accrued morbidity in schizophrenia concerns early identification of that important subgroup (10 - 20%) of FES patients who are refractory to treatment. If these patients could be detected as close to the onset of their illness as possible, alternative treatments could be initiated before further deterioration occurs. While factors such as male gender, early onset of illness, low educational level, affective blunting, premorbid personality disorder and high levels of expressed emotions in family members have been associated with poor outcome,[25] these findings have not been replicated consistently. The FES studies mentioned earlier in this article provide strong evidence that a longer duration of illness before treatment and frequent previous admissions significantly predict poor outcome. There are a number of biological indicators that may predict which patients are at risk for relapse with reduction or discontinuation of maintenance medication.[24] The most promising appears to be dopamine psychostimulant provocative tests — patients displaying transient activation of their symptoms after receiving methylphenidate are likely to relapse.[26] Another risk factor identified by the same investigators is the presence of tardive dyskinesia.

A further matter requiring careful attention in FES is the prevention of side-effects, particularly EPS. Very often, with the initiation of treatment, the development of EPS such as severe dystonia or akathisia can have a profound negative impact on the patient's compliance for years to come.[12] It is important to initiate treatment in FES with low-dosage medication, and carefully titrate up until a clinical improvement is observed, or until side-effects emerge. Because FES patients are particularly likely to develop EPS, a strong case can be made out for the prophylactic use of antiparkinsonian medication in an FES. An alternative would be to consider using a new antipsychotic, with a lower risk of inducing EPS.

The new antipsychotics

Several new antipsychotics such as olanzapine, seroquel, ziprasidone and sertindole are at various stages of development, and should be available for clinical use within the next few years. Only two are currently available, namely clozapine and risperidone. Clozapine, of course, is not new, but its re-introduction to clinical practice after being severely restricted when found in rare cases to cause fatal agranulocytosis has been supported by an enormous amount of new safety and efficacy data. The new antipsychotics can be classified according to their receptor-binding profiles — clozapine, olanzapine and seroquel being multireceptor antagonists and risperidone, ziprasodone and sertindole being dopamine (D_2) - serotonin ($5HT_2$) - norepinephrine (α_1) antagonists.[27]

There is compelling evidence to suggest that the new antipsychotics have distinct advantages over conventional agents. Clozapine is associated with significantly fewer EPS, has a favourable effect across a broad spectrum of symptoms, and is effective in treatment-resistant schizophrenia.[28] Clozapine is also reported to improve cognitive impairment in schizophrenia[29] and to reduce suicidality.[30] Risperidone, in recommended doses, is reported to be more effective than haloperidol in reducing both positive and negative symptoms of schizophrenia and causes fewer EPS than conventional antipsychotics.[31-33] There are also indications that risperidone may be superior to the conventional antipsychotics in refractory schizophrenia.[34]

Experience with these drugs in FES is limited. Szymanski *et al.*[35] have reported a modest outcome in a small cohort of FES patients treated with clozapine relatively early in the course of the illness. Subjects were refractory to conventional antipsychotics in multiple clinical trials. Although none of the patients attained a complete remission, 2 of 10 patients showed a favourable response at 6 weeks and 1 other after 12 weeks. In a large multicentre study,[15] 183 subjects with first-episode schizophreniform disorder were treated with flexible doses of either risperidone or haloperidol for 6 weeks. Efficacy was assessed at weeks 1, 2, 4 and 6 by means of the positive and negative symptom scale (PANSS), clinical global impressions and brief psychiatric rating scale (BPRS). Clinical improvement was defined as a 50% or more reduction in total PANSS scores at endpoint. EPS were rated according to the EPS rating scale. At endpoint both treatment groups showed significant improvement on the PANSS and BPRS. Sixty-three per cent of the patients on risperidone and 56% of those on haloperidol experienced clinical improvement. Risperidone caused significantly fewer and less severe EPS, and significantly fewer patients on risperidone discontinued treatment.

Cost is often given as the major reason for relegating the new antipsychotics to the second, third, or even last line of treatment for schizophrenia. However, the cost of medication is only a very small part of the total costs involved in treating patients with schizophrenia, so the cheapest drug may not provide the most cost-effective treatment. A re-thinking of this approach is likely. Considering that most schizophrenics do poorly with traditional antipsychotics in the long term, and particularly because recent evidence indicates that early and effective treatment and prevention of relapses has enduring favourable effects on outcome, the use of the new antipsychotics at an earlier stage of the illness needs to be considered seriously. Risperidone has proved to be a safe and effective antipsychotic that can be used as first-line treatment. Whether its reported efficacy for negative symptoms is due to a reduced incidence of EPS or whether it actually has a direct effect on primary negative symptoms, is not clear. Further experience will show whether it is also associated with a reduced rate of tardive dyskinesia and neuroleptic malignant syndrome, and whether it shares some of the other reported benefits of clozapine. Although there is abundant evidence that clozapine has a number of advantages over the conventional antipsychotics, the risk of agranulocytosis will probably prevent it from being used as a first-line drug. However, because its efficacy in refractory schizophrenia is well established, and because favourable long-term outcome depends on early response to treatment, it would be unwise to delay unnecessarily before switching non-responsive patients to clozapine. It has been suggested that if there has been no significant response after 3 months of treatment it would be an appropriate time to consider using clozapine.[2]

The antipsychotics currently available will soon be augmented by the introduction of other new compounds. Undoubtedly major revisions in our approach to the treatment of schizophrenia are under way, much the same as was the case with the treatment of depression after the introduction of the selective serotonin re-uptake inhibitors.

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