The Evolving Definition of Treatment Resistance

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Despite the introduction of antipsychotic treatment for schizophrenia, the outcome for many patients has remained poor. This is largely due to the treatment-resistant nature of schizophrenia in some patients and inadequate long-term maintenance treatment. The definition of treatment resistance remains controversial in spite of its importance. This review discusses the importance of treatment resistance and the factors affecting its definition in the light of recent advances in knowledge and treatment. A decade ago, positive symptoms were thought to be the prime outcome measure for schizophrenia and were the standard by which treatment resistance was largely assessed. More recently, however, a wider range of outcome measures has been recognized, including both negative symptoms and cognitive function. All of these outcome measures affect quality of life such that the patient may consider any outcome other than a return to premorbid levels of functioning as inadequate. Furthermore, patient responsiveness should be recognized as a continuum rather than as a dichotomy of response or nonresponse; partial response to treatment may not be accepted as satisfactory. Definitions of treatment resistance should reflect these factors. Patients may benefit from pharmacotherapy with atypical antipsychotics even if they do not meet criteria for narrowly defined treatment resistance. Although clozapine use has often been restricted to treatment-resistant patients, the benefit it bestows outweighs the potential risk of side effects in patients with less stringently defined treatment resistance.
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Schizophrenia is a complex disorder with an impact on most aspects of psychological functioning. It is characterized by a wide spectrum of symptoms; positive symptoms are the most prominent in the acute episode of the illness, but negative symptoms, affective disturbances, and cognitive deficits may all be differentially affected by pharmacotherapy and will have a major impact on patient functioning and quality of life. These factors have only recently been recognized as important outcome measures that should be included in definitions of treatment resistance.

This review discusses the importance of treatment resistance, the wide heterogeneity of response to antipsychotic treatment, the evolving definition of treatment resistance with increasing knowledge of the course of schizophrenia, important outcome measures, and the efficacy of atypical antipsychotics such as clozapine.

THE PROBLEM OF TREATMENT RESISTANCE

Pharmacotherapy has become the cornerstone of treatment for schizophrenia. The introduction of antipsychotic treatment led to a drastic reduction in the number of residents in psychiatric hospitals as acute psychotic symptoms were improved such that many patients could be reintegrated into society. Early studies showed that 3 of 4 patients were markedly improved when treated with antipsychotic therapy compared with only 20% of patients who received placebo.[1] Furthermore, antipsychotic maintenance treatment can prevent relapse, rehospitalization, and a subsequently poor outcome. After 1 year of taking placebo, approximately 3 of 4 first-episode and multiepisode patients with schizophrenia will relapse, compared with only 10% to 20% of patients taking antipsychotic maintenance treatment.[2]

Enthusiasm over the effects of antipsychotics diminished, however, as the prognosis for patients with schizophrenia remained poor. The dramatic effect of antipsychotic treatment on the positive symptoms of schizophrenia probably initially obscured the problems associated with treatment: the poor therapeutic effect on certain aspects of schizophrenia and the problem of accompanying side effects. Westermeyer and Harrow[3] estimated that a maximum of 1 of 4 patients was truly asymptomatic during follow-up, only 1 in 3 had good social integration, 50% to 70% had professional integration problems, 80% were rehospitalized at least once during follow-up, and 10% committed suicide in the first 10 years of the illness, with a 40% to 50% rate of suicide attempts. In the psychiatric population, patients with schizophrenia have the worst prognosis. An alternative assessment of the study from Davis et al.[1] revealed that approximately 3% of patients were worse following antipsychotic treatment, 8%

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experienced no change in their condition, and 20% reported only a minimal improvement.

A recent meta-analysis by Hegarty et al.[4] confirmed that only about 40% of patients with schizophrenia had a favorable outcome (in remission or improved with mild residual symptoms and good professional and social integration) in follow-up studies of at least 1 year in duration. From a sample of 74 patients diagnosed with schizophrenia using Research Diagnostic Criteria, Harrow et al.[5] found that approximately 40% to 50% had a poor outcome, with approximately 30% to 40% of patients still experiencing delusions and hallucinations after 2, 4.5, and 7 to 8 years of follow-up. This poor outcome may be due to both treatment resistance of first-episode patients and relapse of initially responsive patients. Approximately 20% of first-episode patients show no response to 1 year of treatment with a typical antipsychotic.[6]

HETEROGENEITY OF RESPONSE TO TREATMENT

A wide variability of therapeutic effects can be expected in different studies of antipsychotic treatment depending on the diagnostic and inclusion criteria, evaluated symptomatology, and pharmacologic and concomitant psychosocial treatment applied. Furthermore, schizophrenic patients are not a homogeneous group of patients. Heterogeneity may be due to differing diagnostic criteria, the etiopathogenetic mechanisms involved in the patients' psychosis, the stage of the illness (whether the patient is first-episode, has relapsed, or has chronic schizophrenia), comorbid pathology, and sex.

For example, patients defined according to the strict Kraepelinian criteria have a worse outcome than those defined by non-Kraepelinian criteria.[4] A 1983 study by Watt et al.[7] showed that patients with schizophrenia have different clinical courses of illness. During a 5-year follow-up of 121 patients, 16% of patients did not experience a relapse of illness, 32% had repeated episodes but no residual deficit between relapses, 9% had repeated episodes but some residual deficit after each relapse, and the remaining 43% experienced repeated episodes with a growing deficit between relapses. This worst outcome occurred with a lower frequency in first-episode patients (N = 48) than in the overall schizophrenic group, 33% versus 43%, respectively. However, it was much more common in men than in women: 46% of first-episode men (N = 12) compared with only 18% of first-episode women (N = 4).

Comorbid pathology, particularly substance abuse, also affects the course of schizophrenia. Substance abuse induces earlier exacerbation of symptoms, more frequent rehospitalization, more persistent psychotic symptoms, and, thereby, more resistance to treatment.[8]

In order for a patient to be defined as treatment resistant, the patient must have received adequate psychosocial and pharmacologic treatment.

Psychosocial context has an important impact on the symptoms of the patient and on the effects of pharmacotherapy. Since patients are characterized by a vulnerability to stress, overstimulation will exacerbate psychotic symptoms. "Expressed emotion" research has clearly demonstrated the effects of the environment on the evolution of schizophrenic patients and on the interaction between pharmacologic treatment and psychosocial context.[9] Furthermore, strategies for psychosocial rehabilitation have been shown to be effective and important in obtaining substantial behavioral and functional improvement, symptom reduction, and high levels of psychosocial integration.[10]

Although antipsychotics have been in use for 50 years, there has only recently been some consensus about what constitutes adequate treatment. The patient should receive a dose within the therapeutic window. A lower dose may be less effective, while a higher dose may not be more effective but may, on the contrary, obscure the therapeutic effect due to increasing side effects such as extrapyramidal symptoms (EPS). In addition, the dose should be adapted to the particular patient, considering previous therapeutic and side effects experienced by the patient and the patient's stage of illness. For example, first-episode patients are generally more responsive to antipsychotics than patients with chronic schizophrenia, but they may also be more sensitive to adverse effects. Controversy continues as to how long it takes before a clear therapeutic effect with a typical antipsychotic will be shown; however, it is accepted that at least 4 to 6 weeks of treatment are required.

An often underestimated cause of nonresponse or inadequate response to treatment is patient noncompliance with acute or maintenance treatment. Analysis of plasma drug levels can determine whether the concentration is within the therapeutic range and can thereby exclude noncompliance as the reason for treatment failure. Patient and caregiver education, prevention of side effects, and careful monitoring are important to ensure compliance and the long-term success of treatment.

Although conventional antipsychotics do not seem to differ in efficacy when adequately dosed, clinical experience shows that a few patients may respond more favorably to one drug than to another, so switching to a different conventional antipsychotic is an often-used therapeutic strategy for nonresponsive patients. Nevertheless, if a conventional antipsychotic has been used without success, changing to treatment with an atypical antipsychotic is more effective and is increasingly advised.

THE EVOLVING DEFINITION OF TREATMENT RESISTANCE

Clearly, the treatment resistance of patients with schizophrenia is a frequent and important clinical problem. However, treatment resistance is in itself difficult to define, and the criteria remain controversial. Definitions of treatment

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Table 1. Definition of Treatment-Resistant Schizophrenic Patients[a]

Clinical history (previous treatment)
No good level of functioning over the past 5 years
Received 3 periods of treatment in the preceding 5 years with antipsychotics of at least 2 different chemical classes for at least 6 weeks, with an equivalent of at least 1000 mg chlorpromazine daily without significant relief
Cross-sectional
BPRS total score ≥ 45 (18 items, rated from 1–7 [absent to severe])
Rating ≥ 4 on at least 2 of the following BPRS items: conceptual disorganization, unusual thoughts, hallucinatory behavior, suspiciousness
CGI score ≥ 4
Prospective
Failure to reduce BPRS score by > 20%; plus either a posttreatment BPRS score ≥ 35 or CGI score ≥ 3 with 60 mg haloperidol daily for 6 weeks

[a]From reference 12. Abbreviations: BPRS = Brief Psychiatric Rating Scale, CGI = Clinical Global Impressions scale.

resistance differ in several domains: dichotomy (response or nonresponse) versus continuum of response, the type and duration of previous treatment, the psychopathologic symptoms assessed, and whether psychosocial functioning has been evaluated.

In the 1970s, chronic hospitalization for more than 2 years was used as a criterion for nonresponse.[11] However, such patients may have been noncompliant with treatment or hospitalized because adequate psychosocial rehabilitation or alternatives were unavailable. Moreover, severe symptoms or impairment do not always result in chronic hospitalization. Long-term hospital care is becoming less frequent, so using hospitalization as an index for treatment resistance will underestimate the impairment of patients cared for in the community. The restriction of treatment resistance to patients with chronic pathology also fails to recognize treatment-resistant first-episode patients.

Persistence of positive symptoms despite adequate antipsychotic treatment has also been used to characterize nonresponse.[11] However, this approach underestimates the importance of other symptoms. While conventional antipsychotics have a major effect on reducing positive symptoms, new atypical antipsychotics are also effective in improving negative symptoms and cognitive dysfunction. Therefore, recognition and evaluation of poor response with regard to all of these symptoms are important in order to evaluate the efficacy of the new atypical antipsychotics.

In studies such as those from Harrow et al.[5] and Hegarty et al.,[4] a reduction in total symptom score was used to define treatment response, with global evaluation of functioning using the Clinical Global Impressions scale (CGI) or an overall assessment of psychosocial functioning. Although this approach evaluates a broader spectrum of the illness, there is still a risk of underestimating the impact of residual symptoms.

The effectiveness of clozapine in treatment-resistant patients and its subsequent licensing for this indication necessitated a clear definition of treatment resistance. A narrow definition of treatment resistance was introduced in the study by Kane et al.[12] The criteria included aspects of the patients' clinical history, cross-sectional measures, and prospective assessments (Table 1).

The approach of Kane et al.[12] to operationalize treatment resistance has been followed in many trials exploring new therapeutic strategies for treatment-resistant patients. However, in clinical practice, there is probably no need for 3 previous trials with antipsychotics; usually 2 trials or even 1 can be considered sufficient to show treatment resistance. As stated in the American Psychiatric Association treatment guidelines,[13] a trial with clozapine should be considered when patients fail to respond to adequate treatment with at least 1 antipsychotic, except for patients who have a specific contraindication, such as blood dyscrasia or cardiac arrhythmia, or are unable or unwilling to cooperate with monitoring requirements.

The criteria of Kane et al.[12] do not highlight the advantages of new antipsychotic treatments that produce fewer side effects and have a greater effect on a larger spectrum of symptoms, including affective, cognitive, and negative symptoms. The criterion of positive response as a 20% reduction in Brief Psychiatric Rating Scale (BPRS) score not only overemphasizes the importance of positive symptoms, but may also lead to an underestimation of the impact of residual symptoms on the overall functioning, psychosocial integration, and quality of life of the patient. Moreover, such a criterion gives the erroneous impression that a 20% reduction in BPRS score represents a substantial improvement or a satisfactory response, whereas the patient may still have impairment in other areas.

The definition of treatment response provided by Kane et al.[12] also implies that nonresponders constitute a homogeneous group of patients. However, nonresponders show considerable diversity in treatment response from partial response to nonresponse, or even deterioration in symptomatology, disability, and the course of their illness. Consideration of treatment response as a continuum recognizes that many patients partially improve, but will still show important positive and negative symptoms and disabilities that have an important impact on level of functioning, psychosocial integration, and quality of life.

A global rating of the continuum of responsiveness to antipsychotic drug therapy has been designed by an international study group.[14] The study group defined treatment refractoriness as "continuing psychotic symptoms with substantial functional disability and/or behavioral deviances that persist in well-diagnosed persons with schizophrenia despite reasonable and customary pharmacological and psychosocial treatment that has been provided continuously for an adequate time period."[14(pp552–553)] Thus, treatment refractoriness was recognized as a complex construct whose definition should include the psychotic symptoms, functional disability (especially social dysfunction), and

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Table 2. Definition of Treatment Response Levels[a]

Assessment	1 Clinical Remission	2 Partial Remission	3 Slight Resistance	4 Moderate Resistance	5 Severe Resistance	6 Refractory	7 Severely Refractory
CGI score	1 (normal), some negative symptoms	2 (borderline), mild residual positive symptoms	3 (mildly ill), residual positive/ negative symptoms	4 (moderately ill), obvious symptoms	5 (markedly ill), persistent symptoms	6 (severely ill), slight or no symptom reduction, positive/negative symptoms are persistent	7 (most extremely ill), no symptom reduction, high level of positive/ negative symptoms
BPRS score	≤ 2 for all psychotic symptoms	No psychotic items ≥ 3	Not more than 1 psychotic item > 4	4 on 2 psychotic items, total score ≥ 45	4 on at least 3 psychotic items or 5 on 1 psychotic item, total score ≥ 50	6 on at least 1 psychotic item or ≥ 5 on at least 2 psychotic items, total score ≥ 50	7 on at least 1 psychotic item, total score ≥ 50
Living skills survey	No supervision	Occasional supervision	2 or more areas, occasional supervision	4 or more areas, frequent supervision	6 or more areas, frequent supervision	Disruption of all psychosocial areas	All areas, helplessness, disturbing, dangerous, constant supervision

[a]Adapted from reference 14, with permission.

Table 3. Outcome Measures in Schizophrenia[a]

Psychopathology: positive, negative, disorganization
Cognitive function: attention, executive, memory function
Extrapyramidal function: EPS, akathisia, tardive dyskinesia
Interpersonal social function: work/school, independent living
Compliance, hospitalization, suicidal tendencies, aggression
Family, societal burden
Quality of life

[a]Abbreviation: EPS = extrapyramidal symptoms.

behavioral deviances that interfere with psychosocial integration. Moreover, the clinical history of the patient should indicate that the patient had received previous adequate treatment of pharmacotherapy as well as psychosocial treatment and attempts at rehabilitation. In this definition, a clinical history of psychosis for at least 2 years was recommended, although it was recognized that 1 year of unresponsiveness might be an adequate time period. In addition, their criteria specified at least 3 periods of antipsychotic treatment in the preceding 2 years using different chemical classes corresponding to daily dosages ≥ 1000 mg of chlorpromazine, with at least 6 weeks on each treatment with no symptomatic relief. Responsiveness was viewed as a continuum, but dichotomous cutoff thresholds were distinguished to categorize refractoriness for particular studies and purposes. The rating scale combined scores from the CGI scale, the BPRS, and the Independent Living Skills Survey, an assessment of social functioning, to define 7 levels of response, essentially levels of remission, suboptimal response, or refractoriness (Table 2).

In 1992, Meltzer again assessed outcome measures of schizophrenia in light of the advance in schizophrenia knowledge over the previous decade.[15] He stated that it may be more useful to evaluate treatment responsiveness as a continuum, including all relevant outcome criteria, rather than use the strict treatment-resistance criteria set forth by Kane et al.[12] For example, patients with little or no overt psychopathology while receiving antipsychotics may consider their treatment unacceptable because of EPS. Furthermore, patients and caregivers may consider any outcome other than a return to premorbid levels of functioning as inadequate. Outcome measures now considered to be of importance in schizophrenia are psychopathology, cognitive functioning, EPS, interpersonal social function, treatment compliance, hospitalization, suicidal tendencies and aggression, the burden on the family and society, and the overall quality of life for the patient (Table 3).

CONCLUSION

Poor treatment response and treatment resistance present an important problem in schizophrenia research and clinical practice. A clear definition of treatment resistance and the range of persistent symptoms and functional deficits is a cornerstone of schizophrenia research and the identification of appropriate treatment plans. A dichotomous definition that relies on persistent positive symptoms, even after several adequate treatment trials, may be a useful approach for schizophrenia research. However, it does not fully appreciate the impact of residual symptoms and psychosocial problems and will underestimate the number of partially or poorly responding patients.

In clinical practice, to provide adequate therapeutic strategies, symptoms and psychosocial deficits as well as behavioral problems should be broadly assessed using a continuous scale to evaluate fully the psychopathologic spectrum, the degree of impairment, and the burden for patients and their families. The clinician should consider

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the diagnosis of the illness, the patient's premorbid history and previous treatment, the stage of the illness, and an assessment of symptoms, comorbidity, side effects, psychosocial functioning, quality of life, and compliance and tolerability of treatment. Only by having this overview of the patient's illness can one fully appreciate the level of functioning and the overall quality of life of the patient and determine the appropriate therapeutic intervention.

Atypical antipsychotics have a beneficial effect on a broader spectrum of symptoms, induce fewer side effects, and are more effective on residual and poorly responding symptoms than are conventional antipsychotics. Furthermore, atypical antipsychotics will promote and ameliorate psychosocial functioning. Narrowly defined, chronic, treatment-resistant patients with psychotic symptoms are not the only ones who may benefit from such treatment. Indeed, patients with a less-than-satisfactory response to antipsychotic treatment who do not regain a previous level of functioning should be included in trials of the new atypical antipsychotics, as should first-episode patients. Clozapine use has been restricted to patients with severe refractoriness because of the risk of side effects; however, because of the poor quality of life of schizophrenic patients exhibiting residual positive symptoms or those without clear psychotic symptoms but with deficits, depressive symptoms, behavioral problems, and extrapyramidal and subjective side effects, it may be that the risk of side effects will be outweighed by the benefits and advantages of clozapine treatment.

Drug names: chlorpromazine (Thorazine and others), clozapine (Clozaril, Leponex), haloperidol (Haldol and others).

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