History and Current Definitions of Treatment-Resistant Schizophrenia

Helio Elkis

Department and Institute of Psychiatry, University of São Paulo Medical School, University of São Paulo General Hospital, São Paulo, Brazil

Abstract

Soon after the discovery of chlorpromazine in 1950, it was observed that among its users a specific group of patients remained symptomatic and were considered refractory or resistant to phenothiazines. However, the first operational definition of treatment-resistant schizophrenia was only proposed in 1988, in the landmark study which introduced clozapine for the treatment of that condition. The definition evolved due to the introduction of algorithms for the treatment of schizophrenia and, presently, treatment resistance can be defined as persistence of psychotic symptoms after failure to respond to 2 adequate treatment trials with antipsychotics. Clozapine has proven to be the best drug for patients with treatment-resistant schizophrenia, but about 30% of these do not respond to such a drug and are considered as partial responders, clozapine resistant or ‘super-refractory’.

The discovery of chlorpromazine, the first of the first-generation antipsychotics (FGAs) in the 1950s brought new hope for treating schizophrenia, allowing both psychotic symptoms and hospital stays to be reduced and enabling patients to return to a social setting. However, during the subsequent years, it was observed that among chlorpromazine users a specific group of patients remained symptomatic and these were considered refractory or resistant to phenothiazines [1].

Even now, the definition of treatment-resistant schizophrenia (TRS) proves problematic, since schizophrenia is, by definition, a chronic disease, and long-term studies have shown that 80–90% of patients develop some kind of social or occupational dysfunction [2].

Indeed, chronicity is frequently taken as a synonym of refractoriness, and consequently many clinicians believe that refractoriness and complete deterioration is the inevitable outcome of schizophrenia. However, epidemiological studies such as the International Study on Schizophrenia [3] have shown that about 50% of cases have a
favorable outcome, and therefore it is conceivable that the other 50% of population is represented by patients with TRS.

Using parameters to define poor outcome, some authors employed the number of re-hospitalizations or chronic hospitalizations to define TRS [4], but factors such as poor compliance, weak social support programs or a history of violence can keep patients chronically hospitalized without their having TRS [5].

Indeed, in medicine there is a clear distinction between chronicity and refractoriness, because there are various chronic diseases (e.g. diabetes and hypertension) which, despite their chronicity, do in fact respond to treatment, with patients remaining stable at the same doses of hypoglycemic agents or antihypertensives throughout their lives [6].

Sometimes the term ‘TRS’ or ‘refractory schizophrenia’ is mistakenly thought to result from a lack of compliance, and some authors argue that it suggests ‘nothing can be done’, embedding the notion that the patient is resisting the treatment, rather than the illness itself is resistant to treatment, and it has been suggested that the term for ‘incomplete recovery’ be used instead of ‘treatment refractory’ [7]. A detailed discussion of this and other issues regarding compliance may be found in the chapter by Lambert.

In addition to distinguishing the concepts of chronicity and refractoriness, it is necessary to define what is meant by response to treatment, a concept that distinguishes remission from recovery. ‘Response to treatment’ is a reduction in the severity of symptoms, as assessed by some sort of scale. ‘Remission’ means an almost total absence of symptomatology for a certain period of time, whereas ‘recovery’ is the absence of the disease for a long period [8].

For instance, ‘remission’ in rheumatoid arthritis is considered as absence of fatigue, minimal morning stiffness, absence of pain and swelling in joints, and normal hemosedimentation. When used analogously for schizophrenia, ‘remission’ currently is defined as a minimum period of 6 months during which psychotic symptoms, symptoms of disorganization and negative symptoms have low levels of clinical severity [9] corresponding to levels of ≤3 for the respective symptoms on the Brief Psychiatric Rating Scale (BPRS) [10] or the Positive and Negative Syndrome Scale (PANSS) [11].

The concept of TRS sometimes is associated with remission, which would imply an almost complete absence of symptoms, but also is related to response (i.e. reduction in symptoms as compared with a previously established baseline level of severity).

**Prevalence, Clinical and Psychopathological Aspects**

A meta-analysis of the outcome literature of the treatment of schizophrenia encompassing the twentieth century [12] observed that, after the introduction of neuroleptic therapy, only 48% of patients who had chronic schizophrenia had a favorable outcome. In first-episode patients, approximately 20% did not respond to conventional antipsychotic
treatment after 1 year of treatment [13]. Generally, it is assumed that 20–30% of patients who have schizophrenia do not respond to treatment with conventional antipsychotics [14], but some reviews have identified higher rates (up to 60%) [2].

In terms of demographic aspects, Meltzer et al. [15] observed a mean difference of 2 years of age at disease onset together with a predominance of males in patients with TRS as compared with non-TRS patients. Similarly, Henna and Elkis [16] observed that patients who had TRS were predominantly male, with a mean age of onset around 17 years (as compared with around 20 years for patients who responded to treatment), and experienced a higher number of hospitalizations than those who responded to treatment.

Recently Castro and Elkis [4], in a retrospective study, observed that patients taking clozapine (and therefore with TRS) had a mean age of onset of 18 years, while non-refractory patients, who were taking FGA or second-generation antipsychotics (SGAs), had a mean age of onset ranging from 21 to 23 years.

Other authors observed that non-responsive patients differ significantly from non-refractory patients in terms of a higher number of episodes of illness, history of obstetric complications, long duration of untreated psychosis as well as a history of substance abuse [17].

In terms of the psychopathology, some authors assessed homogeneous populations of patients who had TRS using well-known rating scales to detect symptom clusters in an attempt to elicit a distinctive psychopathologic profile of TRS. Thus, Lindenmayer et al. [18] used the PANSS to evaluate 157 patients who had TRS, and found a factor structure similar to their original factor analysis study in TRS patients who were responsive to treatment, i.e. positive, negative, excitement, cognitive and depressive factors [19]. More details about factor analyses of the PANSS are found in the chapter by Lindenmayer and Khan.

Using the BPRS [10] in large sample of patients with TRS, McMahon et al. [20] observed through confirmatory factor analysis that 13 of the 18 items of the BPRS loaded into 4 factors: reality distortion (grandiosity, suspiciousness, hallucinatory behavior, unusual thought content), disorganization (conceptual disorganization, mannerism and posturing, disorientation), negative symptoms (emotional withdrawal, motor retardation, blunted affect) and anxiety/depression (anxiety, guilty feelings, depression).

In the Schizophrenia Program at the Institute of Psychiatry of the University of São Paulo Medical School, we analyzed data from an homogenous population of 96 patients [21], narrowly defined as having TRS based on the criteria of Kane and Meltzer [14] and assessed by an anchored version of the BPRS [22, 23]. Using factor analysis, these investigators found that 16 of the 18 items of the scale clustered into 4 dimensions: negative/disorganization (emotional withdrawal, disorientation, blunted affect, mannerisms and posturing, conceptual disorganization), excitement (excitement, hostility, tension, grandiosity, uncooperativeness), positive factors (unusual thought content, suspiciousness, hallucinatory behavior) and depression (depression,