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REVIEW ARTICLE

Evolution of the Concept of Treatment-resistant Schizophrenia: Toward a Reformulation for Lack of an Adequate Response

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The concept of "resistant schizophrenia" is linked to the development of antipsychotic drugs. Although there were previous attempts, the first definition acknowledged in the scientific literature, was closely linked to the development of clozapine in dichotomic terms of response/no response to previous drug. This article reviews the influence of the psychopharmacologic treatment of schizophrenia on the evolving definition of treatment-resistance. It also addresses other concepts of interest, such as remission and recovery, as well as definitions of schizophrenia in which deterioration is an integral part of the psychopathology, thereby implicitly ruling out the possibility of a complete remission of symptoms. Instead of treatment-resistance, we are suggesting the term "lack of adequate response," which is closer to operational dimensional models that integrate the idea of a continuum with response levels related to an individual's life expectations, and which allow different pharmacological approaches to be integrated.

1. Introduction

Throughout the history of psychiatry, schizophrenia has been one of the most attractive pathologies for clinicians and researchers. The scientific output on etiology, diagnosis and treatment is enormous. Early descriptions spoke of an illness that tended to be chronic and with a poor prognosis. Prevalence studies describe it as stable in time and in different places throughout the world. In a review spanning from 1965 until 2002, Saha et al found a stable prevalence between 0.5% and 0.8%, despite some population variances.[1] As to its evolution and according to Meltzer, 70% of treated patients respond to medication and to psychosocial treatments, with remission of positive symptoms of schizophrenia. However, the remaining 30% are considered treatment-refractory or resistant.[2]

The first breakthroughs in treatment involved the use of shock therapy and electroconvulsive therapy. Possibilities for improvement were glimpsed and terms such as remission appeared, but were not conceptualized, and had very different implications than they currently have. In the mid 1950s, neuroleptic drugs were synthesized, including chlorpromazine, and the possibility of real clinical improvement gained acceptance.[3] Improvement of the positive symptoms of schizophrenia reduced chronic hospitalization in asylums, with a certain re-integration of patients into their family environment.

The introduction of the second-generation (atypical) antipsychotic (SGA) drugs, provided not only for better control of the positive symptoms of schizophrenia, but also for negative and cognitive symptoms, and with fewer side effects. This promised a change in the long-term prognosis and influenced the quality of life of persons suffering from schizophrenia, even though the literature continued to speak of lack of response. Development of the concept of treatment-resistance had begun, and is valid and evolving, even today.

The concept of treatment-resistant schizophrenia was associated with the development of antipsychotic drugs. Although previous attempts had been made, the first definition acknowledged in the scientific literature, was linked to the development of an antipsychotic drug, clozapine. A study carried out in 1988 by Kane et al defined "treatment-resistance" and indicated clozapine as the gold-standard treatment for these patients.[4] This recommendation remains in the clinical guidelines. It is a dichotomous definition of response/no response. Other dimensional definitions, such as by Brenner et al,[5] appeared later, and were more applicable to daily practice. The leverage effect of psychotherapeutic and

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psychosocial interventions has been successively integrated with antipsychotic drugs and resilience to stress factors in the overall response.[6] This has finally led to an integrated biopsychosocial approach and a multi-level assessment of treatment response.

There has also been progress in the knowledge of the pathology. As opposed to previous infection, immunological, and other theories, in 2001, Liebermann et al described the pathophysiology as a disturbance in neurodevelopment with a clinical course in outbreaks leading to progressive deterioration.[7] Other researchers have pointed out the variability in the clinical course of schizophrenia after a first episode, with regard to different factors that influence both the clinical course and response to treatment.[8] One of the most significant among those referred to is duration of untreated psychosis, which may be related to the severity of the disease and be a marker that determines its course, as shown in Figure 1.[9]

This evolution reflects changes in the way treatment-resistance is conceptualized, and ranges from dichotomy to dimensionality. Concepts such as remission, much closer to the idea of recovery, had already been developed in the 21st century. It is worth mentioning that researchers, such as Cabaleiro Goas, had already indicated different levels of remission based on patients' social functioning.[10] Even though this concept was used in the literature, in light of recent advances it has been taken up again with a new meaning. Andreasen et al have introduced the concept of remission as a necessary but insufficient step toward recovery.[11]

2. Analysis of the definition of treatment-resistant schizophrenia

Increased knowledge of schizophrenia has been one of the contributions of drug development, among which is the definition of treatment-resistance. Before this definition, research on treatment-resistance was hindered by a lack of consistency in the concept.[12]

At the beginning of the 20th century, since there were no drugs to control symptoms, the criteria of no response were based on the need to be housed in an asylum. In Spain, for example, Cabaleiro Goas spoke of complete remission in the event that symptoms remitted completely, even with a "defect", but that allowed the affected to live a normal life; incomplete remission if the illness or its "defect" only allowed them a reduced social or family life; and no remission implied that there was no response to treatment and their condition did not allow them to abandon the asylum.[10] The criteria of the time were based on the quality of personal and social functioning.

With the development of drugs in the 1970s, certain quantitative criteria were included, but the idea of functioning remained: chronic hospitalization for more than 2 years was one of the criteria for defining a case as treatment-resistant.[13] Other factors which could influence hospitalization and were not symptoms in themselves, were not taken into account. Another criterion used was the persistence of positive symptoms of schizophrenia, despite appropriate antipsychotic treatment.[13] At this time, the difference between chronicity and drug treatment-resistance did not exist as such.

2.1. The 1988 criteria proposed by Kane et al

At the beginning of the 1980s, some researchers, such as Itil et al, attempted to define "treatment-resistance" by introducing pharmacology into the definition.[14] During this period, Deniker et al also defined "treatment-resistance" as the maintenance of symptoms for $\geq$ 2 years, with standard doses of antipsychotic drugs for 6 months.[15] However, it was following research with clozapine by Kane et al in 1988, that the definitions of "treatment-resistance" and "treatment-refractoriness" were systemized and scientifically validated, and criteria were applied to different studies.[4]

The definition, based on criteria, arose from a pharmacological need, to prove the effectiveness of clozapine on this type of patient and to have it licensed for use on treatment-resistant schizophrenia.[16] In this multicenter study, Kane et al[4] established the criteria, currently still in use with some changes, for the duration of the treatment needed,[17] the number of failed pharmacological tests,[18] and the necessary pharmacological doses,[18,19] spurred by evidence that with doses of chlorpromazine $\geq$ 400 mg/day, 80–90% of the dopaminergic receptors were already blocked.[20] These changes make the criteria less strict. Table 1[4,17–20] lists the changes. These more or less restrictive criteria are currently used in their

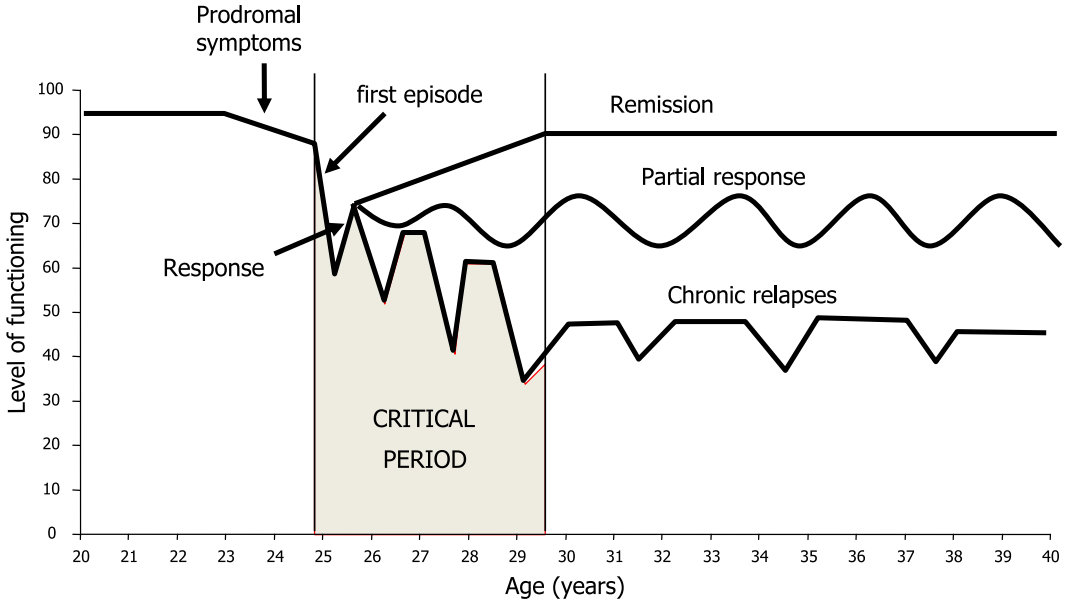

Figure 1 Possible courses after response to treatment in a first episode of schizophrenia.[9,38,39]