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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

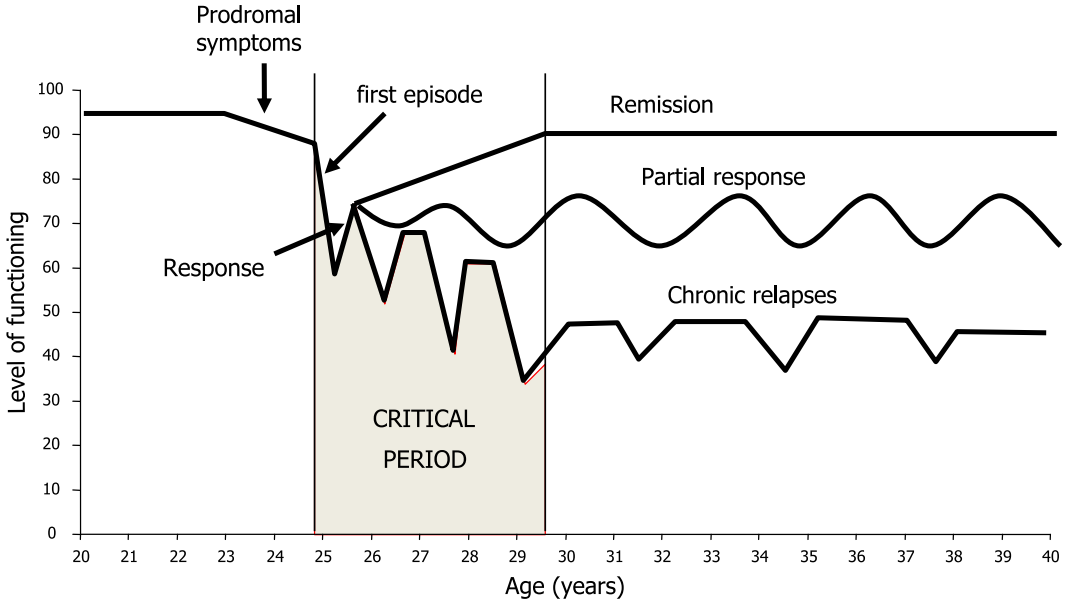

Figure 1 Possible courses after response to treatment in a first episode of schizophrenia.[9,38,39]

Table 1 Kane's criteria for diagnosis of treatment-resistant schizophrenia

Kane's criteria for diagnosis of resistant schizophrenia[4]	Kane's modified criteria for diagnosis of resistant schizophrenia[17–20]
Treatment with different classes of antipsychotics at equal doses of 1000 mg/day of chlorpromazine for at least 3 periods of 6 weeks in the last 5 years without significant clinical improvement.	Treatment with different classes of antipsychotics at equal doses of 400–600 mg/day of chlorpromazine for at least 2 periods of 6 weeks in the last 5 years without significant clinical improvement.
Reduction of at least 20% on the BPRS scale, score > 35 points on the BPRS scale after treatment, CGI score > 3 after treatment with 60 mg/day of haloperidol for 6 weeks.	Reduction of at least 20% on the BPRS scale, score > 35 points on the BPRS scale after treatment, CGI score > 3 after treatment with 60 mg/day of haloperidol for 6 weeks.
BPRS score > 45. Score > 2 on BPRS items of conceptual disorganization, unusual thoughts, hallucinatory behavior and mistrust. CGI score > 4.	BPRS score > 45. Score > 2 on BPRS items of conceptual disorganization, unusual thoughts, hallucinatory behavior and mistrust. CGI score > 4.

BPRS = Brief Psychiatric Rating Scale; CGI = Clinical Global Impression.

application: a more restrictive definition for research purposes, another less restrictive one for developing antipsychotic drugs, and another that is more broadly defined being clinically and practically relevant. This difference in criteria is important since discrepancies arise when it comes to quantifying resistance to treatment.[14] Thus, in 1995, Juárez-Reyes et al[21] estimated prevalence with different criteria, and found a variation reaching 42.9% when less strict criteria were applied, but 12.9% when evaluated with the criteria proposed by Kane et al.

The definition by Kane et al, as well as the previous ones, dichotomously assess response/no response and are discordant with observations in clinical practice, making the definitions incomplete. For instance, data existed to indicate that in the long-term evolution of schizophrenic patients, 80–90% present some degree of social or work impairment, thus many of them respond partially.[14] Other researchers postulate that both the positive response criteria and the 20% reduction in the Brief Psychiatric Rating Scale (BPRS) on which Kane et al's definition is based on, overestimate the importance of positive symptoms of schizophrenia and underestimate the impact of residual symptoms on the overall functioning, social integration and quality of life of patients.[16] Moreover, this definition divides patients into two homogenous groups, without taking into account the heterogeneity that is symptomatic of the illness.

2.2. The 1990 criteria proposed by Brenner et al

Before Kane et al, there were researchers such as May et al, who had made previous attempts at a definition from a dimensional point of view and who took these heterogeneous symptoms and the idea of partial treatment response into greater consideration.[14] They postulated different levels of response, integrating the social consequences of the illness and a psychosocial approach, rather than solely a pharmacological one.[22] Later, in 1990, Brenner et al introduced this concept with greater impact, by adding a vision of continuum to the definition.[5] They defended the existence of different degrees of treatment response, ranging from clinical remission to severe treatment-refractoriness. These researchers defined treatment-refractoriness as the persistence of psychotic symptoms with substantial social dysfunction and/or behavioral disorders, which persist in patients properly diagnosed as schizophrenic after continuous pharmacological and psychosocial treatment within an appropriate period of time.[5] This definition implies that some patients' levels of response may worsen over time, and also takes into account patients' functional social and personal levels, and not just the existence of active symptoms.[3] This definition recommends a history of psychotic symptoms for at $\geq$ 2 years, although it acknowledges that the history of 1 year may be sufficient.[5] At least three periods of antipsychotic treatment are needed in the 2 previous years, administering different drugs with recommended daily doses of $\geq$ 1000 mg of chlorpromazine equivalent for at least 6 weeks without improvement.[5] Scores from different scales are combined and seven levels of response defined. Included are: different levels of remission, suboptimal treatment response and treatment refractoriness.[16] The authors themselves point out the benefits of this definition, which are the need to establish operational multidimensional criteria to enable comparison, to establish the risk/benefit of SGAs, to understand the heterogeneity of schizophrenia, to assess therapeutic needs, and to boost new discoveries.[5] These researchers already proposed combined psychosocial and pharmacological treatments. Table 2[5] lists criteria proposed by Brenner and coworkers.[5]

Table 2 Brenner's criteria for treatment-resistant schizophrenia[5]

Level 1	Clinical remission	No need for a formal rehabilitation program	Rapid response to antipsychotics at recommended doses. Patient may show anhedonia or another negative symptom. CGI normal and score < 2 on BPRS. Good functional level without supervision.
Level 2	Partial remission	No need for a formal rehabilitation program	Rapid reduction of psychotic symptoms. Mild signs of residual psychotic symptoms. CGI 2. None of the BPRS scale items are $\geq$ 3.
Level 3	Light resistance	Need for a rehabilitation program	Slight or incomplete reduction of symptoms with positive and negative residual symptoms. Alteration of social or personal functioning in at least two areas and requiring occasional supervision. No more than one item with a score $\geq$ 4 on the BPRS.
Level 4	Moderate resistance	Need for a rehabilitation program	Reduction of symptoms but with a clear persistence of them, affecting six or more areas of social and personal functioning and requiring frequent supervision. CGI 4. A score of 4 or 2 BPRS items. A BPRS score $\geq$ 45 on the 18-item version and 60 on the 24-item version.
Level 5	Severe resistance	Need for a continuous strategy, individual and oriented toward attempts with atypical antipsychotics and adjuvant treatment	Reduction of symptoms but with a clear persistence of them, affecting six or more areas of social and personal functioning and requiring frequent supervision. CGI 5. A score of 5 on 1 BPRS item or $\geq$ 4 on 3 items. A total BPRS > 50 on the 18-item version and 67 on the 24-item version.
Level 6	Refractoriness	Longer-term hospitalization with pharmacological and psychosocial attempts	Reduction of mild or non-demonstrable symptoms and persistence of positive and negative symptoms with marked alteration in all areas of social and personal functioning. CGI 6. A score of 6 on 1 BPRS item or of $\geq$ 5 on 2 items. Total BPRS score of $\geq$ 5 per level.
Level 7	Severe refractoriness	Longer-term hospitalization with pharmacological and psychosocial attempts	No reduction of symptoms with many positive and negative symptoms associated with behavioral alterations. All areas of social and personal functioning have deteriorated, requiring constant supervision. CGI 7. A score of 7 on 1 BPRS item. Total score of $\geq$ 5 per level

BPRS = Brief Psychiatric Rating Scale; CGI = Clinical Global Impression.

2.3. The 1992 criteria proposed by Meltzer

Meltzer in 1992 set forth the idea from Brenner et al[23] He proposed to assess treatment-resistance according to different parameters: psychopathology, cognitive function, extrapyramidal functions, social functioning, independence and work functioning, quality of life, reinstatement, dependences, cost of the illness, as well as treatment.[24] His criteria are less strict and more useful in clinical practice.

The way treatment-resistance is currently defined, is based on previous ideas and is reflected in treatment algorithms in various clinical guides. According to the current definition, schizophrenia is considered an illness in which, besides the existence of acute symptoms, there is a deterioration of the premorbid state.[25] Clinical guides indicate the need to assess adherence to treatment and that this treatment be appropriate, to re-examine the diagnosis, substance abuse and psychosocial stressors, as well as the use of cognitive behavioral and psychosocial therapies, before considering a patient as treatment-resistant, and to propose treatment algorithms.[26]

2.4. Other related concepts: negative symptoms of schizophrenia and remission

Historically, the more significant symptoms in the definition of treatment-resistance were the ones designated positive symptoms. Negative symptoms of schizophrenia, characterized by the absence of behavior and functions, usually displayed in healthy persons, have typically been considered structural, indicators of poor prognosis, and with poor treatment response.[27] Spanish researchers found a higher correlation between anhedonia and unsociability with poor treatment response, and a significantly higher score in apathy and abulia in treatment-nonresponsive individuals.[27,28] This seems related to the capacity to adapt to work, social and personal surroundings.

It has also played an important role in certain classifications. In 1980, Crow had already classified schizophrenia into two distinct pathological processes: schizophrenia type I and type II, depending on whether positive or negative symptoms of schizophrenia predominate, based on the two types having etiopathology, clinical presentation and a different response to treatment.[29] This has not been replicated consistently. Andreasen developed the Scale for Assessment of Positive Symptoms (SAPS),[30] and the Scale for Assessment of Negative Symptoms (SANS),[31] establishing two types of schizophrenia, positive and negative. Pogue-Geile and Harrow distinguished between two types of negative symptoms of schizophrenia: type A, related to social dysfunction, and type B for the remaining symptoms and social symptoms secondary to adapting to a chronic illness.[32] Carpenter specified the differences between negative symptoms; he defined deficit state as primary and persistent, and secondary as those due to causes other than schizophrenia and which may or may not persist.[33] The Positive and Negative Syndrome Scale (PANSS) was developed to assess schizophrenia in broader dimensions than as a positive/negative syndrome, and integrated these ideas by assessing four (positive, negative, disorganized and relational) different symptoms.[34]

One of the latest contributions was made in April 2003 by a working group, Remission in Schizophrenia Working Group, which came together to develop a definition for remission based on operational criteria. With the help of historical constructs, they defined it based on a single threshold of severity, instead of basing it on a percentage improvement over a specific level of reference. Remission criteria were evaluated based on three dimensions: positive symptoms, negative symptoms and disorganization.[11] These three factors are determinants at the clinic, although other researchers, such as Carpenter and Koenig, indicated that they were preceded by symptoms in social interaction, cognitive function, in affect and in the motivation that seems determinant in long-term morbidity.[35] Carpenter had already written in 1977 that clinical recovery was not synonymous with social recovery. We believe that this idea is linked to what is today known as individual psychosocial functioning.

Encompassing the earlier ideas of the Schizophrenia Working Group, Andreasen et al proposed different scoring items for the PANSS and BPRS scales, divided into three dimensions: psychoticism with delusions and hallucinatory behavior; disorganization, mannerisms and strange attitudes; and negative symptoms with blunted affect, social withdrawal and lack of spontaneity. These dimensional criteria are the most frequently used today to evaluate remission of symptoms, if all items remain at low intensity for ≤ 6 months.[11]

3. Conclusions

3.1. From drug resistance to lack of sufficient response

What has typically been called resistance to antipsychotic treatment is nowadays a fundamental healthcare challenge. It involves deterioration in social adjustment, reduction in the capacity to access rehabilitation programs, and high healthcare costs.[36] Even with overall treatment today, many patients experience variable and fluctuating remission of positive and negative symptoms. In spite of a reduced number of chronic inpatients, this hampers adaptation to the demands of daily life: studies, work, family, partner, social relations, etc.

If we perform a historical assessment of the knowledge acquired on the treatment and clinical course of schizophrenia, we arrive at several conclusions. One is heterogeneity in response, and that we are indeed well aware of many factors on which this heterogeneity depends; i.e., comorbidity, therapeutic non-compliance, factors deriving from the individual metabolism itself, abuse of other substances, and lack of psychosocial support. In many cases, we do not know why some patients receiving overall treatment show partial and fluctuating remission of symptoms, with a negative impact on meeting their objectives. We arrive at another conclusion if we review historical milestones in antipsychotic psychopharmacology, one of the main engines for progress. We find ourselves in a period of stagnation, interrupted by the appearance of different depot formulations of known antipsychotic drugs such as risperidone, olanzapine and paliperidone, which facilitate adherence, the main factor in relapse. However, something else is needed, other than new drugs, for the challenges we face today: negative symptoms, cognitive and social functioning. We must consider what has historically been postulated and what Lieberman and Kopelowicz articulated, speaking of psychiatric advances not only in terms of drugs, but also in rehabilitation and community services, as a stimulus to achieve recovery and restore patients' baseline functioning.[37]

In the clinical practice of today, treatment-resistance cannot be categorically evaluated according to response, or lack thereof, to drug treatment. Setting forth Andreasen's ideas on the concept of remission, we are closer to operational dimensional models that integrate the idea of continuum, and we speak of a lack of sufficient response. We believe that this concept should be more inclusive in its current vision of treatment-resistant schizophrenia, since it could contribute a notion of continuum with response levels up to recovery of premorbid functioning, with regard to the individual's life expectations. Furthermore, it takes up the ideas of Brenner et al and Meltzer by integrating different pharmacological approaches, without denying the importance of drugs, while hoping for

advances in research on pro-cognitive compounds, antipsychotic drugs, etc., which will mark new therapeutic milestones.

Conflicts of interest

The authors declare that they have no competing or financial interests related to the material in the manuscript. Winston W. Shen has reviewed this manuscript and found no conflict of interest.

Disclosures

Juan D. Molina and Ana B. Jiménez-González searched the relevant papers and drafted the manuscript. Francisco López-Muñoz and Fernando Cañas participated in critically reviewing the manuscript on intellectual content and scholarly writing. All authors have read and approved the final manuscript.

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