Review

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Pharmacological treatment resistant schizophrenia

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In the clinical practice, there are three different terms to designate schizophrenic patients who do not improve with antipsychotic medication: treatment-resistant, treatment-refractory and non-respondent patients.

Treatment resistance is neither a synonym of chronicity nor of severity nor seriousness. Therefore, for a patient to be considered resistant, several points must be taken into account. These points are: *a)* whether the schizophrenia is primary or secondary; *b)* its nature *c)* presence of previous substance abuse, and *d)* treatment compliance and tolerance; e*)* presence of minor neurological signs.

The most widely accepted criteria to define pharmacological treatment resistance in schizophrenia were initially developed around 1988 by Kane. Nowadays, the BPRS and Independent Living Skills Survey (ILSS) are the scales used to assess the levels of lack of response or of treatment resistance.

To attain a suitable therapeutic evolution in schizophrenics resistant to treatment in antipsychotic medication assays, the following guidelines must be considered:

- Identifying the symptoms clearly and using medication with a suitable dose and duration.
- Taking into account that treatment resistance can be mistaken for treatment intolerance, non-compliance to treatment, inappropriate social support or inappropriate psychosocial treatment.
- Using up all single therapeutic agents before applying multiple agents.
- Preventing extrapyramidal effects by means of an adequate choice of the primary treatment.
- Maintaining a positive therapeutic attitude.

Key words:
Treatment pharmacological. Resistant. Schizophrenia.

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Esquizofrenia resistente al tratamiento farmacológico

En la práctica clínica son tres los términos para caracterizar a los pacientes esquizofrénicos que no mejoran con medicación antipsicótica: resistencia al tratamiento, tratamiento refractario y no respondedores.

La resistencia al tratamiento no es sinónima de cronicidad ni de severidad o gravedad, de tal manera que para que un paciente sea considerado resistente deben tenerse en cuenta varios puntos: *a)* si la esquizofrenia es primaria o secundaria; *b)* la naturaleza de la misma; *c)* si hubo o no historia de abuso de sustancias; *d)* cumplimiento y tolerancia de los tratamientos, y *e)* presencia de signos neurológicos menores.

Los criterios mayoritariamente aceptados para definir la resistencia al tratamiento en la esquizofrenia fueron desarrollados inicialmente por Kane en 1988. Actualmente para la evaluación de los niveles de falta de respuesta o resistencia al tratamiento se utiliza la escala BPRS y la Independent Living Skills Survey (ILSS).

Para alcanzar una evolución terapéutica favorable en ensayos con fármacos antipsicóticos en pacientes esquizofrénicos resistentes al tratamiento se deben seguir las siguientes directrices:

- Identificar claramente los síntomas y utilizar fármacos en dosificación adecuada y tiempo suficiente.
- Tener en cuenta que la resistencia al tratamiento puede confundirse bien con intolerancia a la medicación, no adherencia al tratamiento, un inadecuado apoyo social o bien un tratamiento psicosocial inapropiado.
- Agotar la utilización de fármacos solos antes que tratamientos farmacológicos combinados.
- Prevenir los efectos extrapiramidales mediante una apropiada elección del tratamiento primario.
- Mantener una actitud terapéutica positiva.

Palabras clave:
Tratamiento farmacológico. Resistencia. Esquizofrenia.

INTRODUCTION

In this review, we focus on the concept of resistance to single treatment. This is done exclusively from the pharmacological point of view, even when it is known that treatment should be multifactorial and that other series of therapies such as psychosocial approaches, which although very effective, above all in chronic psychosis, are difficult to quantify, so that they still lack a univocal methodology.

Although schizophrenia is considered a chronic disease in which treatment never provides a cure, it has been possible to reach significant clinical improvement since the introduction of chlorpromazine and other antipsychotic drugs. As there is no total remission of symptoms, we may consider the existence of different levels of response to treatment and consequently, probably the presence of resistance to treatment, considering that between 5%-25% of schizophrenic patients do not partially or totally respond to antipsychotics without including the 15 % who improve only with placebo.

In the clinical practice, there are three terms that have been used to characterize schizophrenic patients with prominent symptoms who do not improve with antipsychotic drugs: treatment resistant, treatment refractory and treatment non-respondent patients. In general, these terms are used indistinctly.

Three different types of definition have been proposed, according to the objective aimed at:

- *Very restricted definition,* for research objectives aiming to offer well established clinical and paraclinical characterization of a sample of schizophrenic patients particularly resistant to treatment[1-3].
- *Less strict definition,* with research objectives of a new antipsychotic drug whose indication may be treatment refractory schizophrenia.
- *Extended definition*, having practical clinical interest in relationship with strategies to be developed in low treatment responding patients.

DIFFERENTIATION OF THE RESISTANCE CONCEPT

Resistance to treatment is not a synonym of chronicity. Although schizophrenia is a chronic disease, some schizophrenic patients may remain hospitalized for long periods for other reasons than that of being treatment resistant. These may be, for example, for social or family reasons. Collins et al. (1992) find that 50 % of long stay schizophrenic patients do not comply with ERT criteria[4].

Resistance is not always synonymous of severity or seriousness. Some patients whose schizophrenia is not especially severe do not show any type of improvement with treatment. They are often not treated and sometimes not studied because their condition is not serious.

If a schizophrenic patient is considered treatment resistant, the physician should consider the following aspects:

- *Primary or secondary resistance.* Know the disease period in which the resistance is present, differentiating if it is from the first treatments (primary) or in subsequent ones (secondary).
- *Character of the resistance.* It affects all the symptoms (overall resistance) or only the nuclear symptoms (partial resistance).
- *Clinical or personal history prior to onset of the schizophrenia.* It is important to know if the patient has a history of previous substance abuse or abuse during the disease.
- *Somatic examination.* Presence of minor neurological signs.
- Compliance and tolerance of the drug treatments received.

Historic aspects

There are at least four historic aspects that may be considered in treatment resistant schizophrenia: limits of the treatment efficacy, attempts to define therapeutic strategies, first attempts to define the term and first intentions to distinguish the resistance factors.

Limits of treatment efficacy

The first case mentioned in the literature on resistant schizophrenia was described by Bardenat and Sutter in 1938[5] in a patient who received treatment with insulin. After 1952, with the development of classic antipsychotics, a significant improvement was obtained in many schizophrenic patients, however not so much benefit was obtained in some of them. In 1976, for example, Davis[6] described the case of a «fenotiazin-resistant» patient.

Attempts to define therapeutic strategies

Several therapeutic attempts were established from the beginning. Electroconvulsive therapy was one of them, either alone or associated with neuroleptics. Some psychiatrists continued with insulin cures until 1970. However, new therapeutic strategies were established, especially after the appearance of new drugs such as clozapine, amilsupride, etc.[7,8].

First attempts to define the term

Itil et al. proposed a definition of resistant schizophrenic patients as those who maintained active psychotic symp-

toms in spite of 2 years of treatment (or who were taking phenotiazine 6 months) and a dose of chlorpromazine greater than 6,600 mg and of trifluoperazine 80 mg. When testing a new neuroleptic, loxapine, in «refractory schizophrenia» Deniker et al.[9] defined this as that which has been treated with neuroleptics for at least 2 years, at standard dose for six months and no less than three neuroleptics at different times, without noticeable benefit.

First intentions to distinguish resistance factors

Jus et al.[10] stated that neuroleptic resistance in schizophrenic patients could be due to: poor premorbid history, lack of precipitating factors, insidious onset and subtype of hebephrenic or simple schizophrenia.

PRESENT CRITERION

By definition, schizophrenia includes an extensive period with symptoms associated to social incapacity that constitutes a deterioration from the onset of the disease[11]. Long term evolution of this type of patients confirms that 80 %-90 % of these patients have social and occupational incapacity in different degrees. Consequently, given that complete remission of a schizophrenic episode is not common and that most of the patients are partial responders in the best of the cases, a definition of treatment resistant schizophrenia that dichotomizes patients into those whose symptoms have remitted completely versus those others with persistent symptoms who do not improve with antipsychotic medication may not be adequate.

The most accepted criterion to define treatment resistant schizophrenia was initially used by Kane et al.[12] in 1988 due to a multicenter clinical trial with clozapine (MCT). Originally, these criteria included:

Persistent positive symptoms

Value equal to or superior to 4 (moderate) in at least two out of four positive symptoms of the Overall and Gorham BPRS Scale[13]: hallucinatory behavior, unusual thought content, suspiciousness and conceptual disorganization.

Moderately serious disease grade

Assessed according to the BPRS (total score equal to or superior to 45 on an 18 item scale) and value equal to or superior to 4 on Guy's Clinical Global Impression (CGI) scale[14].

Disease persistence

No stable period of good social and/or occupational functioning in the last 5 years: incapacity to maintain a job and establish adequate personal relationships.

Treatment refractory condition

In the last 5 years, the patient has received at least 3 treatment periods with conventional antipsychotics (of at least two chemical varieties) at a dose equal to or superior to 1,000 mg daily of chlorpromazine for 6 weeks, each one of them without significant improvement of the symptoms and failure of improvement in at least 20 % of the total value on the BPRS scale or intolerance to a prospective clinical trial of haloperidol for 6 weeks at a dose of 10-60 mg per day.

The fourth criterion, condition refractory to treatment, was modified from the time it was proposed, because it was verified that failure of 2 trials with drugs was sufficient to be accepted as a treatment resistant criterion[15], especially if this failure to the response occurred after using second generation antipsychotics[16]. It is important to stress the fact that interactions have been documented during the last three decades between treatment responders and the setting in which they live (Fallon and Liberman, 1983; Liberman et al., 1984). Thus, those patients who were in long stay units with less supervision required superior doses of neuroleptics to obtain the same response.

Together with this definition of Kane, there are others that are no less interesting.

That proposed by May et al.[17], and defended by Dencker and Kulhanek (1988) has three advantages (table 1):

Brenner et al.[18] (1990) defined the term treatment refractory schizophrenia as «psychotic symptoms present in persons with adequate diagnosis of schizophrenia, important incapacity of psychic functions and/or abnormal behavior, that persist in spite of reasonable and regular drug and psychosocial treatment for a time period of at least 2 years.» Since then, seven response levels or grades that go from total remission to severity in regards to refractoriness have been established.

For the evaluation of the levels of lack of response or treatment resistance, the BPRS scale and Independent Living Skills Survey (ILSS) are used. The global evaluation of each patient groups the following aspects (table 2).

Table 1 | **May et al.[17] treatment resistance grades**

There are different response levels, from an excellent response (level 1) to severe resistance to treatment (level 6)
They include social consequences of the disease
Not only drug treatment but also the type of pyschosocial intervention conducted are taken into consideration

Table 2 Grades of treatment response and resistance[18]

Identification of up to nine domains in which the patient is assessed according to a scale that groups from «autonomously» until «only with constant care or supervision»
Presence of seven response levels or grades that gradually include: «clinical remission» (two levels), «resistance» (three levels) and «refractory» (two levels)
It includes a quality of life scale

Table 3 Guidelines proposed to determine treatment resistance in schizophrenia

Treatment refractory condition: at least two previous trials of 4 to 6 weeks long and 400 to 600 mg of chlorpromazine (or equivalent) without clinical improvement
Persistence of the disease: more than 5 years without period of good social or occupational functioning
Persistent psychotic symptoms: total score on the BPRS scale greater than 45 (on the 18 item scale) and value greater than 4 (moderate) in at least 2 of 4 items of positive symptoms

However, there have also been other changes regarding the definition of an adequate clinical trial. The different strategies in the psychopharmacological treatment of schizophrenia have aimed at knowing the therapeutic window of the neuroleptics, which depend on their blood levels in blood, in which absorption, transport and metabolism enter into play. Furthermore, other authors suggest that the sum of other drugs such as lithium, propanolol, carbamazepine and benzodiazepines may improve therapeutic response. Generally, it is accepted that a period of 4 to 6 weeks (more than the strict 6 week period) is adequate for a treatment in clinical trial with antipsychotic medication[19]. The recommended dose ranges have also been reviewed. Initially, at least 1,000 mg of chlorpromazine, or its equivalents, was the dose proposed to be used in a trial with conventional antipsychotics. However, doses around 400 mg per day of chlorpromazine are sufficient to block between 80 % and 90 % of the dopamine receptors[20] and higher doses do not produce direct therapeutic benefit, even in patients not responding to treatment[21]. Thus, a 4 to 6 week long trial with 400 to 600 mg of chlorpromazine is presently accepted as the adequate standard dose for treatment in a clinical trial[15].

All these criteria changes are presently being used when defining treatment resistance in clinical trials[21] and also constitute the bases of a relatively recent proposal regarding therapeutic strategy to follow with a schizophrenic patient in whom an attempt is made to optimize accurately his/her clinical response during a specific drug treatment (table 3).

NEGATIVE SYMPTOMS AND COGNITIVE DETERIORATION

Although most of the definitions on resistance to treatment focus their attention on the persistence of positive symptoms in psychosis, there is increasing awareness on the problem of the presence of negative symptoms and cognitive deterioration[22]. Clozapine and other second generation antipsychotics have been shown to be very effective in the reduction of negative symptoms in double blind clinical trials. Thus there is controversy about whether it would be appropriate for the negative symptoms to also form a part of the definition of resistance to treatment. Additionally, deterioration of the cognitive functions especially influence a long term unfavorable course of schizophrenic patients, especially related to occupational aspects and as it is also clear that second generation antipsychotics may improve action in these domains, more strength is also given increasingly to the criterion of inclusion of cognitive functions as an integrating part of the concept of resistance to treatment, since they are very important for optimum clinical functioning.

PREVALENCE

Few studies related with resistance to treatment in schizophrenia are found. Two independent groups have considered this factor in the United States in recent years.

Using an extended interpretation when performing a study with clozapine approved by the FDA in the country of California, Juarez-Reyes et al.[23] studied a sample of 293 patients. These patients were considered resistant to treatment if they fulfilled the following criteria: they were older than 16 years, they had a diagnosis of schizophrenia or schizoaffective disorder, without improvement after two four week long clinical trials with psychodrugs and with doses of 600 mg/day or greater, or they presented late dyskinesia and an index inferior to 61 points on the global functioning assessment. The estimated frequency of resistance to treatment based on this extended criterion was 42.9 %. However, this value decreased to 12.9 % if the criteria established by Kane[12] were used, probably due to the primary incapacity of finding cases with 3 clinical trials without beneficial results.

Essock et al[24] used the following criteria to measure prevalence of resistance to treatment: failure of two 6 week long clinical trials and 1,000 mg/day of chlorpromazine or equivalent, hospitalization of at least four months and a total number of hospitalizations of at least 24 months in the last 5 years. Frequency obtained in a total of 803 patients

admitted to the state hospital of Connecticut with schizophrenia or schizoaffective disorder diagnosis was 48 %.

With these and similar estimations[25], it can be extrapolated that a total of between 200,000 and 500,000 patients with treatment resistance in schizophrenia presently live in the United States. We do not know the figures in Spain.

PATHOPHYSIOLOGY OF TREATMENT RESISTANT SCHIZOPHRENIA

Presently, it is almost universally accepted that pathophysiology of schizophrenia entails alterations of the early processes of neurodevelopment and that it possibly gives rise to the schizophrenic symptoms during adolescence or the years of early adult age. The hypothesis of neurodevelopment is supported by neuropathological evidence (Akbarian et al., 1993, 1995), studies in dizygotic twins (Bracha et al., 1991; Torrey, 1994) and observations of premorbid level of patients who develop schizophrenia (Done et al., 1994; Walker and Levine, 1990). The presence of cerebral structural abnormalities in a large number of schizophrenic patients includes the ventricular system and frontal, temporal and limbic cortexes.

Since the criteria for resistance to treatment have been standardized, research on the neurobiological nature of the problem has been growing[4]. Although the data are not very numerous, evidence of factors of neurodevelopment associated to a poor response to treatment in schizophrenia (Murray, 1994; Bloom, 1993; Sham et al. 1996) has been recently found. Lieberman et al. (1996) state that there is an increase in the ventricular size and decrease in cortical volume among patients classified as resistant, when control subjects are compared with responding patients. Bilder et al.[26] and Stern et al.[27], have also verified that patients with treatment resistant schizophrenia have greater index of cortical atrophy in magnetic resonance (MRI) studies) when compared with patients who have good response to treatment. This is especially true if the patient has a predominance of negative symptoms[28]. The patients with persistent negative symptoms also have a tendency to abnormal cellular migration in the prefrontal cortex[29].

Recent preclinical (Li et al., 1995; Giron et al., 1996) and clinical evidence (Breier et al., 1997; Laruelle et al., 1996) support the importance of synaptic regulation of dopamine (or its glutamate regulating neurotransmitters and GABA) as mediator of schizophrenic disease. This model would explain the poor course of the disease, greater likelihood of recurrences and prolonged time of drug response to the treatment (Lieberman et al., in press).

The disease stages[30] and corresponding pathophysiological conditions include the following stages (fig. 1).

State 1: cortical neuropathology and deficient neuromodulating capacity

The first stage of schizophrenia is the result of genetic or epigenetic causes during pregnancy or in the first moments of perinatal development, that determine a failure in the neuronal development and synaptogenesis processes and the consequent deficit of inhibitory capacity of the cerebral cortex on the subcortical structures. If these abnormalities in development are very numerous or severe, the patients may have an early onset of the disease, the disease may be more severe and they may present resistance to treatment in their first episodes of the disease.

Stage 2: neurochemical activation

Deficiency in the neuronal modulating capacity leads to the second pathophysiological stage that occurs in adolescence and early adult age. In the course of stressing experiences (e.g., family conflicts, school situations, military service, substance abuse), the alterations of the neuronal activity, instead of being compensated so that the equilibrium would be reestablished, progressively have a neuro-

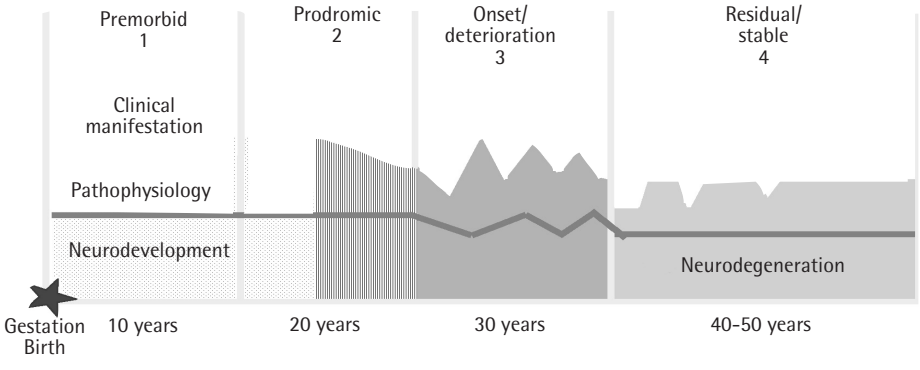

Figure 1 *Disease stages. Table of Sheitman and Lieberman[30].*

chemical activation as a result. This process leads to prodromic and initial phases of schizophrenia.

Stage 3: neurotoxicity

It involves the development of neuronal structural changes, as a consequence of the prolonged neuronal activation or of the effects they product. The result is a persistent morbidity and resistance to treatment.

GUIDELINES

These evidences and the interpretative model presented suggest two large pathways of clinical deterioration in schizophrenia. The first is a consequence related with resistance to treatment that may be directly due to pathological factors of neurodevelopment. The second includes prolonged periods of untreated psychoses during the initial period and/or multiple episodes during the first years of the disease, with low recovery levels.

Endogenous neurochemical activation, consequence of the incapacity to regulate presynaptic dopamine release in the limbic system, may be a useful pathway to understanding the phenomenon of the refractory response that occurs in the schizophrenic patient.

The following clinical practice should be adopted if it is aimed to reach a favorable therapeutic course in trials with antipsychotic drugs in treatment resistant schizophrenic patients (table 4):

- *Clear identification of the symptoms.* Antipsychotics are very useful in the treatment of positive symptoms in psychosis, including hallucinations, delusions and other disorders. The new drugs may also be beneficial for negative symptoms, such as limited socialization, withdrawal and affective blunting, especially if these are secondary to the extrapyramidal symptoms due to the effect of conventional medication. It must also be considered that some drugs, such as clozapine, have been shown to be effective in hostile, aggressive psychotic patients. Thus, if we know for sure what are the specific symptoms a specific drug that is being tested is aimed at, we will know for sure which parameters have benefited and which have not. Furthermore, the global management of resistant schizophrenia is difficult and it should be approached by means of the symptom in most of the cases. If these and the pathophysiology of these are known, we could resolve part of the problems of this entity.
- *Systematic use of drugs in adequate dose and at least for 4-6 weeks.*
- *Consideration that drug intolerance, treatment non-compliance, inadequate social support and inappropriate psychosocial treatment may create appearance of resistance to treatment.* Assessment of these factors should precede the confirmation that a specific drug fails in the treatment. Thus, blood levels of the drug should be obtained to monitor compliance and rule out scarce drug absorption.
- *Exhaust the use of single therapeutic agents before multiple agents.* There is tremendous pressure by the clinicians to find a drug that rapidly solves each one of the problems the patient has. For example, hostility, irritability, insomnia could be considered secondary to psychosis and they would only be solved when a good therapeutic effect of the drug is reached.
- *Prevention of extrapyramidal effects by appropriate choice of treatment.* With the appearance of antipsychotic agents that are clearly effective at doses that do not cause extrapyramidal effects in most of the patients, persistence of adverse effects may be eliminated as an argument of therapeutic failure.
- *Maintain a positive therapeutic attitude.* At present, there are many therapeutic choices with antipsychotic drugs and new drugs are appearing continually every year. Thus, the patients and their family members should consider that there are good reasons for the existence of beneficial treatments, in spite of having a history of severe disease.

Tabla 4 **Guidelines for a favorable therapeutic course of trials with antipsychotic drugs in treatment resistant schizophrenic patients**

Clear identification of the symptoms
Use of drugs in adequate dosage and sufficient time
Consider that drug intolerance, treatment non-compliance, inadequate social support and inappropriate psychosocial treatment may create appearance of resistance to treatment
Exhaust the use of single therapeutic agents before multiple agents
Prevention of extrapyramidal effects by appropriate choice of primary treatment
Maintain a positive therapeutic attitude

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