Review

The evolving concept of Treatment-Resistant Schizophrenia

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Schizophrenia is a chronic disease of body and mind that affects 1% of the population. The existence of the person with schizophrenia should be understood, at least, from two perspectives: one considering the integration of the individual into the social community, another understanding that there is a patient with a medical problem treatable with medications and psychotherapies. There is a large group of patients with 'treatment-resistant schizophrenia," that is, cases in which a minimum degree of remission with conventional treatments is not obtained. These cases have pointed to the fact that even today we still lack an integrative treatment model obtained through the assembling of specific interventions with verifiable effectiveness. The concept of treatment-resistant schizophrenia should have evolved in accordance with the advancing of the currently available knowledge and therapeutic resources. Why hasn't this happened? This article reviews the history of the concept of "resistance" to account for such failure and proposes a methodological approach to overcome this stagnation.

Key words:
Schizophrenia, Resistant schizophrenia, Psychosis, Chronic schizophrenia, Treatment resistant schizophrenia, Antipsychotics, Comorbidity

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La evolución del concepto de Esquizofrenia Resistente al Tratamiento

La esquizofrenia es una enfermedad crónica del cuerpo y de la mente que afecta al 1% de la población. La existencia de la persona con esquizofrenia debe ser entendida, por lo menos, con dos perspectivas: una, la que contempla su integración en la comunidad social; otra, la que entiende que hay un paciente con un problema de salud tratable con medicinas y con psicoterapias. Hay un grupo numeroso de pacientes con presentaciones 'resistentes' de la esquizofrenia, es decir: casos en los que no se obtiene un grado mínimo de remisión con los tratamientos convencionales. Estos casos dejan en evidencia el hecho de que todavía hoy carecemos de un modelo de tratamiento integrador que esté armado a partir de intervenciones específicas cuya eficacia sea verificable. El concepto de 'esquizofrenia resistente' debería haber evolucionado a la par que los conocimientos y los recursos terapéuticos que hoy tenemos. ¿Por qué no ha ocurrido? Este artículo revisa la historia del concepto de 'resistencia' para dar cuenta de tal fracaso y proponer perspectivas metodológicas que nos saquen del estancamiento.

Palabras clave:
Esquizofrenia, Esquizofrenia resistente, Psicosis, Esquizofrenia crónica, Esquizofrenia resistente al tratamiento, Antipsicóticos, Comorbilidad

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INTRODUCTION

Schizophrenia is a chronic disorder of the body and mind that affects 1% of the population.[1] There have been frequent attempts to define some *remission criteria* of the supposed disease,[2] or at least to provide an operational definition of the partial achievements obtained in the treatment of the *disorder*. Unfortunately, complete *remission* of the symptoms (and even less so *duration*) is an unreachable desire for many patients with treatment resistance. In this article, we understand "resistance" as lack of sufficient and verifiable changes of the symptoms after having correctly received conventional treatments. The currently available psychiatric classifications do not define this possible course of the disorder. However, it has been estimated that the cases of treatment-resistant schizophrenia can be 20 to 50%

of the total, according to the definition of "resistance" used.[3, 4] The excessive percentages shown by some investigations may be because they do not distinguish cases with true resistances from those others that have only received inadequate treatment, above all in regards to dosage, compliance and duration.[5]

Schizophrenia entails a qualitative change in the normal development of the individual. Some classical authors refer to this change as a "biographical rupture."[6] After the first symptomatic episode and confirmation of the diagnosis during the case follow-up, work must be done on re-adaptation of the patient and their immediate setting to the new circumstance. Even if complete remission of the symptoms is achieved, in some way the patients will try to express that they no longer perceive themselves as before. This chronic feeling of irreversible transformation can be accompanied by a Posttraumatic Stress Disorder due to the hospitalization and the experience, generally anxiety-producing, of the acute psychotic symptoms.[7] Furthermore, it includes many other psychological and social phenomenon that we cannot explain with only a theory of trauma or of "conflict" of normal psychology.

If we compare the therapies available at present with the past periods, we see that these have multiplied on increasingly more solid scientific basis in most of the developed countries. The objectives in the *recovery* stage after the acute crisis are currently more ambitious and on the level of the expectations of the patients, of their families and of society.[8] We now know that the early-onset of drug treatment and of the psychosocial treatments not only improve the immediate result but also the long-term prognosis.[8, 9] With the advances achieved, the benefits of the therapies continue to be limited, even when we combine drug treatment and psychosocial treatment optimally.[10] In general, there has been progress. In most of the patients, it has been possible to control the positive symptoms for enough time to avoid the amount of interference in the challenges of adolescence and the young age that previously occurred. The treatment of the negative symptoms has become more sophisticated. We have rediscovered the importance of diagnosing and rehabilitating the neuropsychological and executive dysfunctions. Little by little, we are integrating the medical-psychological type actions with the social and familial context actions.[11-15]

However, in a large percentage of patients, that is, between 30 and 50%, response to treatment will not be favorable,[16] or it may be so limited that it will not have any practical consequence in the development of the person, that is, on their possibilities to increase their long-term repertoire of survival strategies that is reflected in the grade of adaptation to social life beyond that of the core family. It is known that this result is related with the nature per se of the disease and that something can be predicted through the prognostic factors described by the cohort studies.[17, 18] With the drug treatments, it is possible to reduce the recurrence risk, which the greater the number, the greater the deterioration. This reduction in risk is 30% per year of treatment maintained without symptoms, although the controversial CATIE study has been publishing some less triumphal data since the year 2005.[19]

The patients who do not improve with any of the conventional treatments pose a special challenge. The expectations for long-term recovery decrease and the *positive symptoms* also persist. This hinders the reinsertion of the patient in the family and community for the psychosocial treatment proposed in any model of comprehensive treatment. That is, the persistence of symptoms what are considered "acute" and "positive" also hinder rehabilitation, besides the "negative" symptoms.

Our questions investigate the concept per se of *resistant schizophrenia*. Does it refer to a subgroup of patients with partial or incomplete recover of the *positive* and/or acute symptoms? Does it propose disease progression in a different way due to the concurrence of additional factors? And if so, what would these factors of poor prognosis be? Is *resistant schizophrenia* a variation of grade, of greater severity, that only becomes clear as such when conventional treatments fail, or is it a qualitative variation of the treatment by itself?

WHAT DO WE UNDERSTAND BY TREATMENT-RESISTANT?

Treatment Resistant or *Refractory Schizophrenia (TRS)* occurs when there is insufficient response to optimum successive treatments.[20] Kane, in 1988, formulated the best-known definition: therapeutic failure to at least three treatment trials with full dose antipsychotics, using 400-600 mg/day of chlorpromazine as reference.[21] Eleven years later, this formula was revised and other criteria added, among them lack of patent adherence to treatment standing out.[22] Currently, some authors propose replacing the term "resistance" with "incomplete recovery," and extend the analysis of the therapeutic intervention to multiple domains of dysfunction beyond the psychiatric syndromes.[23] Therefore, they consider that "non-resistance" also includes complete disappearance of *negative,* cognitive and affective *symptoms* plus complete recovery of the pre-disease functioning.[24] Anecdotically, it has been suggested that '*very poor outcome schizophrenia*' could be a separate disease with a dysfunctional pattern of visual and auditory cortexes different from that described in common schizophrenia.[25] Successively, some more ambitious remission objectives have been added. These blur the original concept of "resistance" and render useless the idea of "remission" for the investigation

of treatments, above all in detriment of the therapies of aspects of the disorder that go beyond the psychiatric semiology. This explains why many modern studies aim to measure the results of a "comprehensive" therapeutic intervention by statistical correlation studies between *variables* (that do not serve to establish *causality* or adapt to the rigorous definition of '*experiment*'). Epistemologically, these variables are *immense* because they operate on different interpretation levels or "logical types." *For example: is it* valid to refer to the effectiveness of a psychosocial therapy using the score changes on the PANSS scale*? Or is it valid* to refer to effectiveness of the antipsychotic drugs considering the "social functionality" scales? Isn't it possible that there are persons with chronic hallucinations who are capable of working and supporting a family? Are there no doubtful histories of single psychotic episode, without current "executive dysfunction" that evolve towards severe social maladaptation?

For most of the investigators, the concept of TRS has a precise meaning. It is the persistence of *positive symptoms*, which are moderate or severe, after correct biological treatment.[26] Recent publications use expressions of the following type: *ultraresistant schizophrenia*[27], *clozapine-resistant schizophrenia*[28-30], *pharmacological treatment resistant schizophrenia*[31] and *neuroleptic-nonresponsive schizophrenic patient.*[32] In accordance with these close definitions, it would be erroneous to classify a patient who does not follow the treatment as TRS, stating that *resistance would then be due to the patient and not to the schizophrenic disease*.[5] We think that this comment is useful to investigate the efficacy of the drugs. However, a useful concept in the investigation may be useless in the real clinical practice, unless we opt for the ideology that separates the *disease* from the *person-patient* and we confuse the *methodological reductionism* of the science with *ontological reductionism.*

There is agreement on differentiating TRS (30% of the cases) from Chronic Schizophrenia (80% of the cases). However, this distinction is problematic. Is a patient with chronic delusion, structured secondarily from some "primary phenomena" or "automatisms" that were relieved with medication "resistant" or "chronic?" And is it in the same as a patient with *delusional perceptions* and third person auditory hallucinations that are not relieved with medication and that do not become structured as *delusional thought,* persisting the originating experience of perplexity and strangeness of ones self? As long as the *positivist psychopathology* (the PANSS scale is its most refined ingenuity) does not incorporate the distinctions made by the old European psychopathology between *primary delusion* and *secondary delusion,* there will be no possibility of delimiting the phenomena and totally distinguishing "resistance" from mere "chronicity."

HOW DO WE MEASURE IT?

Empirical verification of *resistance* is done based on the confirmation of change (or rather: of no change) of the scores obtained from the structured interviews and lists of symptoms designed for the investigation and not for daily work with the patients. The lists simplify the description of the signs and symptoms so that everyone can understand them, so that it can be used by professionals with theoretically divergent positions and heterogeneous paths of qualification in grades of experience. It is not clear (beyond the calibration meetings held prior to multicenter studies) that *validity* and *reliability* of these instruments are maintained even when the evaluator agrees to eliminate much of the doctrinal cultural heritage and of his/her experience in order to be able to score that observed according to the delimited definitions required by the test invented by a colleague having a different doctrinal tendency. Many studies do not describe the qualification of the persons who apply the instrument. Were they grant receivers, inexpert resident physicians, the same psychiatrist signing the article, etc.? Even more, we do not know the *validity* and *reliability* of the instruments in minority or unusual clinical populations, as is the patients with TRS.

HISTORY OF THE IDEA OF TRS

During the decade of the 1980's (see table 1), several experts became aware of the complexity of the idea of occult "resistance." The most mentioned definition of TRS had been that proposed by Kane et al. in the study that ratified the use of clozapine.[21] The criterion was confirmed or ruled out based on three dimensions: 1) *historic*: a history of total or partial absence of response to the previous treatment, having used at least two antipsychotics at adequate doses for sufficient time; 2) *current severity:* the patient should have some level of psychopathological severity according to the scores on the BPRS and CGI; 3) *verification:* insufficient improvement should be observed at present regarding the previous psychopathological levels with the current treatment. It should be taken into account that the definition of Kane is dichotomic (yes or no), which facilitates the processing of information at the expense of not analyzing how psychopathological expression changes, the readaptation of the individual to the disease and the social functionality. Even when these other dimensions of the problem are not ruled out, the definitions of Wilson in 1989[24] and of Keefe in 1991[33] are also dichotomic.

During the decade of the 1990s, Brenner et al.[34, 35] gave an unidimensional definition based on two sub-dimensions. They considered TRS as a *continuum* and they added the sub-dimension of the global reduction of all types of symptoms (not only positive) to the sub-dimension of the social adaptation.

The most modern definitions (see table 1) are guidelines and algorithms that have been reached by consensus which generally include the following criteria: (1) an agreed on number of clinical trials with drugs, (2) type of molecules tested (3) minimum time of treatment duration, (4) adequate minimum dose and (5) verification of an incomplete or insufficient clinical response.[36-39]

According to the Brenner group,[34, 35] something more than the response to drug treatment should be considered. For them it was necessary to incorporate the psychosocial treatment to the definition of "resistance." They distinguished investigation from the clinical practice and resistance to pharmacological treatments from resistance to psychosocial treatments. They suggested a synergic effect between both treatment forms and postulated that the psychosocial approach was of special importance in the case of TRS.

FACTORS OF TREATMENT RESISTANCE OF SCHIZOPHRENIA

Since the pioneer work of Kane, many investigators[40-43] have contributed to the identification of incomplete recovery factories and treatment resistance. (Table 2).

Intrinsic factors

This is the nature per se of the *disorder*, its intrinsic capacity of causing definitive *defect* and *transformation* in the personality after remission of the acute symptoms. The *clinical course* of this disease may have different outcomes, but there will always be *deterioration* of the individual's functionality. If we observe the long-term course of the *psychological reactivity* and *social functioning* of the person with untreated schizophrenia, we will verify that it will correlate in a nonlinear way with the progression of some symptoms that persist during the entire life, in agreement with the unified model of *dementia praecox* that Emil Kraepelin demonstrated in his sixth treaties of psychiatry in 1899.[44] We think that the language used by notorious experts[2, 45] to refer to the irreversible fact of the schizophrenic *process* avoids the problem because it does not clarify, (but also does not expressly deny) that when we define "remission" with a score threshold on the scales of symptoms, it can be deduced that the treatment has reverted the *qualitative change in the existence* of the subject. This qualitative change is, for many, the core aspect of the definition of schizophrenia.[46]. During the last years of life, Kraepelin modified some of his ideas and finally accepted the possibility of the complete remission in a small percentage of cases, in agreement with the follow-up studies of Eugen Bleuler[47] and of the Bonn Group. Applying stricter diagnostic criteria, excluding episodic cases having as *phasic, cycloid, polymorphic* course and of noticeable affective or confusional symptoms, the long-term prognosis of schizophrenia has become unpromising.[48] The current cohort studies show us that, even with a single episode, the *defect* acquired in the personality is not totally repaired.[49, 50] In most of the cases, some degree of social dysfunction remains in regards to the *potential of social status* that the subject had prior to the onset of the disease. Each episode of schizophrenia means a traumatic and long-lasting detention of the psychological development in the young when the investment used aiming for independence and for social ascent should be at its maximum.[51-53] If there were total cure, an enormous effort would be needed to pay back the debt that had been contracted for the years that were not used to consolidate the personality, social position and interpersonal relationships outside of the direct family. If we use the language of the economic sciences, each episode of schizophrenia has an elevated "opportunity cost." This rupture of the existential course escapes the inventories of symptoms and the short-term observation of many clinicians.

There is no clear of semiological profile of the first episode of schizophrenia that has been related with this future event of "resistance." There are clinical factors and course types that have some statistical correlation, but they are not sufficiently defined to formulate a hypothesis. These are age of early onset, gender, duration of the psychotic episode and severity of the deficit syndrome after the first acute episode.[54]

There are few *intrinsic* neurobiological findings of schizophrenia that help to anticipate if there will be "resistance" from the first episode. Past retrospective studies have suggested that ventricular enlargement anticipated a worse prognosis, however the prospective studies have related it with the use of drugs and with other harmful somatic conditions. Better response to the new antipsychotics has been related with cortical atrophy.[5] There are few more findings that have been correlated with "resistance" and it is strange that the few that have been found indicate an immunological hypothesis of psychoses: low plasma homovanillic acid and alteration of the function and concentrations of T cells and of some interleukins.[55]

Methodological factor

The second difficulty in order to identify the problems that we may treat under real work conditions (more than experimental ones: optimum but not always generalizable). If there were agreement regarding this point, it would be easier to exchange experiences in the management of TRS. The *lineal logic*, of cause-effect, feeds the belief that the "real" symptoms of schizophrenia orient the choice of the therapeutic objectives. The *circular* or "cybernetic" logic,

Table 1 Evolution of the operational definitions of the term resistances proposed by different authors

Author	Criterion of Treatment Resistance
Kane, 1988	At least 3 treatment trials with full antipsychotic doses using as reference 400-600 mg of chlorpromazine, without full symptomatic remission episodes during the last 5 years.
Wilson, 1989	Persistence of symptoms after 2.5 years of treatment with three different classes of neuroleptics (dosage of 1000 mg of chlorpromazine equivalents) for 8 weeks in the last 5 years.
Schüssler y cols. 1989	Insufficient improvement after administering neuroleptic treatment for 4 weeks.
Brenner y cols. 1990, Brenner y cols, 1993	Operational definition based on a scale developed by the author, distinguishing three different concepts: remission resistance, refractoriness. They develop a treatment response scale, with seven levels based on the CGI scale, BPRS and a Daily Living Skills scale. They define an intervention period of two years, to be able to diagnose resistance.
Keefe y cols 1991	There is not sufficient improvement after their neuroleptic treatment (40 mg haloperidol/day) during 6 weeks.
APA, 2004	Insufficient response to two clinical trials of 4 or 6 weeks duration using monotherapy with two different second-generation antipsychotics or two trials with a first-generation antipsychotic, if second-generation antipsychotics are not available. It is considered that the patient is treatment-resistant and is a candidate to be treated with clozapine in a clinical trial of 6 weeks with a dose of up to 900 mg/day.
EMEA, 2003[1]	Patients who have an inadequate response after two periods of at least at 6 weeks using neuroleptics of two drug types and with sufficient dosage.

[1]The guidelines for clinical research in schizophrenia of the European Agency suggest a definition for resistant patient to be used when it is aimed to study drugs in this type of patients. Most of the definitions used in the clinical practice are based on the pharmacological resistance criteria or chemoresistance, in which the criterion of change in the symptoms is expressed based on scales or inventories that very and grade of objectivity (for example, BPRS, PANSS or CGI).

Table 2 Factors that influence the concept of resistance

1. Intrinsic factor	a) Descriptive or differential nature or trait of the disease. b) Symptomatic typologies and constitutional and socio-demographic data that increase the likelihood of a worse outcome for the schizophrenia in general.
2. Methodological factor	a) Consequences of methodological reductionism (necessary for positivist research) in the definition of techniques and therapeutic objectives for the daily work in non-selected patients, and under real conditions. b) Consequences of bidirectional and "constructivist" origin of the mental symptoms that emerge during a specific therapist-patient relationship.
3. Biological factors of the individual	a) Pharmacodynamic, pharmogenetic and pharmacokinetic factor. b) Organic and toxicomania comorbidity factor.
4. Psychological and behavioral factors of the individual.	a) Personality factor (it includes the aggressive component). b) Disease awareness factor (BE CAREFUL: therapeutic awareness and compliance are simultaneously placed in the individual factor and in the contextual factor. Compliance also has some relationship with the intrinsic factor of the disease, since part of lack of disease awareness could be 'anosognosia').
5. Contextual factors of each one	a) Violence factor (beyond the individual aggressiveness). b) Family factor (it includes the paradigm of "expressed emotion," but it is more than that). c) Social factor.

more open to a *constructivistic view* of the meeting point between the curer and the patient, shows that the clinician who describes the symptoms of a patient becomes a part of the problem observed. He/she becomes an observer-participant, never neutral, that constitutes together with the observed (that is not a passive object) a syndrome and some goals. Psychiatrists reset the identity per se of experts together with the patients, their families and the persons who in any way participate in the construction and treatment of the problem on a daily basis. It is possible that the therapeutic objectives have been preconsistent choices arising from prejudices and cultural, social and economic interests, independent of the scientific evidence. Perhaps the prejudices select the symptoms that we are predisposed to grasp, and the psychotic patient, with his/her hypersensitive inclination, gives them to us as a present, and thus maintains us with the illusion that some sort of understanding is possible and with a reciprocal sensation of control on the relationship with the other. Couldn't it be that the same occurs in psychiatry as in other professions: that demand shapes a certain type of "professional offer" that assumes the ability to define the problems and needs of others? Could the patient and family modulate the expression based on the expectations they have about the professional who is going to treat them? Mental disease, without rejecting its biological basis, also operates as an ideological construction in which the psychiatrist will never be an external and neutral observer, but an active part of its mechanism.[56, 57] If we obviate this perspective, we waste a good part of our curative potential.

Research suggests that the best treatment of schizophrenia combines pharmacotherapy and psychosocial interventions.[58] However, hope in the recovery of areas such as work and socialization is vain when, in fact, we are obligated to operate with precarious means in lines of treatment that are multiplied and overlapping without coordination,[53] considering as 'holism' that which is mere opportunistic syncretism. This difficulty would be overcome if we worked with personalized, verifiable and *binding* objectives instead of seeking protecting in a *holistic* ideal that no one dares to question or specify: perhaps the professional groups, in accordance with specific parameters and interests, assume the power of clarifying or obscuring their *praxis* according to whether they are inside or outside of the circle.

First, it is necessary to break down the specific factors located in factors or "levels" or "domains" of the TRS. Each fact could be linked with a limited therapeutic objective, extracted from pharmacotherapy, psychotherapy, family therapy, psychoeducation, occupational therapy, etc. A repertoire of very defined problems would appear with their respective specific tasks. This would make it possible to perform follow-up studies of homogeneous groups based on these specific tasks and not based on clinical types or on global therapies. After, we could investigate the relationship between the simple facts and complex facts (intrapsychic dynamics, type of therapy, type of personality, neuropsychological profile, etc.). On the contrary, the "official "clinical guidelines"[59] use these terms: "reduce or eliminate the symptoms," maximize quality of life and adaptive functioning," promote and maintain recovery."

Pharmacodynamic factor

The percentage profile of receptorial activity *in vitro* of each molecule has served to increase, not to void, the first neurobiological hypothesis of schizophrenia that has really had homogeneous consequences in the worldwide clinical practice: dopaminergic neurotransmission dysfunction. This model has recently been propped up by two large-scale naturalistic studies that compare old and modern antipsychotics: that is, the CATIE study[19] and the EUFEST study (the latter including haloperidol and amisulpride, 2 molecules with almost 100% dopaminergic activity)[60]. Kapur and Seeman[61, 62] had already previously postulated, based on functional neuroimaging tests and receptor or receptorial kinetics *in vivo*, that the 'atypicity" of antipsychotics is a function of the percentage of dopaminergic D2 receptor occupation in selective zones of the brain[63] and above all on the velocity with which the drug separate from these receptors. There is no practical need to appeal to other neurotransmission systems to understand the therapeutic response if we are aware that this assumption does not imply an understanding of the etiopathogeny. There are five drugs in use that have a very rapid receptorial dissociation (they would be the "most atypicals" in accordance to the hypotheses of Kapur and Seeman): clozapine, an inexpensive and effective antipsychotic but with uncomfortable dosage; quetiapine, a drug having less neuroleptic potency that has gained protagonism as a polyvalent drug; amisulpride, a European antipsychotic that only binds to dopaminergic receptors (pro-mesocortical dopaminergic action with doses lower than 200 mg/day and anti-mesolimbic dopaminergic action with doses over 400 mg/day); aripiprazole, the only antipsychotic with partial agonistic activity in the dopamine receptors; and paliperidone, metabolite of risperidone that significantly reduces the receptor binding time.

Pharmacogenetic factor

Studies on association between genetic variations, clinical responses and adverse effects[64, 65] will increase knowledge of TRS. We currently lack solid tests on pharmacodynamics and efficacy. We only know the pharmacokinetic consequences of some genetic variants whose knowledge would influence the dosing of each individual but little or nothing on the drug to choose. The

"transfer" of basic investigation to clinical investigation has still not provided practical and generalizable results.

Pharmacokinetic factor

The individual variations of the biological constitution beyond the brain scope modify response to treatment. There are factors that alter digestive absorption, hepatic metabolism, renal elimination, distribution volume and bioavailability. The relationship of metabolism of the psychopharmaceuticals with factors that alter the function of hepatic isoenzymes of the cytochrome P450 is known.[66] There are less sophisticated factors that are equally important: obesity and smoking. It should be remembered that clozapine, the only antipsychotic explicitly indicated in TRS, has many interactions.[67, 68] Among these interactions, such a daily fact as smoking stands out.[69, 70] This can accelerate hepatic metabolism of clozapine and olanzapine until the plasma concentration is reduced by 50%. The high consumption of tobacco among persons with schizophrenia (up to 80% of the patients) may mask this "invisible drug addiction."[71, 72]

Factor of biological comorbidity

Herein, we will consider drug consumption and somatic diseases. The use of substances is frequent in persons with schizophrenia, a fact that clinical trials on treatments tend to avoid, this decreasing the *external validity* of their results.[73] Traditionally, the most frequently used drugs have been tobacco and alcohol, but consumption of other drugs is increasingly more frequent, especially cannabis derivates. Opiate consumption and cocaine is also greater.[74, 75] Independently of the hypothetical anti-psychotic action of opiates, drug consumption in general worsens the prognosis of schizophrenia, either directly, as a harmful biological factor, or indirectly, by interfering with the development of the person.[76] Drug consumption increases the likelihood of relapses[77] and of treatment noncompliance.[78] Special mention should be given to the growing use of cannabis derivates, which increase the risk of having a first episode of psychosis in genetically vulnerable individuals. Continuation of use once the disease has been established worsens the prognosis and is one of the most important factors of "resistance." This agrees with what we know about the impact of cannabinoids on dopaminergic neurotransmission, memory and "executive function."[79-81] Abuse of anticholinergics, prescribed by the psychiatrist per se for the control of some extrapyramidal symptoms that are sometimes exaggerated by the patient to provoke overdosing with euphoretic purposes, is not rare and worsens the cognitive function and increases the risk of relapse.[82] The risk of caffeine is not clear. Some patients consume high amounts, but we do not know whether this is a cause or consequence of the disease. It has not been confirmed that caffeine alone precipitates relapses, but we know that with high doses, the cognitive function is modified, dopaminergic transmission is altered, and that it produces anxiety and even psychotic symptoms. It is suspected that some patients drink coffee to relieve *negative and cognitive symptoms* and to reduce the adverse effects of antipsychotics. Coffee decreases the effectiveness of clozapine, altering its hepatic metabolism.[83-85]

No large-scale studies aimed at testing the best antipsychotics when TRS coexists with drug addiction have been conducted. The best results at present are seen with clozapine, and to a lesser degree, with its analogues (quetiapine and olanzapine), which has been related with possible lower induction of extrapyramidal symptoms, the preferential action in the reward system, sedative effect, less induction of neuroleptic dysphoria and possible antidepressant effect.[86]

Most of the patients with schizophrenia also have somatic diseases. They are often diagnosed late and badly. The causal relationship that some have with schizophrenia, if it exists, should be multifactorial and bidirectional, since it would simultaneously reflect a specific genetic vulnerability, a degenerative process of all the body (where the brain is only a highly interconnected portion with the rest), pro-inflammatory and immunological deregulation states, harmful action of a diet and a style of disorganized life, action of antipsychotic drugs and substance abuse.[87, 88] All of the above, in addition to the limited preparation of the Health Care Services to treat with equity these persons, directly increases the vulnerability of their body and nervous system. Indirectly, pharmacological interactions and antipsychotic treatment dropouts occur due to attribution of side effects and distraction with physical malaise. Metabolic alterations linked to the style of life (diabetes, obesity, hypertension, dyslipidemia, sleep apnea, etc.), may explain the poor result of the treatment when it only focuses on "the mental." We stress that all body alteration is already a mental alteration and also that it could directly harm the nervous system.[89] By inverse reasoning, we understand that some somatic conditions indicate psychic malaise that is expressed by psychosomatic mechanisms. We generally obviate this in persons with schizophrenia because they bewitch us with their "mental" rarenesses. Some simple interventions focused on "the body" (beginning to practice a sport, going out for a walk with the pet, learning to cook to normalize the diet, curing a knee injury that prevents rapid walking, improving sight or impaired hearing, etc.) may sometimes catalyze a general favorable evolution in an individual with TRS who was previously treated for "the mental."[88] The psychosomatic reactions are a signal of body-mind alarm, but which sometime may crystallize in the identity of

subjects whose style of interpersonal relationships is hardly adaptable to the changes in the setting. This could occur in persons with schizophrenia. However, there is even more, since the clear changes in the body of a person affect the identity of those close to him/her and precipitates change in the chain that will affect all of "the physical" and "mental."[90-92]

Human Immunodeficiency Virus and Hepatitis C Virus affect patients with schizophrenia somewhat more. They alter the immunological system, hepatic function, neuronal function and regulation of the cerebral glia. This increases the cognitive deterioration, social exclusion, toxicity and pharmacological interactions.[93-95]

Personality factor

Personality traits are transformed with the disease. *Normally, they accentuate the temperament* component (in the biological sense given to the word by Cloninger).[96] This occurs in such a way that the caricature of the baseline personality may be the only visible zone of some schizophrenias (that is: *heboid*, *simple* and some *residuals*). Then, they dominate the stereotypes of gesture and speech, the limited harmony in the affective reactions, the subtle extravagances without affective irradiation and the slow decline of social efficacy. Those components of the personality acquired late through interaction of the subject with the environment (that which Cloninger calls *character)* are subjected to overexertion and sometimes are accentuated, other times they are toned down and other times they are inverted or become disassociated. However, in every case, they become inflexible, with lack of harmony, and they lose a variety of registries and tones. This process decreases variability and elasticity of the "defense mechanisms" and of the various registries of the *Self*, which decreases the adaptability of the individual to the demands imposed by the environment with growing risk and difficulty beginning in adolescence.

If we observe the grade of integration of the psychic functioning, expressible as adaptability to a changing and challenging surrounding, we will verify that persons with schizophrenia have a much lower stress threshold for activation of *psychotic mental functioning.* Some call this lower *activation threshold* (*dimensional* concept, or at least *dynamic*) "psychotic structure" of the personality (categorial and static concept) as if these could be a configuration of the static, substantial and naturalized subjectivity. However, it stands out that many patients with latent schizophrenia or mildly residual schizophrenia have "borderline" *functioning,* and even a "neurotic" *level* for prolonged periods, in spite of having low *psychotic functioning thresholds.*[97] These overlapping presentations of the disease greatly hinder the diagnosis and promote harsh discussions among the clinicians. In contrast with the idea of "character structure," the idea of "character functioning" implies dynamism, fluctuation and some reversibility in spite of the background schizophrenic process. Thus, we can understand why some persons with TRS do not always show clear or continuous *autistic* withdrawal. More often, they have problems relating with persons that they actively seek out for periods of times, but which are frustrating, inane or excessively challenging.

Currently, a person with schizophrenia can be diagnosed on Axis II in several ways: as if an erroneous diagnosis had been made in the past, and that had already been corrected with the "true" label; as if a "true" comorbidity was acceptable between the schizophrenia and the personality disorders; or as a way of stressing, by using axis II, the influence of the baseline personality in the *pathoplasty* of the psychosis. There is a fourth possibility: all those persons with schizophrenia function *as if* they had a personality disorder when they do not show prominent "positive" psychotic symptoms and when the rest of the symptoms are established after overcoming the acute phase. It is not surprising that the generalized use of antipsychotics is contemporary of the boom of the diagnoses of Personality Disorder. Bleuler already described "atypical," "latent" and "frustrated" presentation which were *rediscovered* several times with a different name (remember, for example, the *pseudoneurotic schizophrenia* of Hoch and Polatin).[98]

The systematic investigation of the personality in schizophrenia has been limited to investigate about some premorbid traits of temperament and character that announce a vulnerability that is postulated to be neurobiological.[99] Are both phenomena *commensurable*, or do they belong to different levels of intellection? On the same level, we have neglected the singularity of the subject. And this subjectivity is decisive to be able to understand many cases of TRS. It serves to orient us in the practical management of the transitional or "adaptive" episodes of the life cycle of any person (for example, the leaps of development towards adolescence or towards the formation of the first stable partner, distorted by the psychotic symptoms but not alien to all of the time coherence of the stages making up the existence of any individual, the complex problem of the "absence of disease awareness;"[100] the loss of treatment adherence;[101, 102] the specific interpersonal difficulties underlying the social withdrawal; some episodes of violence; the pattern of reappearance of the symptoms; and the thematic of secondary that dominate in the chronic phase. Perhaps the vulnerability or schizotaxia[103] that may condition some psychological-reactive vicissitudes of the subject that will also modulate retroactively the biological course of the schizophrenia. If these determine the course of the disease, they should be treated.

Treatment non-compliance factor

How can we know if a patient has TRS if we do not have reliable resources to verify drug dose compliance? If it is *holism* that moves us, we should consider that treatment non-compliance forms a part of the concept of TRS. We know that this occurs in 40-60% of the drug treatments.[104, 105] We know that the psychiatrists are aware of the problem in general but they tend to underestimate the grade of noncompliance of their own patients. By the way, what is the general measurement of noncompliance and non-adherence in psychotherapies and social interventions? These realities occupy much of our daily work and by themselves determine, more than any other factor, the long-term prognosis of schizophrenia.[106-109] An analysis of the causes of non-compliance and non-adherence would exceed the purposes of this article. We stress two ideas: one, that drug therapy non-compliance is only one observable part of a much larger and complex phenomenon that we call "non-adherence." Another one is that non-adherence to psychosocial treatment is a global failure of the therapist who applies it and/or of its theoretical classification or frame and/or its focus or methodology (and not of the patient or family, who are often blamed for showing psychic or systemic "resistances"). We understand that there is a prerequisite in psychosocial treatments, which are expensive and valuable: to attract the patient and family and have them form a bond while the application of a comprehensive therapeutic program is begun with express purposes, and early provisional results that motivate them to continue and with verifiable goals that assure their retention until the end. This is a responsibility that concerns several professionals who become involved in the treatment of persons with schizophrenia. If is honorably assumed, it becomes necessary to measure efficacy (and the risks and costs) of all the psychological, familial, occupational and social therapies, beyond the easy anathema against psychopharmaceuticals, which, in any event, is the only treatment that everyone can see that is prescribed by a professional and this is publically visible. It is unnecessary to state that to achieve drug treatment adherence, psycho-social competence and human quality are necessary, since we may not have anything to with the failure of the molecule, but we cannot avoid our responsibility in the therapeutic alliance that transforms the drug into a *sufficiently good* object for the patient.

Violence factor

Violence casts a shadow over the prognosis and complicates the management of any mental disorder, not only because it can express the severity of the symptoms but also because it prevents applying the best therapies and provokes distrust in the social setting of the patient regarding the difficult solution, hindering the patient's reincorporation into the community. Violent behaviors have usually been associated with TRS. Can we predict them based on the symptoms of the schizophrenia? The response is not clear. The dysphoria secondary to the use of neuroleptics could be behind some cases of aggressiveness, but this is only a hypothesis.[110] *Violence* is a more complex social action that depends on subjective *opinions of value* than the simple state of *aggressiveness,* and it has not been possible to strictly prove a linear causality that relates both with the symptoms of schizophrenia. The studies do not agree on linking the amount of schizophrenic symptoms, drug treatment and *psychopathy.*[111, 112] However, aggressiveness and psychopathic personality traits are associated with limited *insight*, substance abuse and therapeutic noncompliance, so that violence may predict "resistance."[113, 114]

Family factor

The family is not only important during the upbringing of the baby, of the child and of the adolescent. These are development stages that stand out by the psychoanalytic doctrines, psychoevolutive models and the Attachment Theory. The family is an incomparable human group because it functions with intense, long-lasting affective bonds that are also dynamics having a biological as well as psychosocial and cultural root. This is how the "invisible loyalties," insider styles and symbolic legacies that so powerfully articulate the illusion of relational structure that we acquire as children and which, during the rest of our lives, we re-dramatize and transfer on to our descendents, are understood. The individual occupies a position in the present family structure and in the historic narration of lineage. The individual continues to belong to the family, more or less idealized, even after escaping, immigrating, being repudiated or adapted. And after dying.

The "illusion of structure" operates with implicit rules that are transmitted from generation to generation by attachment, learning and socialization processes. Familial dynamics are not simple mental processes that are a product of the subjective interiorizing of speech, dyadic relationships and conflicts of the past, but also continue to operate in the present in the origin family and in the interpersonal relationships that the individual encounters during his/her lifetime: partners, children, friends, workmates, etc. The *child*, understood as an ideal of the parent and grandparents more than as a free individual from birth, is already organized in this *mythical* structure before being born: that is how the family performs the essential mediator function between the psychological individuation processes, and social and cultural processes.[115-117]

The role of the family as an exclusive pathogenic factor of schizophrenia lacks proof (like the remaining causal,

psychological or biological hypotheses, when everything is said). Nowadays, family therapy is left outside of the etiological debate since there is more interest in the factors that perpetuate and worsen the harm already initiated by the self-corrective causal circuits which, paradoxically, convert the attempts to help into factors that worsen the disorder. Family therapy reveals some causes of the "resistance" and formulates a hypothesis to design individualized therapeutic strategies. When the recursive dynamics of communication are modified in the family, the psychosocial performance of the patient improves and the risk of relapse is reduced.[118] Systemic family therapy was born on the fringes (and often against) of Psychoanalysis and Psychiatry that dominated in the decades of the 1950's and 1960's, but it has currently become part of other doctrines and is a treatment that is often used.[119, 122]. Interest is growing on the rigorous investigation of its efficacy and mechanisms, however, there few controlled studies exist.[120] Many attempts have been made to quantify pathogenic, prognostic and therapeutic factors and there is a clamor to return to the use of the psychiatric nosography of the DSM-IV to compare and replicate studies.[121, 122]

The George Brown team, beginning in 1959, found an intermediate pathway between the family perspective (not systemic) and the methodology of the current biomedical research, leaving aside the considerations on the etiology of the disorder or the mechanism of change by the therapy, they observed the evolution of the already established disease in search for prognostic factors regarding relapse that would involve the family setting. Using a structured interview, it was possible to measure the familial dimension, *Expressed Emotion,* that reliably correlated with the relapse rate, duration of the episodes, number of hospitalizations, psychosocial adaptation, severity of the symptoms, etc. It was a measurement with prognostic value that helped to evaluate the progress of the treatment. However, it was not specific to schizophrenia, since high scores were obtained in other chronic diseases. This model has not provided highly effective treatments and is losing popularity.[123, 124]

The family plays an important role in the process of *becoming chronic,* in the relapses and "resistance" to treatment, however, they always have positive potentialities: the family contains elements of *resilience* to be discovered that would save much work of those capable of collaborating with it. If this is well organized, it can be a tool that resolves a TRS.

Social factor

This includes demographic, economical, cultural factors and those of social and work achievement detected by epidemiological follow-up studies of the patients after a first schizophrenia episode as well as the specific conflicts of each patient in their relationship with their surroundings. There is extensive literature in this regards, however the findings are not consistent and their prognostic value unclear. Many studies indicate that the female gender predicts better social adaptation and more benign (more affective) symptoms. However, the concept of "gender" is confusing because it includes different biological, psychological and social variables.[125, 126] The level of social adaptation prior to the first episode (amount and quality of the social relationships and of those of work and the number of years of schooling) has a long-term predictive value and correlation with cognitive and negative symptoms. Although it is not clear if these are markers of state or traits, individual, group and familial psychosocial and psychoeducational interventions are essential to avoid the stagnation of a schizophrenia.[10,12, 127]

DISCUSSION

In the beginning, Kane proposed a TRS model that stressed pharmacological treatment of the symptoms, above all of the *positive symptoms*[128]. However, the idea of drug-resistance as well as the ideas of *remission* and *recovery* were applied in the disease that, by definition, produces some irreversible *defect* in several domains of the functioning of the person in this setting. Nowadays, we know that this *defect* is correlated in grade and in an exact way with the neurobiological findings. However, we continue to ignore its causality pathways and differential repercussion in the different *intellection levels* through which we approach the problem. Therefore, it will continue to occur although we only attend to the *positive symptoms,* which are made up of a *construct* that is not as in reach to observation as it seems (for example, we could increase sensitivity of the study instruments in the search of "automatisms," "basic symptoms close to the substrate," and "attenuated symptoms" or relocate them with the *negative symptoms).*

The change in the symptoms is gradual and not categorical. The categorical is the disease and the total syndrome that accompanies it, which infiltrating the personality and the neuro-cognition maintains a definitive "vulnerability" that makes the subject prone to a singular psychotic form (schizophreniform) of coping with the anguish that the common challenges of existence causes. Furthermore, the symptoms are some *variables* that depend on time and multiple personal and environmental factors that are destined to change. Such occasions of change may go unnoticed if we study the patient, conditioned by some expectations that are limited to the readjustment of the psychotherapy. Without desire to diminish the merit of the "operativation" of Kane (the symptoms disappear or do not disappear), we think that the disadvantages of its *methodological reductionism"* are clear.

We think that the concept of TRS should be broad, without sticking to the single criterion of clinical remission of the positive, negative, general or other symptoms. However, we observe that the "holistic" intention also does not provide more rigorous or more effective treatment models. Persons with schizophrenia are very heterogeneous in regards to the grade of involvement of the different *functioning domains* that we have linked to the ideas of *recovery and resistance*. We think that several *functioning domains* belong to different *intellection levels* in which independent change with specific therapies for each level can be introduced, that is, stating that a drug and psychological therapy do not operate indistinctly within an amalgam of *bio-psycho-social multifactoriality* having a single level with blurred limits, however much they seem to us to be "naturally" complementary and even synergic.[129] If change on one of the levels provokes changes on other levels, such correlation reflects a qualitative change of *complex,* circular, self-corrective, reverberant, systemic *causality.* It is not the *lineal causality* (dignified with the restriction of the *multifactoriality*) that the empirical research having a *positivistic aspect* that presently equally dominates biomedical sciences and psychosocial sciences has made us accustomed to.

When postulating "resistance" criteria, it is well to distinguish the real clinical practice from that of research. For example, the substance abuse disorders should not be an exclusion criterion in research on TRS (with wide definition) if we accept that more than 50% of persons with schizophrenia may be taking these substances.

We have not found works on TRS that dare to differentiate the varied phenomenologies of the *positive symptoms.* The usual instruments (PANSS, BPRS…) avoid the question and hardly organize the semiology into a hierarchy. They lump together the symptoms of greater biological connotation and of greater response to drugs (phenomena close to the "mental automatism" of Clérambault and to the 'basic symptoms close to the substrate" of Huber), together with *secondary positive symptoms* that can be: 1) habits, motor and stereotypal disorders (also verbal) due to a background of noticeable negative or cognitive symptoms; 2) ways of verbalizing emotions, *cenesthopathy*, obsessive type thoughts and malaises of difficult explanation, filtered by the *phraseology* of these *positive symptoms* that seem to so greatly captivate the attention of the psychiatrists; 3) *catathymic* delusions; 4) *understandable* situations and psychological reactions; 5) simulations. Deprived of the subtle differences that were previously promoted by Descriptive Psychopathology of European tradition, we presently group such heterogeneity into some semiological *constructs* of limited, unequivocal and objectified appearance. In this way, the disparity of results and of weak credit of the modern clinical trials of treatments could be explained. We also have not found sure proof of the synergy between the simultaneous drug treatments and the psychosocial ones.

Is TRS a variation of grade, of greater severity or is it a qualitative variant that requires different treatments? The response will depend on the width we use to represent our idea of "resistance." There is consensus that the definition of *remission* should be broadl[2, 129]. This makes it necessary for us to redefine the original concept of TRS, which was created with a practical intention in the 1980's and then had to be adapted to more ambitious goals. Nowadays, the idea of TRS has been blurred and does not generate bold investigations, except for the attempts to ratify multiple drug therapies.[130]

We propose maintaining the original concept but taking advantage of the extensions, without falling into the *holistic* fallacy. Some "resistances" in schizophrenia are attributable to the "resistances" of the institutions and professionals treating it. We often seek protection in words such as: 'global,' 'integral,' 'total,' 'multidisciplinary,' 'multimodal,' 'biopsychosocial,' 'combined' and 'coordinated' to avoid the open debate between professionals following antagonic doctrines, to avoid obstinate realities, to create pseudo-problems in which our specific doctrine can be applied, to avoid the *valid and standardized measurement of effectiveness* of our therapies, and to dissolve the sense of individual responsibility in a *therapeutic team.*

The old taxonomies of schizophrenia have not demonstrated clear utility. Perhaps, a taxonomy of the factors, forms and levels of "resistance" could have an empirically demonstratable practical function (independently of their "truth") and would assign specific functions and personal responsibilities to all the professionals who are around a person with TRS. The first step would be to classify the facts associated to the "resistance" in order to define several *"levels of intellection"* of the problem in operational terms. After, it would be necessary to investigate to what degree the facts of each level or factor predict partial results with *methodologically reductionist therapeutic actions, limited to these events.* Each one of the levels in which the therapeutic failures operate are maintained, but differentiated. One of the fundamentals of the problem is not renounced: the resistance of the *positive symptoms* to the drug treatments. Pragmatism of the therapeutical results is put before the theoretical coherence and etiopathogenic thoughts. There would be at least five factors or *resistance levels:* clinical-symptomatic, biological (pharmacokinetics, pharmacogenetics, of general health, drug usage), individual psychology (personality, violence, adherence), familial and social. The patients can simultaneously use elevated measures in several facts having different levels, but give priority to a single event that opens the way to access a problem that previously seemed to be stagnated, inaccessible or non-existence.

The guiding idea is the *parsimony*, that is, that the lowest possible number of therapeutic acts (if possible only one) is used and that each act occurs before any other, in order to clearly verify its effectiveness, give the patient and family the opportunity to open new pathways with their own talent and make it necessary for us to design "systematically perfect interventions," that is, interventions based on a complex view of the problem that detects the key "facts" on which to apply the minimum and most accurate, personalized action (one for each person and each moment), easy to perform, immediate, tangible and observable by everyone (expert interpretations on the intrapsychic or "on what really happens" is not valid). This minimum change, however sound, should destabilize the patient and circumstances, activate chain reactions and reveal more facts that open other intervention pathways on previously dormant ones.

One example: we have a patient with TRS, morbid obesity (biological level) and severe social withdrawal (social level). Our goals are to have the patient agree to practice some exercise and to relate more with people. Someone will provide guidelines for physical exercise and measure the patient's variation in weight. Then another person will have the patient come to a weekly meeting of persons with schizophrenia and will periodically measure the variation of the size of the person's social network. We can also design a task that works on two levels simultaneously. However, care must be taken. This should be done only if the task meets the two goals without mixing them. For example, we could convince the obese patient to take the responsibility for walking a dog (physical exercise), then measure the changes in their social network (meeting with people who also walk a dog). We cannot dilute these two tasks within a long-term group therapy oriented at the search for *insight*, which at the same time promotes exercise, healthy diet, attachment to the animal and interpersonal relationships. Progress on the two levels worked on precipitate emotional fluctuations (by the new human relationships) and identity crises (stop being very fat, assuming an adult role, etc.) from which latent symptoms are derived that give access to other levels. Then, perhaps we use an antidepressant or introspective psychotherapy. Or, we try antipsychotics that previously failed, since the emotional body-mind of our patients is no longer what it was.

Scales that score the severity of the "resistance" on each level, reporting its *validity* to comparable facts within this level need to be developed. With this information, we can design clinical trials on treatments, avoiding the popular and useless markers that we invoke after failing: "non-adherence," "secondary benefit," "null disease awareness," "lack of motivation," "social problem," "drug resistance," "does not collaborate," "dysfunctional family" and "limited capacity of *insight.*"

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