Chapter 1

Treatment-Resistant Schizophrenia: Prevalence and Risk Factors

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1. Introduction

Despite significant progress in the treatment of schizophrenia in recent decades, the evolution of a large rate of patients suffering from this mental disorder is little influenced by treatment [1]. The management of these patients, so-called treatment resistant, constitutes a public health problem. Indeed, these very symptomatic patients often require long periods of hospitalization [2], and their care consumes a disproportionately large share of total cost management of schizophrenia [3].

Following the renewed interest in clozapine since 1988, thanks to the baseline study on the neuroleptic Kane and al [4], and the development in this period of several explicit criteria defining treatment-resistant schizophrenia (TRS), like those of Kane [4], Dencker and al [5] and Brenner and al [6], some studies have subsequently estimated its prevalence.

The large number and variety of risk factors associated with poor prognosis or poor response to treatment, reported in the literature, suggest that several pathophysiological mechanisms may contribute to the emergence of resistance.

In this work, we tried to shed light on the prevalence of this concept, as well as its risk factors, through a critical review of the literature.

2. Methodology

In our literature review, we conducted a literature search in two databases MEDLINE and PUBMED. We used the following keywords: treatment-resistant, refractory, schizophrenia,

prevalence, Correlates, predictors, poor outcome, Treatment refractoriness, Treatment response, poor prognosis.

For studies estimating the prevalence of TRS, we selected the works that have considered the resistance as a categorical diagnosis, defining it by explicit criteria.

For risk factors of TRS, we selected studies that have specifically studied the risk factors of resistance, and the studies that studied the risk factors of poor prognosis or poor response to treatment.

3. Prevalence of treatment-resistant schizophrenia

3.1. Results

The prevalence of resistant schizophrenia ranged from 5 to 60% (Table 1) in the four studies in the literature. Vanelle only found a low rate of 5% resistance because of too restrictive criteria of resistance corresponding to stages 5 and 6 of Dencker and May defining TRS. The results of the other three studies suggest that an important rate of patients do not derive virtually any benefit of treatment and that the TRS is therefore a true public health problem [7]. Many authors agree on the fact that 1/5 to 1/3 of patients are resistant to treatment [1]. Methodological differences between these different studies concerning inclusion criteria and the TRS criteria were important, which explains the wide variation in the estimate of the prevalence of TRS: 5 to 60%. The study by Juarez-Reyes and al [8] illustrates this fact. Applying the criteria of the FDA (Food and Drugs Administration) for the prescription of Clozapine in the United States of America, Juarez-Reyes et al found in their sample a prevalence of 42.9% of resistant patients, but applying the more restrictive criteria of Kane on the same sample, the prevalence dropped to 12.9%.

These methodological differences reflect a lack of consensus on the concept of TRS, which seems to hamper research in this field, since the studies found were few, relatively old and only conducted between 1990 and 1996.

3.2. Discussion of methodological differences

The methodological differences were related to:

3.2.1. Inclusion criteria

Essock [11] required in his sample only inpatients that must have had a total hospitalization of at least 24 months for the preceding 5 years as inclusion criteria. It is clear that in such sample the prevalence of TRS will be overestimated. By applying FDA criteria for eligibility to Clozapine in this sample, Essock found the highest rate of TRS: 60%. Indeed, if outpatients were including in the sample, prevalence of TRS would be less elevated. Essock [11] justified such restrictive inclusion criteria by the fact "to ensure that Clozapine was most available for

Authors	Inclusion's criteria	Criteria of TRS				Prevalence of TRS
		Number of NLP trial	Minimal duration of NLP trial	Minimal dosage of CPZ or its equivalent	Assessment scales	
Terkelsen (1990) [9]	Retrospective estimates based on three large-scale surveys, of patients in New York State	unspecified	unspecified	unspecified	BPRS CGI	.58 % of inpatients and 24 % of outpatients
Vanelle (. 5995) [10]	566 SKZ or SAD inpatients since at least 6 months disease duration since 3 years	2	3 months	.5000 mg/a day	CGI level 5 and 6 of May and Dencker classification of treatment response	5%
Juarez-Reyes (. 5995) [8]	293 SKZ ou SAD	2	4 weeks	600 mg/a day	BPRS CGI GAF	42.9 +/- 5.9%
Essock (. 5996) [11]	803 SKZ or SAD inpatients since at least 4 months and at least 24 months of hospitalization during the last 5 years disease duration since 5 years	2	6 weeks	.5000 mg/a day	BPRS CGI FDA criteria for eligibility to Clozapine	60%

SKZ: schizophrenia; SAD: schizo-affective disorder; NLP: neuroleptic ; CPZ : Chlorpromazine; BPRS: Brief Psychiatric Rating Scale; CGI: clinical global impressions; GAF: global assessment of functioning.

Table 1. Prevalence of TRS in the literature.

those most in need", because of the high cost of this treatment, and thus he recognized that he did not screen TRS in all potentially patients in need to Clozapine, such as outpatients.

3.2.2. Criteria of TRS

3.2.2.1. Chronic hospitalization

In Vanelle's study [10], which is based on the Dencker and May criteria [5] to define the TRS, the need of continuous hospital stay was an essential criterion of resistance. Such highly

restrictive criteria of resistance may underestimate TRS. This highly restrictive criterion seems explaining the low rate of TRS in Vanelle's study 5 % [10]. Currently, most authors agree that chronic hospitalization is not necessary for criteria of TRS [1].

3.2.2.2. Duration criteria

Persistence of illness for more than 5 years was taken as the duration criteria for TRS by Kane et al [4]. This was most probably the impact of serious side effects of clozapine (drug induced agranulocytosis), which made researchers so stringent about duration criteria. Essock [11] fixed this duration at 5 years and Vanelle [10] at 3 years. The other authors did not specify any duration. Currently, most authors agree that waiting such durations are not necessary and a clinical history of persistent psychosis for at least 2 years is sufficient for TRS [6,12]. Some researchers have mentioned that even one year of unresponsiveness to treatment may be an adequate time period [7].

3.2.2.3. Criteria of adequate drug trial

3.2.2.3.1. Duration of adequate drug trial

This duration ranged from 4 weeks to 3 months between the four studies (Table 1). Most authors agree with the fact a period of 4 to 8 weeks is sufficient to evaluate the efficacy of a therapeutic trial [13-17]. Conley [1] recommended in its definition of TRS established in 2001, a period of 4 to 6 weeks, while the NICE (national institute for clinical excellence) recommends a period of 6 to 8 weeks [18]. Nevertheless, some authors as Vannelle [10], Ciapparelli [19] and Lindenmayer [20] consider that a period less than three months is insufficient to assess the efficacy of a therapeutic trial.

This duration must vary according to symptoms taken into account when assessing the therapeutic trial, because the different symptomatic dimensions do not evolve synchronously. If the assessment of treatment response is based on the positive and negative symptoms, a relatively short period seems sufficient. If the dimensions, such as social functioning, occupational functioning, or quality of life, are included in the scope of the evaluation, a longer period of evaluation should be required. However, the functional dimension of schizophrenia is less specific to treatment response as positive or negative symptoms in a clinical trial, as it can be influenced by several factors other than treatment [21,22].

3.2.2.3.2. Adequate dosage of neuroleptic

Despite the variation of this dose (600 to 1000 mg per day of chlorpromazine equivalents) across studies, it was largely sufficient. Indeed, Kane set the minimum threshold dose, in its definition of resistance, to 1000 mg per day of chlorpromazine equivalent [4]. But the results of more recent studies, using the technique of positron emission tomography, showed that a dose of 400 mg of chlorpromazine daily can block 80-90% of dopamine D2 receptors in the nigrostriatal pathway, and an occupancy rate of 60 to 80% of these receptors is sufficient to obtain a response to neuroleptic treatment [23]. In addition It has been reported that higher doses produce no

direct therapeutic benefit even in patients who are nonresponsive to therapy [24] and do not improve efficacy in acute treatment [25].This dopamine antagonism is considered the main mechanism of action of typical neuroleptics [23].Currently, most authors such as Barnes[13], McEvedy [13], Dixon [26], Kinon [24], Shalev [27] and Conley [1] consider that doses between 400 and 600 mg per day of chlorpromazine equivalents are sufficient.

3.2.2.4. Adequate number of trials

Terkelsen [9] could not assess the adequacy of previous trials in his study because he constructed retrospective estimation based on three large-scale surveys, conducted in 1987 and 1988, of patients in New York State. The remaining three authors (table 1) agree that the failure of two trials is a criterion of treatment resistance, and not three as Kane had proposed in the beginning in his initial definition of TRS. Indeed, the fact that there was only a 3% response rate to prospective haloperidol treatment and a 4% response rate to double blind chlorpromazine treatment in the Multicenter Clozapine Trial led to the belief that failure of two retrospective drug trials would be as effective as 3 in screening for treatment resistance [4]. Additionally, Kinon and al [24] mentioned that subjects who do not respond to 2 adequate antipsychotic trials (1 retrospective and 1 prospective) have less than 7% chance of responding to another trial. The FDA guidelines on clozapine use state that a patient before being treated with clozapine should have failed to respond to two separate trials of antipsychotics. Several guidelines such as APA (American Psychiatric Association) [28], NICE [18], IPAP (The International Psychopharmacology Algorithm Project) [29], and TMAP (the Texas Medication Algorithm Project) [30] also recommended that the number of trials of other antipsychotics that should precede a clozapine trial is 2. Thus, two drug trial failures are now generally accepted as the criterion for treatment resistance.

3.2.2.5. Scales for evaluating response to treatment

With the exception of the Vanelle's study, all of the other studies have used the BPRS as the main tool for assessing the clinical response (Table 1). In this scale the positive psychotic symptoms are the most important. The response to neuroleptic treatment was considered adequate if the score in the BPRS reduction ranges from 20 to 30% as suggested in the literature data [31]. Cognition and subjective perspectives or other illness domains again have not been incorporated into definitions of treatment response in TRS in these studies.

However, according to some authors, the definition of resistant schizophrenia must be multidimensional, and the field to assess during a clinical trial should be extended and include, besides the conventional positive and negative symptoms of schizophrenia, cognitive deficits, quality of life, social reintegration, occupational impairments and behavioral problems [32-35]. But these positions are still controversial. This higher level of requirement is motivated by improving in therapeutic arsenal in the field of schizophrenia as the widespread prescription of Second Generation Antipsychotic (SGA), cognitive remediation and several types of psychotherapy that are effective on certain dimensions of schizophrenia.

3.2.2.6. The question of the type of antipsychotic

The four studies were consistent in the type of neuroleptic. During clinical trials of these studies, only conventional neuroleptics (also called first generation antipsychotics: FGA) are used. The results of these studies, therefore, reflect only the resistance of schizophrenia in this type of neuroleptic. Recently, the evidence that second generation antipsychotics (SGA) are somewhat more effective than traditional medications has opened the question of the type of the drug patient should fail [36]. Currently, most authors [37] and guidelines such as APA (American Psychiatric Association) [28], NICE [18], IPAP [29], TMAP (the Texas Medication Algorithm Project) [30] and Clinical Practice Guidelines for the Treatment of Schizophrenia in Adults of the Department of the COMMONWEALTH OF MASSACHUSETTS [38] agree that failure to respond to second generation antipsychotics should precede a clozapine trial. In the Schizophrenia Algorithm of the International Psychopharmacology Algorithm Project (IPAP) [29] patient is regarded to be refractory if he or she failed to respond to monotherapy with Two trials of Two Different SGA (or Two trials with a FGA, if SGAs are not available). Indeed, atypical antipsychotics cause fewer early and late extrapyramidal neurological side effects, improve adherence to treatment, would be more effective than conventional neuroleptics in negative symptoms, cognitive deficits and mood symptoms, and may be effective in some cases resistant to conventional neuroleptics, but without reaching the effectiveness of clozapine for this indication [39].

3.2.2.7. Recommendations for future studies

Since 1996, the last date of study estimating the prevalence of TRS, there have been changes in treatment practices in schizophrenia, such as the widespread prescription of atypical antipsychotics, or more intensive *deinstitutionalization* of psychiatric cares in schizophrenia, which could change the rate of resistance. There has also been a revision of the criteria of TRS [1] as shown in the comparison of TRS criteria adopted by the four studies estimating the prevalence of TRS to the recent data from the literature given above. New studies estimating the prevalence of TRS and adopting the revised criteria of resistance seem to be necessary. Pending the establishment of a broad consensus on the criteria of TRS, this will be precious for research and therapeutic practice, the criteria of TRS that are currently almost unanimously accepted in the literature are:

- A period of two years, during which the patient does not improve significantly, and has a poor psychosocial functioning, seems reasonable even without long hospital stay.
- During this period, two well-conducted clinical trials have failed. The characteristics of an adequate therapeutic trial would be:
- A period of 4 to 6 weeks each,
- A dose of 400 to 600 mg equivalent of chlorpromazine to classical neuroleptics
- Among the two trials that failed, one should include an atypical antipsychotic.

Even more restrictive criteria, such as Kane, should be reserved for experimental studies evaluating the efficacy of new drugs in resistant schizophrenia.

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4. Risk factors of TRS

In this field, the literature is dominated by studies that have examined factors associated with good or poor prognosis or outcome in general, or factors associated with good or poor response to neuroleptic treatment in particular.

4.1. Risk factors related to the patient

The male gender is among the most documented risk factors of poor prognosis [40]. It was also identified specifically as a factor associated with a poor response to neuroleptic treatment for chronic patients and for patients seen during their first psychotic episode, by numerous studies [41]. This male gender predominance in patients with TRS is explained by a greater sensitivity of dopamine receptors to dopamine antagonism of neuroleptics in women, due to the antidopaminergic effect of natural estrogen [42].

The results of studies correlating the early age of onset and poor outcome are consistent [43,44]. This risk factor was associated with greater dysfunction in prospective studies [45], with poor response to neuroleptics [46-48], with an increased risk of re hospitalization [49] and specifically to the resistance [10]. Schizophrenia has a later onset in females than in males and the difference has been found to be about 5 years in most studies [50] suggesting that the association between early age of onset and poor prognosis, is biased by the variable male gender. However, the fact that the difference in age of onset between men and women disappears in patients with TRS in many studies [44] argues for a direct influence, and independently of gender, of age at onset on treatment response. The association between early age of onset and poor outcome reflects a greater neurodevelopmental insult [51] that can be intensified by environmental factors.

In terms of symptoms, severity of negative symptoms was associated with poor response to treatment in many studies [35,52]. Other clinical aspects of schizophrenia were associated with poor prognosis in the literature, as asociality [53] inappropriate or blunted affects [35,53], the low level of premorbid functioning [54], a high degree of minor neurological signs [55], the absence of affective symptoms [56,57], negative formal thought [52], excessive summertime (July) and clustering of birthdates [58], morbid polydypsia [59], and a less severe overall basic symptomatology (before starting treatment) [60].

In the psychological level, insight, poor coping, and some personality traits such as low social skills, a lack of impulse control, and an intolerance of frustration, alogia would be factors of poor response to psychosocial treatment [61-63].

4.2. Family and socio-environmental risk factors

The presence of family history of schizophrenia would be a poor prognostic factor [64]. A high emotional expressiveness in the family environment was related to higher risk of relapses [65]. A history of obstetric complications is more common in patients not responding to neuroleptic treatment [66]. The absence of precipitating factors [35] and a history of substance abuse [67-70] were associated with poor response to treatment.

4.3. Risk factors associated with cognitive deficits

Several literature reviews have summarized the evidence for associations between functional outcome and cognitive deficits [71-73]. These reviews have regarded ranks of functional outcome measures, including measures of skill acquisition in psychosocial rehabilitation treatment, demonstration of ability to solve simulated interpersonal problems, and community (social and occupational) functioning. The reviews indicated consistent and highly significant relationships between ranks of key cognitive constructs such as episodic memory, immediate / working memory, vigilance, and executive functions, and functional outcome in schizophrenia. The effect sizes of these relationships tended to be in the medium to wide range.

According to several studies, the severity of cognitive deficits is equally or more important than positive or negative symptoms to predict prognosis in schizophrenia [74].

4.4. Para clinical risk factors

4.4.1. The data of brain neuroimaging

The ventricular enlargement is the variable most studied in this field. Over the last three decades, earlier computerized tomography and then MRI, cross sectional studies including chronic patients have found an association between ventricular enlargement and poor outcome [75-77]. Several longitudinal studies conducted during periods of 1 to 5 years of chronic patients [78,79] or first psychotic episode patients [77,80] confirmed these structural changes in the brain and found that they were progressive over the course of illness.

For the gray matter, reduction in total volume or located reduction in certain regions such as the frontal, temporal and occipital cortex and ventral thalamus were identified [77]. In addition, volumes of the putamen, especially dorsal and in the right hemisphere, showed increases in patients with better outcomes, whereas putamen volumes in patients with poor outcome did not differ from those in healthy comparison subjects [81]. Expansion of the putamen is known to occur as a result of antipsychotic treatment, so that failure to expand in patients with poor outcome may be related to their resistance to treatment [77].

Abnormalities of white matter located especially at the frontal and temporal lobe of the right hemisphere were associated with poor outcome [77].

The results of longitudinal studies suggest that these brain volume changes seem to be progressive, and occurred at an early stage of the illness [82].

Dynamic neuroimaging data found that lower pre-treatment striatal metabolism predicted better clinical response to neuroleptic treatment and that drug responders showed a greater increase in striatal metabolism after haloperidol therapy [83-85].

4.4.2. The biology data

In the literature, a smaller increase in plasma levels of prolactin [86,87], and a smaller decrease in plasma homovanillic acid [88-91] following administration of neuroleptic, were associated

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with poor response treatment. A lower baseline plasma levels of homovanillic acid (before the administration of a neuroleptic), was also associated with poor response to treatment [35,92]. A lack of clinical change after administration of amphetamine (central dopamine agonist) was associated with decreased response to antipsychotics [93]. A blunted response of growth hormone after stimulation with apomorphine [94] has been associated with poor prognosis.

All these factors reflect a poorer response to central dopaminergic action of dopamine antagonist antipsychotics. The hyperactivity of central dopaminergic mesolimbic pathway remains the predominant mechanism that explains the positive symptoms of schizophrenia [39].

4.4.3. The data of electrophysiology

The MMN (mismatch negativity) is an early component of auditory evoked potential, recorded after a disruptive auditory stimulus. The peak of MMN occurs after 100 to 150 milliseconds after the stimulus. Abnormally increased MMN amplitude, as well as abnormal MMN topographical distribution, was associated with a poor functional outcome in schizophrenia [95]. These anomalies reflect pre-attentive deficit process (or automatic attention), related to neuropathological changes in the auditory cortex in schizophrenia [95].

4.4.4. The Electrodermal Activity (EDA)

Some studies have found that heightened electrodermal activity, as indicated by frequent orienting responses to innocuous stimuli, elevated skin conductance level (SCL) and frequent nonspecific skin conductance responses (NS-SCR), is associated with most often poor symptomatic, social and occupational outcome in schizophrenic patients [96].

4.5. Risk factors associated with treatment

The initial duration of untreated psychosis, namely the time gap between the onset of psychotic symptoms and first treatment, also called DUP, is among the most studied risk factors for poor outcome during the last 2 decades [97]. Evidence from both retrospective and prospective studies suggests that a longer duration of untreated psychosis in the early stage of schizophrenia is associated with a longer time to remission and a lower level of recovery, a greater likelihood of relapse and a worse overall outcome [98]. Perkins in a recent meta-analysis has retained a total of 43 publications from 28 sites. He found that shorter DUP was associated with greater response to antipsychotic treatment, as measured by severity of global psychopathology, positive symptoms, negative symptoms, and functional outcomes [97].These findings are frequently interpreted as a consequence of a more intense and rapid progression of a neurodegenerative process in the first years of untreated illness [99].

Response to treatment, at least in some cases, appears to decrease over psychotic relapses. As a result patients have lower rates of remission and longer duration to achieve it [100]. Lieberman and colleagues [101] measured time to remission over three successive psychotic episodes and found that the time to reach remission more than tripled between the first and third episode.

Moreover, the absence of a significant and rapid reduction of symptoms during the first days of neuroleptic treatment (3 to 7 days) [60], the dysphoric subjective response type at an initial dose of neuroleptic [60], a bad alliance with the therapist [63], the occurrence of neurological side effects such as parkinsonism [102], akathisia [10] or tardive dyskinesia [102], predict a poor response to treatment.

4.6. Methodological considerations

In our literature review we have considered the factors influencing the prognosis and response to treatment as factors that may explain the resistance. This choice can be criticized. On the one hand, a poor prognosis or a poor response to neuroleptic treatment is not synonymous with therapeutic resistance. On the other hand, the prognosis is a broader concept that the response to treatment and thus the factors influencing prognosis and those influencing treatment response can be inter-related but not necessarily identical [60]. Accordingly, it is important to consider these potential factors of resistance with caution.

Tools for evaluating the response to treatment or prognosis varied widely, limiting their comparability. Consensus specifying tools for assessing treatment response and prognosis in schizophrenia is therefore of great interest for research in this field [60]. The criteria for remission in schizophrenia proposed by Andreasen et al [103] can be a great help for future studies [104].

In this area of research, the results of longitudinal studies examining schizophrenic patients prospectively from their first psychotic episode are more reliable than cross-sectional studies retrospectively examining chronic patients [102]. Indeed, in samples of chronic patients examined retrospectively, there is firstly an overrepresentation of poor responders or patients with less favorable prognosis, and secondly, a greater heterogeneity because these chronic patients are at different stages of the disease and were exposed for varying periods at different neuroleptics. While in samples of patients followed from their first psychotic episode in longitudinal studies, there is a greater representation of the broad spectrum of response to treatment or prognosis, and a greater homogeneity because patients are at the same stages of the disease (the first months or years of illness) and the exposure to neuroleptics was controlled [102].

Some risk factors of TRS are known to be interrelated, like poor premorbid sociosexual functioning [77] and cognitive deficits that are related to severity of the negative symptoms. At end of design studies with methodological rigor use of statistical techniques such as multiple regression and the development of more complex predictive models is needed for future studies in this area.

4.7. The pathophysiology of TRS

The pathophysiology of TRS is still unclear. Some risk factors for TRS cited above as the low level of premorbid adjustment, male gender, severity of primary negative symptoms, the greater frequency of obstetric complications, the high degree of minor neurological signs, and the vulnerability to develop tardive dyskinesia, suggest a neurodevelopmental origin [98].

These neurodevelopmental factors are more frequently found in patients resistant to treatment from the first clinical trial. Moreover, these factors may have an additive effect, i.e. there should be coexistence of a critical number of such factors for there to be resistance [98]. According to some authors [59,105,106] these factors are the characteristics of a more severe subtype of schizophrenia (Kraepelinian schizophrenia) less influenced by neuroleptic treatment.

However, some patients worsen over the course of their illness either because of its progression or because they become less responsive to treatment [101]. Other TRS risk factors mentioned above as DUP, progressive changes in brain volumes in early stage of illness and the deterioration of treatment response over relapses, support the hypothesis that the resistance would be secondary to a neurodegenerative process, which alters the response to treatment in a progressive manner, and not to a static and finished neurodevelopmental process [99]. Candidate's neurons for the seat of this neurodegeneration include dopaminergic projections to the cortex, and glutamatergic cortico-cortical projections. This neurodegeneration is due to excessive glutamatergic excitation (excitotoxicity) triggered by the disease, involving the NMDA subtype of glutamate receptor that is coupled to an ion channel for calcium. This excessive excitation induces an excess of intracellular calcium, which activates certain intracellular enzymes which dangerously begin to produce free radicals that destroy the cell [39].

For other authors, these two hypotheses, neurodevelopmental and neurodegenerative, are not mutually exclusive, but in fact they are complementary [98]. Each comes at different stages of the disease in the genesis of resistance to treatment. However, the neurodegenerative hypothesis is more optimistic, because it suggests that treatment resistance is not inevitable, it does not follow the law of all or nothing, at least for some patients, and it would be possible to protect patients against the development of resistance to treatment by receiving early effective and continuous treatment.

4.8. The perspectives

Some risk factors for TRS cited in this literature review, are promising and interesting, and require a particular interest in future studies because they offer an more positive and optimistic approach of the concept of TRS.

4.8.1. The initial duration of untreated psychosis

It is a potentially modifiable risk factor, offering hope for effective therapeutic intervention to avoid resistance by shortening this duration. Indeed, some preliminary studies have found that shortening this period is possible by means of early detection programs [107], and that early intervention can favorably influence the prognosis of schizophrenia [108,109]. Additionally, evidence for a neuroprotective effect of some forms of early treatment such as atypical antipsychotics is beginning to emerge. Atypical antipsychotics may counteract some of the progressive deteriorative effects by enhancing synaptic plasticity and cellular resilience [99]. Finally, understanding the mechanism by which duration of untreated psychosis influences prognosis may lead to better understanding of the pathophysiology of schizophrenia and to improved current treatment strategies [97].

4.8.2. Cognitive deficits

Cognitive impairment has emerged as an important new target in schizophrenia therapeutics in light of evidence that cognitive deficits are critically related to the functional of disability that is characteristic of the illness. The cognitive impairment is a risk factor for TRS that is potentially accessible to efficient therapeutic interventions. Indeed, in addition to atypical antipsychotics that are more effective in improving cognitive deficits than classical antipsychotics [39], there is now enough evidence that some rehabilitation therapies such as cognitive remediation - a cognitive computerized training - can change and improve these deficits [110], and thus it is another promising way forward.

4.8.3. Some paraclinical tests

The mismatch negativity (MMN) is an electrophysiological recording that could predict poor outcome in patients with schizophrenia. It has the advantage of being harmless, quick and easy to made, with low cost, and can be coupled with functional neuroimaging (fMRI) to increase its spatial resolution [95,111]. Like the mismatch negativity, research can provide "biomarkers" associated with prognosis or response to treatment. Predicting precociously a poor outcome using such convenient test will give the therapist the opportunity to optimize treatment at the first trial.

4.8.4. The glutamate hypothesis for schizophrenia

The promising findings of researches on the glutamate hypothesis in pathophysiology and treatment of schizophrenia allow hope for having future drugs modulating glutamatergic neurotransmission (such as NMDA-receptor agonists) that seem to be promising in difficult-to-improve symptoms as cognitive impairments and negative symptoms [112,113]

4.8.5. The need for future studies

Setrn and al found in there review of the literature about predictors of response to neuroleptic treatment in schizophrenia, that predictive models explained less then 80 % and more frequently less than 40 % of the outcome variance. These findings suggest that there are other factors influencing the prognosis of schizophrenia, which are still unknown [60], hence there is an important need for further studies in this area.

5. Conclusion

TRS remains a challenge for clinical practice and research. It is an undeniable and frequent clinic reality and a real public health problem. For research, having a wide consensus defining the boundaries of TRS is important for comparability and reliability of future studies. TRS is a heterogeneous entity, and has a multifactorial determinism. It is not, at least for some patients, a fatality, but rather the culmination of several risk factors, some of which seem to be

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accessible to effective therapeutic interventions. According to this opinion, TRS would be partly preventable and reversible.

Nomenclature

TRS : treatment-resistant schizophrenia;

SKZ: schizophrenia;

SAD: schizo-affective disorder;

NLP: neuroleptic;

CPZ: Chlorpromazine;

BPRS: Brief Psychiatric Rating Scale;

CGI: Clinical global impressions;

GAF: Global assessment of functioning;

SGA: Second generation antipsychotics;

FGA: first generation antipsychotics;

APA: American Psychiatric Association;

NICE: National institute for clinical excellence;

IPAP: The International Psychopharmacology Algorithm Project;

TMAP: The Texas Medication Algorithm Project

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