

Biology of Schizophrenia: Is Treatment Refractoriness Synonymous with Severity of Illness [A.K.A. Is This a Drug Efficacy Problem or an Expression of Severe Illness?]

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We would like to start this chapter by describing three severe cases of schizophrenia where treatment resistance developed at different time points of the evolution or natural history of disorder.

Case report 1—AB is a man of 34 years who developed his first psychotic symptoms at the age of 17 years. He has a history of neurodevelopmental abnormalities such as birth complications and motor and language retardation as well as use of cannabis which triggered his psychotic with concomitant mood swings. Due to this he was considered to have bipolar disorder and was admitted for the first time and treated according to such diagnosis, i.e., with antipsychotics and mood stabilizers but was discharged with no improvement. He was then subsequently admitted five more times due to the presence of clear persecutory delusions, auditory hallucinations, thought disorganization, and agitation without mood features. In one of the episodes he hit his mother in the chest and menaced his father with a knife. Patient was diagnosed as having paranoid schizophrenia due to the characteristics of the psychotic episodes and absence of concomitant mood symptoms.

He has been treated with six different antipsychotics during this period (haloperidol, trifluoperazine, olanzapine, risperidone, quetiapine, and aripiprazol) without satisfactory response with persistence of persecutory delusions and auditory hallucinations. The patient was again admitted and then defined as having treatment for resistant schizophrenia, and clozapine monotherapy was introduced with progressive doses, reaching 500 mg/day. The patient was discharged and after some weeks responded to treatment, achieving full remission at 6 months. He presently

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takes daily doses of 400 mg of clozapine and is studying law and the relationship with family is very satisfactory.

Case report 2—CD. This is a 45-year-old male patient who started showing first symptoms of schizophrenia by the age of 25. Patient has no history of birth complications or use of drugs. He had some mild difficulties during high school and especially during his university course, concluding a 4 years course on administration business in 7 years. The first symptoms and subsequent psychotic episodes were characterized by the presence of suspiciousness, paranoid ideas, and intense delusional perception. However, these episodes were of mild severity and the patient had never been admitted into a psychiatric hospital. He has been treated with a series of conventional antipsychotics (haloperidol, pimozide, trifluoperazine) as well as atypical antipsychotics (amisulpride and aripiprazol) with partial response, maintaining mild persistent psychotic symptoms, especially delusional symptoms, but with no substantial impact on patient's behavior. However, the patient developed predominance of negative symptoms characterized by blunted affect, avolition, and anhedonia which cause impairment of his social and occupational functions. Antidepressants such as imipramine and fluoxetine have shown evidence of efficacy over negative symptoms and therefore were added to antipsychotics (Singh et al. 2010).

Due to the exacerbation of his delusional perceptions it was decided that the patient should be treated with clozapine which reached 300 mg/day with remission of psychotic symptoms after a couple of weeks. However the severity of negative symptoms continues to represent a major issue in patient's life, who still complains about fatigue, anhedonia, and lack of drive. Due to this a trial with lamotrigine was recently started based on the evidence that it is an effective clozapine augmentation drug (Tiihonen et al. 2009).

Case Report 3—EF. This is a 50-year-old male patient with a history of schizophrenia which started when he was 15 years old, after heavy use of drugs such as cannabis, cocaine, and LSD. His aunt had a diagnosis of schizophrenia which was so severe that she was treated with leucotomy almost 60 years ago, when this surgery was allowed in Brazil. At the time of the first examination he weighed 90 kg and was 167 cm tall (MCI = 32.3).

He was treated only with conventional antipsychotics during 20 years and during this period was admitted four times into psychiatric hospitals. His disorder was characterized initially by auditory command hallucinations when he hit his own head and developed a traumatic cataract. He also showed disorganized behavior, laughing without reason and with outburst of pronounced aggressiveness towards members of the family. He also tried to cut his penis with a knife.

It was necessary to place the patient in a room outside his house with a person specially hired to take care of him. In terms of treatment he received atypical antipsychotics such as aripiprazol, due to his obesity, at doses of 40 mg/day, but he did not respond at all. Subsequently risperidone was introduced reaching 12 mg/daily for several weeks, but without substantial response as well. Clozapine was then initiated and patient responded partially with 800 mg/daily with reduction of aggressiveness and improvement of sociality. However command voices remained

present and it was decided to augment clozapine with ECT. He is presently much better taking 700 mg/daily of clozapine and receiving ECT sessions twice a week. Also, he had a substantial reduction in his weight (75 kg, MCI = 26.9).

In case number 1 resistance to antipsychotic developed early, with the patient showing an unsatisfactory response since the beginning of treatment. Case number 2 represents a classical chronic patient with schizophrenia who has predominance of negative symptoms and functional impairment but where psychotic symptoms represent an active dimension of psychopathology with important impact on his behavior. Case number 3 represents the extreme of resistance with patient responding partially to clozapine and developing what we call super-refractoriness (Buckley et al. 2001; Henna Neto and Elkis 2007).

Therefore such cases illustrate a spectrum of resistance which may appear in the beginning of the disorder as well as at the chronic phase of schizophrenia and can reach extremes of great severity and impairment of functioning.

Resistance to treatment continues to be one of the most important issues in terms of the treatment of schizophrenia, and the items discussed below represent an attempt to encompass this complex phenomenon.

2.1 Treatment Response and Treatment Resistance

It is well established that a certain proportion of patients with schizophrenia do not respond adequately to antipsychotic treatment and such patients are defined to have Treatment Resistance Schizophrenia (TRS). However, the definition of TRS proves problematic to this day, implying various connotations.

Generally TRS is mistaken by chronicity. In fact chronicity frequently is taken as a synonym of refractoriness, and, consequently, many clinicians believe that refractoriness is the inevitable outcome of schizophrenia. However epidemiological studies such as the International Study on Schizophrenia have shown that about 50 % of the cases of schizophrenia do respond to treatment and have a favorable outcome in terms of remission of symptoms and maintaining certain level of functioning (Harrison et al. 2001).

Schizophrenia is a chronic disorder and it is important to make a distinction between chronicity and refractoriness, since there are various chronic diseases, as for example, diabetes and hypertension, that, despite their chronicity, do in fact respond to treatment, with patients remaining stable using the same doses of hypoglycemic agents or antihypertensive drugs throughout their lives (Elkis 2010).

What is the meaning of response to treatment? A simple definition is the reduction in the severity of symptoms, as assessed by some sort of scale (Leucht and Kane 2006). This definition implies that a certain instrument must be chosen to measure the level of response as defined by a certain threshold or cutoff point (Leucht et al. 2009). For example, the first criteria which defined refractoriness in schizophrenia established that patients should be considered responsive to clozapine if there was a reduction of 20 % or more of the BPRS (Kane et al. 1988).

In fact response is a key concept in defining resistance and a recent systematic review of 33 studies found that definitions of TRS vary extensively but have in common the following components or dimensions (Suzuki et al. 2011):

- Failure to respond to 1–3 previous antipsychotic trials, with therapeutic doses, within certain duration
- Prospective treatment with another antipsychotic
- Evaluation of treatment response of prospective treatment with certain instruments (e.g. PANSS or BPRS)

Definitions of TRS based on algorithms such as those proposed by the American Psychiatric Association (APA) (Lehman et al. 2004) or the International Psychopharmacology Algorithm Project (IPAP) (<http://www.ipap.org>) (Elkis 2007) simplify clinical decisions since they propose that a patient should be considered to have TRS if he or she does not respond to at least two trials with antipsychotics, with adequate doses, with 4–6 weeks duration.

It is also important to mention that response should not be confounded with remission since sometimes TRS is associated with the idea of lack of remission, generally conceived as a complete absence of symptom. Actually remission is defined as the presence of a group of symptoms within a certain level or threshold of severity, during a defined period of time (Leucht et al. 2009). In the case of schizophrenia, “remission” currently is defined as a minimum period of 6 months during which psychotic symptoms, symptoms of disorganization, and negative symptoms have low levels of clinical severity and impact on patient’s behavior (Andreasen et al. 2005).

Finally TRS cannot be mistakenly confounded as the result from a lack of adherence to treatment since patients considered to be resistant can actually be non-adherent (Correll et al. 2011) and the distinction between treatment resistance and resistance to treatment must be carefully evaluated (Lambert 2010).

2.2 Is the Failure to Respond to Antipsychotics a Manifestation of Brain Neurodevelopmental or Neurodegenerative/Neuroprogressive Processes?

The neurodevelopmental model proposes that schizophrenia represents the end stage of abnormal developmental processes that began years before the onset of illness (Rapoport et al. 2012) with neurodevelopmental abnormalities giving rise to the symptoms of schizophrenia during adolescence or early adulthood through the interaction of genetic and environmental factors (Sheitman and Lieberman 1998; Murray et al. 2008).

Neurodegenerative processes otherwise represent progressive brain disease of the nervous system that are initiated by specific biochemical changes which have a genetic basis (Jarskog and Gilmore 2006). Schizophrenia was primarily regarded as a neurodegenerative process with a deteriorating course (“dementia praecox”); however, such processes are considered limited, leading to the concept of neuroprogression, which is defined as the pathological reorganization of the central nervous

system along the course of several mental disorders (Jarskog and Gilmore 2006; Gama et al. 2013).

Sheitman and Lieberman were the first to propose a model where TRS could be regarded as the result of neurodevelopmental and neurodegenerative processes through the lifespan. According to this model resistance to antipsychotic drugs would develop at certain time point of the evolution of schizophrenia based on three stages: cortical neuropathology and deficient neuromodulatory capacity, neurochemical sensitization, and subsequent neurotoxicity (Sheitman and Lieberman 1998).

In this model, cortical neuropathology and deficient neuromodulatory capacity would be the result of genetic and/or epigenetic factors and would occur during the fetal gestation and early perinatal development. Neurochemical sensitization would be expression of a deficiency in neuromodulatory capacity which occurs in adolescence or early adulthood and would be triggered by environmental factors such as stress or substance abuse while neurotoxicity occurs in the residual phase of the development of schizophrenia and is associated with neuronal changes or neuronal loss (Sheitman and Lieberman 1998).

Various levels of evidence have shown that some neurodevelopmental factors may be associated with treatment response, as for example, genes, lower levels of premorbid function, early age of onset, male gender, as well as brain abnormalities (Sheitman and Lieberman 1998). Some of them are summarized below.

2.3 Genetics

It is well known that response to drugs is mediated by genes. The ability of antipsychotics to improve the symptoms of schizophrenia is dependent on its antagonist and reverse agonist activities at different neuroreceptors, and some genetic association studies of resistant-schizophrenia have focused on different pharmacodynamic factors (Luca et al. 2010). Some genetic studies have shown an association between response to antipsychotics or TRS and candidate genes such as 5HT receptors, cytochrome families, and dopamine receptors (Inada et al. 2003; Cordeiro et al. 2006; Luca et al. 2010; Hotta et al. 2011).

The COMT (Catechol-Orto-Methyltransferase) is key enzyme in the metabolism of dopamine, which is known to be deregulated in schizophrenia. It is located in the cytogenetic band of 22q11.2 on chromosome 22. In terms of its polymorphisms it has been shown that a G→A transition in the codon 158 of the COMT gene results in the substitution of valine to methionine (Inada et al. 2003).

This COMT Val158Met polymorphism has been extensively studied in association with aggressive behavior, violence, suicide, and use of cannabis in patients with schizophrenia (Inada et al. 2003; Hosak 2007; Henquet et al. 2008). Using a very restrictive definition for TRS (patients hospitalized for 1 year and receiving daily the equivalent of 1,000 mg of chlorpromazine during this period), Inada et al. compared 100 patients with schizophrenia with 201 healthy controls and observed no association between COMT polymorphism or alleles (H and L) with

the diagnosis of schizophrenia, but the rate of TRS tended to be higher in patients with COMT L/L genotype than in those without TRS (Inada et al. 2003).

It is well known that the serotonin system (5HT) plays a key role in the mechanisms of action of antipsychotics and consequently in terms of treatment response as well as cognitive impairment (Meltzer et al. 2003, 2012; Meltzer 2010). The HTR3A, HTR2A, and HTR4 were investigated in 101 Japanese patients defined as having TRS based on the Inada's et al. stringent criteria (Inada et al. 2003) as compared with 239 non-TRS. The investigators found no association between the single marker analysis of those genes and in the haplotype analysis of HTR3A and HTR4. However, the daily neuroleptic dosage is higher in patients with T/T genotype of the HTR3A polymorphism (Ji et al. 2008).

Among these genes the DISC-1 (Disrupted-In-Schizophrenia), which, along with Neuregulin-1-ErbB4, plays a key role in neurodevelopment and is considered a candidate gene for schizophrenia (Jaaro-Peled et al. 2009), was investigated through four Single Nucleotide Polymorphisms (SNPs) in 32 patients diagnosed with TRS as compared with 95 non-TRS patients, but no association was found between DISC-1 and TRS (Hotta et al. 2011).

The association between 384 markers (SNPs) from candidate genes was investigated in 85 patients defined as having TRS, according to APA definition of treatment resistance (Lehman et al. 2004), and compared with 115 non-TRS. The investigators found a significant trend with the SNP rs2152324 in the NALCN gene, but after False Discovery Rate (FDR) correction, the *p*-value showed to be not significant (Teo et al. 2012).

The role of inflammation has been investigated for a long time in TRS (Lin et al. 1998; Maes et al. 2002), but recently the gene FAS, which plays a key role in this association, was investigated in 96 patients, defined as having TRS by Kane et al. criteria (Kane et al. 1988), in comparison with 77 non-TRS patients. The researchers found a significant association between the SNP rs7085850 and two haplotypes that were significantly associated with TRS in this sample (Jia et al. 2011).

2.4 Brain Abnormalities

Early studies with CT scans have demonstrated an inverse relationship between the degree of ventricular enlargement and treatment response (Weinberger et al. 1979). Many subsequent CT studies tried to replicate these findings, but a first meta-analysis of these early studies as well as a critical review of this subject found no relationship between ventricular enlargement and treatment response in patients with schizophrenia (Friedman et al. 1992; Borgio et al. 2010).

In an early MRI study Lawrie et al. compared patients responsive with resistant and found that poorly responsive patients had lower volumes of most brain structures than treatment responders, but no particular specific brain region was associated with poor response (Lawrie et al. 1995).

However, recent studies in patients whose illness is progressive and resistant to treatment—termed poor outcome patients or having “Kraepelinian schizophrenia”—have shown abnormalities such as ventricular enlargement and decrease in gray matter as well as in the corpus callosum size, internal capsule, and putamen (Buchsbaum et al. 2003; Mitelman et al. 2007, 2009a, b, c, 2010; Mitelman and Buchsbaum 2007).

Lack of response to clozapine was initially related to cortical atrophy in some computed tomography studies (Friedman et al. 1991), but such finding was not replicated in magnetic resonance imaging studies (Borgio et al. 2010).

2.5 Is the Failure to Respond to Antipsychotics a Manifestation of Abnormal Neurotransmission?

It is well known that dopaminergic dysfunction underlies the majority of symptoms of schizophrenia (Howes and Kapur 2009) and that efficacy of antipsychotic is related to the degree of D2 occupancy (Seeman 1995). Patients with schizophrenia show and increase amphetamine-induced dopamine release in the striatum, especially in those who are drug-naïve (Javitt and Laruelle 2006) and Single Photon Emission Computed Tomography (SPECT) studies showed that higher levels of dopamine at baseline were significantly associated with greater improvement of positive symptoms after 6 weeks of antipsychotic treatment (Abi-Dargham et al. 2000).

Demjaha and colleagues compared 12 TRS patients with 12 non-TRS patients (responders), as well as 12 controls, in terms of their capacity of dopamine synthesis using ^{18}F -DOPA Positron Emission Tomography (PET). All patients were treated with non-clozapine antipsychotics. Patients with TRS showed similar levels of dopamine synthesis compared with normal controls but a lesser capacity than patients who responded to treatment (Demjaha et al. 2012).

Conclusions

Although this brief overview enumerates diverse neurobiological changes in patients with treatment refractory schizophrenia, none of these represent—alone or collectively—a distinct “neurobiological” signature of refractory schizophrenia. While it appears intuitive that worsening and prolonged psychosis would over time lead to fundamental brain changes [in line with a “Kraepelinian” typology], in reality this is hard to either refute or confirm scientifically. The neuroplastic and also potentially neurotoxic effects of antipsychotic medications add another level of complexity to these considerations.

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A Clinical Conundrum

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