

## Recent Advances in Treatment Resistant Schizophrenia - Pharmacological, Non-Pharmacological, Genetic and Neuroanatomical Aspects

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### ABSTRACT

Schizophrenia is the most common within a spectrum of clinically similar conditions, including schizoaffective disorder, schizotypal disorder and acute and transient psychotic disorders. 1% of the population meet diagnostic criteria for the disorder over their lifetime. The aetiology is complex and multifactorial involving genetic, environmental factors, neurodevelopment insults and several neurotransmitter systems.

Treatment Resistant Schizophrenia represents severe and persistent, unremitting illness as judged by symptom, neurocognitive and disability criteria. Failure to respond to at least 2 classes of antipsychotics in optimal doses over 6-8 weeks is considered Treatment Resistant Schizophrenia.

**Method :** Extensive literature on TRS was reviewed using medline, cochrane and pubmed search engines. Internationally recognised evidence-based guidelines were reviewed and information synthesised.

**Conclusions:** Clozapine remains the gold standard treatment with its unique properties. Other non-pharmacological and psychosocial interventions are being increasingly evaluated. Despite the recent advances, management of TRS continues to be a challenge.

The author has no conflict of interest with any organisation and hopes to present an unbiased view.

### INTRODUCTION:

Schizophrenia is a complex disorder of brain function with wide variation in symptoms and signs, and in the course of the illness. Schizophrenia is the most common and most important disorder within a spectrum of clinically similar (and possibly genetically related) conditions, which include schizoaffective disorder, schizotypal disorder and acute transient psychotic disorders.<sup>1</sup> The term 'schizophrenia' includes a range of clinical presentations and personal experiences that result from complex interactions between genes and the environment, and are influenced by the person's reaction to their experience of the disorder.

Variation in the incidence and prevalence of schizophrenia between populations is greater than was once believed.<sup>2</sup> As many as 1% of people meet diagnostic criteria for the disorder over their lifetime. In terms of the global burden of disease and disability, schizophrenia ranks among the top 10 disorders worldwide.<sup>3</sup>

Schizophrenia is a complex, multifactorial disorder. Its aetiology has a major genetic component involving multiple genes of small effect, individual assortments of rare mutations and molecular pathways that are likely to be heterogeneous, both within and across populations.<sup>4</sup> Environmental factors, ranging from neurodevelopmental insults (e.g. maternal

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pregnancy and birth complications) to psychosocial adversity and substance misuse, interact with genetic susceptibility to produce widespread phenotypic variation.<sup>5</sup>

The 'social defeat' hypothesis draws together various environmental risk factors to explain how they might lead to schizophrenia.<sup>6</sup> Precursors of schizophrenia, including developmental delays, cognitive abnormalities, attenuated symptoms and odd behaviour, may appear very early in life.

Most research into schizophrenia is based on the highly unlikely assumption that schizophrenia is a single, uniform disorder. Research into the various forms of schizophrenia has been assisted by the conceptual tool of endophenotypes, which are heritable, objectively measurable biological traits that co-segregate with clinical illness in pedigrees and may also be expressed in unaffected members. Endophenotypes include distinct patterns on neuropsychological tests of cognitive function, brain electrophysiological measures and neuroimaging variables.<sup>7</sup>

The social and economic costs of schizophrenia are disproportionately high, relative to its incidence and prevalence. Schizophrenia is associated with a greater burden of long-term disability than any other mental disorder.

In most developed countries, the direct costs of schizophrenia (incurred by hospital or community-based treatment, supervised accommodation and related services) amount to 1.4–2.8% of national health care expenditure and up to 20% of the direct costs of all mental health conditions.

Over the last decade, a clinical staging model for mental illnesses has been developed,<sup>8</sup> which proposes that the course of illness is a continuum.

Clinical staging models assume that treatments offered earlier in the course of an illness have the potential to be safer, more acceptable, more effective and more affordable than those offered later.

### **Treatment Resistant Schizophrenia:**

Treatment Resistant Schizophrenia represents severe, persistent or unremitting illness (stage 4), as judged by symptoms, neurocognition and disability criteria

Clinical remission in schizophrenia is not uncommon, based on the findings of studies that have applied objective criteria.<sup>9</sup> However, a substantial minority of people with schizophrenia have persisting disabling and distressing symptoms. Apparent treatment resistance should be a trigger to reassess the treatment plan.

Management of TRS continues to be a challenge. Efforts have been made to achieve a common definition of TRS. There has been some progress in terms of understanding neurochemical mechanisms, structural changes and functional brain changes in TRS.

Clozapine continues to be gold standard in treatment of TRS.

Partial response to Clozapine remains the most difficult to treat despite interventions such as augmentation strategies and non-pharmacological treatment. When treatment resistance has been clearly demonstrated, clozapine should be offered within 6–12 months.

### **Resistance, Response and Remission :**

Schizophrenia is a chronic disorder with psychopathological dimensions - positive,

negative, disorganisation, cognitive and affective symptoms. The illness leads to significant disability- work, relationships and academic.

International study on schizophrenia concluded that 48% with chronic schizophrenia had favourable outcome.<sup>10</sup> Most of the longitudinal studies suggest that 30-40% patients with schizophrenia do not respond to treatment.

Treatment Response refers to clinically significant improvement of psychopathology measured by BPRS/PANSS (reduction of 20 % from baseline) and measures of functionality (FACT-SCZ/GAF) Response refers to score of 2 or 1 in the CGI-Change OR  $\geq 20$  points on FACT-SCZ or  $\geq 20\%$  decrease on BPRS or PANSS.

Partial Response is a score of 3 on CGI-Change OR 10 to 20 points increase on FACT-SCZ or GAF OR  $\geq 10\%$  reduction on the BPRS or PANSS.

What is treatment resistance? A well-documented failure to respond to  $\geq 2$  antipsychotics, clearly documented history of treatment failure of  $\geq 1$  antipsychotic plus prospective validation of treatment failure with another antipsychotic (different from the one that previously failed). Dose and duration: each treatment with  $\geq 600$  chlorpromazine equivalents (CPZE) per day for  $\geq 6$  weeks.

Lack of improvement in reducing CGI22  $\geq 4$  AND a score of  $\leq 49$  on FACT-SCZ or  $\leq 50$  on the GAF.

#### **Current consensus:**

1. History of failure of at least 2 antipsychotic trials (one of them with an atypical antipsychotic) with adequate doses, with 4 to 6 weeks' duration, without satisfactory

response, particularly in terms of persistence of psychotic symptoms.

2. High levels of psychopathology, particularly presence of psychotic symptoms that have an impact on the patient's conduct and functionality.
3. Presence of suicidality, violence, and substance abuse.

Samara and colleagues meta-analytically reviewed the duration of a series of trials in patients with schizophrenia and found that those who do not respond in the first 2 weeks are unlikely to respond later, a finding that may in the future modify the definition of Treatment Resistant Schizophrenia.<sup>11</sup>

#### **Clinical features of TRS:**

Some investigators propose a mean difference in the disease onset, predominance of the male gender and a higher number of hospitalizations in patients with Treatment Resistant Schizophrenia compared to those without Treatment Resistant Schizophrenia.

Other correlates of Treatment Resistance are duration of illness, poor premorbid functioning, family history of schizophrenia, an absence of precipitating factors, and a history of substance abuse.

#### **Etiology of TRS:**

The following stages have been proposed in the development of TRS:

1. Cortical pathology and deficient neuromodulatory capacity due to genetic/epigenetic etiologic factors occurring during childhood

2. Neurochemical sensitization leading to dopamine release and development of psychotic episodes occurring during adolescence, and
3. Neurotoxicity with consequent development of structural neuronal changes in adulthood.

Cortical neuropathology and deficient neuromodulatory capacity- the result of genetic and/or epigenetic factors during fetal gestation and early perinatal development.

Neurochemical sensitization - expression of a deficiency in neuromodulatory capacity that occurs in adolescence or early adulthood, triggered by environmental factors such as stress or substance abuse, Neurotoxicity occurs in the residual phase of the development of schizophrenia and is associated with neuronal changes or neuronal loss.<sup>12</sup>

#### **Structural abnormalities in TRS:**

Patients with TRS show a higher reduction of the Pre Frontal Cortical volume when compared with non-TRS.

#### **Functional abnormalities in TRS:**

A review on functional neuroimaging studies was undertaken in patients with TRS V/S healthy controls V/S non-TRS: TRS- hypo metabolism in the Pre Frontal Cortex and hyper-metabolism in the basal ganglia were observed.<sup>13</sup>

#### **Treatment of TRS:**

### **PHARMACOLOGICAL**

**CLOZAPINE:** In a meta-analysis that included 150 trials and 21,533 participants- clozapine, amisulpride, risperidone, and olanzapine proved to be superior to haloperidol, a standard antipsychotic

for the treatment of schizophrenia, with clozapine showing the highest efficacy in terms of improvement of positive, negative, depressive, and total symptoms.<sup>14</sup>

Phase 2 Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, 99 patients who had not responded to atypical antipsychotics in the previous phase were assigned to clozapine, olanzapine, quetiapine, or risperidone. Patients assigned to clozapine had greater reductions in the PANSS total score as well as the lowest discontinuation.<sup>15</sup>

#### **CutLass study:**

136 patients with schizophrenia who showed a poor response to 2 or more antipsychotics were randomly assigned to clozapine or to another SGA (risperidone, olanzapine, quetiapine, or amisulpride). Clozapine proved to be superior in terms of reduction of the PANSS but not in quality of life, an important effectiveness outcome.<sup>16</sup>

#### **Non-pharmacological biological interventions:**

Transcranial magnetic stimulation (TMS) particularly for resistant auditory hallucinations, as well as persistent negative symptoms, has been extensively reviewed with some promising results but it is not formally indicated to be used in daily routine clinical practice for patients with TRS.<sup>17</sup>

ECT in TRS was reviewed with inclusion of 9 uncontrolled studies. Other reviews have shown the ECT is used as an augmentation strategy, particularly for incomplete responders to clozapine and the number of controlled studies is scarce.<sup>18</sup>

RCT in which patients with partial response to clozapine were assigned to ECT plus clozapine or treatment as usual (TAU). Patients who were

considered non-responders of the clozapine group received an 8-week open trial of ECT (crossover phase). ECT was performed 3 times per week for the first 4 weeks and twice weekly for the last 4 weeks. Response was defined as 40% reduction in symptoms on BPRS and CGI. Fifty percent of patients of the ECT group responded to treatment, whereas none of the patients of the TAU showed any improvement.<sup>19</sup>

### **Evidence for Psychosocial interventions in Treatment Resistant Schizophrenia:**

#### **Cognitive behavioral therapy (CBT):**

A meta-analysis of 12 RCTs showed that, when compared with controls, patients with medication-resistant psychosis who have received CBT improved significantly in terms of psychotic symptoms as well as general symptoms.<sup>19</sup>

Cognitive Remediation Therapy is designed to improve neurocognitive abilities such as attention, working memory, cognitive flexibility and planning and executive functioning which leads to improved psychosocial functioning (RCTs and meta-analysis). CRT is a set of cognitive drills/interventions designed to enhance cognitive functioning.<sup>20</sup>

#### **Social Cognitive Intervention Training:**

Social cognition is a set of cognitive processes applied to recognition, understanding, accurate processing and effective use of social cues in real-world situations. In schizophrenia research, social cognition comprises the following domains : emotional perception, theory of mind and attributional style. SCIT participants have improved social cognitive measures and have better self-reported social relationships.<sup>21</sup>

### **CONCLUSION:**

Despite considerable recent advances, management of Treatment Resistant Schizophrenia continues to be challenge. Attempts have been made to have a common definition of TRS. Neurochemical mechanisms, particularly in terms of dopaminergic and glutaminergic neurotransmission are gradually being understood. Clozapine continues to be the gold standard for the treatment of TRS. Non-pharmacological biological interventions such as TMS or ECT have been trialled with varying degrees of success. Psychosocial interventions such as CRT and SCIT need further evaluation.

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