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Treatment resistant schizophrenia: Course of brain structure and function

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ABSTRACT

Approximately 30% of people with schizophrenia manifest a minimal response to conventional and atypical antipsychotic medications and manifest continuous symptoms of psychosis, with this condition referred to as "treatment resistant schizophrenia (TRS)". There are several neurobiological consequences of continuous psychosis, including regional cortical atrophy and ventricular enlargement. Pharmacological treatments are available for TRS, with at least 1/3 of patients responding to treatment with clozapine. In this paper we review the evidence regarding the course of treatment resistant schizophrenia, as well as changes in brain structure and function in psychosis and on the possible role of clozapine treatment in altering cortical deterioration in patients with TRS.

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Although the majority of patients with schizophrenia experience a beneficial effect from treatment with antipsychotic medications, there exists a substantial minority who do not experience a good clinical response. The common term for this subgroup of patients is "treatment-resistant" patients, despite the fact that patients who are adherent to their treatments are not "resisting" the interventions offered. There are several important issues in the domain of treatment resistant schizophrenia. These include the developmental course of treatment resistance, including its onset and potential worsening over time. Related to this important topic, is the issue of whether there are biological changes, including cortical deterioration, occurring in the context of repeated relapses and the development of treatment resistance. This question has received substantial attention recently, with several long-term follow-up studies of the early course of antipsychotic treatment and the correlates of this course recently published. In the cases where successful pharmacological treatment of treatment resistant symptoms occurs, it is important to understand whether this treatment arrests deterioration in the cortex. We will consider the course of cortical changes and their response to successful and unsuccessful attempts to reduce symptomatic burden treatment resistant schizophrenia.

1. Definition of treatment resistance

Although the concept of treatment resistance has been around since the 1960s (Itil et al., 1966), leading to a variety of attempts at the treatment of this condition, the leading current definition, or the 'Kane

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criteria,' defines treatment resistance with three broad criteria (Kane et al., 1988). First, the patient must fail to respond to three or more adequate trials of antipsychotic treatment within the last 5 years, including medications from two distinct classes with dosing greater than or equal to the equivalent of 1000 mg/day of chlorpromazine. With the advent of second generation antipsychotic medications, it is now broadly accepted that failures to respond to three or more atypical medications or 2 atypical medications plus a conventional medication define treatment resistance (Suzuki et al., 2011).

Further, at least with two of the critical psychosis symptoms of conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content must score at least 4 (moderate) in severity on a continuous basis. Lastly, the patient has evidence of substantial current symptoms despite current optimized treatment to which the patient is adherent, defined as a score greater than or equal to 45 on the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham, 1962), which would likely be a score on the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987) of 90 or more.

Therefore, treatment resistance is generally focused on psychosis and disorganization, and may manifest as complete non-response or minimal benefit to treatment with medications to which the majority of patients have a beneficial response (Tracey et al., 2013). Treatment resistance is not subtle and should be differentiated from partial or incomplete response, where patients experience either moderate improvements with residual or episodic (breakthrough) psychotic symptoms or persistence of a single psychotic symptom, such as delusions or hallucinations, despite successful treatment of their other symptomatic features.

In considering treatment resistance, it is also important to ensure that non-response is not actually nonadherence, which is prevalent in schizophrenia (Marder, 2003) and begins at the time of the first episode (Casiero et al., 2012; Robinson et al., 1999a, 1999b). Both relapse after successful treatment or persistent symptoms despite treatment may actually be caused by not taking medication at all or by taking it in an inconsistent or limited manner. It is challenging to make sure that patients are taking their medications. Prior to designating a patient treatment resistant, it is important to evaluate adherence as comprehensively as possible. This would include examination of refill patterns, input from informants, and possible observation while hospitalized with an acute exacerbation.

Because this definition of treatment resistance is chiefly based on clinical symptoms, many have recommended incorporating assessment of psychosocial factors, including medication adherence and substance abuse in the definition. For example, Suzuki et al. (2012) suggested also requiring global functional impairments defined by the Clinical Global Impression Severity Scale (CGI-S), the Functional Assessment for Comprehensive Treatment of Schizophrenia (FACT-Sz) scale, and/or the Global Assessment of Functioning (GAF). Consideration of everyday functioning and other clinical features of the illness is very important (i.e., motivation, insight, cooperativeness); many patients whose symptoms are clinically responsive remain disabled and have multiple elements of poor functional outcome (Strassnig and Harvey, 2014). Treatment resistant patients with current conceptualizations have functional deficits as well as persistent symptoms despite treatment. It also is important to conceptually separate the consideration of impairments in everyday functioning and persistent clinical symptoms. The two do not necessarily overlap. Successful treatment of clinical symptoms does not assure disability reduction and functional remission may occur in the presence of persistent psychosis (Harvey and Bellack, 2009). Regardless of the assessment strategies used and the factors considered, we agree that patients be considered treatment resistant only if both the clinical and functional outcomes are both poor.

A concurrently developed conceptualization of treatment resistance was focused on just this global and multidimensional impairment. First described by Keefe et al. (1987), the "Kraepelinian" conceptualization was focused on catastrophic disability as well as failures in treatment response to antipsychotic medications. Those criteria identified a subgroup with wide ranging deficits in everyday functioning, being dependent on others for all of their needs for at least a 5-year period, while concurrently manifesting no evidence of symptomatic response despite adequate treatment during this period. These patients were described as having a greater family history of schizophrenia-related conditions as well as having cortical abnormalities detected with neuroimaging, including asymmetries of cerebral ventricles. We will return to this group when we discuss the neurobiological consequences of persistent treatment resistance on brain structure and function. It is important to note that this conceptualization was developed immediately prior to the re-introduction of clozapine into the US and has largely been supplanted by the definitions of treatment resistance described above. It is of interest, however, that convergence of functional disability and lack of treatment response converges across different conceptions of very poor outcome in schizophrenia.

Disability in TRS patients may be associated with greater cognitive impairments compared to other patients. For instance, De Bartolomeis et al. (2013) and Frydecka et al. (2016) reported greater cognitive impairments in TRS patients than in treatment responsive patients. Further, negative symptoms were also more severe and associated with TRS status as well. Iasevoli et al. (2016) studied 118 patients with TRS and other conditions, finding that TRS patients were considerably more impaired on everyday functioning than non-TRS patients with schizophrenia as well as mood and anxiety disordered patients. Both clinical symptoms and cognitive performance were considerably worse than in treatment responsive patients, leading the authors to suggest that TRS may be a separate diagnostic entity. Thus, multiple previously replicated predictors of poor functional outcome, including cognitive deficits and negative symptoms (Galderisi et al., 2014; Strassnig et al., 2015), accompany the TRS syndrome.

1.1. Origins of treatment resistance

Considerable evidence suggests that most patients with schizophrenia manifest a positive response to their first treatment with antipsychotic medication (Robinson et al., 1999b). This response appears quite robust and affects as many as 90% of patients within their first months of treatment, according to the results of the first Hillside Hospital study. Recent studies have suggested that there may be more variability in treatment response than suggested by the Hillside Hospital studies. For instance, Nordon et al. (2014) found that in a sample of 467 patients, 249 had a good clinical response and 133 were found to be remaining mildly ill after treatment. Only 4.9% remained severely ill. Although Nordon et al., consider their residually mildly ill group to be "non-responsive", those cases would not meet the current criteria for TRS because their symptoms are too mild. Another group with milder initial baseline symptoms ($n = 62$) had an initial response but did not sustain it over time. These results are consistent with those by Levine and Rabinowitz (2010), who found that mildly ill patients often did not manifest good treatment response. Further, in their large-scale clinical trial ($n > 400$), there were about 20% of cases whose treatment response was minimal enough at 6 months to consider them as potentially TRS. In a follow-up study of a national sample of psychiatric admissions ($n = 2290$), Levine et al. (2011) reported that approximately 12% of patients manifested a refractory course starting at the first episode, with another 30% or so who developed a refractory course over time.

Both the rate and time course of treatment response show evidence of worsening after the first relapse with as many as 1/3 of patients showing evidence of treatment resistance within the first five years of illness (Levine et al., 2011; Lieberman et al., 1996). Thus, treatment resistance appears to develop after at last one or more successful treatments in the majority of TRS cases over time, approximately doubling to tripling in prevalence compared to the first episode over the lifetime