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EDITORIAL

Reconsidering the Term "Treatment Resistant Schizophrenia"

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Schizophrenia is a serious mental illness with an onset typically in late adolescence or early adulthood, which is often, but not always, followed by recurrent symptoms and persistent disability across the lifespan. The heterogeneity of outcomes, from sustained recovery to lifelong impairment, has long challenged clinicians and researchers and has motivated efforts to stratify patients by their degree of treatment response. Central to these efforts is the concept of "treatment resistant schizophrenia" (TRS). A 2017 expert consensus report defined TRS as referring to persons with a diagnosis of schizophrenia who have not responded adequately to at least two courses of different antipsychotic medications administered in doses equivalent to at least 600 mg of chlorpromazine per day, each for at least 6 weeks, with the patient taking at least 80% of prescribed doses over both periods. Adequate response is operationalized as at least a 20% reduction in symptom severity, with residual positive symptoms and functional impairment rated no more than mild.[1]

Originally intended as a guide for research studies, the TRS designation is highly problematic when applied to clinical practice. While it may have some utility, most importantly as a guide to the initiation of clozapine,[2] I argue that the term is conceptually flawed, clinically counterproductive, and potentially harmful to the patients it purports to classify.

The Definition is Systematically Narrow and Imposes a False Dichotomy

The TRS definition centers on positive symptoms (hallucinations, delusions, and disorganization) while largely excluding the clinical domains that most consistently drive long-term disability.[3] Persistent negative symptoms such as amotivation, anhedonia, and blunted affect are not incorporated into the definition, partly because no effective treatments for these symptoms currently exist.[4] This means that a patient with debilitating amotivation and social withdrawal may not meet TRS criteria despite having severe illness. Similarly, cognitive deficits, among the strongest predictors of functional outcome,[5] remain outside the definitional framework. Social functioning, arguably the most important clinical outcome, is multi-determined and frequently impaired even in patients whose positive symptoms are adequately controlled.

The definition also imposes a false dichotomy. As the expert report noted, treatment resistance is not truly binary yet in practice the term is used that way, implying that those who do not meet criteria are "treatment responsive." This obscures a reality in which most patients with schizophrenia are better but not well in response to antipsychotic medication and experience a continuous gradient of partial response, residual symptoms, and functional limitations. TRS also does not apply meaningfully to the group of patients who have dramatic recoveries in response to clozapine. TRS is estimated to apply to approximately 30% of persons with schizophrenia,[3] yet this figure is almost certainly an underestimate. Some TRS prevalence estimates are based on clozapine registry enrollment[6] and thus are inherently conservative as clozapine remains underutilized.[7] These estimates are further undermined by longitudinal population-based data. For example, the Suffolk County Mental Health Project, which enrolled persons hospitalized with first-episode psychosis in a defined geographic region between 1989 and 1995, found at 25-year follow-up that only 13% of those with schizophrenia-spectrum disorders had achieved remission and only 5% met criteria for recovery.[8] Even allowing for underutilization evidence-based treatments in that era, outcomes of this severity are difficult to reconcile with a 30% prevalence of "treatment resistance."

The Term Mislocates the Source of Failure

Perhaps the most consequential problem with "treatment resistant schizophrenia" is the implicit causal narrative it constructs. The connotation of the word "resistant" attributes non-response to a property of the patient or their illness, resistance, rather than to the inadequacy of available

treatments or failures in their delivery. One reading of the term, though not the intended one, is that the patient has actively repelled or opposed treatment. A more defensible reading, that the illness itself has some intrinsic property of resistance, is marginally more accurate but still misleading because it implies that the deficit lies with the patient's biology rather than with the limits of our pharmacological armamentarium.

The more accurate statement is this: for a substantial proportion of persons with schizophrenia, we have not yet developed treatments that are sufficiently effective or sufficiently acceptable, and we have not consistently delivered even the treatments we do have. Clozapine, the most effective antipsychotic for TRS, is chronically underutilized,[7] as are long-acting injectable antipsychotic medications.[9] Specialized psychosocial interventions with demonstrated efficacy are inconsistently available.[10] The therapeutic relationships necessary to sustain long-term engagement and collaboration are often not cultivated.[11] Describing the resulting poor outcomes as "treatment resistance" redirects attention from these systemic shortfalls and places the burden of failure on the patient.

This framing also fails to account for the heterogeneity of schizophrenia. Patients grouped under a single diagnostic label almost certainly represent multiple pathophysiological subtypes.[12] For patients whose illness is driven by mechanisms other than those targeted by available antipsychotics, "resistance" to those agents is not a property of the patient; it is a predictable consequence of mismatched treatment.

The Term is Stigmatizing and Psychologically Harmful to Patients

The diagnosis of schizophrenia itself is among the most stigmatized in medicine; there have been sustained arguments within the field that the disorder should be renamed on precisely these grounds.[13] "Treatment resistant" adds a further negative attribution layered atop an already burdensome label. The companion term, "pseudo-resistance," used when non-response is attributed to medication nonadherence or pharmacokinetic factors rather than true treatment failure, is particularly problematic: it implies that the patient has been disingenuous about their experience of illness or their engagement with treatment. The proposed designation "ultra treatment resistant" for patients who fail to respond to clozapine further intensifies this stigmatization.[14]

The impact of this terminology on persons with schizophrenia has received very little systematic attention. Understandably, the term TRS may suggest to patients that they are untreatable. One qualitative study reported that patients with schizophrenia who received a TRS assessment experienced it as damaging to their sense of self and their hope for recovery.[15] In the current era in which the inclusion of persons with lived experience is actively promoted in both research and clinical care, the viewpoints of persons with schizophrenia should be sought about this terminology.

The Term Exists Outside a Meaningful Continuum of Outcomes

Over the past two decades, the concept of "recovery" has been applied to the experience of living with schizophrenia,[16,17] with efforts now underway to standardize its definition.[18] Unlike TRS, recovery is not defined in terms of response to specific treatments; it is patient-centered, encompassing symptom severity, life productivity, and a sense of meaning or purpose despite any ongoing symptoms. The TRS designation and the recovery framework thus represent two concepts at opposite ends of an uncharted continuum, with no standardized language or measurement tools to describe the many patients who are between these endpoints. It is instructive to examine the approach to clinical status and illness severity employed in other chronic disorders. For many diseases with uncertain etiologies and heterogeneous courses, standardized severity rating systems have been developed that track patients longitudinally regardless of treatment status. Parkinson's disease has the Unified Parkinson's Disease Rating Scale[19] and multiple sclerosis the Expanded Disability Status Scale[20] In contrast, schizophrenia has the 100-point Global Assessment of Functioning (GAF)[21] and the 7-point Clinical Global Impression,[22] neither of which is disease-specific, is routinely used in clinical settings, or has demonstrated adequate reliability outside of research contexts. (The GAF was omitted from the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) in part for these reasons.)

Developing a schizophrenia-specific severity and outcome rating system that spans the full continuum, from severe and persistent illness symptoms to sustained recovery, would be methodologically challenging and may be an aspirational rather than near-term goal. However, the extensive conceptual groundwork already developed in both the TRS and recovery literatures, as well as the global rating scales, could serve as the foundation for such an instrument. The instrument would more accurately characterize a patient's status and could include quantification of key positive and negative symptoms and functioning. The measure could also allow for the description of contributing factors to suboptimal outcomes (eg, medication nonadherence, clozapine intolerance, lack of social support) and resist the reductive binary that "treatment resistant" currently imposes.

Conclusion

The term "treatment resistant schizophrenia" has directed attention toward patients who may benefit from clozapine or other intensive interventions and has focused research on a group with particularly poor outcomes. However, the concept underestimates the true prevalence of patients who do not achieve optimal outcomes, excludes the clinical domains most relevant to long-term disability, misattributes treatment failure to patient or illness characteristics rather than to the limits of available treatments and their delivery, carries stigmatizing implications for patients, and does not provide

a framework for describing the full range of outcomes in schizophrenia. The field would be better served by language and measurement tools that characterize the continuum of illness and recovery and that locate responsibility for improvement where it more accurately belongs, in the development of more effective treatments and in the consistent implementation of those we already have.

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Conflict of Interest

The author has no conflicts of interest to declare.

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