Using Treatment Response to Subtype Schizophrenia: Proposal for a New Paradigm in Classification

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Introduction

Phenomenology and Diagnosis

The treatment and classification of schizophrenia continue to represent an enormous challenge. Phenomenology and outcome remain the basis of present classification systems although both are heterogeneous and overlap with other psychiatric disorders.1,2 Efforts are in place for change; eg, the Working Group on Classification of Psychotic Disorders for ICD-11 has recommended omitting the traditional subtypes such as paranoid, catatonic, etc., in accordance with DSM-5, the major argument being lack of clinical utility in routine clinical practice.3,4 We believe the changes advocated do not go far enough because classification still relies heavily on symptom clusters. Adding severity and course specifiers, as is the case in the ICD-11 draft, or multiple dimensions (DSM-V) may represent more of a challenge than benefit for clinicians in their busy daily practices. Moreover, the reliability and predictive validity of these specifiers and domains are not well established and, possibly, not substantively better than the subtypes that have been abandoned.

Alternative Strategies

Biological. The search continues for biological markers that are both sensitive and specific diagnostically, a search made more difficult by the lack of an etiological basis to inform phenotypic classification. However, to date other means of classification (eg, laboratory, physiologic, and genetic), utilized in most areas of medicine, continue to remain elusive in the field of psychiatry. That we are witnessing a broader research framework bridging diagnostic groups may appear to fly in the face of such an approach,5 but the 2 positions are not necessarily incongruous. There are disadvantages to research working within the same restrictive framework that serves clinical care well by, ideally, superimposing evidence-based treatment algorithms upon clearly established diagnostic categories.

Clinical Staging

Clinical staging, incorporated by medicine for many years now, brings into play illness severity, prognosis, and choice of treatment.6 More recently, such a model has been proposed for schizophrenia, with 5 stages that move individuals from at-risk to severe, persistent, and unremitting.7 In terms of advantages, it allows for earlier intervention by accommodating attenuated symptoms as an early stage; the case is also made that such an approach offers greater opportunity to deal with apparently contradictory findings, which may actually reflect illness progression. Clinical staging has garnered success in medicine, particularly oncology, but it faces its own challenges in psychiatry. Examples include the ambiguity of the stages (eg, first episode vs chronic schizophrenia) and the low conversion rate in prodromal samples.8

Treatment Response

Building on such an approach, we propose a model that instead examines treatment response, a strategy that may offer advantages. Response to a particular treatment, or lack thereof, is certainly used for diagnostic purposes in other areas of medicine, one such example being the classification of Diabetes Mellitus (DM) in ICD-10, which includes Insulin Dependent DM (E10-14) and Non-Insulin Dependent DM (E11). Other categories, such as Malnutrition Related DM (E-12), further highlight the pragmatic nature of diagnostic criteria employed using this strategy.9 There are similar examples for numerous other medical illnesses where medications form the basis of clinical decision making.10,11 This type
of approach also sets the stage for distinguishing variations of the illness that may represent differences in underlying pathophysiology although such links are not always so clearly defined.12 Clozapine and its unique position in treatment-resistant schizophrenia is a good example of this; although the relationship has been clearly established, mechanisms of action and their implications regarding underlying pathophysiology remain unclear.13

Proposed Schizophrenia Subtypes Based on Treatment Response

The introduction of antipsychotic medications revolutionized the treatment of schizophrenia although there has been little progress since. Despite a number of “typical” antipsychotics and a growing number of newer “atypical” agents, there is general agreement that, notwithstanding side effects and clozapine’s unique superiority in refractory schizophrenia, differences in efficacy between drugs are not substantiated.14 Current evidence suggests we have 3 levels of response that can be dissociated: response to an antipsychotic other than clozapine15,16; response to clozapine17–19; and suboptimal response to both.

This knowledge has been embraced by the field and translated to treatment guidelines.20 Drawing upon research to date, criteria generally dictate 2 failed antipsychotic trials before the designation of treatment resistance and recommendation of clozapine.21 In those who demonstrate suboptimal response to clozapine, there is a paucity of evidence to suggest any particular intervention, including augmentation with other agents, is effective, leading to the suggestion that these individuals may constitute an “ultrarresistant” form of schizophrenia.22

Based on these patterns of response, we suggest the following subtypes and nomenclature: (1) Schizophrenia-Antipsychotic Responsive; (2) Schizophrenia-Clozapine Responsive; and (3) Schizophrenia-Clozapine Resistant. From a clinical standpoint, these groups appear to have face validity, and in fact, we have evidence at this point allowing us to estimate the comparative size of each sample. Current data suggest approximately 70%–80% of patients will constitute the Schizophrenia-Antipsychotic Responsive group,15 whereas approximately 30%–60% of those remaining will prove to be Schizophrenia-Clozapine Responsive,17–19 leaving the remainder as Schizophrenia-Clozapine Resistant.

Linking Subtypes to Pharmacology and Pathophysiology

Using treatment response acknowledges the central role of antipsychotics in schizophrenia, sidestepping the theoretical debates that arise with mechanistic models. From the standpoint of treatment-resistant schizophrenia, the numerous newer antipsychotics that hoped to replicate clozapine’s efficacy, while avoiding its adverse effects, have not achieved this. Current theories, including concomitant 5-HT2 binding and D2 transience, cannot explain why clozapine remains pharmacologically unique.

At the same time, employing such an approach does provide a platform for revisiting mechanisms of action based on clearly distinct patterns of response/nonresponse. It is appealing to surmise that the larger group of so-called responders (Schizophrenia-Antipsychotic Responsive) are “D2 responsive” given D2 antagonism is the one pharmacological feature inextricably linked to antipsychotic activity.23 However, even this explanation must strive to explain why individuals failing 1 antipsychotic, excepting clozapine, may respond to another, albeit at a considerably lower rate.15 Clozapine too exhibits D2 blockade,24 though this does not adequately define its unique efficacy because these same individuals have failed treatment with nonclozapine compounds that all share in common this feature. Similarly, popular theories posited to explain atypicality (eg, greater 5-HT2 vs D2 antagonism; D2 transience) cannot account for clozapine’s unique clinical profile because other atypical agents share each of these features but do not parallel clozapine clinically.25 Alternative mechanisms have been hypothesized (eg, glutamate), but it remains that the pharmacological features of clozapine accounting for its unique properties clinically are not well understood. In the case of Schizophrenia-Clozapine Resistant, we have no effective treatments currently, making it even more difficult to speculate regarding underlying pathophysiology.

Challenges in Subtyping Schizophrenia Based on Treatment Response

Ironically, our proposal comes at the same time the field is embracing a broader definition of schizophrenia, one that incorporates multiple symptom domains. Further, this shift parallels an increased focus on functional vs clinical recovery, with evidence already available suggesting that features other than positive symptoms play a greater role in functional outcomes.26

We hold to our reasoning, however, based on several lines of thinking. Antipsychotics quickly established themselves as the cornerstone of treatment in schizophrenia because psychosis is central to this illness.20 Treatment-resistant schizophrenia is first and foremost about poorly controlled positive symptoms; the crux of definitions is persistence of positive symptoms in the face of adequate antipsychotic trials.17,21 On this point, thinking regarding antipsychotics seems to have drifted in the last several decades, perhaps fuelled by the hope (and claims) that these drugs would be “antischizophrenic” rather than merely antipsychotics.25 In fact, their impact on these other symptom domains is modest at best. The approach of developing an antipsychotic with broad spectrum symptom improvement continues although we are witnessing a shift to symptom-specific drugs that
constitute add-on strategies to existing antipsychotic treatment.28

It is important that the 3 subgroups proposed here are relatively discreet and, ideally, trait rather than state dependent. Our own work, which follows individuals from the earliest stages of treatment, has established that treatment resistance can be observed from the illness’ onset.13 Unlike relapses, associated with psychotic exacerbation and transient in nature, treatment-resistant schizophrenia appears stable and poorly responsive to treatments other than clozapine. It is also of note that clozapine does not appear unique outside of this subpopulation.29 Although it is often continued in the third group (Schizophrenia-Clozapine Resistant), this may be a decision of convenience; it takes considerable effort to move patients to clozapine, and it is a drug routinely identified as the treatment of “last resort.” This said, current evidence has failed to establish any treatment as consistently effective in this sample.30

There are practical challenges to the approach we propose. Many individuals are not willing to start clozapine or may not tolerate it, making an adequate clinical trial impossible. Criteria for treatment-resistant schizophrenia and clozapine resistance exist,172122 but aspects remain vaguely defined (eg, previous antipsychotic effectiveness; level of functioning). Similarly, there is a need to clearly establish treatment response. We argue that it be operationalized and at a threshold exceeding partial, suboptimal response; to this end, we support the argument for a 50% Brief Psychiatric Rating Scale (BPRS)/Positive and Negative Syndrome Scale (PANSS) reduction, which translates to a score of 2 on Clinical Global Impression-Global Improvement (ie, CGI-I, much improved).31 In very ill patients, there is the possibility that they could demonstrate response, but still remain quite symptomatic. One means of addressing this would be to couple the CGI-I and CGI-Severity (CGI-S) scores, and identify those who are at particular threshold in terms of severity (eg, ≥4—moderately ill) as Schizophrenia-Clozapine Eligible. Such a strategy would also provide a threshold for establishing candidacy for clozapine when background information regarding treatment response cannot be easily obtained, or in the case of individuals who meet criteria for clozapine but, for whatever reason, do not undertake or complete an adequate trial. The CGI in particular is conducive to busy clinical settings demanding a brief, simple measurement tool. Although such scales address more immediate drug response, over the longer term remission criteria can also be implemented.32

Schizophrenia represents a lifelong illness, and treatment response/remission can wax and wane. This must be distinguished from response per se; numerous factors can contribute to what appears as evolving treatment resistance or attenuated response, such as poor adherence and substance abuse.3334 There is evidence that multiple relapses have biological consequences and are associated with diminished response across episodes.3537 Alternatively, it has been hypothesized that schizophrenia is characterized by different trajectories,38 evident in the earliest stages of psychosis, an idea in keeping with the conceptualization of schizophrenia as a heterogeneous group of disorders.

Conclusion

Notwithstanding the aforementioned concerns, there are compelling arguments for adapting the proposed strategy. For those working with schizophrenia, it provides a simple and clinically relevant model that has face validity. It highlights what is central to the management of schizophrenia, ie, antipsychotic treatment/response, and evidence has clearly established that better symptom control translates to improved functional recovery.39 The proposed classification system also ensures that refractory psychosis continues as a priority by highlighting both treatment-resistant schizophrenia and clozapine resistance, requiring the field to acknowledge unmet needs in antipsychotic development. In addition, it reinforces an evidence-based approach that capitalizes on what we know to this point. The importance of clozapine in treatment-resistant schizophrenia is re-emphasized, and the need to move individuals through antipsychotic trials and to clozapine in a timely fashion (which is still not occurring)40 is underscored. From the standpoint of antipsychotic development, the field has stalled, and this approach, clearly delineating subtypes of psychosis based on treatment response, provides a more sophisticated framework for evaluating alternative strategies. A first step in research would be clearly establishing the clinical criteria/thresholds that distinguish these groups; thereafter, they can be used to define study samples that can be evaluated using the same research strategies presently in place (pharmacological, neuropsychological, electrophysiological, imaging, and genetic), with similar goals (eg, endophenotypes and biomarkers).

References


