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Eliminate Schizophrenia

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Abstract

"Schizophrenia" is used as a unitary diagnostic term for an illness that is extremely heterogeneous in its etiology, pathophysiology, presentation, and trajectory. Furthermore, the presence of psychosis—its hallmark characteristic—can be observed in individuals with other diagnoses, and biologically- and computationally-defined psychosis biotypes differ from those associated with DSM diagnoses and yield different treatment predictions. We argue that *schizophrenia* is not only stigmatizing as a label, it is not useful as a diagnostic term, a disease concept, or a construct for scientific research. Until we are able to delineate a range of dysfunctions across molecular/cellular and/or macrocircuit levels that map onto psychosis-proneness and indicate optimal treatment pathways, we propose to eliminate *schizophrenia* and replace it with a new nomenclature as an interim solution. Similar to what is done with other broad descriptive disease concepts in medicine which are defined by hallmark clinical features and then further subtyped (e.g., sickle cell anemia, iron deficiency anemia), we propose that psychosis spectrum illnesses (PSIs) be characterized by their temporal characteristics, relevant modifying/causal and symptom features, and treatment responsiveness.

> We have discussed this topic in my "lived experience" PEPPNET group (Prodrome and Early Psychosis Program Network). The consensus is that [schizophrenia] is not a helpful diagnosis.
>
> --Nancy Howe, parent of a son with a persistent psychotic illness

Schizophrenia is not a useful diagnostic term

The word "diagnosis" derives from the Greek for "discern or distinguish," indicating that when we make a diagnosis, we discern what is present in the patient and we distinguish what sets them apart from other causes of their symptoms and/or from healthy people. A diagnostic term ideally indicates what is not functioning and discerns the underlying cause: for example, aplastic anemia vs. sickle cell anemia vs. iron deficiency anemia.

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The word *schizophrenia* — split mind — neither indicates what is malfunctioning nor discerns the cause of that malfunction from other potential causes. Nothing in modern science indicates that the mind or the brain are split into pieces when an individual meets diagnostic criteria for schizophrenia. Worse, the term has gained a pejorative and error-prone set of associations in the public mind and it is almost impossible to use the diagnosis with a patient, family member, or health care provider without creating a cloud of nihilism. Two recent large surveys of stakeholders show that roughly 75% favor a name change, with the hope of reducing stigma and discrimination(Lasalvia et al., 2021; Mesholam-Gately et al., 2021). But beyond the laudable goal of reducing stigma for individuals with lived experience, we argue that it is time to provide a more rational conceptual and semantic substrate for clinicians and researchers.

Schizophrenia is not a useful disease concept for clinicians

As every clinician and researcher knows, individuals diagnosed with "schizophrenia" manifest an extremely heterogeneous ensemble of clinical presentations, treatment response patterns, and short and long-term trajectories. As noted for the DSM-V revisions: "Based on the absence of clear boundaries around the condition, and the multiplicity of implicated etiological factors and pathophysiological mechanisms, schizophrenia is likely to be a conglomerate of multiple disorders" (Tandon et al., 2013). Indeed, a large number of genes of small effect combine with various deleterious environmental exposures to induce an ensemble of neural system dysfunctions that then result in the symptoms and behaviors in the diagnostic checklist: what Cannon terms the "watershed" phenomenon (Cannon, 2016).

If the purpose of a disease concept is to indicate aspects of underlying pathology, narrow down treatment options, and/or inform prognosis, then *schizophrenia* is not a useful entity. For broad descriptive disease concepts in medicine defined by a hallmark set of clinical findings, such as breast cancer or diabetes, modern diagnostic systems distinguish among subtypes based on etiologic and/or pathologic features: invasive ductal carcinoma, HER-2 enriched breast cancer, severe autoimmune diabetes, mild obesity-related diabetes. Clarifying the subtype determines the optimal course of treatment. We have no such reliable and valid subtypes for schizophrenia (yet). Even more perplexing, the situation is reversed: the hallmark defining presence of a psychosis syndrome can often be found across a number of different broad etiologic and diagnostic categories: schizophrenia, schizoaffective disorder, bipolar disorder, delusional disorder, post-traumatic stress reactions, autism spectrum disorder.

Schizophrenia is not useful as a construct for scientific research

In fact, biologically and computationally defined biotypes of psychosis phenotypes are represented by an admixture of individuals carrying diagnoses of schizophrenia, schizoaffective disorder, and bipolar disorder with psychosis (Clementz et al., 2020). These findings—along with research showing that it is possible to study a transdiagnostic group of individuals and derive dimensionality-reduced symptom axes that map onto distinct, reproducible brain maps with potential individualized clinical applications (Ji et al., 2021)—highlight the glaring research limitations of "schizophrenia". It may very well be that it is

not merely a conglomerate of multiple disorders, but a conglomerate of an almost infinite combination of genetic, molecular, synaptic, microcircuit, macrocircuit, cognitive, meta-cognitive and environmental vulnerabilities that manifest a high degree of interindividual variation. The repeated and costly failures of clinical trials of many new compounds aiming to treat schizophrenia may be attributed to this heterogeneity, which dilutes the study cohorts' biological receptivity to any given compound.

Even more frustrating, research into biological mechanisms of a psychiatric illness depends on the use of non-human animal models of disease features, but there is no animal model that captures even the most elemental aspects of "schizophrenia." (While this is arguably true of all psychiatric illnesses, it is especially so with psychosis symptoms). Pre-clinical studies are obliged to narrow their focus to singular but nonspecific features such as cognitive dysfunction or social interaction impairment or amphetamine-induced hyperlocomotion and to hope that this might apply to some aspects of the complex syndromes observed in humans.

Eliminate *schizophrenia*-- and then what?

Early 20th-century "dementia" subsumed a wide variety of presentations and etiologies that have since been sub-categorized: Alzheimer's disease, fronto-temporal neurocognitive disorder, Lewy body disease, etc.—all differentiated based on brain region/system dysfunction, histology, and characteristic clinical features… And all benefitting from differentiated clinical and research programs. A decade ago, the argument was made to eliminate the uninformative and stigmatizing word *dementia* as a diagnostic term in favor of more medically specific and semantically neutral labels, such as neurocognitive disorder (Jellinger, 2010). We argue that it is now time to eliminate *schizophrenia* for the same reasons– but with additional goals in mind.

Our ultimate aim as a field is to derive a neurophysiology-based nosology grounded in an understanding of the brain's underlying pathology, compensatory mechanisms, and treatment needs. For example, psychosis syndromes characterized by fronto-striatal dysconnectivity may be especially responsive to D2-antagonist antipsychotics as compared to those that are not (Kim et al., 2019). With sustained research focus, we will be able to delineate a range of additional malfunctions (and compensations) across molecular/cellular and/or macrocircuit levels that map onto psychosis-proneness and indicate optimal treatment pathways-- and possibly, though not necessarily, map onto different phenomenological presentations.

In the meantime, what can we do? In thoughtful clinical practice, we rely on psychiatric formulations: the various biological, social, and psychological factors that have contributed to a patient's particular presentation at a particular time. "Persistent visual and tactile hallucinations plus delusions of being followed occurring over the past 2 years in this 16 year old homeless female with a significant sexual trauma history"… "Intermittent auditory hallucinations and paranoia about brain implants occurring with an insidious onset over the past 6 months in this 21 year old male college student with an impoverished social network". These are richly informative clinical descriptors. They provide a veridical and actionable

framework for capturing the complexity of an individual's experience, but they cannot fully replace a diagnostic system. Individuals, family members, and health care workers still need a shared shorthand vocabulary, and researchers require some form of rational categorization in order to carry out meaningful human studies, at least until we obtain validation and a new naming convention for the complex multi-variate biotypes being defined computationally in current investigations.

We suggest that an interim step forward will be to develop a nomenclature similar, for example, to what is done for anemia. Just as the defining feature of anemia is a lack of healthy red blood cells, we could start with the defining feature of psychosis symptoms (psyche= mind, osis= disorder). In one recent survey, "psychosis spectrum syndrome" was the name change favored by clinicians and researchers, while those with lived experience noted the stigmatizing connotations of "psychosis" and preferred terms that highlighted "mental health suffering" (Mesholam-Gately et al., 2021). We thus suggest *psychosis spectrum illness (PSI)* as a compromise. By using the term *illness* rather than *disorder* we refer to the suffering, and by using the acronym *PSI*, we minimize use of the word "psychosis." Labels such as *schizophrenia* and *schizoaffective disorder* would be replaced with *PSI*, which would be further characterized by key temporal features, such as the age of onset, whether onset was acute vs. insidious, and the phase of illness (for these certainly reflect important pathophysiologic factors; Table 1). But just as anemia is further specified by etiologic/descriptive modifiers, such as iron deficiency vs. sickle cell anemia, the nature of the PSI could be further specified by noting relevant causal/modifying features, predominant symptoms, and treatment responsiveness. "First episode of psychosis" has entered into common clinical parlance, but "first episode of PSI, insidious onset, with pervasive delusions and comorbid cannabis use" has even more usefulness for clinical care and research.

A future where we can imagine biologically- and computationally-based biotyping that will inform clinical care appears to be close at hand. In the meantime, as we await further investigation and validation of the emerging data, we can employ a more rational, descriptive, and practical approach to distinguishing and discerning the many ways that psychosis-proneness manifests itself in human beings. The dedicated individuals who seek our treatment recommendations abd volunteer for our research studies deserve nothing less than for us to eliminate *schizophrenia*.

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Table 1:

Practical descriptive nomenclature that could be used for psychosis spectrum illnesses (PSIs): Temporal descriptors, possible causal/modifying features, predominant symptoms, and treatment response.

Temporal Descriptors	***Modifying/ causal risk factors***	***Predominant symptoms***	***Treatment response***
Symptom Onset: --Acute/ Insidious --Childhood/Adolescent/Adult Course: --Single Episode --Intermittent --Remitting/Relapsing --Persistent Illness Phase: --Clinical High Risk --First episode --Recent-onset/Early Phase --Ongoing --Recovered	*Significant trauma history* *Affective diathesis* *Substance use* *Traumatic brain injury*	*Hallucinations* *Delusions* *Disorganization* *Cognitive Impairment* *Expressive deficits* *Avolition/asociality* *Psychomotor symptoms* *Somatic symptoms* *Atypical features (e.g. visual hallucinations in the absence of other symptoms)* *Obsessive-compulsive symptoms* *Affective dysregulation* *Mood symptoms* *Suicidality*	*D2-antagonist-responsive* *D2-antagonist nonresponsive* *Clozapine-responsive* *Mood stabilizer-responsive* *Treatment resistant/refractory*

Examples of how such a new nomenclature could be applied to 4 different cases, all of whom would meet DSM criteria for “schizophrenia”. Key temporal features are noted first, followed by key modifying descriptors:

- Persistent PSI, insidious onset; *with hallucinations/delusions*
- Intermittent PSI, childhood onset; *with strong trauma history; atypical features*
- Intermittent PSI, adult onset, recovery phase; *with mood symptoms; D2-antagonist responsive*
- Remitting/relapsing PSI, acute onset during adolescence, ongoing; *with comorbid cannabis use; disorganization/avolition/ cognitive impairment; clozapine-responsive*