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Are mental disorders orphan diseases?

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"All happy families are alike; each unhappy family is unhappy in its own way."

— Leo Tolstoy, *Anna Karenina*

We often begin our research articles and grant applications by citing the high prevalence of the mental disorders that we are investigating, the assumption being that the higher the prevalence, the more impactful the research. On the other end of the spectrum are rare or orphan diseases, some of which have been observed in only a few cases around the world. These orphan diseases are often poorly researched because of the low public health and commercial impact the research might have. However, in the last few years, advances, often driven by progress in scientific knowledge, advocacy, legislation and changes in funding models, have led to significant progress in improving care for people with orphan diseases. In this editorial we argue that it is possible, and potentially beneficial, to conceive psychiatric disorders as aggregates of orphan diseases sharing "surface" characteristics. This shift in conception might be advantageous, as it emphasizes the uniqueness of each case rather than the "surface" commonalities shared by a large group of patients.

What is a rare or orphan disease?

A rare disease is defined by its prevalence, which is fewer than 1 person per 2000 individuals according to the European definition and fewer than 1 person per 1200 according to the American definition.¹ Throughout the world, more than 5000 rare diseases have already been identified and classified. Because of their rarity, they often lack a market large enough to stimulate research and support for discovering specific treatment, hence the denomination of orphan diseases. Orphan diseases mainly begin in childhood and are of genetic origin in the vast majority of cases.² However, several other pathogenic processes (e.g., immune, tumour, poisoning, chronic infection and teratogenic processes) may be implicated, and in a significant number of cases, orphan diseases have unknown etiologies.³ These diseases have varying severity profiles: some are lethal, the majority are serious,

and some have more subtle clinical consequences.² Orphan diseases can manifest themselves in any form of symptoms by affecting cognitive, physical, mental, behavioural, sensory and other abilities. The rarity of orphan diseases, taken individually, does not imply that their collective impact is minimal; on the contrary, these rare diseases affect 6%–8% of the world's population. In the province of Quebec alone, 500 000 people are estimated to suffer from these types of diseases.³ A list of rare diseases can be found on the National Organization for Rare Disorders website (rarediseases.org).

Orphan diseases can lead to significant physical and mental impairments, major gaps in patients' autonomy and function, and psychosocial and emotional effects on the patients' families. It is not uncommon for the phenotypic patterns of these diseases to lead to academic difficulties, inability to work, social exclusion, emotional isolation, discrimination and stigmatization.¹ Treatments for orphan diseases are rarely effective and, in the vast majority of cases, aim strictly at symptoms to improve quality of life. The absence of curative treatment leads to substantial mental burden on patients and their families and to a lack of therapeutic hope.² The intensity of this burden was assessed via a questionnaire sent to 2500 patients afflicted with chronic diseases, 8.2% of whom had rare diseases. Patients with orphan diseases were those who described the worst experience in terms of loss of social and economic status as well as the management of and access to medical care.²

The rarity of orphan diseases leads to significant obstacles, including delayed diagnosis, management based on little scientific evidence, and lack of knowledge about the course of the disease and prognosis. The scarcity of financial interest and, accordingly, of research on these different diseases by pharmaceutical companies also leads to inequity in access to pharmacological treatment.^{2,4} Notwithstanding these difficulties, specific treatments have been developed for some orphan diseases, particularly since the *Orphan Drug Act* was passed in the United States in 1983.⁵ However, most drugs used to treat orphan diseases are very expensive and are often not covered by private or public insurance plans. The financial burden of these treatments rests on the affected individuals and their families.

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Could psychiatric disorders be considered orphan diseases?

The description of orphan diseases presented in the previous section suggests striking similarities with psychiatric disorders and raises the question of whether psychiatric disorders should also be considered orphan diseases. The main objection to this proposition would be that psychiatric disorders are not rare, and their prevalence is usually in the 1 to 2 digits of percent. However, it is also arguable that these prevalence rates are based on “surface characteristics” of what we currently define as disorders in psychiatry. It is possible that if we consider “deeper” characteristics of psychiatric disorders based on specific biological and environmental mechanisms and their interactions, the apparent commonalities will dissolve into a multitude of unique rare diseases.

Psychiatry, like many areas of medicine, has defined, organized and classified its diagnostic categories according to clinical manifestations. The medical tradition of grouping constellations of symptoms that frequently occurred together and hypothesizing that these symptoms stemmed from a single underlying pathological process began in England in the 18th century with the physician Thomas Sydenham and was perfected in the 19th century by the German pathologist Rudolph Virchow.⁶ This focus on symptoms and their evolution to infer distinct pathological conditions with different clinical manifestations was also adopted in the 19th century by Emil Kraepelin and profoundly changed the course of history of psychiatry.

Kraepelin, a German psychiatrist and director of the Munich Psychiatric Clinic, tried to situate psychiatry in a biological and medical context, considering mental disorders as manifestations of organic brain pathology.⁶ He also used the symptoms and their evolution to propose diagnostic categories representing distinct underlying pathophysiological processes. For Kraepelin, symptom progression and patient prognosis were essential to differentiate various diseases.

The Kraepelinian classification at that time confronted a heterogeneous, disorganized psychiatric field without a consensual diagnostic system to categorize mental disorders.⁶ The lack of a shared vision by the scientific community on how to classify various clinical presentations led to a multitude of different classification systems. On one hand, some classified any cluster of symptoms as a distinct disorder, leading to hundreds of different categories; on the other hand, others perceived all mental disorders and all the different constellations of symptoms as variations of a single disorder: psychosis.⁶ Anchored by DSM-III, psychiatry and its classification system are still defined by categorical syndromes created from groups of symptoms and signs that tend to cluster together.

Advances in mechanistic understanding of mental disorders

Advances in immunology, functional brain imaging and genetics over the last 40 years have raised many questions about the pathophysiology and the classification of mental disorders. When the DSM-III was published in 1980, the scientific

literature contained 21 articles on the subject of biomarkers in psychiatry. Four decades later, more than 1550 articles have been written and published on this topic.⁷ The search for objective means to define the disorders and their underlying pathophysiological processes intends to find answers on the etiology of the different mental disorders in order to develop new therapeutic avenues and to clarify patients' prognosis. Advances in human genetics have led to the identification of millions of genetic variations, including single nucleotide polymorphisms (SNPs; variation of a single base pair) and copy number variation of a gene or chromosome segment (due to duplication or deletion), partly explaining the differences in susceptibility to disease.⁸ Genetic psychiatric studies conducted in recent years have elucidated multiple SNPs and rare copy number variants of certain DNA segments found more frequently in patients with schizophrenia, bipolar disorder, attention-deficit/hyperactivity disorder and autism than in the general population.⁷ An overview of the genetic architecture of these disorders is emerging, and it is now accepted that a large part of the genetic risk associated with each of these diseases comes from a very large number of genetic variants, each imparting a relatively small effect. It has long been known that the etiology of these disorders is partly genetic, but it is now understood that the hereditary component of each of these disorders is distributed over hundreds or even thousands of genetic polymorphisms.⁷ Under this scenario of genetic complexity, it is possible that the genetic vulnerability signature of each patient is unique and, as such, each patient will be a singleton. It is also possible that epigenetic variations, both driven by environmental factors and generationally transmitted, could add to the singularity of each patient. Notwithstanding this uniqueness, genome-wide association studies have also suggested that the genetic vulnerability of various psychiatric disorders, as determined by their polygenic risk score, are correlated, which brings into question the pertinence of clustering patients on the basis of “surface” clinical characteristics.

Advances in morphological and functional imaging, along with advances in neurosciences, have undoubtedly brought light to anatomic and connectivity dysfunctions between different brain regions in the genesis of mental illnesses. For example, an association between disturbances in brain development and schizophrenia has been reported.⁹ For more than 20 years, some experts have argued that the symptoms of schizophrenia were the result of alterations in the connection of different brain regions due to genetic variants — a hypothesis that has gained ground in recent years because of the availability of advanced imaging and genetic techniques.¹⁰ Here again, while some commonalities among patients are real, the interindividual differences in the same diagnosis category remain the rule rather than the exception.

The last decade has also seen the development of a new clinical and research field in the domain of encephalitis and immunological disorders that can lead to neuropsychiatric disorders. Studies in different medical disciplines have reported a wide variety of causes of acute and chronic noninfectious encephalitis;¹¹ for example, anti-NMDAR antibody encephalitis (glutamate NMDA anti-receptor) and

anti-VGKC antibody encephalitis (voltage-dependent potassium channel), now mainly divided into leucine-rich glioma inactivated protein[LGI-1] and contactin-associated protein 2[CASPR2]), have been singled out and well described. In addition, a significant portion of acute noninfectious encephalitis cases has been associated with unknown autoimmune and inflammatory disorders sensitive to immunotherapies.¹¹ These findings have raised awareness of organic causes linked to acute psychiatric pictures, usually manifesting as psychotic disorders, and have added a layer of complexity to the search for the biological basis underlying different mental disorders.

All these biological lines of evidence suggest that a possibly very large number of unique pathways exist that can lead to similar behavioural manifestations and functional deteriorations that are currently grouped under the same psychiatric disorder. For example, there is now ample evidence that deletion of the 22q11 chromosomal segment and variations in complement component C4 are associated with increased risk for schizophrenia.^{12,13} The prevalence of these abnormalities is quite low in the general population, which might be compatible with the definition of rare diseases for each one of them. This rarity may in turn hamper the search for specific treatments for these 2 putative rare forms of schizophrenia, thus implying that 22q11 and the C4 forms of schizophrenia fit the description of orphan diseases. Autism is another good example. Recent analyses confirm the existence of subtypes of autism-spectrum disorders that differ in their genetic architecture.¹⁴ Eventually, it will be possible to link specific cognitive, intellectual, emotional and psychopathological phenotypes to specific structural mutations with variable penetrance or rare polymorphisms and exomic mutations that will represent genetic subtypes of heterogeneous disorders.

The unique complexity of patients with mental disorders

It is important to note that psychiatry will probably never fit into a strictly biological mechanistic framework and a purely medical model of illnesses. The risk for different psychopathologies extends beyond the genome, immunity disorders or cerebral dysfunctions to integrate the unique biological makeup of every patient with personal experiences, psychological and physical trauma, temperament and resilience, and access to a support network. Some of the biological mechanisms underlying this integration are starting to be unravelled by studying the epigenome. To better understand the association between biological risk factors and the environment (including the psychological characteristics) of each individual and how these shape the clinical manifestations of each patient, we may need to change our classical view of mental disorders.

Although useful, our current categories of psychiatric disorders based on different constellations of signs and symptoms have potentially slowed psychiatric research and decreased our ability to make reliable progress by grouping very different patients (and losing the uniqueness of each). Changing our vision of mental illnesses could dramatically

change psychiatric research and practice. Within the same diagnostic category, psychiatric patients express very different phenotypic, symptomatic and severity profiles that may be rooted in unique genetic variations modified by distinct environmental factors, including past experiences that vary greatly among patients. Perceiving each patient as carrying a rare disease with specific (and possibly unique) genetic makeup as well as unique environmental contingencies could lead clinicians to perceive each psychiatric patient as unique and, in turn, lead clinicians to inquire about genetic, neuropsychological, symptom, intellectual, inflammatory, vocational and social profiles more frequently. Such an individualized assessment would lead to specific social, familial, psychological and pharmacotherapeutic interventions with the objective of maximizing participation in occupational and educational activities and increasing the sense of that individual being an active participant in society. These interventions aim at positive changes in patients' biological predispositions, psychological and behavioural characteristics and environment. For instance, several studies have shown the potential benefits of cognitive remediation interventions on employability, capacity to function at work and real-world community activities in individuals with schizophrenia.^{15,16} Even more interestingly, the results of genetic testing could even identify carriers of specific alleles predicting the response to psychosocial interventions. For example, Breitborde and colleagues showed that patients with first-episode psychosis who were carriers of a specific allele involved in memory and cognitive plasticity showed significant improvement after receiving a metacognitive remediation therapy, whereas noncarriers did not respond to the intervention.¹⁷

Conclusion

This way of perceiving mental disorders and the developing interest in advancing personalized medical interventions¹⁸ could offer more individualized treatment to refine prognostic assessments and advance research accordingly. Psychiatry, with its whole arsenal of interventions (e.g., pharmacological, psychological, social) could then be considered the flagship of individualized medicine rather than a 19th century model of medicine. Under this paradigmatic shift, our best introduction to grant applications would then be, for example, "The C4 form of schizophrenia is a rare disease that requires focused and intensive investigation/intervention." Correlatively, our clinical attitude will shift from considering our patients as elements of a large nebulous syndrome to considering them as individuals with various and unique needs.

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