Review article

Beyond the DSM: trends in psychiatry diagnoses

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Abstract

Background: Although widely used in clinical practice and research, Diagnostic and Statistical Manual of Mental Disorders (DSM) diagnoses have low validity: patients with different mental disorders can share similar symptoms, while those with the same diagnosis might have different symptoms. In fact, the DSM diagnostic system has been considered one of the main obstacles for further development of psychiatric research. Recently, it has been proposed that psychiatry nosology should be reframed according to a biologically-based etiology. **Objectives:** To review present and past endeavors of establishing an etiology-based nosology. **Methods:** Comprehensive review of articles on the topic. **Results:** From Hippocrates onwards, multiple attempts have been undertaken aiming to move etiology and nosology closer. The most recent efforts are represented by Developmental Psychopathology (DP) and the Research Domain Criteria (RDoC), which presents an operational matrix recommended to be used in clinical research instead of the DSM diagnoses. **Discussion:** The DSM-based nosology is faulty. RDoC and DP might be interesting alternatives for an etiology-based nosology. However, while DP has already brought promising results, RDoC is a novel proposal, whose advantages and disadvantages should gradually be identified in the upcoming years.

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Introduction

Diagnostic construct heterogeneity is one of the main challenges in psychiatric research and practice[1-6]. For example, according to the Diagnostic and Statistical Manual of Mental Disorders (DSM), major depressive disorder (MDD) is composed by two main symptoms (depressed mood and anhedonia), one of them being necessary for diagnosis. In addition, MDD should also present 5 or more symptoms out of 9 (Table 1). It is possible, therefore, that two patients diagnosed with depression do not have a single common symptom. This issue is also valid for other psychiatric disorders such as bipolar disorder, schizophrenia, anxiety disorders, trauma-related disorders and obsessive-compulsive disorder[1]. Moreover, DSM does not consider for diagnostic formulation clinical aspects such as age, sex, comorbidities and duration of disease[7].

Heterogeneity is an issue for several reasons. Patients with the same diagnosis – although presenting different symptoms – will be treated similarly in clinical practice and in socioeconomic aspects (e.g., private insurance reimbursement, social security, access to health services). In clinical research, such patients are grouped together and compared to controls in studies investigating biomarkers, populational studies, and randomized clinical trials. Partly due to heterogeneity, most studies have presented negative results[3].

Therefore, it is key to reappraise psychiatric nosology. In fact, a recurring suggestion has been that psychiatric nosology should be based on the etiology of mental disorders, similarly to mainstream medicine[8]. However, there are several obstacles in this approach. In this article, I discuss the challenges and advances of this integration. Initially, I present general concepts on nosology and etiology and a historical review on the attempts for their integration. After that, the limitations of the current models are discussed. Finally, the concepts from two recent approaches are presented – the *Research Domain Criteria* (RDOC) and the Developmental Psychopathology (DP) framework – which might be helpful in the effort to develop an etiology-based nosology.

Nosology of mental disorders

Nosological categorizations can be organized into 3 major dimensions. One of them distinguishes between cause and description. The medical model traditionally opts for the former. However, as the causes of mental disorders are not known, the psychiatry nosological classification is based on clinical description, using operational criteria (i.e., a diagnosis is composed based on standardized criteria, as exemplified in Table 1) and eventually considering the course and prognosis of the described syndrome. This approach, present in the current DSM models, has problems such as the overlap between different diagnoses of signs and symptoms, which can also present distinct phenomenologies (e.g., depressed mood due to bereavement, hypothyroidism, or a depressive syndrome)[4].

Table 1. Major depressive disorder operational criteria

A. 5 or more of the following symptoms have been present during the same 2-week period; at least one of the symptoms is (1) or (2) 1. Depressed mood 2. Anhedonia 3. Weight or appetite changes 4. Insomnia/ hypersomnia 5. Psychomotor agitation/retardation 6. Fatigue or loss of energy 7. Feelings of worthlessness or guilt 8. Concentration difficulties 9. Thoughts of dying
B. Symptoms cause significant distress or impairment
C. Episode not attributable to a medical condition
E. No previous (hypo)manic episode(s)

The table shows the operational criteria for major depressive disorder. Adapted from the 5th version of the Diagnostic and Statistical Manual of Mental Disorders[7].

In addition, disorders can be classified categorically or continuously. Discrete categories are useful for physicians as the patients' disease is clearly delimitated and, therefore, a treatment can be straightforwardly established. The dimensional model, in turn, allows to examine all individuals (healthy subjects and patients) according to a spectrum and thus to collect more data. It is also a more "natural" representation for clinical symptoms that do not present a clear distinction between normal and pathological[9].

The last dimension is between essentialism and nominalism. In the essentialist perspective, mental disorders are "natural types" that can be identified and categorized. The nominalist perspective considers

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that mental disorders are categories created for convenience, not reflecting something that "exists" naturally. "Moderate nominalism" admits that mental disorders "exist", but also that their classification and taxonomy involve practical and operational aspects[10].

Considering these dimensions, commonly used mental disorder frameworks can be identified, such as the "disease" (essentialist and categorical, understanding mental disorder as an organic and cerebral disease), the "altered function" (dimensional, assumes that mental disorder is caused by the loss or damage of a function in the brain) and the "biopsychosocial" (proposed by Engel and Meyer, arguing that psychological and social causes are as important as biological ones for both the etiology and the nosology of mental disorders – this model is essentialist and categorical, although it is balanced in the causalism/descriptivism dimension) models[10].

Etiology of mental disorders

In a systematic review of articles that investigated the etiology of mental disorders, Kendler[11] identified three main approaches, which are focused on the biological (e.g., genetic, epigenetic, molecular, neurochemistry and neuroimaging studies), psychological (studies exploring neuropsychological traits, personality traits, cognition, and psychiatric symptoms) or environmental (focused on the individual, family, society, culture or community) aspects. Studies in these categories have been fairly distributed, with a slight preponderance of biological studies. Also, 1/3 of the studies evaluated more than one category (e.g., neuroimaging with neuropsychology, genetics with environment). From these findings, the author described some common paradigms used in the investigation of etiological factors of mental disorders.

The first one is the *identification of multiple risk factors at different levels.* This paradigm assumes that, since the effect of a risk factor is small, several risk factors, at different levels, should be identified to "sum up the different causes" of a disorder. This approach does not support one specific category, as the importance of a factor will be solely determined by its effect size[11]. This paradigm, however, has two issues. One is methodological: risk factors variables can be confounding variables or epiphenomena. In addition, although the paradigm is theoretically pluralistic, researchers might end up valuing more the etiological factors that they are mostly familiar with[11].

The second paradigm – *elucidation of causal mechanisms* – is employed in mechanistic studies. It uses a pragmatic approach to identify risk factors and cause-effect mechanisms[11]. This paradigm also has some issues, one of them being its reductionist approach. In addition, the "causal" factor can be a variable of confusion. In fact, this type of study, which generally uses a cross-sectional design, is prone to this type of bias. Another difficulty of this model is the need for a valid nosological system[11]. For example, the finding of an overactivation of the amygdala in patients with depression does not necessarily imply that this finding has etiological value as it is also observed in other disorders. In addition, depression itself is a heterogeneous construct[12].

Nosology and etiology in Psychiatry: an historical overview

The earliest nosological classifications of mental disorders took place in ancient Greece. Hippocrates proposed that the temperaments of men would be caused by four humors: yellow bile, black bile, blood, and phlegm. The black bile would generate a melancholy temper, observed in philosophers and poets. At excessive levels, black bile would lead to melancholy[13]. This classification system is an etiological one, since mental diagnoses derive from their causes.

In the Middle Ages, insanity and madness were assumed to be caused either by the free will of individuals or by the influence of malevolent spirits. Thus, there would be no etiology, since the symptoms of the mind did not come from the body, but from either a moral or spiritual deviation[13].

In Renaissance, the Ancient and Middle Ages concepts of mental disorder coexisted[13]. This apparent contradiction is consistent with Rene Descartes' works (1596-1650), which defined the ontology of mind based on the mind-body dualism: there would be the *res cogitans,* produced by the mind, and the *res extensa*, the material reality[14].

Psychiatry emerges as a medical discipline between the eighteenth and nineteenth centuries. Psychiatrists were the physicians able to distinguish "insanities" from "nervous diseases"[13]. Patients with insanities (a concept that probably encompassed the current diagnoses of schizophrenia, dementia, mental retardation, epilepsy, and affective psychoses) were those who lost contact with reality and, therefore, must be alienated from society. Patients with nervous diseases (hysteria, anxious and depressive disorders, neuroses) in turn, were those who could live in society[14].

Interestingly, "insanities" would not present an etiological cause, being caused by moral or spiritual defects, whereas the etiology of nervous diseases would be the nerves and the nervous system[13,14]. Afterwards this pattern was reversed, with the identification of the cause of general paralysis and the neuropathological findings of Alzheimer's Disease; which lead to further investigation on the etiology of insanities. In contrast, with the birth of psychoanalysis, nervous diseases were no longer associated with organic etiologies[13,14].

At the beginning of the twentieth century, the Franco-German school of psychiatry advocated that mental disorders should be classified according to their cause. Pinel, the father of modern psychiatry, argued that "insane" patients suffered from natural processes and not from moral or spiritual deviations. In agreement, Emil Kraepelin and Eugen Bleuler organized a taxonomy of mental disorders[13].

According to its psychopathological presentation and course, madness was divided into *dementia praecox* and manic-depressive psychosis. Jaspers, in his book General Psychopathology, organized psychiatric disorders in three groups: Group I included cerebral disorders such as brain tumors and meningitis, group II was represented by the psychotic disorders (schizophrenia, epilepsy and manic-depressive psychosis), and group III encompassed the personality disorders. Thus, mental illnesses started to be understood as having an organic etiology and to be organized nosologically from this assumption[15].

Karl Jaspers argued that mental disorders should be described from both a comprehensive (*verstehen*) and an explanatory (*erklären*) perspective. This distinction is also known as the 1st vs. 3rd person problem, i.e., the experience of one in relation to one's disorder (in "first person") that is not appreciated by an etiology-based nosological framework (in "third person")[16]. According to Jasper, the comprehensive approach should access the individual's hermeneutic circle, psychic phenomena, and meaningful associations. To this end, the clinician must use a phenomenological approach, without causal preconceptions – the "pure appreciation of the facts". The *erklären*, in turn, is the causal, "genetic" explanation of mental disorders[15,16].

The early 20th century organicist view had psychoanalysis as its counterpoint, which was initially developed by Freud. Psychoanalysis claims that most mental phenomena originate from individual psychic conflicts, not from biological causes. In this context, "nervous" diseases would have a psychological cause due to processes such as psychic conflicts, defense mechanisms and latent or manifest contents[15].

Emergence of DSM

The 1st version of the DSM, elaborated in 1952, was originated from the US military classification manual used in World War Two. This manual prioritized the classification and selection of soldiers mentally fit to go and remain at war, as well as to treat their mental disorders. The psychiatrists attending these soldiers, therefore, dealt mainly with dynamic and "neurotic" disorders. Thus, DSM-I contained terms such as "psychoneurotic neuroses" and "psychophysiological reactions". Nevertheless, DSM-I, as well as the

DSM-II, also included biological diagnoses and some concepts of the Kraepelian classification[17].

The first two DSM versions used no operational criteria. Rather, psychiatrists would have to decide, according to their best judgment, whether the presence of a symptom was severe enough to formulate a diagnosis. Due to this subjectivity, diagnoses in the early DSM versions had low reproducibility[15]. In fact, studies conducted in the 1970s showed that different psychiatrists, using DSM-II, would often perform distinct diagnosis for patients exhibiting similar symptoms. In addition, Rosenhan's pseudo-patient experiment showed that healthy volunteers, when describing false but vague mental symptoms, were diagnosed with severe mental disorders such as manic-depressive psychosis or schizophrenia[18].

In 1974, a task force led by Robert Spitzer aimed to compile a new version of the DSM consistent with the International Classification of Diseases (ICD), which was mostly used outside the United States. This proposal was also consistent with the onset of clinical psychiatric research that required well-defined diagnostic constructs. The DSM-III also incorporated the findings from the *Research Diagnostic Criteria* (RDC) and the Feighner criteria studies[6]. DSM-III adopted a neo-Krapelenian model, using categorical and operational diagnoses, theoretically more accurate and replicable than in previous DSM versions. However, DSM-III is considered "atheoretical", i.e., without an etiological (biological or psychological) basis. The DSM-IV, developed in 1994, was similar to DSM-III in this regard[6].

The 3rd and 4th versions of DSM brought important advances in contemporary psychiatric research, and lead to an increase of the psychopathological, epidemiological and therapeutic knowledge of mental disorders. However, DSM also brought several "side effects", such as diagnostic "reification", low validity of constructs, lack of integration with etiological advances, and exponential increase in the diagnosis of comorbidities[6].

Despite these issues, the 5th version of DSM, presented in 2013, maintained the same operational structure, with only minor changes. The task force decided not to modify it substantially as this could invalidate prior and ongoing research based on earlier DSM versions[19]. Thus, DSM-5, frustrating some researchers, was "more of the same" of its previous versions.

Challenges of traditional models for the integration between nosology and etiology

From its 2nd version onwards, DSM has been focusing on *reliability*, i.e., in performing diagnoses based on reliable constructs that produce similar results when applied by different evaluators. On the other hand, being "atheoretical", DSM have not primarily aimed for *validity*, i.e., to which extent a given syndrome really represents the phenomenon being observed[20]. In fact, there are several types of diagnostic "validity". The *face* validity is subjective and presupposes that there is a "natural type" to be measured. Operational validity is objective and can be divided into validity of the *construct* (how much the instrument actually measures the construct and no other symptoms – for example, if a depression scale measures depression and not anxiety), of the *content* (if the instrument measures all the aspects of what is being assessed – for example, if a depression scale measures all symptoms of depression) and of the *criterion* (if an independent, but theoretically related to the construct, instrument is associated with the construct – for example, if the measure of "neuroticism" – independent of the construct of depression – is associated with depression)[20].

Concomitantly to DSM-III, Robins and Guze presented five criteria to ascertain the validity of a disorder. They were (1) identification and accurate description of signs and symptoms; (2) delimitation and exclusion of other disorders; (3) investigation of biological and etiological correlates (laboratory tests); (4) follow-up studies; (5) family studies. Subsequently, other criteria were added such as response to treatment and construct stability over time[21].

Epidemiological studies further observed that criteria (1) and (2) could not be confirmed using DSM, as an accurate description of signs and symptoms was not necessary according to its operational criteria[22]. Moreover, there are only a few pathognomonic psychiatric symptoms, most of them being shared by several mental disorders.

Several studies have been carried out in the past decades looking for biomarkers that could distinguish and delimit mental disorders. In this context, these studies aim to determine rare points between diagnoses as to "carve nature at its joints"[23].

Initial studies in genetic psychiatry envisioned to find "causative" genes for mental disorders, particularly for those with a possible strong biological basis, such as schizophrenia and bipolar disorder. However, although family studies have indeed identified some risk genes, the effect size of these associations has been very low. Furthermore, most identified genes are not specific to a particular mental disorder[23].

Also in accordance to Robins and Guze's proposal, neuroimaging studies have been conducted searching for "neural signatures"[2] of mental disorders, i.e., structural or functional patterns that could be specifically associated with a disorder. However, the results of these studies also presented small effect sizes, being of little relevance from a clinical perspective[2].

Several authors claim that the failure of psychiatric studies to identify "neural signatures" and to "carve nature at its joints" is due to the current nosological system and its heterogeneous diagnosis. In fact, if two patients diagnosed with depression may not present a single common symptom, it is unlikely that they will share neural signatures or risk genes. In addition, diagnoses present a significant overlap of symptoms and, therefore, different diagnoses might share mutual neural signatures and risk genes.

Proposals for an integration between etiology and nosology

Research Domain Criteria (RDoC)

While DSM-5 followed the same path of DSM-IV, the National Institute of Mental Health (NIMH) champions a fresh proposal through the *Research Domain Criteria* (RDoC), which aims to *"develop, for research purposes, new ways of classifying mental disorders based on dimensions of observable behavior and neurobiological measures"*[5].

According to the NIMH, DSM-IV not only presents critical issues such as reification, lack of face validity, abundance of psychiatric comorbidities, and extreme diagnostic heterogeneity, but also discourages novel methods of research, favoring the standard "mental disorder vs. healthy control" comparison model[3]. Ultimately, these issues would lead to a delay in the development of new therapies, since heterogeneous diagnoses decrease the signal-to-noise ratio. Finally, DSM categorical system would inhibit a transdiagnostic approach to examine the causes of common endophenotypes shared by different disorders[3].

The RDoC defends that, at least for research purposes, the classic model of associating etiological findings to nosological syndromes should be discarded. On the contrary, RDoC initially associates signs and symptoms with endophenotypes to further identify etiologies. For instance, symptoms of fear and anxiety are both associated with HPA system hyperactivity. Thus, these symptoms may have common etiologies. In other words, while the most common model of current research is to compare patients with healthy controls aiming to identify a disease-related biomarker, one of the models proposed by RDoC is to associate signs and symptoms (regardless of diagnosis, and even including healthy controls) with endophenotypes to identify common biomarkers.

The RDoC is based on 7 pillars[5]: (1) to use a translational perspective, exploring several clinical syndromes simultaneously; (2) to use a dimensional model, from normal to pathological; (3) to develop valid and replicable methods for measuring signs and symptoms; (4) in clinical trials, to have as an outcome variable a behavioral or neural response and not a diagnostic scale; (5) to be

an integrative model, also considering behavior and neural circuits; (6) to define nosological constructs for research applicability; (7) to conduct research not tied to DSM categories.

The RDoC matrix is composed of 5 domains, each of which having subdomains (Table 2):

1) Domain of negative valence: fear, anxiety, sustained threat, loss, frustration in the absence of reward;

2) Domain of positive valence: approximation, response to reward, sustained response to reward (persistence), reward-based learning, habit;

3) Cognitive systems: attention, perception, operational memory, declarative memory, language, cognitive control;

4) Systems for social processes: affiliation and attachment, social communication, perception and knowledge of the self, perception and knowledge of others;

5) Activation systems: activation (*arousal*), biological rhythms, sleep-wake cycle.

Each subdomain can be further investigated in different levels. For example, fear can be investigated at the genetic and epigenetic (BDNF, 5-HT), molecular (BDNF, serotonin), cellular (GABA neurons), neural (amygdala), physiological (heart rate variability), and behavioral (response inhibition) levels, using self-reported scales, and through paradigms (e.g., the Trier test).

The objective of the RDoC, therefore, is to offer an ongoing work proposal, with constant improvement and incorporation of new findings, which provides an experimental, etiology-based classification for developing psychiatric research and nosology. According to NIMH, one of the outcomes of RDoC may be the modification of current nosological systems to improve diagnosis, treatment, and ultimately prevention and cure of mental disorders [3,5].

Developmental Psychopathology framework

According to Rutter[24], Developmental Psychopathology (DP) is a conceptual model that involves a series of research methods focusing on psychopathological and developmental characteristics to ask questions about mechanisms and processes. DP has several assumptions, such as the expectation of diagnostic continuities and discontinuities; a focus on both risk and protective factors (resilience); age as an ambiguous variable that reflects both biological maturation and accumulation of experiences; and the investigation of direct and indirect mechanisms of disease[25]. DP also contributes to the debate of categorical vs. dimensional classification by highlighting the continuities and discontinuities of various mental disorders. For instance, intellectual disability has a continuity between mild intellectual disability and normality, but a discontinuity in cases of severe and profound intellectual disability, the latter presenting relatively better defined etiologies[24].

DP, similarly to the RDoC, recognizes the need for a paradigm shift in the current concepts of nosology and psychiatric research. Thus, DP and RDoC approaches are less exclusive than complementary. However, RDoC has a clearer preference for the biological etiology of mental disorders and the identification of transdiagnostic endophenotypes and biomarkers; whereas PD considers biopsychosocial aspects and proposes the study of the individual throughout development.

DP, differently from RDoC, is a research model used in psychiatry for a longer time and has already presented results – for instance, findings related to the influence of psychopathology and child behavior in adult psychopathology, the importance of childhood traumas (abuse, deprivation) as risk factors for mental disorders in adults, the interaction between genetic load and environmental characteristics (gene-environment interaction) in the incidence of mental disorders, and the importance of parental psychopathology in mental disorders of childhood and adolescence[24,26].

The challenges of the DP framework include greater understanding of the mechanisms that lead to the onset of mental disorders in some patients, but not all, that present early adverse experiences or risk genotypes[24,26]. In this context, the influence of gender and age in the etiology of mental disorders is poorly understood. Another challenge is to understand how the environment "*gets inside the skin*" and induce epigenetic and neuroendocrine changes. Gene-environment studies revealed, for example, increased risk for depression according to the genotype and the environment, but not the underlying biological mechanisms involved[24,26].

Integration between the 1st and 3rd the person perspectives

Finally, another proposal concerning an etiology-based nosology system focuses on the integration between the perspectives of the subject and the object[16]. For instance, Kapur[27] proposes that psychosis is a "state of aberrant salience". The author argues that the dopaminergic system "provides salience" to environmental stimuli. In a physiological state, the hedonic motivation or attention to a stimulus is regulated by dopaminergic activity. In psychosis, dopaminergic activity is aberrant, providing salience to neutral internal and external stimuli, giving rise, respectively, to delusions and hallucinations. Antipsychotics, by decreasing dopaminergic activity, would tune down the significance of these stimuli, allowing them to be re-signified by the patient. In Kapur's proposal, the "cause" of a mental disorder is therefore presented from the perspective of the 1st person. Theoretically, this integrative vision could help to reduce the stigma of mental disorders and clinical treatment, as it explains to patients the causes of their illness[11].

Conclusion

The DSM-based nosological classification has been widely used in the last four decades. It was developed in response to criticisms that argued that psychiatric constructs presented poor reliability. Presently, both DSM critics and supporters agree that the validity of its diagnostic constructs is low.

Despite DSM contributions to the advancement of psychiatric research, it is currently considered as an obstacle to future progress, since its constructs are heterogeneous and the signs and symptoms that define a syndrome overlap. Another issue is comorbidity: patients commonly have 2 or more diagnoses, which further confirm the low diagnostic validity and the impossibility of "carving nature at its joints". Etiology-focused research, such as risk genotypes and neural signatures, showed poor results in identifying risk factors useful for clinical practice and in proposing pathological mechanisms for mental disorders. Moreover, little progress has been observed in the development of new treatments for major mental disorders in the last 20 years.

Recently, an etiology-based nosology system, in agreement with mainstream medicine, has been advocated for psychiatry. RDoC

Table 2. Research domain criteria (RDoC) framework

Systems	Genes	Molecules	Cells	Circuits	Phisiology	Behavior	Self- reports	Paradigms
Negative valence								
Positive valence								
Cognition								
Social processes								
Arousal/modulation								

Adapted from Cuthbert (2015)[3].

proposes that psychiatry research should abandon the categorical diagnoses of DSM as to investigate the signs, symptoms and endophenotypes that occur in healthy individuals and in patients with different psychopathologies. According to RDoC creators, this novel framework will aid in identifying mental disorders etiologies, subsequently defining reliable and valid nosological constructs.

DP, in turn, uses research methods and concepts focused on the influence of early life events and risk genotypes as etiological factors for mental disorders. Although not rejecting the DSM, DP findings have been contributing to a review of current nosology based on etiology.

In summary, the proposal of an integration between nosology and etiology has brought heated debates in academia as it leads to fundamental discussions in Psychiatry – essentially, what a mental disorder is. Apart from this debate, most researchers agree that the nosological model is faulty for several reasons and, in this context, the proposals of RDOC and DP might be interesting alternatives for an etiology-based nosology. However, while the PD framework has already brought promising results, RDoC is a novel proposal, whose advantages and disadvantages will gradually be identified in the upcoming years.

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