Original article

Do *DSM* classifications help or hinder drug development?

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Development and regulatory approval of psychotropic drugs targets individuals with syndromes described in the current *Diagnostic and Statistical Manual of Mental Disorders (DSM)*. This helps drug developers and regulators to communicate with prescribers, and prescribers to match a specific psychotropic with the individual patient(s) most likely to benefit from it. However, this practice has been criticized on the grounds that *DSM* syndromes are too heterogenous biologically, and the effects of psychotropics are too nonspecific to allow for an effective match. This review considers the advantages and disadvantages of the current practice and the possible alternatives. It concludes that efforts should be made to explore psychotropic development transdiagnostically, free of the *DSM* boundaries. However, currently there exists no alternative diagnostic system that is clearly superior to the *DSM* in terms of communications between the stakeholders in drug development.

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Introduction

After a flurry of novel psychotropics in the 1980s and 1990s, which had a moderately superior tolerability profile compared with existing drugs, the 2000s have been characterized by a stagnation of productivity in drug development. The presumed stagnation has been lamented in editorials[1,2] and attributed to a lack of pathophysiological understanding of the brain's normal and abnormal functioning, difficulties in identifying targets, poor translation from animal models to human ones, the absence of biological markers, and the high financial risks associated with CNS drug development. Adherence to diagnostic systems which were not specifically designed for drug development, such as the *Diagnostic and Statistical Manual of Mental Disorders (DSM),* has also been suggested as a major reason for the paucity of novel psychotropics.[3,4]

The use of diagnostic systems including the *DSM* is the medical profession's attempt to classify and circumscribe clinical presentations in the belief that such classification will facilitate matching a specific disease and treatment for an individual patient and optimize the clinical benefits. Diagnosis is based on the similarity of the symptoms and test results of the individual patient to a known pathophysiological process, and on known interactions between the process and the therapeutic intervention.

As health care provision has evolved beyond the traditional doctor-patient interaction, diagnostic systems have also been employed to communicate between the various stakeholders of health care provision: patients, their families, clinicians, academic researchers, insurers, the pharmaceutical industry, and government agencies. The Food and Drug Administration (FDA) and the European Medicines Agency (EMA) employ the *DSM* classification to support

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evaluation of new drug applications (NDAs). Therefore, the *DSM* strongly affects the kinds of trial design and patient population used in support of the NDAs. Once a decision is made to approve a psychotropic for marketing, the communication between regulators, prescribers, and patients takes place via the Summaries of Product Characterisrics (SPC), or the labels accompanying the approved drug. A review of the SPCs and labels issued by the FDA and EMA between 2000 and 2013 indicates that depending on the context, the *DSM* was mentioned in relation to between 45% and 90% of the approved psychotropics.[5]

DSM will remain a useful tool for drug development, yet all stakeholders should be aware of its limitations and maintain the necessary flexibility

The first, and probably the only, significant revision of the original *DSM-I* version, published in 1952, occurred in the 1980s when *DSM-III* abandoned the vague psychodynamic explanation to mental illnesses and focused exclusively on detailed phenomenological descriptions. *DSM-5* was characterized by good reliability so that health care providers and researchers worldwide could easily communicate. However, because of the very slow progress in neurosciences and the large gaps in understanding the biology of mental illnesses, *DSM* has added very little to the validity of the diagnosis, a limitation fully acknowledged by its authors[6] and commentators.[7]

The current version, *DSM-5* is based on field trials[8] and an evolving consensus. The consensus is affected by slow, incremental scientific progress, but also by social developments, and, unavoidably, by the personal views of the participants in the consensus groups.

Unfortunately, psychiatric diagnosis has lagged behind the rest of the medical disciplines. Since it is easier to understand how liquids are pumped through tubes, and how O_2 and CO_2 are exchanged, than how emotions and thoughts emerge, it is no wonder that the matching of diagnosis, pathophysiology, and treatment in cardiovascular medicine, for example, is superior to that in psychiatry—though far from perfect. To appreciate the difference, just imagine that before the multiple causes of dyspnea were understood, it would have been observed, serendipitously, that a compound with diuretic proprieties occasionally ameliorated dyspnea and improved the quality of life and work functioning of dyspneic patients. Imagine now, what results of a trial of this diuretic drug, enrolling all patients with dyspnea, poor quality of life, and poor work functioning would look like, or how unpredictable the clinical response to such a drug would be.

Family and molecular genetic studies have posed the strongest challenge to the biological validity of *DSM* classifications, and to the idea that these classifications represent discrete entities that can distinguish between aberrant and normal behaviors and emotions. *DSM-III* and *-IV* were based on a hierarchical system, in which an individual cannot receive two concurrent diagnoses. Occasionally a concurrent diagnosis is labeled comorbidity. Yet, this is inconsistent with clinical observations[9] and with genetic studies that show considerable overlap between *DSM*-listed syndromes. The average genetic correlation is >0.20 between schizophrenia, bipolar disorder, major depressive disorder (MDD), ADHD, anorexia nervosa, obsessive–compulsive disorder, autism spectrum disorder, and Tourette syndrome, and 0.70 between schizophrenia and manic-depressive illness.[10] To address this limitation *DSM-5* assigns a severity dimension to most of the syndromes, making the current classification not only qualitative but also quantitative.

The critiques and the justifications of drug development based on *DSM*

General

Mental health professionals and, hopefully, the public at large, understand that psychiatric classification is not based on known pathophysiological processes but on imperfect, phenomenological constructs called syndromes. Yet, in daily clinical practice and in administrative procedures, these syndromes are treated as true natural elements, depending on which binary decisions are taken. This occurs despite the fact that no pathophysiological processes at the molecular, cellular, or circuit level can be attributed to any specific *DSM* entity. Nevertheless, NDAs based on which psychotropics are approved for marketing are supported by trials conducted in specific *DSM* popula-

tions, such as sufferers of schizophrenia, MDD, or generalized anxiety disorder (GAD). Understandably, the process of developing, approving, and marketing psychotropics based on *DSM* classifications has attracted an overabundance of criticism.

Heterogeneity within diagnostic groups

The most frequent and probably valid criticism is that *DSM* entities do not reflect true biological processes, but fail to "carve nature at the joints" (Plato). Under the descriptive umbrellas of schizophrenia, depression, or anxiety—on a continuum between normality and disease—there probably exists many heterogenous biological processes. Are two schizophrenic individuals, one with an IQ of 105, persistent auditory hallucinations, and mildly declining social functioning, and another with an IQ of 85, severe thought disorder, mild paranoid ideation, and severely declining vocational functioning affected by the same pathophysiologic process? Are two individuals with MDD, one suffering from severely depressed mood, hypersomnia, hyperphagia, motor retardation, poor concentration, and nihilistic ideas, and another with moderately dysphoric mood, insomnia, motor agitation, poor concentration, and very severe anxiety affected by the same pathophysiologic process?

Overlap between diagnostic groups

To further complicate matters, symptomatic manifestations of syndromes with a distinct *DSM* diagnosis tend to overlap. Most MDD patients are anxious, and most patients who meet the criteria for GAD are unhappy. Patients who meet criteria for schizophrenia are often depressed, and patients who meet criteria for depression are occasionally psychotic. If indeed several pathophysiological processes are contained within the same diagnostic class, it explains why only a minority of the target population included in randomized controlled trials (RCTs) or treated in clinical practice, responds to the treatment. Were all or the majority of the patients who meet *DSM* criteria for MDD affected by the same pathophysiologic process, it could be expected that all or most would respond to the same treatment and not only <30% as indicated by RCTs.[3] This is not surprising if one considers that phenomenological description in the *DSM* is attempting to reflect the end result of close to 1 trillion neural connections, their interactions with genetic programing, functionally and dynamically changing proteins, and environmental effects.

Disconnect between psychotropics and *DSM* diagnosis

Further evidence of the disconnect between *DSM* diagnosis and specific pathohistological process is the fact that in daily clinical practice, psychotropics are prescribed regardless of the specific *DSM* diagnosis.[11] Drugs which block dopamine (DA) and serotonin ($5HT_2$) receptors, originally developed and approved for marketing in schizophrenia, are prescribed for almost all *DSM* syndromes. Similarly, selective serotonin reuptake inhibitors (SSRIs) were first developed and indicated in MDD, and later in anxiety disorders and post-traumatic stress disorder (PTSD). For example, quetiapine is prescribed as a hypnotic at approximately 50 mg/day, as an antidepressant at 150 to 300 mg/day, as a mood stabilizer at 400 mg/day, and as an antipsychotic at >600 mg/day.

The advent of modern psychopharmacology and of phenomenologically-based diagnostic system(s), starting with *DSM-III*, has inadvertently created mutual validation between diagnosis and psychotropic drugs (see ref 12, p 241). Along these lines, DA receptor-blocking antipsychotics are indicated for schizophrenic psychosis, and individuals whose psychosis ameliorated in the course of antipsychotic administration are likely to be diagnosed with schizophrenia. A similar relationship has been postulated between MDD and tricyclics (TCAs) or selective serotonin reuptake inhibitors (SSRIs). At the time, the simplistic explanation that specific psychotropics reverse a putative monoaminergic neurotransmitter disturbance, which is central in the mental illness for which the drug has been indicated, was hardly disputed. DA hyperactivity, later to be replaced by DA dysregulation,[13] was at the basis of the DA-blocking drugs' beneficial effect in schizophrenia. A similar dysregulation of noradrenergic/serotonergic neurotransmission was invoked to account for SSRI and TCA benefits in MDD.[14] Although hundreds of nonreplicable and negative studies been published since, and the field has moved into genetic markers such as single nucleotide polymorphisms and copy number variations, the simplistic monoaminergic hypotheses, which emerged in the 1970s, have not yet been fully dislodged.

Splitting and lumping

The most vociferous critics of drug development and of regulatory approval based on *DSM* syndromes have raised the possibility that stakeholders in the treatment of mental illnesses unnecessarily split and repackage syndromes to

justify psychotropic overprescribing. According to this view, for example, the definition of MDD in *DSM-III* and subsequent revisions is overinclusive, comprising individuals with transient sadness. Furthermore, by lumping melancholic depression with mild-to-moderate anxious depression into MDD, *DSM-5* has created a widely heterogenous syndrome devoid of biological common ground.[15] This on the one hand, accounts for the large proportion of MDD patients treated with antidepressants who do not respond to treatment.[16] On the other hand, a considerable number of individuals who are clearly in need of treatment will not get it because they will never meet any *DSM* criteria for a mental illness. For example, almost 80% of youngsters frequenting Schizophrenia Prodromal Clinics and considered at high risk for schizophrenia will never progress to schizophrenia and many will never suffer from a classifiable mental illness. Yet, they manifest apathy, avolition, dysthymia, and negative symptoms, to name a few.[17] A departure from the *DSM*-driven drug development or a more flexible approach would be an incentive to develop drugs for such populations.

Disease-centered approached vs drug-centered approach

A few scientists have called into question the disease-centered approach, by which psychotropics are indicated for specific psychotic disorders or for MDD or GAD, and propose a drug-centered approach. The claim is that substances with psychotropic properties do not reverse an imbalance or an abnormality, which is responsible for the aberrant behaviors or emotions, but rather create a de novo mental status in both ill and healthy individuals. For example, amphetamine-like compounds improve temporary concentration and sociability in healthy individuals and in Alzheimer's disease or post-stroke apathy/social withdrawal.[18] Likewise, DA-blocking psychotropics reduce reactivity to environment stimuli or internal emotions in healthy individuals and in almost all disorders classified by *DSM*. Also, effective psychotropic drugs such as benzodiazepines have been developed much before the modern diagnostic systems existed, and were prescribed, transdiagnostically, to individuals who do not qualify for any *DSM* diagnosis, individuals suffering from insomnia, anxiety, depressed mood or psychotic agitation.[19] To fully understand and take advantage of the effects of psychotropics, a drug-centered approach is suggested. Accordingly, trials involving normal controls (Phase 1 of development) should be much more extensive than the current practice and only when all the effects and adverse effects on normal behavior are well understood should psychiatric patients be involved in trials.

The monoaminergic hypothesis and *DSM*

It is reasonable to assume that the link between *DSM* diagnosis and indicated psychotropics has gained popularity because in the late 1970s the field was trying to make the best of the available scientific knowledge and to replace the scientifically ambiguous psychoanalytic explanations to the etiology of major mental disorders. While it was clear that the monoaminergic hypotheses explaining the link between psychotropics and major mental disorders would not replicate the link between spirochete, penicillin, and the mental manifestation of syphilis,[20] it still reflected plausible, incremental scientific progress. This in turn allowed the providers of mental health care the comfort of leaning on what appeared to be solid scientific foundations which also fitted the medical model.

In daily clinical practice, patients approach physicians with the expectation that they may get relief from their pain and anguish. The providers of mental health care, and in particular psychiatrists, are aware that on one hand they operate in an environment of high diagnostic and therapeutic uncertainty, and on the other hand, that the therapeutic response to any psychotropic drug represents the sum of both the drugs' pharmacological effect and the placebo effect. Clearly, acknowledgement of the poor link between the psychotropic mechanism of action and the assigned *DSM* diagnosis would deprive patients of the full power of the placebo effect.[21]

The weak relationship between *DSM* psychiatric syndromes and psychotropics indicated for them, has not been ignored by regulators. Paul Leber, MD, who headed the relevant division of the FDA between the early 1980s and late 1990s, fully acknowledged that the *DSM* syndromes were poor reflections of true biological processes, if at all. In his view, the *DSM* was an expedient, available way in which the FDA could communicate to practicing prescribers about the general characteristics of the patient populations most likely to benefit from a particular psychotropic (see ref 15, pp 22). Along the same lines, the EMA is continuously updating its development recommendations to address transdiagnostic development.[22]

Potential solutions

The general idea for revising the relationship between psychiatric syndromes and drug development is to (a) identify basic symptoms that manifest trans-diagnostically across *DSM* syndromes, (b) identify biological circuits or genetic-molecular processes and markers common to these manifestations, and (c) devise therapeutic interventions that engage targets common to these circuits and/or genetic-molecular processes.

Research Domain Criteria (RDoC)
Research Domain Criteria (RDoC) is an initiative of the US National Institute of Mental Health (NIMH), and is such an approach. It proposes to divide current *DSM* syndromes into simpler, more basic, observable manifestations, for which measurable physiological correlates can be devised (see article by Cuthbert in this issue, p XX). The assumption is that observable behaviors and emotions, and their respective neurobiological measurable correlates, span across multiple *DSM* disorders.

The RDoC includes five domains: Negative Valence or response to threats, Positive Valence or response to expected rewards, Cognitive Systems, Social Processes, and Arousal/Regulatory Systems. The Negative Valence construct, or potential threat/anxieties, is present in *DSM* under phobia, panic, social anxiety, PTSD, and GAD, as well as in schizophrenia, autism spectrum disorders, MDD, and substance use disorders. Genetic, neurochemical, imaging, electrophysiological, observational, and self-reported data all converge upon commonalities in the abovementioned *DSM* syndromes.[4] Benzodiazepines, which bring partial relief in all syndromes related to Negative Valence, are widely prescribed in clinical practice.

Impairment in Cognitive Systems, from very mild to severe, manifest in almost all *DSM* syndromes.[23] It is unclear whether manifestation of cognitive impairments such as for example, these manifested in schizophrenia, reflects the coincidental occurrence of two abnormalities in the same individual—psychosis and cognitive impairment—or derives from the same biological abnormality.[24] Assuming the former, it is likely that the same pharmacological intervention could improve cognition in individuals at the lower level of normality without a *DSM* disorder, as well as in cognitively impaired individuals with schizophrenia, MDD, or any other mental disorder[25,26] along the lines of a drug-centered approach.[27]

Psychiatric Ratings using Intermediate Stratified Markers
Psychiatric Ratings using Intermediate Stratified Markers (PRISM) is a European Union-funded initiative, similar to the RDoC, intended to investigate the common and the distinct biological background of social withdrawal in schizophrenia, MDD, and Alzheimer disease (AD), and to design the regulatory path to develop drugs for social withdrawal across syndromes.[28] Social withdrawal is among the earlier, often persistent and disabling manifestations of schizophrenia, MDD, and progressive brain degenerative disorders such as AD; hence the need to investigate treatment for this condition.

However, social withdrawal is a complex behavior which can be modulated by aging, concomitant medical diseases, and social, vocational, and economic circumstances. A more basic component of social withdrawal is disturbance in motivation which, like social withdrawal, is manifested in stroke,[29] traumatic brain injury,[30] schizophrenia, and MDD.[31] Disturbance in motivation has created a nomenclature conundrum for both researchers and clinicians such as apathy, avolition, anhedonia, negative symptoms. While each label reflects a slightly different clinical manifestation, there is a large phenomenological and biological overlap in particular between apathy, avolition, and anhedonia.

Apathy, avolition, and anhedonia reflect an abnormality in which reward is processed in order to motivate behavior. To motivate behavior, it is necessary to be able to anticipate reward, generate options for behavior, evaluate the options in terms of effort/risks and other costs all this versus the potential rewards. Any disruption along this chain might generate apathy and/or anhedonia and therefore can be a target of putative treatment. DA, noradrenaline (NE) and serotonin neurotransmission was shown to play a role along this chain suggesting that pharmacological manipulation of the neurotransmission might have a beneficial effect.[32] Apathy and anhedonia manifests in >19 *DSM-5* syndromes.[33] Looking beyond the restrictions of the *DSM* system, it might be possible to develop a drug to treat to treat these conditions trans-diagnostically. L-dopa[34] methylphenidate,[35] bupropion,[36] and modafinil[37] are examples of drugs which affect monoaminergic neurotransmission and have been used in single case series as well in some RCTs

in an attempt to treat apathy/avolition. Although a large number of reports of individual patients benefiting from such interventions exist, and a large RCT with methylphenidate is ongoing,[38] for the moment, none of these drugs has produced consistent benefits. A sigma$_2$/5HT$_{2A}$ antagonist compound currently in development has shown superiority over placebo in negative symptoms in schizophrenia, including apathy,[39] which translated into improvements in social performances.[40] If indeed this type of compound can affect a specific component of apathy it is reasonable that future studies investigate its effect in apathy associated with brain degenerative disorders, MDD, and other developmental disorders.

Conclusions

The current trend to identify basic symptoms that manifest transdiagnostically, investigate biological circuits or genetic-molecular processes and markers common to these manifestations, and develop drugs that engage targets common to these transdiagnostic circuits and/or genetic-molecular processes should be encouraged. *DSM* and similar classifications should be mainly used for communication as they were initially intended.

However, several notes of caution are pertinent before reliance on *DSM* classification as a guide to drug development is abandoned. First, decomposing complex behaviors and emotions like the ones reflected by *DSM* into basic functions such as working memory and then relating it to a biological marker such as reactivity as measured during a functional magnetic resonance imaging (fMRI) as suggested by the RDoC initiative is not the end of the road (Weinberger, in this issue p XX). Individuals with similar fMRI reactivity can manifest distinctly diverse phenomenology.[41]

The attractive hypothesis of one cause for one disease pioneered by Koch and Pasteur has been disappointing in explaining the causes of mental illnesses.[42] Genetic and genetic environmental interaction studies have demonstrated that the same phenomenological manifestation can result from almost infinite numbers of combinations of single-nucleotide polymorphisms (SNPs), frequently reacting to ever-changing environmental circumstances. A much better understanding of the normal and abnormal brain functioning is necessary before diagnostic classifications can truly reflect pathophysiology. Second, for any novel classification to be helpful it has to be first adopted by the community of prescribers. Currently, terms like RDoC Negative or Positive Valence do not define a patient population for whom the average prescriber can prescribe a specific psychotropic. It is likely that for the foreseeable future *DSM* will remain a useful tool for drug development, yet all stakeholders should be aware of its limitations and maintain the necessary flexibility to develop, approve, and use in clinical practice psychotropics which might be effective transdiagnostically. ■

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