What Did We Learn from Research on Comorbidity In Psychiatry? Advantages and Limitations in the Forthcoming DSM-V Era

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Abstract: Despite the large amount of research conducted in this area over the last two decades, comorbidity of psychiatric disorders remains a topic of major practical and theoretical significance.

Official diagnostic and therapeutic guidelines of psychiatric disorders still do not provide clinicians and researchers with any treatment-specific indications for those cases presenting with psychiatric comorbidity. We will discuss the diagnostic improvement brought about, in clinical practice, by the punctual and refined recognition of threshold and subthreshold comorbidity. From such a perspective, diagnostic procedures and forthcoming systems of classification of mental disorders should attempt to combine descriptive, categorical and dimensional approaches, addressing more attention to the cross-sectional and longitudinal analysis of nuclear, subclinical, and atypical symptoms that may represent a pattern of either full-blown or partially expressed psychiatric comorbidity. This should certainly be regarded as a positive development. Parallel, continuous critical challenge seems to be vital in this area, in order to prevent dangerous trivializations and misunderstandings.

Keywords: DSM-V, comorbidity, spectrum, anxiety, mood disorders.

I. HISTORICAL PERSPECTIVES ON COMORBIDITY TOWARDS DSM-V

Despite the large amount of research conducted in this area over the last two decades, comorbidity of psychiatric disorders remains a topic of major practical and theoretical significance [1-4]. As more systematic attention has been devoted to psychiatric diagnosis in general, psychiatric comorbidity has imposed increasing consideration, and the high frequency of multiple diagnoses has discredited the popular assumption in the 70' and 80' [5, 6] that a particular patient is unlikely to have more than one disorder. However, even after its fine-tuning through successive editions, the current edition, DSM-IV [7], represents only a fraction of clinical reality. In DSM-IV-TR [8], clinicians find categories defined appropriately by descriptive, observable definitions; they also find that the boundaries of any given category are an inadequate match with the patients they treat. Within this context, the presence of Axis I and II psychiatric comorbidity and the frequent presentation of atypical and subclinical symptoms are probable major reasons for failure to match patients with the DSM-IV's discrete, categorical, prototypes of mental illness.

Given the short history of the term comorbidity, there are a surprisingly large number of definitions. Feinstein [9] coined the term comorbidity to mean "any distinct additional clinical entity that has existed or that may occur during the clinical course of a patient who has the index disease under study." Strictly speaking, use of the term is restricted to diseases or disorders, not symptoms. Symptoms can associate or co-occur, but they are not comorbid with disorders or with each other. In psychiatric epidemiology, the term comorbid is used somewhat differently, the emphasis being on relative risk. When a patient has a particular index disorder, there may be a relatively greater or lesser risk of other disorders being diagnosed or other symptoms observed.

Clinical studies also use the concept of comorbidity in the sense that more than one disorder can be diagnosed in the same individual. In addition, any individual who meets the full diagnostic criteria for only one disorder may still have an increased frequency of symptoms from other categories, but to an extent that is insufficient to diagnose another disorder. Diagnostic studies may identify symptoms or relationships between syndromes that improve diagnostic precision by increasing the discriminant power of diagnostic criteria.

Kaplan and Feinstein [10] also introduced a number of distinctions about types of comorbidity to clarify the concepts of comorbidity that arise in medicine in general and, possibly, in psychiatry. They distinguished between pathogenic, diagnostic, and prognostic comorbidity. Pathogenic comorbidity arises when a particular disease leads to certain other complications or diseases, which are therefore considered to be etiologically related. Diagnostic comorbidity is likely whenever diagnostic criteria are based on patterns of symptoms that are individually nonspecific. Disorders that predispose the patient to develop other disorders have prognostic comorbidity.

It is often difficult to distinguish these subtypes of comorbidity, however, unless the pathogenesis of the disorder is well understood, which rarely happens with psychiatric disorders. The proper terminology—comorbidity versus some other word or phrase—is not unanimously accepted. George Winokur [11], for example, preferred co-syndromal

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or use of the primary–secondary distinction over comorbid. The multiple uses of the primary– secondary distinction have been further discussed extensively in Maser *et al.* [12]. In medical terms, comorbidity conveys, at least in part, the notion of a disease process. Disease is produced by pathogens, but despite the suspicion of many, as said before, there are very few pathogens known to underlie the mental disorders described in DSM-IV. Co-syndromal is a more technically accurate term, and the temporal definition of the primary– secondary distinction has value. We could also use the term co-occurrence or concomitance or, more simply, association. Notwithstanding, in line with current usage, we shall continue with the term *comorbid* in relation to mental illnesses, even when there is no known pathogen.

In psychiatry, comorbidity appears to be the rule rather than the exception. Numerous studies of clinical samples of inpatients and outpatients [13-17] have evidenced the large proportion of patients who simultaneously meet diagnostic criteria for more than a single disorder, both within axis I and between axes I and II of the DSM-III-R [18]. Similarly, multiple diagnoses within individual subjects appear to be quite frequent in epidemiological surveys conducted in the general population [19-21].

Two major approaches have been employed to classify multiple diagnoses within a single individual: (1) assignment of a primary and secondary diagnosis based on order of onset; and (2) application of hierarchical diagnostic systems in which one condition is inferred to supersede the other. The former approach is preferable because no preconceived etiological assumptions regarding the relationships between disorders are necessary. However, the primary–secondary distinction may be difficult to apply to the assignment of retrospectively ascertained lifetime diagnoses, which require accurate determination of the age of onset of disorders that often emerge in an insidious manner. The latter approach has not been applied consistently across studies because of difference in the hierarchical structure of the diagnostic systems employed. Moreover, hierarchical relationships may often belie clinical data. The elimination of hierarchical relationships between many of the disorders in the DSM-III-R [18] criteria facilitated the assessment of relationships between two or more disorders.

Within this framework, it is plausible that we will not see substantial changes in the forthcoming DSM-V (http://www.dsm5.org). More emphasis will be certainly given to a dimensional characterization for each individual diagnosis. In other words, in the DSM-V it will be partially acknowledged the potential utility of incorporating dimensional elements into our diagnostic classification systems. However, no strong proposals are likely to emerge with regard to exactly how dimensional classification will interface with DSM classical diagnostic approach. In particular, we will see the introduction of dimensional severity ratings to the extant diagnostic categories and/or the constituent symptom criteria. Compared to more drastic approaches (e.g., multi-dimensional assessment, in which categorical diagnostic labels are subsequently imposed on the basis of quantitative algorithms), the "severity" specifiers introduced in the DSM-V for most anxiety and mood disorders would be relatively practical because the categorical system would remain

intact and the dimensional rating system could be optional in settings where its implementation is less feasible (e.g., primary care).

Several potential advantages of this 'not-full' dimensional approach were noted including the ability to address key shortcomings and sources of unreliability in the DSM, such as its failure to convey disorder severity as well as other clinically significant features that are either subsumed by other disorders (e.g., GAD in mood disorders and PTSD) or fall just below conventional thresholds due to a DSM technicality (e.g., subclinical or NOS diagnoses where the clinical presentation is a symptom or two short of a formal disorder). Moreover, because the dimensional ratings would be added to the current diagnostic categories, this approach would have other advantages including: (a) its basis on a pre-existing and widely studied set of constructs; and (b) the ability to retain functional analytic and temporal (duration) aspects of diagnosis that are difficult to capture in a purely psychometric approach (See Table **1** below).

Such an approach will provide a standardized assessment system that would foster across-site comparability in the

Table 1. Rationale for Severity Measure for Panic Disorder*

Panic Disorder Severity Scale-Self Report
Seven items rated on 0-4 severity scales: panic attack frequency, panic attack distress, anticipatory anxiety, agoraphobic avoidance, interoceptive avoidance, work/home impairment, and social impairment.

*From the proposed revision section for Panic Disorder (http://www.dsm5.org /ProposedRevision)

study of dimensional models of psychopathology. Therefore, this approach could be regarded as a prudent "first step" in the direction of the feasibility of more ambitious dimensional systems.

Nonetheless, the DSM-V initial proposal is not without immediately apparent limitations. For instance, as noted earlier, "difference in patient report" (i.e., patient gives different information to independent interviewers in response to inquiries about the presence, severity, or duration of symptoms) is a very common source of diagnostic unreliability that would be relevant to dimensional clinical assessment. In fact, because the dimensional ratings would simply be added onto the existing criteria sets, most sources of unreliability present in the current diagnostic system would continue to be germane (e.g., measurement error associated with vaguely operationalized symptom criteria and differential diagnosis decision rules; see GAD example in preceding paragraph). Perhaps more importantly, because the various disorder categories would remain unchanged, a dimensional system of this nature would not address the problem of high diagnostic comorbidity.

II. THRESHOLD AND SUBTHRESHOLD COMORBIDITY

During the last two decades, most epidemiological and clinical studies on comorbidity, focused on "threshold" comorbidities; that is, the coexistence of two or more DSM-IV Axis I disorders in the same individual in a defined period of time (lifetime, 6 months, 1 month).

Table 2. Possible Explanations for the Co-occurrence of Two or more Comorbid Psychiatric Disorders

Both Disorders are Reflection of the Same Phenomenon
1. Both conditions are reflections of the same phenomenon.
2. One of the two conditions is a mere reflection of the other.
3. One of the two induces changes that lead to the other.
Common Factor for Both Disorders
1. Vulnerability hypothesis.
Artefact of Diagnostic Criteria
1. Comorbidity due to overlapping criteria.
2. Comorbidity due to one disorder encompassing the other.
The Comorbid Disorders are Two Separate Entities
1. They can be either one or the other.
2. They may appear together (comorbidity viewpoint).
3. Each can appear at threshold or subthreshold level. Any combination is possible (mixture subsyndromal viewpoint).
4. Comorbidity is a common final pathway of two distinct conditions.

Adapted from Klein and Riso (22).

In spite of the large amount of studies, it is still unclear whether the co-occurrence of two or more mental disorders in the same person reflects the presence of pathophysiologically independent entities.

High levels of comorbidity raise questions about the specificity and the boundaries of certain diagnostic categories and provide important clues to the etiology, pathophysiology, and phenomenology of both the index and comorbid disorders. Klein and Riso [22] argued that there are at least four theoretical models of comorbidity that may explain the simultaneous co-occurrence of two or more mental disorders in the same individual: comorbidity due to sampling bias, artifacts of diagnostic criteria, drawing boundaries in the wrong place, and common etiological relationships (see Table **2**). The concept of comorbidity is a valid and important clinical construct to capture and depict different components of psychopathology.

The amount of comorbidity may be influenced in different ways. First, the exclusion of hierarchical rules in the classification of mental disorders and the separation of a more pervasive condition into more specific conditions may increase comorbidity rates. Second, the period of time through an individual's lifespan when a disorder is present can affect comorbidity. Third, the definition of a threshold for a diagnosis may also sensitively affect levels of comorbidity as low threshold tends to increase prevalence rates, while high threshold tends to decrease prevalence rates.

This issue becomes problematic when considering "subthreshold" comorbidities. Clinical correlates of subthreshold forms of anxiety and their relationship with other mental disorders have not, to our knowledge, been investigated systematically.

Krueger and Marcon (2) supported a liability spectrum model of comorbidity. According to their theorization, spe-cific mental disorders are understood as manifestations of latent liability factors that explain comorbidity by virtue of their impact on multiple disorders. This theory is based on application of modern statistical models to vast samples of individuals. Nevertheless, from a clinical perspective this approach is not so distant from reappraisals of older theorizations. For example, it was argued that in the majority of patients with a "neurotic syndrome," symptoms drawn from two or more diagnostic categories on the basis of predominant features would often be found. In such cases, the diagnostic groups may overlap or fade into another. Therefore, neurotic disorders have been hypothesized to occur generally among individuals who show deviations along a number of independent dimensions, which may predispose them to anxiety, obsessive symptoms, or depressive disorders, as well as other emotional disorders. In many cases, it may be difficult to disentangle the specific components of such neurotic syndromes [23].

III. IMPLICATIONS OF SPECTRUM APPROACH FOR COMORBIDITY

The difficulty, if not the impossibility, of classifying many patients with multiple disorders into one of the DSM categories has spawned a variety of other procedures to cope with clinical reality. These include use of the primary–secondary distinction, multiple diagnoses, use of both axes I and II, associated features of a disorder, and the spectrum of a disorder concept [24-28]. The term spectrum has been traditionally used to underlie relationships among clusters of symptoms or to place defined syndromes in relation to one another. In the 90's, the "Spectrum Model" of psychiatric disorders evolved (initially with the "panic-agoraphobic spectrum") at the University of Pisa, and has been further developed in collaboration with researchers from the University of Pittsburgh and elsewhere in the United States (www.spectrum-project.org) [29]. In a broader way, such a Model can bring coherence to complex psychiatric symptoms, and include: (1) core, atypical, and subclinical symptoms of the primary axis I disorder; (2) signs, isolated symptoms, symptom cluster, and behavioural patterns related to the core symptoms that may be prodromal, may represent a precursor of a not-yet fully expressed condition, or may be sequelae of a previously full-fledged disorder; and (3) temperamental and/or personality traits. . This approach has the potential to answer to various problems that arise by splitting disorders into narrow, distinct, nonoverlapping diagnostic entities, like: (1) failure to encompass subthreshold and atypical symptomatology; (2) artificial enhancement of comorbid diagnosis; and (3) failure to replicate genetic markers of narrow, restrictive phenotypes. Furthermore, the spectrum approach gives clinical weight to low-severity and isolated symptoms that either appear alone or occur concomitantly with a major disorder [30-33].

Spectrum symptomatology may be viewed as the part of the iceberg that is hidden beneath the surface of the water, while the core, diagnostic criteria symptoms represent the obvious, visible portion. Of course, the various conditions may evidence substantial overlap in terms of individual symptoms, and symptoms of mood spectrum may overlap with anxiety disorders spectrum symptoms [34, 35], substance abuse [36], as well as with what we have termed the

separation anxiety spectrum [37], and derealisation/depersonalization symptoms [38, 39].

Potential uses for the spectrum approach may include the improvement of treatment selection, development of better strategies for outcomes measurement, monitoring the course of illnesses, strengthening of therapeutic alliances, and improvement in subtyping of patients for clinical, biological, and genetic research [40].

IV. IMPLICATIONS FOR TREATMENT AND FUTURE DIRECTIONS

In spite of general awareness that the term 'comorbidity' is a straining word for the clinician, conceptually, it is still clearly important in patient management and treatment. Failure to classify and analyze comorbid disease can create misleading clinical statistics and may cause spurious comparisons during the planning and evaluation of treatment for patients. Comorbidity can alter the clinical course of patients with the same diagnosis by affecting the time of detection, prognostic anticipations, therapeutic selection, and post-therapeutic outcome of an index diagnosis. Also, the presence of soft signs and symptoms belonging to the spectrum of other disorders (observed over a lifetime) if systematically overlooked, may lead to a bias in selecting an appropriate treatment strategy. For example, in a hypothetical trial for an anti-panic medication, a panic patient, who has obsessive symptoms but lacks one symptom to fulfil the criteria for OCD, is included in the trials as well as a patient without obsessive traits. Practical consequences may include poor knowledge about the spectrum of action of the treatment, difficulty in predicting response to the treatment, and/or atypical outcomes.

The DSM-IV does not suggest specific treatments for each disorder category and subcategory. However, modern treatment researchers—psychosocial and psychopharmacological—have attempted to design treatments tailored to specific DSM categories. The strategy links treatment to diagnosis, and we may expect this strategy to succeed to the extent that the targeted DSM-IV classification is valid. It is possible that treatment researchers will successfully design treatments that fit DSM-IV categories but fail to treat their patients successfully because the categories do not completely represent the patients. To the extent that comorbidity presents a challenge to the official nomenclature, it presents a similar challenge to treatments designed and targeted for DSM categories.

Clinicians who seek only the diagnostic criteria for a specific disorder, with rigid adherence to the DSM-IV diagnostic criteria, and by extension, the DSM-IV categories, will probably miss a more global perspective of the entire pathology. Such a narrow perspective is mainly justified in research, but is unacceptable in clinical practice. The DSM-IV was conceived, at least in part, as a research tool, allowing common, standardized, and atheoretical communication among clinical investigators. But the DSM-IV is also used as a clinical manual when the practitioner is face to face with the patient. A more integrative approach that takes comorbidity into account should not only reflect a more valid psychiatric classification, but should also improve treatment and treatment outcome.

Evidence for the dramatic intrusion of comorbidity phenomena (axis I and spectrum comorbidity) in psychiatry has been derived from several sources, including epidemiological, pharmacological, clinical, and genetic studies. Despite this broad body of evidence, proponents of the categorical approach do not take into account subclinical symptomatology that coexists with the disorder, overlooking the complex degree of mixture among the different symptoms [41].

We have discussed the diagnostic improvement brought about by the punctual and refined recognition of subclinical and atypical comorbidity. Another relevant consequence involves therapeutic strategy, as comorbid syndromes often require different acute, continuation, and maintenance doses as well as a distinct timing of administration and suspension of the treatment. It is not difficult to believe that drug targets in the brain are different in different patients; for example, a patient with a pure disorder compared to a patient with the same disorder plus spectrum symptoms of panic and/or obsessive-compulsive disorder. However, official guidelines for the therapy of depression and bipolar disorders still do not provide clinicians and researchers with any treatment-specific indications, devoting relatively little attention to the clinical importance of comorbidity, treatment strategies, and outcome. Also, the reliability of clinical trials can be questioned in light of a more descriptive approach as pharmacological trials are usually conducted with patients whose symptomatology fits a particular diagnosis coded by standardized criteria.

Diagnostic procedures should attempt to combine descriptive, categorical and dimensional approaches, addressing more attention to the cross-sectional and longitudinal analysis of nuclear, subclinical, and atypical symptoms that may represent a pattern of full-blown and partially expressed comorbidity. Within this conceptual framework, psychopathology can be more specifically approached in clinical terms of either individualized treatment or prevention. Furthermore, some traditional points of weakness of clinical psychiatry and psychology, for example, chronic forms of illness and treatment-resistant depressions, may be contrasted more successfully.

CONFLICT OF INTEREST

The author confirms that this article content has no conflicts of interest.

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