There are no patients without comorbidity

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In 1980, a small task force of the American Psychiatric Association (APA) produced a new classification of psychiatric diagnoses, the DSM-III, addressing the need to define operational criteria for mental “disorders”. Being aware of the difficulties in formulating valid disease models due to the lack of knowledge about the pathogenesis of most psychiatric “disorders”, the drafters of DSM-III recognized the intrinsic limitations of the proposed constructs, which were considered no more than hypotheses to be validated through research. Over the next 40 years, a lot of research has been conducted and the results have been almost unequivocal: the proposed diagnostic categories are not valid as they identify heterogeneous syndromes in terms of pathogenesis, clinical course and treatment response. Even the idea that operational criteria would lead to good diagnostic reliability proved to be optimistic in research settings, if not wishful thinking in clinical practice.

The approach just described has favoured the proliferation of diagnostic categories, leading to the creation of a few hundred possible “disorders” with blurred, confusing boundaries. Some disorders, while describing the same patient from different perspectives, are inserted into separate chapters; for example, generalized social phobia is placed among the anxiety disorders, while the avoidant personality is to be found among the personality disorders. At the same time, complex clinical presentations with a broad constellation of symptoms may lead to multiple diagnoses in the same subject. Especially in clinical settings, most patients receive multiple diagnoses – a procedure that dramatically raises estimates of "comorbidity", which becomes the rule rather than the exception. As a result, many cases receive different diagnoses from different observers, depending on the training of the doctor who writes the diagnosis rather than directly reflecting their clinical picture.

Although these limitations have been widely acknowledged by many clinicians and researchers, in 2013 the DSM-5 international task force ended up by proposing substantially the same diagnostic categories as those presented in the previous editions (Vieta, 2016). The minor changes proposed, often aimed at broadening certain categories and narrowing others, were the result of political bargaining between the "supporters" of each diagnosis, rather than the result of the research evidence. Of course, a "political consensus" between the experts is hardly likely to achieve progress; it has, in fact, never done so in the history of human knowledge. What is surprising, however, is an attitude of grandeur displayed by the committee, which defines the DSM-5 as “an essential tool upon which (sic!) both research and clinical practice must be founded”. In spite of the huge amount of evidence that supports the opposite view, the suggested “mental disorders” end up being considered by the task force as real diseases, with supposed distinct and homogeneous pathogenesis and therapeutic implications.

Some Authors argue that psychiatric comorbidities often constitute an artefact due to current diagnostic systems (Maj, 2005). The presence of comorbidity in almost all patients with psychiatric

disorders observed in clinical settings seems to strengthen this hypothesis. Mood and anxiety disorders are the conditions most often found in comorbidity, but high rates of comorbidity are also found with neurodevelopmental, substance use, eating and personality disorders. Bipolar disorder has been confirmed in several meta-analyses to be highly comorbid, mainly with anxiety, eating, and substance use disorders (Loftus et al., 2020; McIntyre et al., 2020). The more attenuated forms of the bipolar spectrum, such as cyclothymia, largely overlap with cluster B or C personality disorders. Furthermore, patients with neurodevelopmental disorders (e.g., autism spectrum disorders, attention-deficit/hyperactivity disorder), through various developmental pathways, evolve and then develop complex clinical pictures in adult life that are often diagnosed as comorbid psychotic, mood, personality, anxiety, eating, and substance use disorders (Perugi et al., 2019).

Comorbidity with substance use disorders (dual diagnosis) is today observed in a large proportion of patients with mood and psychotic disorders. Compared to those without this comorbidity, patients with dual diagnosis have shown differences in many variables, including reduced treatment response to specific medications for mood or psychotic symptoms (Krause et al., 2019). Drug addiction and addictive behaviors (including many eating disorders) increase rapidly during adolescence, peaking in the early to mid 20s', and are present in almost all mood and psychotic patients with a history of neurodevelopmental disorders, such as attention-deficit/hyperactivity disorder and/or emotional dysregulation (Perugi et al., 2019). Future etiological hypotheses, diagnostic models and therapeutic strategies need to go beyond the current nosography by addressing the developmental processes underlying these complex (multiple "comorbid") clinical presentations.

In conclusion, with current diagnostic systems, almost all psychiatric patients end up receiving multiple diagnoses, which may vary from physician to physician. In addition, artificially dividing a complex clinical condition with demarcations that do not exist in nature prevents a holistic approach to patients and encourages unwarranted polypharmacy.

The use of 'wrong' definitions for largely overlapping phenotypes is certainly one of the main reasons why research on brain biochemistry, refined techniques of neuroimage and molecular genetics did not provide the desired results, so failing to validate or improve diagnostic and therapeutic models for mental disorders. In other words, when using the current diagnostic categories it may not be unusual to find patients with the same disorder showing differences in biological markers, and patients with different disorders sharing much of the hypothetical pathogenetic chain. Nonetheless, this information is still helpful to the clinician. We don't always expect similar responses when treating patients with the same syndrome. For example, many depressed patients may feel better when they take an antidepressant, while others do not respond at all, or get worse, becoming suicidal; it is feasible that they have different responses to the drug, but there's still a chance

they do not have the same disease. On the other hand, patients with different clinical pictures could improve with the prescription of the same medication, confirming the non-specific and transdiagnostic action of many psychotropic drugs, as well as the low validity of current diagnostic categories (Solmi et al., 2020).

Relying exclusively on the current diagnostic categories seems to be an insurmountable obstacle, not only for the understanding of the pathogenesis of mental diseases, but also for the discovery and implementation of new therapeutic tools. Indeed, the current diagnostic categories, tailored to the potential response to existing drugs, are a barrier to the development of new therapeutic strategies.

After the introduction of new-generation antidepressants and antipsychotics, which were not really different, but in many cases more manageable than their predecessors, psychiatry has reached a condition of real "therapeutic stagnation" (Schumann et al., 2014). It is unlikely that a drug, even if very effective in a small subset of patients with a certain disorder or with several disorders underlying common factors, can prove to be effective in all patients who meet the criteria of that disorder and, thus, be patented. In addition, the comparative and efficacy studies concerning physical or psychological therapies are strongly limited by the use of categories built specifically for pharmacological and/or cognitive-behavioural interventions. For example, severe and psychotic mixed states and catatonia, which are classically recognized to be non-responsive to drugs, but may respond very well to electroconvulsive therapy (ECT)(Perugi et al., 2020; Valentí et al., 2008), in DSM-5 are just considered as specifiers.

In our view, the correct assessment of a psychiatric patient is favoured by the use of a widely syndromic model based on descriptive psychopathology and, whenever possible, on known or hypothesized neurophysiological foundations. Despite the difficulties encountered in formulating valid models of disease, a syndromic and ‘transdiagnostic’ approach could provide an alternative pathway for the clinical framing of the individual patient, so favouring the use of targeted therapies. This is the essence of ‘personalized’ psychiatry, which may make possible a feasible perspective for the development of a new taxonomy of mental illnesses.

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