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### Mental health: Transdiagnosis versus comorbidity

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#### Abstract

**Background and objectives:** With the old concept of unitary psychosis as a precedent, it is quite usual nowadays to speculate with a similar and much more generalised concept in the mental health field: “transdiagnosis”.

**Methods:** This study is an original narrative, qualitative research, containing inclusive and interpretative components. It will present a critical analysis and provide a reasoned technical opinion on selected, high-quality scientific literature.

**Results:** With regard to the nosotaxis of mental illness, in the near future, a biomarker-based nosology will be a key component of a foreseeable and innovative precision psychiatry. Alternatively, the so-called hierarchical taxonomy of psychopathology, as well as other similar models, tends to be based on legitimate considerations that lack proper evidence. The relatively new and widespread transdiagnostic conception transcends and even completely side-lines the limits of traditional diagnosis. Although they tend to represent the “latest trend” on psychological approaches, transdiagnostic propositions have not yet adequately proven their validity. These common dissenting proposals generally choose the dimensional in the constant debate with the categorical. To date, much of the supposedly transdiagnostic work has only investigated symptoms, and not disorders, has looked at only one disorder, or has not provided scientifically and clinically sound information.

**Conclusion:** Scientific evidence has unequivocally demonstrated the need to routinely consider physical and mental comorbid pathologies from multidisciplinary approaches. The classical medical concept of comorbidity cannot currently be replaced by the alternative, frequent concept of transdiagnosis.

**Keywords:** Biomarker; Comorbidity; Mental Health; Nosology; Transdiagnosis Mental Health: Transdiagnosis Versus Comorbidity

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## Introduction

As a branch of nosology or nosography (description), nosotaxy (classification) of mental, behavioural and neurodevelopmental disorders has its limitations. There is considerable heterogeneity in cataloguing of symptomatology, pathophysiology and aetiology. So far there are few and rather mediocre, clear links between most diagnoses and neurobiological findings. It is well accepted, however, that both environmental and genetic factors contribute to the development of these and many other types of disorders.

There are numerous psychotherapeutic programmes that are effective, when carried out by competent practitioners, in subjects with different associated psychopathological diagnoses at the same time. The same is true for psychopharmacological treatments, which can be similar across multiple pathologies and comorbidities. Furthermore, however, the same is true not only for psychiatry, but also for treatments recommended or indicated for various illnesses across the entire, very broad field of medicine.

It is worth bearing in mind what could be considered the anti-nosographic conception from last century by psychiatrists Joseph Guislain and others, such as Spanish psychiatrist Bartolomé Llopi, of “single psychosis” or “unitary psychosis” [1,2]. Such considerations, however, have not to date survived in the scientific community. As it has been for years, it is nowadays again quite usual to speculate in the specific field of mental health using a similar, far more generalised concept, one dubbed with the neologism “transdiagnosis”. Below, we will address this question.

## Material and Methods

This study is based on the most recent, relevant international, high-quality, related scientific literature. It is not a review conventional. This is original narrative and qualitative research, using integrative, interpretative components. I

will offer a critical analysis, along with a reasoned, expert health opinion, based on the best selected technical literature.

The research design is flexible, but the descriptive and analytical process has been constant, referring to the real-world environment. We have scrutinised the databases of *PubMed/Medline*, *Scilit-Scientific Literature* and others. Published information on nosology and classification of mental disorders is immense and wide-ranging. Thus, we have aimed to make this contribution as meta-synthetic, rigorous, panoramic and up-to-date as possible.

## Results

### • Nosotaxy for mental disorders

Biological classification projects for these disorders such as become are underway [3]. In the near future, biomarker-based nosology, possibly including the digital ones just proposed [4], both at the onset of the disorder and even before its clinical manifestations, will be crucial. Biomarkers are defined as anatomical, biochemical or physiological features that are specific to certain disorders or syndromes. Yet one particular attempt has failed: that of finding the wide range of biological and neurocognitive findings that were supposed to help in the search for biomarkers for obsessive-compulsive disorder [5].

Likewise, with a focus on diagnosis and individualised treatment in the emerging, multidisciplinary category of “precision psychiatry”, the utility has been proposed of the new, ultra-high field magnetic resonance imaging (MRI) technology (7 tesla or higher) [6]. Thus, one also tends to think of the foreseeable, upcoming and renewed speciality as a new “technological psychiatry”. This type of MRI could become a diagnostic tool for monitoring the levels of certain metabolites in people who are psychiatrically predicted to be at high risk of developing psychosis.

Taken together, the multimodal neuroimaging perspective may potentially improve the validity of psychopathological diagnoses [7]. Reduced effective connectivity of the anterior insula with the dorsolateral prefrontal cortex is manifested by depressive symptoms, and the inhibitory effect of that cortex on the insula itself is particularly reflected in the paranoid symptoms of schizophrenia [8]. On the other hand, structural abnormalities in the fronto-striatal-limbic and fronto-parietal networks are primary features in patients suffering from the first episode of recurrent major depressive disorder, and may become a promising target for therapeutic interventions [9].

The pioneering public-private initiative *Brain Research Through Advancing Innovative Neurotechnologies* was launched years ago in the US. This project continues to assume that knowledge and mapping of central neural circuits will transform our understanding of multiple behaviours, perceptions, thoughts and emotions [10]. This will be vital for clinical neuroscientific psychophysiology, of enormous significance for current and, above all, future psychiatry and clinical psychology. In particular and at the present time, psychology as a science is rich in paradoxes.

Innovative neurotechnology, including transient neurotechnology, includes artificial devices integrated with neural tissue to mitigate the morbidity burden inherent in neurological and mental disorders. For its part, the ENIGMA-Anxiety Working Group, a global alliance of forty-three countries, has created a synergy at the intersection of mental health and clinical neuroscience [11]. Some call this synergy “translational” to emphasise the interaction between different disciplines.

- Transdiagnosis in psychopathology?

The multifaceted and increasingly common term “transdiagnosis” attempts to describe features that are common to several nosological entities. The concept transcends the boundaries of traditional diagnosis, and even bypasses them altogether. It often focuses on the

disruption of the likewise novel, broad and commonplace notion of “emotional regulation”. Emotion dysregulation refers to complex affective reactions to certain stimuli, which may be similar in different diagnoses [12].

A so-called “hierarchical taxonomy in psychopathology” (HiTOP) is also being advocated, which is an alternative quantitative nosological system to the current ones [13]. The system is based on covariation of symptoms and when they are similar it groups them together to reduce heterogeneity. It establishes a total of six spectra or dimensions in the form of a continuum from normality to pathology. A spectral model including physical diseases [14] can be easily developed, but this do not prove to be actually true. New theoretical approaches to understanding and measuring psychopathological variables have also been proposed, such as the so-called “network analysis” [15]. These and other diverse patterns are variations on traditional biomedicalism, and are furthermore often “anti-biological”.

Indeed, in many places and also in Spain (EU), in order to understand an excessive number and variety of mental disorders, most behavioural and cognitive psychological models reject their biological basis. They avoid it in favour of the socio-environmental, cultural basis and of personal psyche, the latter understood as a product of the former. This happens above all with the practices, assumptions and professional criteria of those who are not officially specialised in clinical practice. It should be kept in mind that there is no clinical psychology speciality that is European, nor American, in scope. It currently exists as a state-regulated health speciality solely in Spain.

Non-specialised psychologists are generalist psychologists – i.e. those who are exclusively graduate or undergraduate psychologists. This includes graduates in “general health psychology”, who have completed a Master’s degree in health psychology. The latter qualification also exists only in Spain. General health psychologists often misleadingly and

confusingly consider, and promote themselves as “specialised psychotherapists”. Indeed, they will only be recognised as such by those who wish to do so, as psychotherapeutic practice is not specifically regulated [16-18]. In medicine, the same is true for general practitioners or other specialties other than psychiatry, which is an official speciality in Spain and the rest of the EU.

Transdiagnostic arguments which are based on solely psychologicistic grounds, preferably with patterns provided by experimental psychology, are also used. Even more philosophical arguments, or else those based on common structural and functional brain neuroimaging in different disorders are used as well [19]. It has been proposed that the increased volume of the putamen, part of the striatum, may reflect a transdiagnostic marker of familial vulnerability to the appearance of symptoms of different psychopathological categories [20]. Whether the putative marker is transdiagnostic rather than of merely comorbidity is an aprioristic and therefore arbitrary decision on the part of the respective authors.

There are indeed similar structural brain abnormalities in different mental pathologies and, in fact, a shared morphometric signature is being sought [21]. Thus, different psychopathologies may involve to varying degrees the same or similar biological substrates of any kind, whether influential or determinant. Non-biological causal factors, such as psychosocial factors, will often also be common. In any case, correlation does not imply aetiology. That said, on the whole, transdiagnostic models of clustered symptoms have not yet adequately proven their validity, even though they are generally stated and assumed to have done so.

With a differing social perception of health, transhumanist-posthumanist philosophical-scientific-social proposals, understood as the nihilist side of modernity, emerged from the end of the last century. The related concept of postmodernism, a detractor of the rationalism that was representative of modernism, is critical

and sceptical of great constructions of thought. For postmodernism, such diagnoses of mental disorders based primarily on their clinical manifestation through signs, symptoms and pathochrony are of that order.

In psychopathology and in medicine in general, as noted above, sharing an aetiopathogenic neurobiological mechanism does not at all imply a transdiagnostic perspective, or a transtheoretical or theoretical integration model, but is entirely compatible with the traditional comorbidity perspective. For specialised clinical psychology in Spain, evidence demonstrating the empirical efficacy and usefulness of specific psychological interventions in certain psychopathological syndromes takes precedence over schools and speculations or theories. The same is true for psychiatry and, in addition, regarding psychopharmacotherapies.

This is, in short, the very topical and commonplace debate between the categorical and the dimensional, an issue of particular importance in relation to mental health. However, it should be emphasised that future categorisations of mental disorders will have to be based on the underlying neuroscience, genetics and epigenetics, rather than exclusively on psychopathology, and therefore need not be particularly symptomatic or dimensional.

The above can affect a multitude of “atypical” praxes that are supposedly therapeutic, or that are clearly pseudo-psychotherapies. This is to be understood as para-scientific interventions which, with “fractal fallacies”, deviate from the most recognised treatments.

The recent *Research Domain Criteria* (RDoC) theoretical framework helps to interpret neuroscience research results, facilitating the detection of differences in genotypes and endophenotypes. It is based on the observation of functional dimensions rather than categorical diagnoses. It is also intended to contribute in the future to a better understanding of the physiopathological mechanisms and

developmental alterations responsible for certain mental pathologies [22].

Similarly, the RDoC model aims to support a precision medical approach to psychiatry in particular, as discussed in the previous subsection. It understands that psychopathology takes place in the domain of the central nervous system. However, this model is still too open-ended and furthermore hypothetical to be useful in the current clinical setting.

There is a growing need to deploy theoretical and practical models that help to better understand the complexity of mental disorders, as well as the mechanism of their evolution and progression. As has been pointed out here, not everyone agrees with the current biomedical model in use, which they consider reductionist because it is too mechanical and deterministic [23].

Even so, criticisms of the historical epistemological construct represented by the biomedical model are based more on reasonable desires for a better, innovative framing of mental disorders than on clear scientific evidence. It is possible, therefore, that we are basically dealing with alternative phenomenological projects which are, above all, speculative, theoretical and based on the supposed discovery of certain disorders which, in a utopian form, would be central or pluri-generators of others.

The psychological disorders most investigated from a transdiagnostic perspective are emotional disorders, i.e. those formally recognised as anxiety and depressive disorders. Specific, consistent and significant associations have been reported between the symptomatology of major depressive disorder, panic disorder and post-traumatic stress disorder [24].

A unified protocol for the transdiagnostic treatment of so-called emotional disorders has also been developed at the University of Oxford (UK), from which more are being derived [25].

Likewise, the *Critical Psychiatry Network* (1999, UK) is strongly critical of biologism and the dominant biomedical model in therapeutic practice.

There are obviously a multitude of psychopharmacological and psychological treatments that are effective for a wide range of mental disorders. Among psychotherapies, the transdiagnostic usefulness of cognitive-behavioural psychotherapy is often emphasised [26,27]. It is also worth recalling the emotion-focused humanistic therapy or experiential psychotherapy of Leslie S. Greenberg, as well as the above-mentioned unified protocol for transdiagnostic treatment by David Barlow, among others. And also the (perhaps pretentiously named) “third generation” therapy, acceptance and commitment therapy (ACT), by Hayes et al, which is on the very borderline of a scientific philosophical stance based on positive science.

Overall, however, the transdiagnostic approach in mental health has so far not generated a credible paradigm shift that can and should affect nosological classification and clinical-therapeutic interventions [28]. It claims to be innovative, evidence-based and up-to-date, but this is far from being a reality, at least not yet. Transdiagnostic research relies more on rediscoveries than real innovations, and is affected by conceptual biases. So far, the transdiagnostic approach in mental health confuses what it should explain with what it explains and demonstrates.

- Comorbidity of mental disorders

Comorbidity, multimorbidity or associated morbidity, first in psychiatry and then in clinical psychology, is a medical term coined in 1970 [29]. Technically, a pathology is considered to be the set of symptoms of a disease or disorder, and symptoms are its manifestation. As a general rule, however, occasional or permanent psychological characteristics of individuals will not constitute a symptom of any disorder. So intellectual, character, emotional and personality

idiosyncrasies, whether or not they are frequent or prominent, need not be indicative of problems that are diagnosable as typical disorders. In general, however, prominent personal psychological conditions with a more negative social significance will be colloquially typified as revealing some hypothetical or confirmed mental disorder. This will be especially true among ordinary people and professionals who are not specialised in mental health.

To date, many studies claiming to be transdiagnostic have investigated merely symptoms and not disorders, or focussed on a single disorder, or do not provide adequate information on any disorder. However, in clinical practice it is very important to assess comorbidities and not just principal diagnoses, which will not necessarily mean that there is a transdiagnostic condition in such cases, but a concurrent condition. In mental health, comorbidities are indeed the norm rather than the exception [30], and are associated with poorer outcomes and more complex clinical management.

For pathologies that are typically neurological, numerous cognitive, affective, behavioural and perceptual symptoms also imply multiple psychopathological diagnoses [31]. Psychological stressors are common risk factors for so-called functional or psychogenic neurological disorders, which may even lead to persistent disabilities over time. In particular, this is usually the case with multiple psychogenic movement disorders and specifically with conversion disorders [32]. We need not recall that for any branch of medicine, including psychiatry, a symptom is not equivalent to a specific diagnostic assessment.

In any case, and by way of example, there is no doubt from scientifically proven models that adult hippocampal neurogenesis is important for learning and memory, and that it is affected in diseases associated with cognitive impairment, depressive and anxiety disorders [33]. It should be noted, however, that significant comorbidity between personality,

anxiety and depressive disorders appears not to be adequately identified in routine diagnostic assessment alone [34].

Relative to other primarily somatic disorders, approximately 40% of people with inflammatory bowel disease experience psychopathological comorbidities. In subjects with European ancestry the status of these comorbidities may depend on genetic influences, as has been recently published [35]. In another recent study based on data from almost the entire population of adolescents and adults in the Federal Republic of Germany, the comorbid status of persons diagnosed with depression is comprehensively illustrated. This may help to raise awareness of the strong interconnectedness of depression with all other mental disorders and with a considerable number of somatic illnesses [36].

The high comorbidity or grouping of certain mental disorders partly reflects superimposed paths of genetic risks, suggesting a shared genetic architecture. Therefore, remodelling the way in which diagnoses are made has been proposed [37]. It is presupposed that there is a reduced number of common processes to very diverse pathologies. However, this does not imply that, in general, it is about particular evolutive ways of basic disorders, as the transdiagnostic alternative claims it to be. However, the genetic assessment of patients with serious psychopathologies, particularly of patients with mental, neurological or neuroevolutionary multiple cerebral phenotypes, must be considered [38].

The association between physical comorbidity and psychiatric re-hospitalisations is still a poorly understood phenomenon. It appears that primarily comorbid somatic illnesses are more common among patients who are readmitted for psychological causes compared with those who are psychiatric inpatients only once [39]. On the other hand, physical illness requiring hospital admission is likely to be a trigger for mental pathology and a generator of demand for specific care [40].

In short, the current non-axial categorical model, *The Diagnostic and Statistical Manual of Mental Disorders* (DSM-5), published by the American Psychiatric Association, is clearly conditioned by numerous factors and is of a rather regulatory nature. It is based on criteria of inclusion and exclusion, for clinical as well as statistical and research purposes. However, it also makes the possibility explicit of a complementary dimensional-categorical model for personality disorders in its section on emerging models.

The World Health Organisation's *International Classification of Diseases* (ICD-11), which is the global standard for recording health information, also has limitations, although to a lesser extent. It is the current approach, globally agreed upon, cross-cultural and guidance-orientated. Certain more dimensional perspectives, in particular for personality disorders and primary psychoses, have been incorporated into this classification [41]. Although the DSM-5 and ICD-11 have drawbacks, this does not demonstrate the favourableness and validity of the many alternative transdiagnostic approaches such as those described above.

Scientific evidence unequivocally supports the need to routinely monitor both physical and mental comorbid conditions in a multidisciplinary approach [42–44]. Comorbidity among mental disorders is widespread and this risk will persist over time [45]. This has been recognised as a key cross-cutting issue by Cochrane Review Groups in the *Mental Health and Neuroscience Network*, which includes, among others, *Cochrane Common Mental Disorders* and *Cochrane Dementia and Cognitive Improvement*.

## Conclusions

Despite the obvious problems currently posed by categorical diagnoses, it is premature, from the viewpoint of the best scientific knowledge, to propose nosological and nosotaxic alternatives based on dimensional approaches.

The latter, however, are likely to complement the categorical ones in some way in the future.

Comorbidity between different mental disorders is common and long-lasting. Most forthcoming and well-founded clinical predictions will underline the growing importance of so-called precision psychiatry or technological psychiatry. For this “new psychiatry”, neurotechnology will be crucial. By extension, the same may apply to clinical psychology as a formal speciality.

Commonly referred to as transdiagnosis, it transcends traditional limitations, often using the novel concept of emotional regulation. In short, they are all variations or alternatives to the traditional biomedical model and are generally “anti-biological” proposals.

In the ongoing debate between the categorical and the dimensional, the transdiagnostic models of psychopathological symptoms grouped together are mainly of so-called emotional disorders. Transdiagnostic biological markers, which could be called comorbidity markers, have also been proposed. Future categorisations of most mental disorders will have to be based primarily on neuroscience, genetics and epigenetics.

In today's clinical practice it is very important to assess comorbidities in a multidisciplinary approach, not merely the main diagnoses. Although transdiagnostic models are fashionable in the specific field of mental health, they do not seem to be a valid alternative to the current categorical ones, which are more grounded in relevant and ongoing scientific knowledge.

Finally, paradoxically, it can be stated that the transdiagnostic approach also categorises, classifies and labels certain theoretically predetermined psychopathological processes. This, in conclusion, is not in line with the evidence-based, unbiased, professional mental assessment which is typical of the scientific method.

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