Towards a scientific taxonomy of depression

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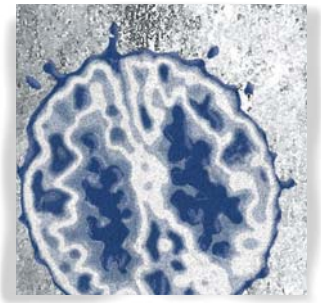

Many concepts have been introduced into the classification of depression, including manic-depressive/bipolar disorder depression, etc. Kraepelin's original concept of manic-depressive disorder has evolved into the concept of polarity, and bipolar and unipolar disorders. Psychiatric classification is characterized by an inflation of the diagnostic categories, including subtypes of depression. This rapid multiplier effect is primarily descriptive, and there is a need to rethink, in a pragmatic fashion, the classification system, in order to develop one that is likely to be of utility and which has a scientific basis. Is the time now right to ask whether there are essential conditions relevant to depression? I think that it is, and here I will introduce the notion with two such conditions. The first is early life stress disorder, and the second vascular depression. These conditions have reached a point where the data supports them as distinct entities. In this paper, the rationale for this is discussed.

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Background

The concept of depression as a disease goes back a long way. Hippocrates described melancholia as a condition in which patients had fears and despondencies for a long time.[1] Robert Burton's book, *Anatomy of Melancholy*, from 1621, is a most interesting read, and many of the descriptions are still applicable.[2] In the last 200 years many concepts have been introduced into the classification of depression, including manic-depressive disorder/insanity,[3] bipolar disorder,[4] and depression.[5,6] Kraepelin's original concept of manic-depressive disorder has evolved into the concept of polarity, and bipolar and depressive disorders. During the last century, psychiatric classification has been characterized by an inflation of diagnostic categories, and this includes the numerous subtypes of depression (see the plethora of DSM classification systems). Severity, duration, and recurrence are used as bases for classification. This rapid multiplier effect is primarily descriptive, and there is a need to rethink, in a pragmatic fashion, the classification system in order to create one that is likely to be of utility and based on science.

As we move towards a classification of depression for this century, it is worth taking a look at the basics of what "disease" is. Disease is an attribute of the patient. The major reason for having a disease label is to convey information in shortened form to others, such that it provides

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key information on the nature and perhaps the treatment of the condition. So, if someone states that a patient has chronic obstructive pulmonary disease, everyone else knows what this means. Disease is conceptualized and taught as an invariant concept, but it is not one. It is fluid, influenced by societal ideas that change with time and in response to scientific trends. There are many definitions of disease, but one practical and easily understandable way to define it is to consider disease "as a state that places individuals at increased risk of adverse consequences." [7] A particular disease refers to the sum of the abnormal elements, such as symptoms, course, signs, laboratory findings, radiological and genetic information, etc, shown by a definable entity, in terms of which they differ from the norm (and from other entities) and in such a manner as to place the subject at risk of adverse consequences.[8] This definition explains the factual implications of the names of diseases when used in diagnostic statements. It relies on comparison with observable norms.[8] Diagnosis is the act of labeling someone as diseased; it reflects the probability that the patient has a disease.

Ideally, the characteristic or group of characteristics specifying the group of patients should be based on the existing state of knowledge.[8] Deviations from the norm, and consequent risk, may or may not require formal statistical information. The classification of adverse consequences includes physical morbidity, mortality, and functional impairment.[9] Most psychiatric diseases place patients at an increased but variable risk for functional morbidity, and only rarely influence mortality. Advances in knowledge should result in the definition of characteristics. The question is, how do we incorporate new knowledge and develop new classification systems? The redefined diseases are unlikely to be identical with the old, and could be a radical departure from the previous definition. Depression research is entering a phase in which redefinitions are likely to occur, and therefore ground rules can be helpful. Explicit ground rules can make the process of "creating" diseases more transparent.

Defining psychiatric disease in a nominalist tradition

There are two methods of labeling disease. Nominalist and essentialist. Nominalists label symptoms with a disease name, and etiology is not a factor. The current approach to depression follows the symptom- and course-based identification of syndromes/diseases. In this tradition, the names of diseases are an easy way of briefly stating the status of symptoms and signs as well as course. The causes in this type of classification can be elusive. Say, for instance, we find that patients with disease X, eg, major depression, have an abnormal genetic marker. We can use the data and develop them as a test to identify specificity, sensitivity, etc. However, this approach relates the changes only to that initial definition. If the definition was not accurate in the first place, then it becomes a problem. It can lead to a test for that condition, but it does not change the definition of that condition based on a presumed cause. Now let us say that the test is a mutation in a gene, and that mutation links not just to depression but to anxiety disorder, bipolar disorder, attention deficit disorder, etc then a symptom-based approach will be disadvantageous. It is likely not to change our understanding, and may be an impediment to better identification of subjects and treatments. An example of an essentialist identification is Hepatitis B or C. Here, there is no link to symptoms or signs—just to the cause. The doctor's skill then consists in identifying the causal disease and prescribing the appropriate treatment. This concept of disease is not yet applicable in a broad sense to psychiatry, because much less is known, and causation is likely to be multifactorial. However, as evidence of causation develops, an essentialist mentality can move the field forward.

The *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (*DSM-IV*) points out that "there is no assumption that each category of mental disorder is a completely discrete entity with absolute boundaries dividing it from other mental disorders or from no mental disorder" (p 21),[10] but the mere fact that a diagnostic concept is listed, official, and provided with a precise definition makes it appear robust and specific. Definitions are stated to become codified and reified without an examination of the fundamental validity. Robins and Guze[11] proposed formal criteria for establishing the validity of psychiatric diagnoses; however few of the entities in DSM meet these criteria. As Kendell and others have pointed out, it is likely that the concept of a nominalist description of disease in the psychiatric context as a distinct entity may not be relevant.[6] One of the hallmarks for symptom- and course-based identification is to demonstrate points of nonoverlap between similar syndromes.[9,11] The points of rarity between psychiatric diseases defined in a nominalist tradition are not as distinct

as one would like. On the other hand, an essentialist classification may be very relevant. We have recently noted a system for defining a condition as a disease.

Criteria for defining disease

The first and obvious criterion is that the condition should be one that leads to a risk for adverse outcomes—either mortality or functional impairment.[12]

The second is where an identifiable characteristic genetic or environmental factor or pathology can be clearly defined. This characteristic should separate the entity from similar entities, in terms of at least one of the following criteria:

1. Clinical symptoms
2. Course and outcome
3. Familial pattern
4. Treatment response.

The differentiation should be clinically significant. Clinical significance may have to be adjudicated by collective groups. The failure to separate may change over time as additional information is developed, and may go through a stage where the characteristic is considered as a subentity.[12,13]

Is the time right to ask whether there are potential essentialist conditions relevant to depression? I think it is, and I would like to introduce the notion of two such categories. The first is early life stress disorder, and the second vascular depression; both these entities have reached a point where the data appears to support their consideration as distinct entities that are clinically significant.

Early life stress disorder

Early life stress disorder meets the essential requirements for what should be called a specific entity. The past decade has seen an increasing awareness of the presence and high incidence of child maltreatment.[14] The National Center of Child Abuse and Neglect reports approximately 1.5 million cases of child maltreatment annually in the United States; half of these cases represent neglect, and 700 000 cases are of sexual, physical, or emotional abuse. In addition to child maltreatment, children often experience other losses, such as the loss of a parent.[15] Thus, early childhood stress is quite common. In a random sample of 1442 subjects from the United States, 14.2% of men and 32.3%, of women reported childhood sexual abuse, and 22.2% of males and 19.5%, of females reported physical abuse.[16] Childhood sexual and physical abuse is common in the general population. So what do we know about the effect of childhood stress?

There is overwhelming evidence that early life stress constitutes a major risk factor for depression. Increased rates of major depression, post-traumatic stress disorder (PTSD), attention-deficit/hyperactivity disorder, and other behavioral disorders have been reported for maltreated children (eg, refs 17,18). A community-based study of adult women revealed that those with a history of childhood sexual or physical abuse had more symptoms of depression and anxiety and more frequently attempted suicide than women without a history of childhood abuse.[19] Others have reported that major depression and anxiety disorders, including panic disorder and PTSD, are frequent in adults with a history of childhood abuse (eg, refs 20,21). Similar findings have been reported for other instances of early life stress. For example, early parental loss has been found to be related to unipolar and bipolar depression, as well as anxiety disorders, beyond familial or genetic factors.[22]

One could argue therefore that early adverse experiences may "shape" a preexisting genetic vulnerability to stress and disease, resulting in a stable phenotype, with a certain risk of developing one syndrome or another in response to further stress exposure. One can argue that this constitutes the essential component of disease, ie, it is state that places an individual at an increased risk for adverse consequences.

This state can be defined as distinct from the rest of the population, and in addition can be differentiated on the following bases.

Clinical

By definition these individuals can exhibit a plethora of symptoms ranging from anxiety, violent behavior, depression, personality disorder, drug abuse, etc. As noted above, an overview of the literature shows that individuals who suffer abuse or neglect as children are more likely to be depressed, to experience other types of psychiatric illness, to have more physical symptoms, and to engage in drug and alcohol abuse. Clearly, additional work is needed to differentiate features. In fact when one works with these patients it is interesting to note the flux in symptom course and features over time. In real life, few of these patients are likely to be true to any one current diagnostic (DSM) entity.

Course and outcome

Childhood abuse strongly predicts poor psychiatric and physical health outcomes in adulthood. Individuals with a history of childhood abuse, particularly sexual abuse, are more likely than individuals with no history of abuse to become high utilizers of medical care and emergency services.

Biological

Findings in children

Neuroendocrine dysfunction in children with early life stress is highly variable, and likely influenced by multiple factors. This could be because a stable phenotype of altered stress vulnerability may not yet have developed in children. Some studies report decreased salivary cortisol concentrations in the morning or a lack of decline of cortisol toward the evening, evidence of an altered circadian rhythm of the hypothalamo-pituitary-adrenal (HPA) axis.[23-25] Cortisol concentrations are related to symptoms of depression. Serotonergic dysfunction is also seen in abused children.[26] In contrast to findings in adult depression and PTSD, normal hippocampal volumes have been observed in maltreated children with PTSD,[27] although smaller ratios of *N*-acetylasparate to creatine have been found in the anterior cingulate of abused children with PTSD.[28]

Findings in adults

A limited number of retrospective studies have evaluated the long-term consequences of early life stress in adults. Lemieux and Coe[29] observed increased 24-hour urinary cortisol excretion in women with a history of childhood sexual abuse and PTSD. These findings, interestingly, are opposite to findings in Vietnam veterans and Holocaust survivors with PTSD.[30] Increased plasma cortisol concentrations are seen amongst patients who experienced the death of a parent in childhood.[31] On the other hand, women with a history of childhood sexual abuse were found to show hypersuppression of salivary cortisol concentrations in response to a low dose of dexamethasone.[32] These data, even if they are variable, are consistent with the notion that childhood abuse leaves a scar in the stress response axis. Heim et al found that abused women exhibit markedly increased plasma acetylcholine (ACTH) responses to psychosocial laboratory stress and in response to corticotrophin-releasing factor (CRF) compared with control subjects and depressed women without early life stress.[33] Similar changes are seen in the sympathetic response.[29,34] These findings are consistent with findings from animal studies, suggesting that the stress axis is sensitized after early life stress in humans that could be due to an increased risk for psychopathology. Decreased hippocampal volumes have been measured in adults with perinatal trauma and adult women with child abuse and PTSD.[35] It is unclear whether this is secondary to the trauma or pre-existent.

Treatment

Obviously the treatment of this entity has to be directed towards prevention. However, it also has implications for medication treatment. In one study, 681 patients with chronic forms of major depression were treated with an antidepressant (nefazodone), Cognitive Behavioral Analysis System of Psychotherapy (CBASP), or the combination. Overall, the effects of the antidepressant alone and psychotherapy alone were equal, and significantly less effective than combination treatment. However, among those with a history of early childhood trauma (loss of parents at an early age, physical or sexual abuse, or neglect), psychotherapy alone was superior to antidepressant monotherapy.[36] Moreover, the combination of psychotherapy and pharmacotherapy was only marginally superior to psychotherapy alone among the childhood abuse cohort. This clearly has implications for managing depression in the context of maltreatment. In fact, this is one of the strongest arguments for defining early life stress disorder as a distinct entity. Without definitions and codification, the implications of research findings will not be well translated, either for research or for clinical purposes.

We do not have knowledge of many aspects of this entity. That is, we do not know what the early features are, or what the gene /environment interaction is. For example, catechol-O-methyl trasferase (COMT) variation has been implicated in predilection to violence in the context of trauma and serotonin transporter genetic variation to depression with the same context, ie, depending on the genetic background, stress produces a different expression.[37] It is likely that clinical features of this entity will not be just syndromal depression or symptoms of PTSD but likely will include anxiety, aggression, and other fea-

tures not typically considered in the current DSM context or labeled as comorbidity.

Why the need to define early life stress disorder as an entity?

The reason for calling a particular feature an entity brings focus and attention. Thus, instead of evaluating patients with depression and stating that a high proportion suffered from trauma, and then stating that they have high comorbidity etc, it reverses the focus and the thinking pattern to a potential cause and the varied manifestations of that cause. By implication, this can lead to a focused search for understanding biology, better assessment of risk prognosis, genetic and social factors, and thereby better treatment and prevention. Given the high estimated rates of this condition, such a focus is imperative at both the research and clinical ends.

Vascular depression

The concept of vascular depression and its potential labeling gives us cause to reflect on the state of labeling psychiatric disorders and the challenges that lie ahead. The concept of vascular depression is not a new idea. Gaupp (1905) as quoted by F. Post[38] described elderly patients with depression secondary to arteriosclerosis. Many had persistent apathy and depressed mood. These early findings were based purely on clinical evidence of cerebral vascular lesions, typically strokes. Magnetic resonance imaging (MRI) and other imaging techniques have allowed depiction of subtle but surprisingly widespread structural brain change in vivo.

Our group and others have previously introduced the notion of vascular depression (we initially used the term arteriosclerotic depression),[39-41] and more precisely subcortical ischemic depression (SID). The broader definition of vascular depression encompasses both depression related to stroke and cardiac disease, and perhaps even hypertension. SID describes a more specific process, is analogous to a recent description of subcortical ischemic vascular dementia,[42] and is similar to what has previously been termed MRI-defined vascular depression.[40] We proposed that diagnostic criteria[43] may be more specific to this entity than the more broadly defined vascular depression. The clinical syndrome meets requirements for diagnostic validity.[44] SID has a clinical description, can be identified through laboratory studies (MRI), can be delimited from other disorders, is not associated with familial factors (for depression), and the changes seen on MRI can influence outcomes longitudinally.[45] The supporting evidence includes the following points. Deep white matter and subcortical lesions as evidence of ischemic disease are more common in elderly depressed patients than healthy elderly control subjects.[46-48] This has also been demonstrated in community populations.[49] Family history of mental illness is significantly less common amongst these patients compared with those without these MRI changes. Large prospective studies have shown that subcortical lesions may be associated with persistence or worsening of depressive symptoms over time.[50] There have also been preliminary studies associating new onset of depression with worsening subcortical disease,[51,52] and worsening of lesion severity is associated with poor depression outcomes.[53] There is also evidence of pathophysiological and neuroanatomical specificity, wherein lesions contributing to depression occur in the basal ganglia and frontal regions.[53,54] The ischemic nature of these lesions has also been shown,[54] and supports data associating severity of subcortical lesions with vascular risk factors such as hypertension,[55-57] and the development of late-onset depression with a history of hypertension.[58]

This description of vascular depression can be incorporated into our current nomenclature system. We took an existing entity, major depression, and developed additional requirements specifying the criteria needed to call it vascular depression or subcortical ischemic vascular depression (SIVD). One significant limitation of this nominalist approach is that it circumscribes the definition to a previously described phenomenon, and presumes that the depression related to this disease process is akin to that noted in the previously described criteria. This approach, although initially useful, is limiting and incomplete. It does not reflect the fact that the disease process is complex, and therefore can manifest with not just lower grades of depression, but also other phenomena including cognitive impairment, dementia psychoses, and possibly mania at some point during the process and in some cases concurrently. The danger is illustrated by the tale of the five blind men and their description of the elephant. The same entity is described in different ways, based on the vantage point. The other approach would be to recognize subcortical ischemic vascular disease as the disease entity (see ref 58). Mood disturbances associated with SID may clearly include the full criteria for major depression, bipolar disorder,[59] or dysthymia. In

addition, less severe or chronic mood disturbances are likely associated with subcortical ischemia; however, with the exception of International Classification of Diseases (ICD) minor depression, our current diagnostic nomenclature does not well capture these other disturbances. Other manifestations of SID include mild cognitive impairment, dementia, stroke, falls, and psychoses.

Thus, labeling SID as the disease changes the emphasis to a disease process and therefore brings into focus the treatment of the disease process, recognizing varying manifestations and progression, for example, from mild cognitive impairment and/or depression to dementia. This focus now allows for the exploration of the causes of the disease process, and thereby enhances the likelihood of developing treatments that are more specific. This process has started for this entity from a neurological and geriatric medicine perspective. The varied clinical symptoms expressed will obviously need symptomatic treatment as is the case for depression, anxiety, mania, or dementia. This will allow the development of trials specific to this population, to assess the response patterns and suitability of different treatment approaches. This focus also allows the development of treatment and prevention approaches aimed towards the underlying causes. In the case of SID the causes are likely to be manifold in most instances. In some cases there may be just one cause, for example cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). When the cause is identified, ie, CADASIL due to Notch 3 mutation, then the primary disease entity should be the causal entity. This is an example where the labeling moves from symptom to disease process and eventually to a causal level.[60] As psychiatry moves from a purely phenomenological symptom course-based approach and follows the trends in medicine, our nomenclature will have to move toward a disease process and/or causally based nomenclature. The time for this change appears to be rapidly approaching. At this time, research is suggesting that some genes are risk factors for what have until now been regarded as unrelated syndromes. Most patients with psychiatric disease may have many attributable causes; in that case, common disease process-based descriptions will need to be developed, just as in the case of SIVD.

Conclusion

I have used two conditions to suggest a potential new taxonomy for depression. The one striking aspect of defining it on this basis is dropping the word "comorbidity" in this context. When we classify using a non-nominalist approach, the basic terminology is altered. Common co-occurrence of disorders gives us clues that could be helpful in looking for antecedents, and at the same time tell us that perhaps our current method is blinding our vision. As we open our eyes and look at emerging data in a nonbiased light, other conditions will emerge that could be useful in conveying information and treating patients. One cautionary note is the danger of overinterpreting genetic information. As potential genes at risk for one or more depressive disorders are identified and developed, defining the level of harm attributable to the gene is important, because any behavior associated with a genetic abnormality is in danger of being construed as disease-associated. This can overemphasize the genetic contribution of any one gene to disease etiology, and may lexicalize behavior patterns with unfortunate consequences. Patients with a genetic variation who are at minimal or no increased risk for adverse consequences should not be labeled as diseased. If the definition of disease is based solely on a genetic abnormality rather than on a clear specification of the risk, the label may harm the patient. ❑

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Hacia una taxonomía científica de la depresión

Dentro de la clasificación de la depresión se han introducido muchos conceptos, incluyendo el trastorno depresivo maníacodepresivo/bipolar, etc. El concepto original de Kraepelin de trastorno maníaco-depresivo ha evolucionado hacia el concepto de polaridad en el trastorno bipolar y unipolar. La clasificación psiquiátrica está caracterizada por una inflación de las categorías diagnósticas, incluyendo diversos subtipos de depresión. Este rápido efecto multiplicador es primariamente descriptivo y es necesario repensar de una manera pragmática el sistema de clasificación, en orden a desarrollar alguno que se espera sea útil y que cuente con bases científicas. ¿Es ahora el momento adecuado para preguntarse si existen condiciones de base que puedan ser relevantes para la depresión? Yo pienso que sí, y aquí yo introduciré esta noción con dos de estas condiciones. La primera es el trastorno por estrés precoz en la vida, y la segunda es la depresión vascular. Estas condiciones han alcanzado un nivel en que los datos obtenidos las sustentan como entidades distintas. En este artículo se discuten los fundamentos de esto.

Vers une taxonomie scientifique de la dépression

La classification de la dépression inclut de nombreuses notions, dont celles de troubles maniacodépressifs/dépression bipolaire etc. Le concept original de trouble maniacodépressif de Kraepelin a évolué vers l'idée de polarité, et de troubles uni- ou bipolaires. La classification psychiatrique se caractérise par l'inflation de différentes catégories diagnostiques comme celle des sous-types de dépression, cet effet multiplicateur étant essentiellement descriptif. Le système de classification doit être repensé de façon pragmatique sur des bases scientifiques afin de pouvoir être utile. Est-ce le bon moment pour se demander si certains états pathologiques sont essentiels dans la dépression ? Je pense que oui, et je vais le démontrer avec deux exemples : le premier est le stress précoce en début de vie, et le second est la dépression vasculaire, deux manifestations considérées par les données comme des entités distinctes. Cet article propose la démonstration des deux exemples.

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