The Dimensional Approach to Clinical Psychopharmacology: A Polysemous Concept

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The last decade has seen significant progress in the development and specific clinical application of selective psychotropes. The dimensional approach to clinical psychopharmacology views the behavioral targets of psychotropes as phenomena existing on a continuum and as components, in varying degrees, of most psychopathologies. The modern concept of dimension has been used in different contexts. In psychology it has a mathematical sense, whereas in biological psychiatry it is associated more with biological function. This paper reviews these two concepts and the recent models attempting to merge them into one. The heuristic value of the dimensional approach, as well as some of its pitfalls and new avenues of research, are discussed.

Key Words: dimensional pychopharmacology, dimension, factorial analysis.

Hopefully, Helen of Troy did not rely exclusively on pharmacological remedies to alleviate Telemachus and his friends' sorrows and music catharsis was widely employed in homeric symposia.

Georgotas 1988

The last decade has seen significant progress in the development and clinical application of selective psychotropics. These new drugs have shed light on some inadequacies of categorical diagnostic systems, such as the current classification of the American Psychiatric Association (APA 1987) or the World Health Organization (WHO 1977), since their behavioral targets are often transnosographic phenomena observed in different diagnostic categories (van Praag et al 1987), within which there are wide variations in drug-induced behavioral reactions. In contrast, the so-called dimensional approach views the various behavioral effects of psychotropes as qualitatively different constructs each existing on a continuum and as components in varying degrees of most psychopathologies (Jouvent 1989). This paper will briefly review the different concepts and issues related to dimensional approaches.

The dimensional approach to clinical psychopharmacology is extremely attractive but also controversial. Even though this concept is being more and more utilized, its current significance is not unequivocal. However, the notion of dimension itself is not new, and the opposition of categorical and dimensional perspectives merely represents recent developments in an older and more extensive philosophical debate about the nature of disease. In ancient Greece, the Platonic school postulated that diseases should be categorized into distinct entities, whereas the rival Hippocratic school conceptualized disease as a dimensional outgrowth from premorbid characteristics (Akiskal 1989). Although many psychiatric pathologies, such as melancholia, mania and paranoia, were described in ancient times, it was

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not until the nineteenth century, and primarily in Europe, that modern nosological entities were described. In Pinel's time in France, a major goal for nosology was to differentiate the manifestations associated with early discharge from the hospital from those associated with long-term institutional care. Systematic clinical descriptions were grouped into syndromes — idiocy, dementia, melancholia, paranoia, catatonia, hebephrenia — that ultimately entered in the Kraepelinian typology. This marked the beginning of scientific psychiatry.

The introduction of neuroleptics by Delay and Denniker (1953) led to a shift in attitudes toward diagnosis. As Askiskal explains (1989), the availability of a treatment that could not only contain the unacceptable behaviors of psychotics, but reduce or even eliminate symptoms, created the desire to provide the largest number of patients with treatment. The nosological boundaries of schizophrenia were enlarged to include even borderline disorders. These broad criteria dominated North American psychiatry until this trend was reversed in the 1970s by the documented effectiveness of lithium for recurrent or cyclic mood disorders and the discovery of tardive dyskinesia in affectively ill patients exposed to neuroleptics. The need to make a careful differential diagnosis between schizophrenia and mood disorders then appeared increasingly important. This categorical approach had to contend, however, with an overlap of clinically observed symptoms in mental disorders even when criteria were carefully defined. Some authors like van Praag (van Praag and Leijnse 1965; van Praag et al 1975; van Praag et al 1987) have advocated a dimensional approach since the sixties, but the development of increasing numbers of psychotropic medications and the production of ever more selective agents thrust psychiatry forward into another phase. Categories such as "depression" are today clearly unsatisfactory to provide guidelines for the sound prescription of the available psychotropics. On the other hand, at this stage the dimensional approach does not offer a simple answer to these problems, partly because it has been used in a number of contexts with different interpretations of the term. For example, in psychology it is applied mainly in a mathematical sense, whereas in biological psychiatry the notion of dimension is more associated with biological function. As will become evident in the discussion to follow, the attempts to merge these two views are not without difficulty.

THE DIMENSIONAL APPROACH IN PSYCHOLOGY

Psychology has offered important support to psychiatry through the development of personality theories and the use of quantitative approaches to issues. Psychologists have constructed scales for thousands of variables representing different aspects of behavior and have been confronted with the challenge of uncovering fundamental personality dimensions to order the multiplicity of personality descriptors and to serve as a personality classification scheme describing complex patterns (Stelmack 1991). This multivariate method springs from the work of Galton (1888), Spearman (1904) and Thurstone (1947) who developed factor analysis. The Galton tradition, enriched by the contributions of many psychomathematicians, and more recently by the use of computers, has given clinical researchers remarkably enhanced access to tools for addressing problems that were previously unapproachable. Thus, the use of factor analysis allows the isolation of a small number of underlying influences responsible for observed relationships of covariation among variables.

The method of factor analysis helps to predict the variance in large number of variables by identifying the variance in a limited number of underlying variables. Factorial models of personality describe personality as the association of stable traits and use concepts such as surface traits and source traits, as defined by Cattell (1980). A surface trait is a set of behaviors that are seen to appear and disappear together and as such represents a simple correlation cluster. A psychiatric syndrome is a surface trait. In contrast, the source trait is defined as a simple structure factor, a dimension, that may be mathematically identified by factor analysis. Thus a syndrome (surface trait) is only a constellation of symptoms that evolve concurrently in time, whereas a dimension (source trait) is considered as an underlying variable with observable manifestations influenced by this dimension. Theoretically, pathology is either an extreme deviation in a particular dimension on a normal continuum or an extreme combination of malfunctioning dimensions that are not so deviate individually. Considering a given dimension, people are only quantitatively different. What we see as the qualitative and unique richness of personality results from the combination of several dimensions. Empirical factor analyses consistently indicate three major dimensions of normal personality variation in the general population. Eysenck's well-known scales distinguish between the three dimensions of neuroticism, extraversion-introversion, and psychoticism (Eysenck and Eysenck 1976). These dimensions are uncorrelated with one another. Similarly, Gray (1982) found three independent dimensions by factor analysis of DSM-III personality disorder categories but they do not correspond well with the dimensions of normal personalities (Cloninger 1987). In general, factorial personality models have had a limited impact on clinical psychiatry.

In the last few decades progress in psychopharmacology has led psychiatrists to develop psychopathological rating scales in order to quantify and compare psychiatric states. In this effort the methods elaborated by psychologists since the beginning of the century, particularly factor analysis, have been exclusively used. However, these rating scales have been constructed with a categorical perspective, eg., the classical Hamilton Depression Rating Scale (Hamilton 1960) was designed to quantify the intensity of a depressive state diagnosed using nosological criteria. Nevertheless, in some cases factor analysis of psychopathological rating scales has allowed the definition of clinical dimensions in

the psychologists' understanding of this term. The distinction between negative and positive aspects of schizophrenia is based mainly on the identification of such dimensions by multivariate analyses of rating scales, such as the Scale for the Assessment of Negative Symptoms (SANS, Andreasen and Olsen 1982), the Scale for the Assessment of Positive Symptoms (SAPS, Andreasen and Olsen 1982), and the Positive and Negative Syndrome Scale for schizophrenia (PANSS, Kay et al 1987). With respect to depression, the Depressive Retardation Rating scale (Widlocher 1983), is designed to assess only one dimension of depressive symptomatology — psychomotor retardation — considered by Widlöcher as having core importance in affective disorders. Principal component analysis has confirmed the stable unidimensional structure of this scale. Furthermore, all items of this scale measure the same clinical entity, retardation, and could therefore be a good index of efficacy for selective drugs acting on this dimension. Similarly, depressive mood was studied by Jouvent (Jouvent et al 1988) who observed qualitative differences in the mood of depressed patients. Using a multivariate approach, he analyzed and confirmed the heterogeneity of the concept of mood using principal component analysis and distinguished five factors of clinical interest. Mood is no longer considered as a global notion, but may be assessed with more precision and more clinical relevance with dimensions such as emotional blunting, emotional hyperexpressivity, and irritability.

Cattell (1980) himself had foreseen the importance of developing dimensional rating instruments when he wrote that "the measurement of relatively pure states, that when combined, describes the complex state of a person at a given moment, has considerable importance for both psychiatric therapies and pharmacology. Previously, in ataractic drug research, the precision on the part of the chemist has been matched by a rather vague evaluation on the part of psychologists with regard to the nature and measurement of the state induced by drugs." We must emphasize at this point, that the dimensions discussed above are not transnosographic. However, a growing number of studies have attempted to demonstrate the transnosographic character of clinical dimensions such as emotional blunting or impulsivity. Therefore, quantitative psychopathology of states, stemming from a categorical framework, have evolved with the use of psychological methodology and have integrated psychological concepts and ideas on dimensionality.

THE DIMENSIONAL APPROACH IN BIOLOGICAL PSYCHIATRY

In biological psychiatry, a dimension represents the behavioral expression of an underlying biological function. Van Praag (1987) has proposed the term "functional/dimensional" approach in contrast with the classical "categorical/nosological" one. In the functional/dimensional approach, the behavioral dimensions are not validated by a mathematical demonstration of a simple factorial structure, but rather by the correlation observed between a set of behavioral manifestations and a biological parameter. To illustrate this approach, some evidence used by psychiatrists to link behavioral dimensions and systems will be briefly reviewed.

The role of monoaminergic neurotransmitters in psychiatric disorders has been studied for decades. However, more recently the development of specific serotonergic medications and the accumulation of evidence from clinical drug trials suggesting the efficacy of these medications in treating a variety of psychiatric categories of illnesses, like depression, anxiety, obsessive-compulsive disorder as well as disorders like migraine (Peroutka et al 1989), has kindled renewed interest in this biogenic amine. Serotonergic neurons, like the noradrenergic and dopaminergic, arise from the brainstem and project to a large number of forebrain structures (neocortex, cingulate gyrus, hippocampus, amygdala and striatum; Azmitia et al 1991). Considering the multiplicity of serotonergic projections, it is not surprising that this system has been extensively studied and implicated in a variety of functions and integrated behaviors. Historically, 5-hydroxyindoleacetic acid (5-HIAA), a metabolite of serotonin, was the first metabolite examined in depression. Ashcroft et al (1966) were the first to report a decreased level of 5-HIAA in the CSF of untreated depressed patients. However, when Goodwin and Jamison (1990) reviewed twenty-five controlled studies of baseline CSF 5-HIAA in depression, they found only seven reporting significant lower levels, one showing significantly higher levels, and the rest showing no directional trends. These negative results led several authors to hypothesize that the serotonin metabolite found in CSF may be related to certain aspects of depression rather than to this mood disorder considered globally. In fact, one of the most replicated findings in biological psychiatry is the association between suicide and low CSF 5-HIAA (Asberg et al 1976; van Praag 1986; Banki et al 1984). These studies further suggested that low 5-HIAA levels are associated with suicides characterized by violent and impulsive acts. This hypothesis is reinforced by the findings that 5-HIAA levels are inversely correlated with psychometric measures of aggression and impulsivity (Brown et al 1979), and that low 5-HIAA levels have been found in impulsive murderers without a suicidal history (Linnoila et al 1982). Moreover, the association between suicide and serotonin metabolites has been observed in a variety of diagnostic groups other than depressed patients, including personality disorders (Brown et al 1979, 1982) and schizophrenia (Ninan et al 1984). Therefore serotonin and its behavioral correlates is a good example of the conceptual shift from research indicating a link between neurotransmitter dysfunction and a categorical entity (depression) to the hypothesis of a connection between serotonin and a clinical dimension (impulsivity). Moreover, while clinical studies solidly associate low 5-HIAA levels and impulsivity, some studies on monkeys (Higley et al 1990) have shown that high 5-HIAA levels are correlated with introverted behavior. This observation has led to the hypo-

thesis that there exists a continuous behavioral dimension, with impulsivity at one end and introversion and inhibition at the other, which is linked to serotonergic neuronal system activity.

As we have discussed, using this approach several investigators have attempted to conceptualize the brain-behavior relationships by defining behavioral dimensions and their neurobiological basis. Brown and Van Praag (Van Praag et al 1991), in their proposed dimensional model of psychopathological dysfunction, present evidence to implicate serotonin in disturbed aggression regulation and heightened anxiety, and dopamine in drive reduction. Tentatively, since evidence for the role of noradrenalin is not as clear, they link noradrenergic dysfunction to anhedonia. In their model, they assume that these dysfunctions interact, but no systematic data are available concerning the quantification of these interactions. However, the authors emphasize that these disturbances in drive, anxiety, aggression regulation, and in anhedonia, are by no means specific to a categorical psychiatric disorder like depression or schizophrenia, but are also seen in other behavioral and neurological disorders. Recently, Cloninger (1987) has proposed a model for the biological study of personality disorders that implies that the underlying structure of normal adaptive traits is the same as that of most maladaptive personality traits. He introduced a system of personality variants based on three dimensions linked to monoaminergic systems: novelty seeking related to dopamine, harm avoidance related to serotonin, and reward dependence related to noradrenaline. For Cloninger these systems are functionally interconnected, and as a result of these interconnections he hypothesizes that integrated patterns of differential responses to punishment, reward and novelty are created.

Another dimensional model recently proposed links DSM-III-R axis I and axis II disorders. Siever and Davis (1991) explore four dimensions and propose treatment strategies based on an hypothesized monoaminergic system dysfunction, namely, 1) the cognitive/perceptual organization dimension which relates to schizophrenia and to schizotypal personality disorder and would be modulated by dopamine. The authors suggest that some schizotypal patients could benefit from neuroleptic treatment, but they use psychotic symptoms as their criteria for treatment instead of impairment of the cognitive/perceptual dimension per se; 2) the impulsivity/aggression dimension, which is related to serotonin and noradrenaline dysfunction; 3) the affective instability dimension tentatively based on "catecholamine instability"; and finally, 4) the anxiety/inhibition dimension, which is possibly related to GABA or noradrenaline dysfunction. Their model needs further confirmation and external validation, but the authors make the interesting suggestion that the pathophysiology of psychiatric disorders may transcend the categorical division of DSM-III-R axis I and II, and that a dimensional model may provide a superior organizational principle associated more closely with external validators — such as biological correlates, treatment response, and clinical course — than a simple categorical approach.

COMMENT

The dimension derived from the factor analysis of a psychopathological rating scale and the behavioral dimension counterpart of a biological function are not synonymous. Moreover, clinical aspects of drive reduction, harm avoidance or anxiety/inhibition remain to be described as well as their relationships with the clinical concepts delineated by the psychopathological rating scales. Further questions remain regarding how will these dimensions relate to psychopathology classically described in discrete categories.

On the other hand, it appears evident that the recent progress in neurobiology and the growing complexity of neurotransmission models would preclude the use of expressions such as "serotonin dysfunction" as if it were a unitary dimension. Such an expression would be reductionist given that an ever growing number of 5-HT receptor subtypes are being identified. In this context, some investigators attempt to correlate therapeutical indications of the newer drugs to specific receptor subtypes (Peroutka et al 1989). However, this inevitably raises questions, such as: Is the concept of a serotonergic or dopaminergic dimension already defunct? Should a new behaviorial dimension be defined for each new receptor subtype?

Still, the model of dimensional psychopharmacology remains extremely attractive from many points of view. The inability of previous works to indicate a curative, etiological effect of psychotropes in such heterogenous disorders as depression or schizophrenia has undoubtedly played a role in the growing interest in a dimensional approach. The dimensional approach may, at the behavioral level of analysis, offer a more precise description of the effects of psychotropes (Jouvent 1989). The new molecules can no longer be classified within the classical categories of neuroleptics, anxiolytics and antidepressants. For example, 5HT1-A agonists such as gepirone and buspirone have both anxiolytic and antidepressant effects (Eison 1989). It therefore becomes necessary to define specific behavioral/clinical dimensions modified by these specific drugs. These dimensions are observed in various diagnostic categories, and this transnosographic presentation will help psychiatrists understand how these drugs correct a neurobiological dysfunction and the corresponding behavioral disturbance, much like a β-blocker will correct tachycardia, whatever its etiology. Moreover, the dimensional effect means that a β-blocker always has the same unidirectional effect on the dimension "cardiac rhythm," but that its therapeutic relevance will depend on the initial state of the patient's rhythm.

On the other hand, from a practical point of view all the dimensional models imply that more than one dimension will be affected at the same time in a given patient, and the interactions between the dimensions remain poorly defined. This means that the clinician will have to assess many dimensions simultaneously — a situation which may create difficulty for psychiatrists accustomed to making a global evaluation of the state of the patient. Moreover, it implies logically that each disturbed dimension will receive

its specific treatment. Such polypharmacotherapy might present practical problems and raise protest and reluctance from both the patient and the psychiatrist wanting to find "the" treatment. It also necessitates defining the threshold at which treatment becomes necessary.

One of the difficulties encountered by the dimensional approach in psychopharmacology derives from the fact that we correlate neuronal systems with complex integrated behaviors too readily. There may well exist levels of analysis yet undefined that would help fill the gaps between neurotransmitter actions and human behavior. A promising approach lies in the definition of more elementary aspects of behavior which are, hopefully, characterized by a less complicated biological base. Such intermediate levels of analysis between clinical dimensions and neuronal systems might be found in the application of concepts and methods of experimental psychology. The recent progress in cognitive psychology will conceivably provide psychiatry with finer tools for the study of subtle aspects of human functioning.

CONCLUSION

Psychiatry has reached a new phase in its development and history. The availability of new therapeutic tools always triggers a period of fruitful theoretical thinking. The classical categorical approach has proved insufficient to assess and understand transnosographic disturbances, such as impulsivity or anhedonia. The dimensional approach has heuristic value, but is not without its own pitfalls. Finally, defining quantifiable dimensions does not suggest that it is only the measurable that counts. Difficultly in the quantification of concepts will always be part of psychiatry's reality and history. Progress in psychiatry shall be best realized by the integration of ideas and experiment.

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