*British Journal of Psychiatry* (1996), **168** (suppl. 30), 129–134

# Comorbidity (Psycho) Analysed

H. M. VAN PRAAG

Many psychiatric patients seem to suffer from a multitude of psychiatric disorders. The term 'comorbidity' was introduced to characterise that situation. This term, however, is multi-interpretable and thus conceals more than it clarifies. Five interpretations of the concept of comorbidity are discussed, in conjunction with the consequences their validity would have for psychiatric research, in particular for the biological branch. If the term comorbidity continues to be used without further qualification, it will slow down the process of conceptualisation of novel research strategies in experimental psychiatry, which is so urgently needed.

## Comorbidity, the mascot of neonosologists

Comorbidity is a pet concept of psychiatry in the 1990s. We seem to have rediscovered the obvious and adorned it with an intriguing name. The psychopathology of an individual patient frequently does not fit the definition of a particular disorder as defined by the classification system in force. Rather it resembles a patchwork of components derived from several different disorders or diagnostic entities. Even more disturbing, more often than not, an individual psychiatric patient seems to suffer simultaneously from a multitude of disorders. Two or three DSM–III-based axis 1 diagnoses and the same number of axis 2 diagnoses are the rule rather than the exception. Each of those diagnostic entities is considered to be sufficiently discrete as to warrant the search for such characteristics as pathophysiological substrate, epidemiology, specific treatment, and outcome.

This is true today as much as it was true before DSM–III. After DSM–III had been introduced, the concept of comorbidity was embraced by neonosologists. It became a mascot of sorts because it seemed to explain a clinical reality that did not tally with the categorical views on mental pathology. In essence, mascots are stereotypes dressed up with magical notions, and so is this one. It conceals the complexity of clinical realities with a simple, would-be explanation. In fact, such complex clinical conditions allow several interpretations, each of which has different implications for psychiatric research in general, and for the biological branch in particular. The term comorbidity blurs rather than clarifies the diagnostic problem we have to deal with. As it is being used today, the mascot will bring psychiatry little luck.

What, then, are the different ways in which the concept of comorbidity can be interpreted?

## Interpretation 1: disorders abound

In psychiatry we face the situation that many patients indeed suffer simultaneously from several discrete disorders. In those cases the term comorbidity could be used appropriately.

If this interpretation is correct, the future of experimental psychiatry would be utterly bleak. It is hard to imagine how one could study such fields as pathogenesis, epidemiology, treatment and outcome of a given disorder if it generally appears among a host of other disorders.

This interpretation, however, seems unlikely. The chance of a group of unrelated disorders occurring in the same individual is small, and accordingly, is in no medical discipline a frequent event. It is hard to imagine that psychiatry would be an exception. Rather, the apparent accumulation of psychiatric disorders in individual patients seems to be a product of the way mental disturbances are being categorised, drawing borders where no genuine distinctions exist (van Praag, 1995*b*).

## Interpretation 2: hierarchical order

This explanation is that one of the various psychiatric syndromes occurring in a given patient is primary, and the others are derivatives, i.e. secondary to the key disturbances. Depression, for instance, could be the primary syndrome, and concurrent symptoms relating to obsessive–compulsive disorders (OCD), panic disorder, generalised anxiety disorder (GAD), or alcoholism could be derivatives.



https://doi.org/10.1192/S0007125000298516 Published online by Cambridge University Press

Such a relationship can be best understood within a biological frame of reference. The primary syndrome would be the immediate expression of key cerebral disturbances, while the secondary manifestations are linked to neuronal perturbations consequential upon the key disturbances. One could understand such an interrelation also from a psychological vantage point and assume that the depressive condition weakens coping and integrative abilities, causing secondary decompensations in psychological domains which, although vulnerable, under normal conditions can be kept under control.

In some patients this interpretation seems plausible. In a study of 15 patients with vital depression (comparable to the DSM–III diagnosis major depression, melancholic type) and concurrent OCD, both conditions disappeared together with electroconvulsive therapy (ECT) in six patients; in three patients the depression responded completely, the OCD symptoms only partially. In the remaining six patients OCD persisted while the depression responded to ECT partially or completely. Since OCD as such is no indication for ECT, it seems likely that OCD occurred secondary to depression in the patients who responded to ECT.

In cases in which such a hierarchical, intersyndromal relation exists, biological research would be seriously hampered as long as no certainty exists about the hierarchical order of the syndromes. Resolving that issue should have the highest priority, and treatment studies with more and less selective therapeutic interventions seem particularly suited to this end. Until that is accomplished, it would be impossible to evaluate the pathogenetic significance of biological findings occurring in psychiatric disorders.

### Interpretation 3: the offspring of a defective persona

In many, if not most, patients, psychiatric symptoms (i.e. abnormal behavioural and experiential phenomena that do not belong to the regular psychological repertoire of an individual) and more or less stable personality pathology go hand in hand. In other words, combinations of axes 1 and 2 diagnoses are particularly frequent. Why this is so could be explained in various ways. Firstly, their co-occurrence could be fortuitous. Secondly, they could often be generated simultaneously but independently. Finally, axes 1 and 2 diagnoses could be causally related, in that the personality pathology is responsible for the current psychopathology or *vice versa*; that axis 1 pathology leads to personality pathology.

Co-occurrence of axes 1 and 2 diagnoses is too frequent as to make their independent existence a plausible proposition. The third explanation seems more acceptable and provides another example of a vertical (i.e. hierarchical) relationship between the various components of a given psychiatric condition. In most patients personality pathology precedes current psychopathology, suggesting that personality factors may contribute to the occurrence of psychiatric disorders. The negative impact of personality pathology on treatment outcome of several psychiatric disorders points in the same direction (Baer *et al*, 1992; Tyrer *et al*, 1993; Reich & Vasile, 1993; Wade *et al*, 1993). This does not, of course, exclude the possibility that, occasionally, personality pathology originates from or deteriorates through serious or recurrent psychopathology.

In the heyday of psychoanalysis, a causal connection between axes 1 and 2 diagnoses was taken for granted. The key question was not whether, but how, they interrelate. This bias regularly led, via tortuous reasoning, to ponderous aetiological constructions. When empirical research, and particularly biological research, assumed an ever stronger position in psychiatry, the interest in this recalcitrant question waned. Research efforts focused on psychopathological syndromes and disorders. The question of the aetiological weight of personality pathology moved to the fringes of experimental psychiatry. This amounts to scientific avoidance behaviour (van Praag, 1992*a*, 1992*c*).

The assumption that axis 1 pathology often coexists with personality pathology because they hang causally together has important consequences for biological psychiatry. It would mean that biological variables found in psychiatric disorders should not only be correlated with psychiatric disorders, psychiatric syndromes, and components of those syndromes, but likewise with personality disorders and personality traits. If a relationship with personality pathology were to be established, the issue becomes urgent whether the axes 1 and 2 pathologies are merely coexistent or interrelated.

Furthermore, it should be explored whether the biological disturbance is state- or trait-dependent. Its trait character would speak in favour of a link with personality pathology. Biological research in psychiatry should thus invariably be longitudinal, at least in those disorders that tend to remit.

Finally, personality disorders without concomitant axis 1 pathology should be studied biologically in their own right. If a biological variable observed in a patient with combined axes 1 and 2 pathologies

https://doi.org/10.1192/S0007125000298516 Published online by Cambridge University Press

was also present in patients showing the personality pathology only, this would strongly suggest axis 2, and not axis 1, pathology to be the behavioural correlate.

### Interpretation 4: one stem, many branches

The multitude of disorders or psychopathological syndromes or parts of syndromes observed in an individual patient reflect the various manifestations of a single biological abnormality. In other words, the disorders/syndromes are interdependent but not in a hierarchical fashion, as in the previous two interpretations, but horizontally.

A global deficit in serotonin (5-hydroxytryptamine, 5-HT) synthesis would provide a hypothetical, but telling, example. The number of 5-HT-containing nerve cells is small. The fibres of these neurons, however, branch out over large areas of the brain and the brain stem. The receptor on which serotonin acts, moreover, is not a uniform structure but there exists at least ten different subtypes, each probably involved in the regulation of diverse functions. Hence a global 5-HT deficit would perturb a variety of brain regions and neuronal circuits, and the assumption that a multitude of psychological domains would thus be affected is plausible.

Indeed, substantial evidence implicates 5-HT systems in the regulation of such diverse psychological domains as anxiety, mood, perception, aggression and impulse control (Bleich *et al*, 1988; Delgado *et al*, 1990; van Praag *et al*, 1990; Caldecott-Hazard *et al*, 1991; Siever *et al*, 1991; van Praag, 1991; Benkert *et al*, 1993; Ohuoha *et al*, 1993; van Praag, 1995*a*). Accordingly one would expect a 5-HT deficit to generate a variety of psychological dysfunctions, and a drug correcting that deficit to exercise therapeutic effects in various psychiatric conditions. Indeed, the group of selective 5-HT reuptake inhibitors, increasing 5-HT availability in the central nervous system and facilitating 5-HT transmission, has shown therapeutic efficacy in such diverse conditions as depression, panic disorder, OCD, aggressive behaviour, and certain personality disorders (Coccaro & Siever, 1985; Kahn & van Praag, 1992; Gitlin, 1993; Hollister & Claghorn, 1993; Song *et al*, 1993).

If valid, the implications of this model for biological psychiatry would be profound. Rather than focusing research on the biological determinants of disease entities such as schizophrenia or major depression, the focus of biological psychiatric research must in that case be shifted toward the study of the psychological correlates of particular neuronal systems, in this instance those in which 5-HT serves as a transmitter. One would expect to find 5-HT disturbances in those mental disorders in which the alleged 5-HT-related psychological functions are severely disturbed. The latter hypothesis, then, should be studied in the next phase of the research design.

Finally, the question of the "hierarchical position" of the 5-HT-related features of the mental disorder under investigation should be addressed. They could be primary symptoms, positioned in the core of that psychiatric condition and directly related to its pathophysiology, or secondary symptoms (i.e. derivatives of the core symptoms). In the former case they should be targets of therapeutic interventions, in the latter case their elimination would at best lead to a partial improvement.

This interpretation would thus turn biological psychiatry away from a more or less monocausal premise – searching for 'markers' and eventually the 'cause' of a mental disorder – toward a multicausal model geared toward elucidation of the complexity of biological dysfunctions presumed to underlie a particular psychiatric condition, which is viewed as a composition of psychological dysfunctions (van Praag, 1996).

### Interpretation 5: nosology abandoned

Mental disorders can be conceived as reaction patterns to noxious stimuli, with considerable interindividual variability and little consistency, rather than as discrete and separate entities. The noxious stimulus might be of a biological or psychological nature, could come from within or without, and might be genetically transmitted or acquired during life. They have in common that an individual cannot cope with them, physically and/or psychologically. According to this model the co-occurrence of various, discrete mental disorders is mainly appearance. In fact we deal with ever-changing composites of pychopathological features.

In this model, symptomatological variability of individual psychiatric conditions could be understood in the following manner. Noxious stimuli (i.e. stimuli an individual is unable to assimilate) will perturb a variety of neuronal circuits and hence a variety of psychological systems. The extent to which the various neuronal circuits will be involved varies individually, and consequently psychiatric conditions will lack symptomatological consistency and predictability. Instead, the components of these psychopathological clusters will vary in intensity and prominence over time, so that within subjects

https://doi.org/10.1192/S0007125000298516 Published online by Cambridge University Press

and between subjects their appearance is as variable as the shape of clouds in the sky.

The measure of neuronal disruption a noxious stimulus will generate is contingent on a number of factors. Most important are the intrinsic qualities of the stimulus and the resilience of the brain and of the personality structure. Some stimuli are disruptive for most people, others only for susceptible ones. Increased vulnerability could be due to personality imperfections or to neuronal defects, causing certain brain circuits to function marginally or deficiently. An equilibrium just maintained under normal conditions will then be deranged if demand is increased.

This interpretation, if valid, would have the most profound consequences of all for biological psychiatry. The search for markers and eventually causes of discrete mental disorders would be largely futile. The farthest one could go would be to group the multitude of reaction patterns in a limited number of diagnostic basins, such as the group of the psychotic, the dementing, and the affective reaction forms, each of which, however, would show considerable heterogeneity. As much as it is futile to search for the antecedents and characteristics of, for instance, the group of abdominal disorders, it would equally lack wisdom to hope for the discovery of, for instance, the pathogenesis of affective reaction forms.

Within the scope of this model, the focus of biological psychiatric research has to shift from the alleged mental 'disorders', to disordered psychological domains. Schizophrenia, panic disorder or major depression as such will not be studied, but disturbances in perception, information processing in mood regulation, in anxiety regulation, in impulse control, to mention only a few. A biology of psychological dysfunctions as they occur in mental disorders would thus be the ultimate goal of biological psychiatric research.

The impact this interpretation of comorbidity would have on the application and scientific development of psychotropic drugs would be no less dramatic (van Praag *et al*, 1987; van Praag, 1990, 1993). Instead of prescribing drugs categorically to treat a particular disorder such as schizophrenia, they would be prescribed because particular psychological dysfunctions are prominent, such as disturbances in mood regulation, in anxiety regulation, or in level of initiative. Functional psychopharmacology would generally imply that, for a given patient, several drugs would be prescribed simultaneously. One would practice goal-directed, dysfunction-oriented polypharmacy, much the same as the cardiologist does in a case of myocardial infarction. The myocardial infarction is not treated, but the resulting cardiac dysfunctions are, each with a rather specific agent.

It would, of course, be inappropriate to prescribe drugs for each and every psychopathological constitutent of a given reaction form. The development of a functional psychopharmacology presupposes renewed scientific interest in weighing psychiatric symptoms according to their diagnostic 'weight'. In diagnosing pneumonia, the symptom cough has a higher rank order than the symptom fatigue. In diagnosing a morbid condition, internists "verticalise" symptomatology.

In present day psychiatry, on the other hand, we tend to group symptoms horizontally as if they were all of equal diagnostic weight. This probably constitutes a serious primitivisation of the diagnostic process, since it seems much more likely that in a given psychiatric state some symptoms are a direct reflection of the underlying pathophysiological process, while others are derivatives (see Interpretation 2).

The former symptoms, which Bleuler (1922) called "primary", should be traced and studied as to their pathogenesis. They would be the proper targets in the search for new psychopharmacological agents. A case in point is the concept of 5-HT-related, anxiety/aggression-driven depression, which we recently introduced (van Praag, 1992*b*, 1995*a*). Primary symptoms in this diagnostic category, the hypothesis reads, are anxiety and aggression; the pathogenesis of this condition is thought to involve disordered 5-HT metabolism, and proper treatment would require drugs that regulate anxiety and/or aggression via regulation of 5-HT circuits. Functional psychopharmacology, implying dysfunction-oriented polypharmacy, presupposes that the symptoms of a particular psychiatric disorder have been 'verticalised' (i.e. grouped according to their relation to the pathophysiology of the disorder) (van Praag, 1992*a*, *b*).

Strongly nosologically oriented as present-day psychiatry is, the present *Zeitgeist* leaves little room for the philosophy underlying this view on comorbidity. This is regrettable because it provides novel ways to interpret psychopathology, to search for the behavioural correlates of biological disturbances, and to develop psychoactive drugs.

## Conclusions

The term comorbidity, then, appears to be multi-interpretable. Consequently it conceals more than it clarifies, if used without further qualification. The first four interpretations are by no means mutually

https://doi.org/10.1192/S0007125000298516 Published online by Cambridge University Press

exclusive. Their validity might vary with the type of psychiatric condition. It is even conceivable that, for the same type of condition in various patients, different interpretations are valid.

The last interpretation discussed is of a different quality and is irreconcilable with the others. It relinquishes the philosophy of nosology and adopts a flexible, highly individualised way of interpreting and diagnosing psychiatric conditions. Adolph Meyer advocated this model, but in the present neonosological era it is not held in great respect (Meyer, 1957). However, its heuristic value is considerable, because it provides neat explanations both for the syndromal heterogeneity of psychiatric conditions and for the nosological aspecificity of most, if not all, biological concomitants so far. Moreover, conceiving of mental disorders as reaction forms leads necessarily to a dimensional approach of diagnosing those conditions. The systematic application of dimensional dissection of psychiatric conditions is, I consider, indispensible to save psychiatric diagnosing from desiccation (van Praag, 1992*a*).

The systematic study of what it means that psychiatric disorders, categorically defined, so frequently occur in concert is urgent, since without a better understanding of this dilemma, biological psychiatric research is at risk, drifting ever closer toward diagnostic irrelevance. There are several ways in which this thorny issue can be approached.

The diagnosis and classification of mental disorders must be two-tracked, i.e. both categorically and dimensionally based. The dimensional diagnosis comprises a detailed account of the psychological dysfunctions of which a given psychiatric condition is composed. Biological variables should be studied as to their categorical or functional specificity.

Moreover, biological disturbances in mental disorders should routinely be studied longitudinally, not only cross-sectionally. Only in this way can one hope to resolve the issue of whether they are linked to current psychopathology or to concomitant (or underlying) personality disorders. To elucidate this question further, the biology of personality disorder should be studied in its own right. If a biological variable observed in a patient with an axis 1 as well as an axis 2 diagnosis also occurs in a patient with a similar personality disorder only, the personality disorder is its most likely behavioural correlate.

Another approach in attempting to shed light on the comorbidity problem is to study psychiatric conditions that show considerable overlap in phenomenology and prevalence, such as the mood, anxiety, and certain personality disorders, collectively, as if they constituted one diagnostic 'basin'. In this way one could assess whether a particular biological variable is indeed 'disorder-linked' or rather 'basin-linked' (specific for a group of disorders or to a common characteristic of that group). 'Basin-linkage' would support the reaction-form model of psychiatric disorders.

Finally we should study the way in which the various syndromal components of a particular psychiatric condition are interrelated. They could be vertically related, i.e. hierarchically related (being the direct or indirect consequences of the pathophysiology of the disorder), horizontally related (being the different manifestations of a common biochemical dysfunction), or they could be unrelated, being independent pathological manifestations.

These questions can be approached with clinical methods. One could, for instance, study the appearance of syndromal components of a particular psychiatric condition over time. It is conceivable that components appearing first are primary, and those coming later are derivative phenomena. Biological studies can also contribute to this differentiation. To this end, emphasis should be put on studying the rare 'pure' conditions, in which a particular well-defined syndrome occurs alone. Let us suppose now that evidence for a 5-HT deficit has been found in a complex psychiatric condition with components of vital depression, GAD and OCD. If those biochemical disturbances are also evident in 'pure' vital depression but not in 'pure' GAD and OCD, this would suggest a hierarchical relationship of the syndromal components. If these disturbances were to be found in OCD and GAD as well, this would rather argue in favour of their horizontal relationship.

Psychopharmacology, finally, could contribute in differentiating between a horizontal relationship of syndromal components and their mutually independent existence. If in the given example a compound that selectively increases 5-HT availability eliminated or ameliorated the multisyndromal psychiatric condition entirely, this would suggest that they are interconnected, either horizontally or vertically. If only one psychopathological component responded, it would be more likely that that component exists independently.

In summary, the term comorbidity, overused and unclear as it is, slows down conceptualisation of new research strategies in experimental psychiatry. Analysing the complex load it covers, it could, on the other hand, usher in a new era of diagnosing mental disorders in a more sophisticated way, and of studying their biological roots.

https://doi.org/10.1192/S0007125000298516 Published online by Cambridge University Press

## References


BAER, L., JENIKE, M. A., BLACK, D. W., *et al* (1992) Effect of axis II diagnoses on treatment outcome with clomipramine in 55 patients with obsessive–compulsive disorder. *Archives of General Psychiatry*, **49**, 862–866.

BENKERT, O., WETZEL, H. & SZEGEDI, A. (1993) Serotonin dysfunction syndromes: a functional common denominator for classification of depression, anxiety, and obsessive–compulsive disorder. *International Clinical Psychopharmacology*, **8** (suppl. 1), 3–14.

BLEICH, A., BROWN, S. L., KAHN, R. S., *et al* (1988) The role of serotonin in schizophrenia. *Schizophrenia Bulletin*, **14**, 297–315.

BLEULER, E. (1922) *Lehrbuch der Psychiatrie. Vierte Auflage*. Berlin: Verlaq von Julius Springer.

CALDECOTT-HAZARD, S., GUZE, B. H., KLING, M. A., *et al* (1991) Clinical and biochemical aspects of depressive disorders: I. Introduction, classification, and research techniques. *Synapse*, **8**, 185–211.

COCCARO, E. F. & SIEVER, L. J. (1985) Second generation antidepressants: a comparative review. *Journal of Clinical Pharmacology*, **25**, 241–260.

DELGADO, P. L., CHARNEY, D. S., PRICE, L. H., *et al* (1990) Serotonin function and the mechanism of antidepressant action. *Archives of General Psychiatry*, **47**, 411–418.

GITLIN, M. J. (1993) Pharmacotherapy of personality disorders: conceptual framework and clinical strategies. *Journal of Clinical Psychopharmacology*, **13**, 343–353.

HOLLISTER, L. E. & CLAGHORN, J. L. (1993) New antidepressants. *Annual Reviews of Pharmacology and Toxicology*, **32**, 165–177.

KAHN, R. S. & VAN PRAAG, H. M. (1992) Panic disorder: a biological perspective. *European Neuropsychopharmacology*, **2**, 1–20.

MEYER, A. (1957) *Psychobiology: A Science of Man*. Springfield, IL: Charles C. Thomas.

OHUOHA, D. C., HYDE, T. M. & KLEINMAN, J. E. (1993) The role of serotonin in schizophrenia: an overview of the nomenclature, distribution and alterations of serotonin receptors in the central nervous system. *Psychopharmacology*, **112**, S5–S15.

REICH, J. H. & VASILE, R. G. (1993) Effect of personality disorders on the treatment outcome of axis I conditions: an update. *Journal of Nervous and Mental Disease*, **181**, 475–484.

SIEVER, L. J., KAHN, R. S., LAWLOR, B. A., *et al* (1991) Critical issues in defining the role of serotonin in psychiatric disorders. *Pharmacological Reviews*, **43**, 509–525.

SONG, F., FREEMANTLE, N., SHELDON, T. A., *et al* (1993) Selective serotonin reuptake inhibitors: meta-analysis of efficacy and acceptability. *British Medical Journal*, **306**, 683–687.

TYRER, P., SEIVEWRIGHT, N., FERGUSON, B., *et al* (1993) The Nottingham study of neurotic disorder. Effect of personality status on response to drug treatment, cognitive therapy and self-help over two years. *British Journal of Psychiatry*, **162**, 219–226.

VAN PRAAG, H. M. (1990) Two-tier diagnosing in psychiatry. *Psychiatric Research*, **34**, 1–11.

——— (1991) Serotonergic dysfunction and aggression control. *Psychological Medicine*, **21**, 15–19.

——— (1992*a*) *Make Believes in Psychiatry of the Perils of Progress*. New York: Brunner Mazel.

——— (1992*b*) About the centrality of mood lowering in mood disorders. *European Neuropsychopharmacology*, **2**, 393–402.

——— (1992*c*) Reconquest of the subjective. Against the waining of psychiatric diagnosing. *British Journal of Psychiatry*, **160**, 266–271.

——— (1993) Diagnosis, the rate-limiting factor of biological depression research. *Neuropsychobiology*, **28**, 197–206.

——— (1995*a*) Serotonin-related, anxiety/aggression-driven stressor-precipitated depression. A psycho-biological hypothesis. *European Psychiatry*, in press.

——— (1995*b*) Concerns about depressions. *European Psychiatry*, **10**, 269–275.

——— (1996) Over the mainstream. Diagnostic requirements for biological psychiatric research. *European Psychiatry*, in press.

———, KAHN, R., ASNIS, G. M., *et al* (1987) Denosologization of biological psychiatry or the specificity of 5-HT disturbances in psychiatric disorders. *Journal of Affective Disorders*, **13**, 1–8.

———, ASNIS, G. M., KAHN, R. S., *et al* (1990) Monoamines and abnormal behaviour. A multi-aminergic perspective. *British Journal of Psychiatry*, **157**, 723–734.

WADE, S. L., MONROE, S. M. & MICHELSON, L. K. (1993) Chronic life stress and treatment outcome in agoraphobia with panic attacks. *American Journal of Psychiatry*, **150**, 1491–1495.


**Herman M. van Praag**, MD, Department of Psychiatry, State University of Limburg, P. Debyelaan 25, Postbus 5800, 6202 AZ Maastricht, Netherlands

https://doi.org/10.1192/S0007125000298516 Published online by Cambridge University Press