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Psychiatric comorbidity and causal disease models

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ABSTRACT

In psychiatry, comorbidity is the rule rather than the exception. Up to 45% of all patients are classified as having more than one psychiatric disorder. These high rates of comorbidity have led to a debate concerning the interpretation of this phenomenon. Some authors emphasize the problematic character of the high rates of comorbidity because they indicate absent zones of rarities. Others consider comorbid conditions to be a validator for a particular reclassification of diseases. In this paper we will show that those at first sight contrasting interpretations of comorbidity are based on similar assumptions about disease models. The underlying ideas are that firstly high rates of comorbidity are the result of the absence of causally defined diseases in psychiatry, and second that causal disease models are preferable to non-causal disease models. We will argue that there are good reasons to seek after causal understanding of psychiatric disorders, but that causal disease models will not rule out high rates of comorbidity — neither in psychiatry, nor in medicine in general. By bringing to the fore these underlying assumptions, we hope to clear the ground for a different understanding of comorbidity, and of models for psychiatric diseases.

Introduction

Recently, large epidemiological studies have showed that roughly one quarter to one third of the population suffered from a psychiatric disorder in the past year. Of this group of patients, 35 to 45% satisfied the criteria for two or even more psychiatric disorders, and thus suffer from comorbidity (Bijl, et al., 1998; Jacobi, et al., 2004; Kessler, et al., 2005). This high co-occurrence of mental disorders has led to a debate concerning its background and interpretation. Why do we find these high co-occurrence rates of psychiatric disorders? First, the definition of comorbidity (Kraemer, et al., 2007; Maj, 2005a; Vella, et al., 2000) and the measurement methods upon which they are based have been called into question (Batstra, et al., 2002; de Groot, et al., 2003). A second part of the debate focuses on the artificiality versus reality of comorbidity (Aragona, 2009; Maj, 2005b; Vella, et al., 2000; Zachar, 2009): are the high rates of comorbidity real or an artifact of the classification system in psychiatry? For instance, are they a consequence of considerable symptom overlap between disorders (Cramer, et al., 2010)? The third part of the discussion – the part we will focus on in this paper – concerns the interpretation of the comorbidity rates: should they be regarded as a problem for the validity of psychiatric disorders (Kendell and Jablensky, 2003) or should they be welcomed as a validator for reclassifying them (Andrews, et al., 2009b)?

The concept of comorbidity was first introduced in medicine by Feinstein in 1970. Feinstein, at that time professor of Medicine and Epidemiology at Yale University, was involved in cancer research. He described comorbidity as “any additional co-existing ailment” in a patient with a particular index disease (Feinstein, 1970, p.467). With the index disease he meant the disease being subject of study, e.g. primary cancer of the lung. Under co-existing ailments he understood roughly factors influencing the condition of the patient apart from the index disease, such as diabetes mellitus, pneumonia or even pregnancy. The main reason for this interest in comorbidity was his conviction that treatment results could not be evaluated without taking this into account. Since the 1980s–1990s comorbidity research in psychiatry took flight (Batstra, et al., 2002; Krueger and Markon, 2006). Large studies were set up to determine the prevalence of psychiatric disorders, specifically including comorbidity patterns. As stated above, comorbidity rates were found to be remarkably high, and clearly above what can be expected by chance.

Interestingly, the high rates of comorbidity in psychiatry are interpreted in notably different, sometimes opposite, ways. In this paper we will specifically focus on the interpretations of comorbidity as a validator (Andrews, et al., 2009b) versus comorbidity as a problem (Kendell and Jablensky, 2003). By reconstructing the arguments for the two different positions, we will show that both positions in fact rest upon the same assumptions about psychiatric disease models. That is, both positions presuppose (i) that there is a relationship between psychiatric comorbidity estimates and the absence of causal disease models in psychiatry, and (ii) that causal disease models are preferable to

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non-causal disease classifications. So, on a fundamental level, there is practically no disagreement between the two positions. In the following paragraphs we will discuss these contrasting views with the aim to bring to the fore the shared ideas underlying both the problem and validator position. Afterwards, we will reflect upon those shared ideas: why is there such a preference for causal disease models? And is the assumed relationship between comorbidity and causal disease models reasonable? Hereby, we hope to clear the ground for a more productive discussion on comorbidity and on psychiatric disease modeling more in general.

Comorbidity as a validator

In the development of the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM 5), the possibility of grouping all current diagnoses into five clusters is investigated (Andrews et al., 2009a, 2009b; Carpenter, et al., 2009; Goldberg, et al., 2009; Krueger and South, 2009; Sachdev, et al., 2009). The reason for this attempt is the complexity of the current system for clinical use: the DSM is far from parsimonious with 16 major categories comprising some 160 diagnoses. The hope is that a limited number of clusters could facilitate both research and clinical practice. Eleven criteria, the so-called validators, are used to decide which diseases should be clustered. Andrews et al. roughly divide them into 'causal risk factors' and 'aspects of the clinical picture'. For instance, if two diseases share genes, neural substrates, or environmental risk factors, then there are arguments to group them in the same cluster. Likewise, high rates of comorbidity count as a criterion for grouping two diseases in one cluster and are "used as a systematic way of examining the relationships between disorders in terms of the risk and clinical factors" (Andrews, et al., 2009b, p.1995). How do the authors defend this use of comorbidity? As we will see in the reconstruction of the argument, the assumption of a common causal structure for different diseases is of vital importance. The argument to use comorbidity patterns as a criterion in reclassifying psychiatric diseases is the following.

Abduction

The fact in need of explanation is that the two diseases d1 and d2 occur far more frequently than their separate frequencies suggest, i.e. they have high rates of comorbidity.

If there is a common cause C for the two diseases d1 and d2, then their high rates of comorbidity are to be expected.

Therefore, it is plausible that the two diseases d1 and d2 have a common cause C.

Advice for disease classification

A disease classification based on a common cause C has important benefits: it will "emphasize risk factors, increase clinical utility, and potentiate research into the cause and prevention of mental disorders" (Andrews, et al., 2009b, p.1999).

If diseases d1 and d2 have high rates of comorbidity, then it is plausible that they have a common cause C (see Abduction).

Therefore, a disease classification that groups diseases d1 and d2 together has important benefits.

Thus, a high rate of comorbidity of two diseases indicates the existence of a common causal background and therefore those diseases should be clustered. It follows that Andrews et al. prefer a classification based on C to a classification not based on C. A complicating factor in understanding the argument is that C is not neatly defined, as the following terms are used for C: common cause (Kraemer, et al., 2007), risk factors for disorders in a cluster, common etiological agent, and existence of higher-order dimensions of psychopathology (Andrews, et al., 2009b). Nevertheless, it is clear that at least some notion of causality underlies the justification of comorbidity as a criterion ('validator') in reclassifying diseases.

Comorbidity as a problem

Kendell and Jablensky see comorbidity in a different way (2003, p.7): "Comorbidity poses a further problem that is becoming increasingly clamant as its full extent is revealed by community studies." That is, the scale of comorbidity between for instance anxiety disorders, depression and addictive syndromes has repeatedly been found to be exceptionally high (Kessler, et al., 2005; Sullivan and Kendler, 1998), which led to increasing disenchantment with the assumption that these diseases are discrete entities. But, what exactly is the problem that comorbidity poses? The answer becomes clear when we unravel the argument starting from the assumption about valid diagnoses:

A diagnosis is valid if and only if it satisfies at least one condition out of 1 and 2 (Kendell and Jablensky, 2003):

1. The defining syndrome, i.e. a set of signs and symptoms, can be separated from neighboring syndromes by a zone of rarity. This criterion means that two syndromes A and B are valid if some individuals in a population suffer from the symptoms of syndrome A, while other individuals have the symptoms of syndrome B, but not many individuals suffer from a mixture of symptoms of syndromes A and B. In this case there is a zone of rarity, which can be demonstrated by statistical techniques such as latent class analyses. The absence of a zone of rarity entails that syndromes A and B are highly comorbid, and that syndrome A cannot be separated from syndrome B in terms of the symptoms suffered by patients.
2. Fundamental, qualitative criteria are part of the disease definition, without being part of other disease definitions with a similar syndrome. Fundamental criteria are "physiological, anatomical, histological, chromosomal, or molecular" abnormalities (p.8). Examples of psychiatric diseases satisfying this category are for instance Down's syndrome, Huntington, Creutzfeld Jacob and fragile X syndrome.

Next, Kendell and Jablensky argue that in psychiatry there are scarcely valid diagnoses. First, most disorders do not satisfy condition 2, since they are defined solely by a set of symptoms. Therefore, most psychiatric disorders have to meet condition 1 in order to be valid. Whether current psychiatric disorders meet condition 1 is doubtful. The few attempts which have been done to demonstrate a zone of rarity have ended in failure, i.e. have not shown a statistical difference between defining symptom sets (Van Loo, et al., forthcoming). Furthermore, the high rates of psychiatric comorbidity could indicate that zones of rarity are not existing.

So, comorbidity poses a problem since it indicates that zones of rarity are lacking between the defining symptom sets of psychiatric disorders. In other words, comorbidity shows that our sets of symptoms cannot be statistically separated from each other. But why is that a problem? Kendell and Jablensky say that if condition 1 is not met, disease definitions will most likely not "survive successful exploration of their biological substrate" (p.8). And "…a diagnostic class … is valid, in the sense of delineating a specific, *necessary, and sufficient biological mechanism*" (p.7). Thus, ultimately, comorbidity is a problem for Kendell and Jablensky since it indicates that most psychiatric disorders do not delineate a necessary, and sufficient biological mechanism (NSBM). Obviously, it follows that the authors prefer a diagnostic class based on this NSBM to a class not based on NSBM.

Comparison of both positions

Interestingly, if we compare the validator versus problem position, eventually the same assumptions regarding comorbidity and causal disease models underlie these both diverging positions. After all, Andrews et al. regard comorbidity as a criterion for reclassifying psychiatric