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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.

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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, Creutzfeldt 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

disorders as (i) comorbidity is an indicator of a common causal structure (C) of diseases and in our current classification system diseases do not coincide with C. Yet, (ii) a classification based on C is preferred to a classification not based on C. Comparably, the evaluation of comorbidity as a problem is justified by the assumptions that (i) comorbidity is an indicator of the fact that current diagnoses do not coincide with a necessary and sufficient biological mechanism (NSBM), while (ii) a classification based on a NSBM is preferred to a class not based on a NSBM. Thus, in principle, both views (i) assume a relationship between psychiatric comorbidity and the absence of causal disease models in current psychiatry, and (ii) endorse a model, in which diseases are defined in terms of their causes. In the end, those positions, which are *prima facie* opposite, can be traced back to the same assumptions. The main difference between both positions concerns their views on the usefulness of the current disease categories. Kendell and Jablensky doubt the value of the current categories in delineating separate syndromes with a specific accompanying biological mechanism whereas Andrews et al. superimpose a new structure on the current categories and thus have less doubt on their usefulness. Nevertheless, the positions are similar concerning important assumptions on causal disease models and comorbidity. Those assumptions will be discussed in the remainder of this paper.

The preference for causal models of disease

Causal models of disease clearly have huge advantages. In the first place, they offer a large increase in understanding and explanation of diseases. Secondly, they increase opportunities to interfere in disease processes. The easiest way to illustrate those advantages is on the basis of the monocausal disease model, in which diseases are defined in terms of a single necessary and sufficient cause. As we saw, this is the model defended by Kendell and Jablensky. A cause is necessary when the disease does not occur without the presence of the cause. A cause is sufficient when the presence of the cause indeed will lead to the disease (Broadbent, 2009; Carter, 2003). E.g., for tuberculosis (TB), infection with tubercle bacillus is necessary (one cannot have TB without the infection) and sufficient for TB to be present. A monocausal model of disease is advantageous as, in the presence of only one cause, all therapeutic or preventive measures in one case should be effective in a second case (Carter, 2003). However, even multifactorial disease models, in which more than one causal mechanism is at stake (Broadbent, 2009), do increase our understanding and offer treatment possibilities as is illustrated by all preventive measures for noncommunicable diseases (Alwan and Agis, 2011). The drive for Kendell and Jablensky for NSBM disease models may be aimed too high, but the quest for causal understanding of disorders is indeed laudable.

Although causal disease models are in principle to advantage, in reality, diseases are defined in a broad variety of ways. In psychiatry, the classification of diseases is almost entirely based on the combinations of symptoms since the introduction of the DSM III in 1980. In the DSM I and II, the description of disorders was so general and brief, that clinicians had to decide largely by themselves whether a patient could be characterized as having the disease or not (Spitzer, 1980). As a consequence it was impossible to assess the efficacy of psychiatric treatments, since criteria for both diagnosis and treatment outcome were lacking (Kendler, et al., 2010). Thus, there was a need for a more standardized way to classify patients with psychiatric disorders. However, there was much disagreement on the causes of psychiatric disorders. For instance, Freudian oriented psychiatrists ascribed symptoms to defensive operations keeping internal conflicts out of consciousness, while other psychiatrists ascribed panic complaints to biological mechanisms or learned avoidance responses. For the advancement of diagnostic consensus among psychiatrists, it seemed more fruitful to exclude causality from diagnoses altogether (Spitzer, 1980). The idea was that the discovery of causal mechanisms and treatment possibilities would benefit from classifying patients in a standardized way based on symptoms.

Nowadays, symptomatic classification of psychiatric disorders is still employed, and not exclusively in psychiatry.

In medicine in general, before the 19th century causal disease models did not exist: extensive lists of causes of a varied nature could lead to one disease. For instance, pneumonia could be caused by contusions of the throat, depression, cooling, or violent effort and fatigue. However, in the 19th century disease modeling shifted. Defining diseases in terms of their causes – instead of their symptoms – turned out to be very fruitful. Once a disease like childbed fever was defined not in terms of symptoms as fever and endometritis, but as a disease due to decaying organic matter, rates of death dropped dramatically (Carter, 2003). Since that time, many diseases have been redefined in terms of their causes.

At the moment, medical diseases are defined in terms of causes but also in many other ways. Some diseases are defined in terms of a certain abnormal state of affairs. Diabetes mellitus, for instance, is “characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both” (American Diabetes Association, 2012, p.264). Another example is heart failure, “a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood” (Hunt, et al., 2009, p.e397). Other diseases are defined in terms of a set of symptoms (e.g., migraine, inflammatory bowel syndrome). Exclusively monocausal or even multifactorial disease models are far from medical reality. The comorbidity debate shows that this fact has not diminished the need for causal disease models in psychiatry.

Causal models of disease and comorbidity

In the previous sections we found that high rates of comorbidity are considered to show that current diagnoses do not coincide with their causes. But what would happen if we defined all diseases in terms of their causes? What kind of comorbidity patterns would then be expected? Would a classification system with exclusively causally defined diseases lead to chance expected comorbidity rates (i.e. $p(d1 \wedge d2) = p(d1)p(d2)$)?

The necessary condition for this to happen is to define diseases in a causally independent way, viz. to exclude by definition all possible causal connections between two diseases. In that case, diseases cannot have common causes, risk factors, nor influence each other's occurrence. This, however, seems a strange condition for the majority of medical diseases. Many diseases are causally connected in several ways. Diabetes mellitus and heart failure, two common diseases mentioned above, co-occur regularly (McMurray and Pfeffer, 2005) and can be used as an example to illustrate possible causal connections between diseases (Fig. 1). First, there are common causes or risk factors for both diseases such as hemochromatosis (American Diabetes Association, 2012; Hunt, et al., 2009). Second, consequences of the one may be causes of the other, as is illustrated by for instance diabetic cardiomyopathy (Boudina and Abel, 2007). Even monocausally defined diseases may have causal links through shared basal mechanisms as protein–protein interactions (Park, et al., 2011) or since the one may increase the chances for the other as in case of HIV and TB (Kwan and Ernst, 2011). Thus, to expect that comorbidity rates will follow chance if we define diseases in terms of causes is expecting too much.

Conclusion

The high rates of comorbidity in psychiatry have led to different and opposing interpretations concerning the meaning of this phenomenon. In this paper, we showed that at least part of the debate concerning comorbidity actually focuses on the wrong subject. Fundamentally, the discussion does not concern comorbidity but the existing models for psychiatric diseases. Therefore, the core issue is what models to adopt for psychiatry. A preference for causal disease models, which have for some time been absent in psychiatry, is underlying both interpretations of comorbidity as a problem versus a validator.

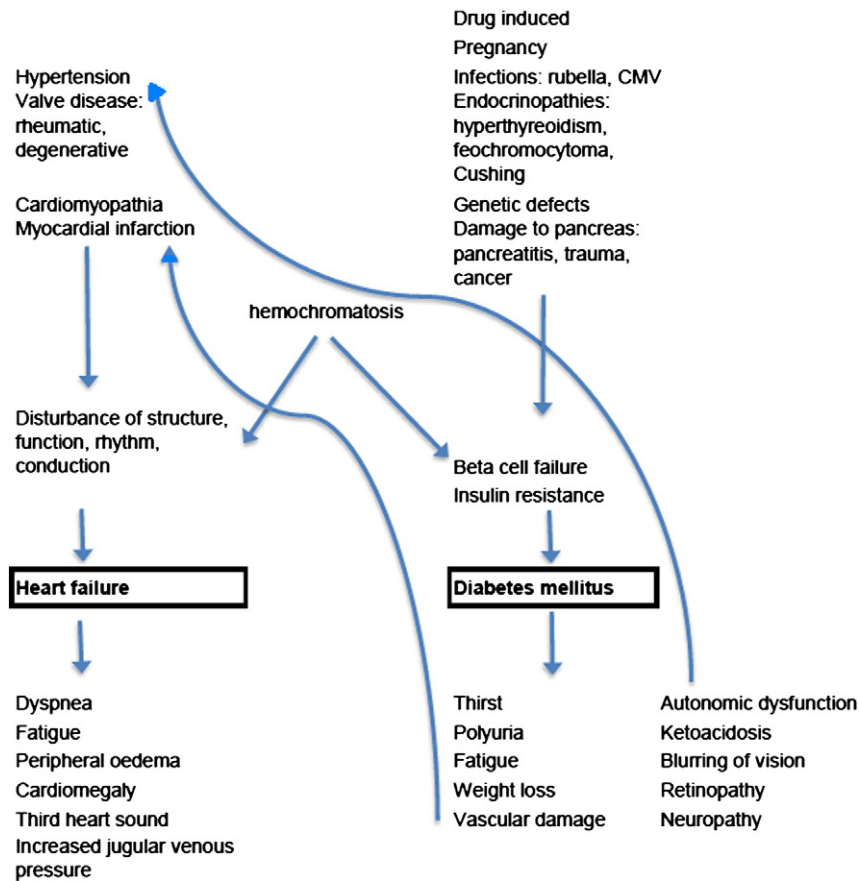


Fig. 1. Causal connections between heart failure and diabetes mellitus.

In terms of usefulness there are great advantages of disease definitions based upon their causes. It increases understanding and possibilities to interfere in undesirable processes. However, we have shown that also in medicine in general a diversity of non-causal disease definitions is used. Furthermore, there are many connections between causally defined diseases underlying the high rates of comorbidity in medicine. The only way to achieve chance expected rates of comorbidity is by defining diseases in terms of completely independent causes. This is quite unlikely, even when we proceed and find out more and more about causal mechanisms of disorders.

Important open ends remain after clarifying this debate on comorbidity. First, the term ‘common cause’ is vague. For sure, the discussed authors do not mean that ‘any cause’ should be adopted in a disease model for psychiatric diseases. However, what counts as a relevant cause for a disease model is an unanswered question. A second open end is the more exact connection between disease models, causal or non-causal, and comorbidity. We argued that at least some comorbidity remains, also in case of causal disease models. But to what extent do the high rates of comorbidity result from the absence of causality in disease models? Those issues will be addressed in a next paper, concerning the role of causality in disease models and the interplay between disease models, population characteristics and comorbidity.

As in other fields of medicine, psychiatric comorbidity will remain a fact of life. The term was originally introduced by Feinstein because it was helpful in the interpretation and generalization of findings from clinical trials. He acknowledged that patients with more diseases might have different treatment outcomes than patients with only one disease. We showed that, currently, the concept of comorbidity functions as an indicator for the absence of causal mechanisms in psychiatric disease definitions, which has a number of disadvantages. The search for causal disease models could resolve part of the problem of Feinstein, since an

increase in our understanding of causal mechanisms can help us focus and evaluate treatments despite the remaining rates of comorbidity.

Conflict of interest statement

The authors declare no conflict of interest.

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