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COMORBIDITIES AND PSYCHOTIC ILLNESS. Part 1: Philosophy and clinical consequences

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SUMMARY

This article aims at addressing the implications of defining 'comorbidity' within the field of psychiatry. We have looked at the standard definition of comorbidity and then discussed whether this definition can be applied to comorbidities in psychiatry. While comorbidities in physical illness are clearly the coexistence of two independent illnesses, Comorbidities in Mental illness are the result of the polygenic nature of mental illnesses, especially in psychotic illness whether schizophrenia or bipolar disorder. As a consequence, often the comorbidities of psychiatric illness are caused by two conditions which have in common the presence of particular single nucleotide polymorphisms (snps), which regulate the metabolism of neurotransmitters or the presence of neurotrophic factors . Thus inevitably, many such comorbidities are inextricably linked. We discuss the consequences of this form of comorbidity for the description, classification, and risk profile of mental illness.

Key words: *comorbidity - psychiatric illness - single nucleotide polimorphisms - neurotrophic factors*

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INTRODUCTION

In order to define comorbidity as is generally used, we referred to its definition and description in Wikipedia, in order to use a defenition which is commonly and easily available. Here we found that there are differences in the term's use in general medicine and in psychiatry which lead to some controversy. Hence in the first few paragraphs of this article we depend on the discussion as illustrated by Wikipedia.In medicine, comorbidity can be described as two disorders of different oetiology which coexist in the same person.It has been usual to also use this definition in mental health. Thus, in medicine, the term "comorbid" can mean either several medical conditions existing simultaneously but independently with another condition, or it may mean the existence of several related medical conditions (Valderas 2009).

In psychiatry and related subjects, comorbidity refers to the presence of more than one diagnosis which occur in the same person at the same time.

The reality is that, in psychiatric classification, comorbidity does not necessarily imean the presence of multiple diseases, but instead the term comorbidity may simply demonstrate that currently we are not able to provide a single diagnosis which accounts for all the symptoms (First 2005).

DEFINING COMORBIDITY

It is the case that in the DSM Axis I, Major Depressive Disorder is a very common only listed as a comorbid disorder.

This is hardly surprising because if a person is mentally ill, that person may very well be low in mood due to the consequences of the illness itself.

On the other hand, the Axis II personality disorders are often criticized because the rates when these are described as comorbidities are seen as excessively high, suggesting that these categories of mental illness may be too imprecisely described to be usefully valid for diagnostic purposes and, therefore not useful in deciding how treatment resources need to be deployed.

This problem is illustrated by the difficulty in the differential diagnosis between Borderline PD and Bipolar Disorder (Agius 2012). It is in situations like this that the possibility of discribing both conditions as being co-morbid which sometimes suggests that the concept of co-morbidity may be used to deal with the presence of symptoms which cannot easily be fitted into conventional diagnostic criteria of eithe condition.

The term 'comorbidity' is relatively new. It was introduced into medicine by Feinstein (1970) to describe cases in which a 'distinct additional clinical entity' (Feinstein 1970) occurred in a patient who had an ongoing main medical condition.

The term 'comorbidity' has recently become very common in psychiatry,but it has been argued that its use to indicate the presence of two or more psychiatric diagnoses occuring together may be to be incorrect because in many cases it is doubtful whether the two diagnoses are in reality two different clinical conditions or are in fact multiple manifestations of a single clinical condition.

The view has been expressed that because '"the use of imprecise language may lead to correspondingly

imprecise thinking', this usage of the term 'comorbidity' should probably be avoided" (Maj 2005).

It has ben argued that psychiatric comorbidity is a conceptual anomaly which has led to a crisis in psychiatric classification (Aragona 2009), and a review of this question has described comorbidity as 'an epistemological challenge to modern psychiatry' (Jakovljević 2012).

COMORBIDITY AND PSYCHOTIC ILLNESS

Psychotic illnesses are classically divided across the 'Schizophrenia Spectrum' into two groups; Schizophrenia and Bipolar Disorder, with a group lieing between these poles called 'Schizoaffective' which have both the characteristics of schizophreniform illness (positive and negative symptoms) and those of mood disorders.

This seems to be reflected in the genetic makeup of each individual patient, so that, given that the genetics of psychosis is polygenic (Craddock 2005), patients with psychotic illness have a each a collection of single nucleotide polymorphisms (snps) so that the genes patients have are reflected in the illness they get (Craddock 2005).

The implication of this is that, in psychotic illness, one can describe, as McGorry (in his training manual for early intervention in psychosis) and many psychologists do, each illness as a group of overlapping syndromes; Positive symptoms, Negative symptoms, which when severe can be described as the 'deficit syndrome', manic symptoms, depressive symptoms, which if severe could be described as melancholia.

Arguably, then, each of these groups of symptoms can be described as a syndrome in their own right, which exists in each patient 'comorbidly' with the other syndromes. There is one factor which however binds them together- that many of the snps concerned- those involved with COMT, MAO, and BDNF for example will, by their very nature of their function in cathecolamine metabolism (COMT and MAO) or in neurogenesis (BDNF) affect all the different syndromes, and can thus be seen as unifying factors causing these symptoms within each patient-so that, indeed 'the genes patients have are reflected in the illness they get'.

Other symptoms exist in psychotic patients which must be seen as co-morbid. These include Drug and Alcohol Abuse, which leads to the concept of 'Dual Diagnosis', anxiety disorders and Post Traumatic stress disorder, which, it has been suggested, may be iatrogenic as a result of the admisson of young persons coersively into hospital (McGorry 1991).

With anxiety disorders we must also include Obsessive Compulsive Disorder. Anxiety can be an important factor in psychotic illness- verging into severe paranoia.

There is an important overlap of OCD symptoms in Psychotic illness ,affecting about 4% of patients (Jones 2006) which often leads to important diagnostic disputation an to whether the patient has severe OCD with some psychotic symptoms or whether the patient has schizophrenia with some obsessive traits.

OCD traits have been described in At Risk Mental States, First Episodes and in Chronic Schizophrenia, in other words at all stages of psychotic illness (Zink 2014).

It goes without saying, again that both Serotonin and Dopamine pathways are involved in Anxiety and OCD as well as psychosis, and that they modulate each other , thus giving rise to the possible co-morbidity (Milad 2012).

The same may be said of PTSD, however McGorry and others point out that PTSD can be an iatrogenic co-morbidity; caused by trauma during the diagnostic and admission process, and that more patient friendly procedures could reduce this risk (McGorry 1991).

On the other side of the schizophrenia spectrum, in bipolar disorder, co-morbidities can occur frequently, in both bipolar I and Bipolar II patients, and have an important influence on prognosis. Anxiety disorders are known to be frequent comorbid factors in bipolar patients, and they worsen the prognosis (Pakpoor 2013).

Recently, a genetic link between comorbid anxiety disorders (AD) and bipolar II disorders (BP-II) has been described (Wang 2014). It has been suggested that the genes involved in metabolizing dopamine and encoding dopamine receptors, such as aldehyde dehydrogenase 2 (ALDH2) and dopamine D2 receptor (DRD2) genes, may be important to the pathogenesis of BP-II comorbid with Anxiety Disorders (Wang 2014). Wang et al. showed that there is a statistically significant association between the dopamine D2 receptor (DRD2) Taq-I A1/A2 genotype and Bipolar II with Anxiety Disorder (Wang 2014). Furthermore Wang showed that there was a significant interaction of the DRD2 Taq-I A1/A1 and the ALDH2*1*1 genotypes in BP-II without AD (Wang 2014).

Thus Wang et al. demonstrated that 'there is a unique genetic distinction between BP-II with and without Anxiety Disorder' (Wang 2014), and they also showed that there is an association between DRD2 Taq-I A1/A2 genotype and BP-II with AD(Wang 2014). Wang et al. also showed that there is evidence that the ALDH2 and DRD2 genes interact in BP-II, particularly BP-II without AD (Wang 2014).

We are pleased that the work of Wang et al, cited above came to light while we were drafting this article, as it indeed illustrates that genes involved in dopamine metabolism and in production of D2 receptors are directly involved in the condition 'Bipolar Disorder with comorbid anxiety.

This work will support the general argument about comorbidities which we will make in the conclusion of this article.

OCD is a common comorbidity. These patients are difficult to treat, as high dose SSRIs, useful for OCD, can make bipolar illness worse. Recent studies suggest that mood stabilisation is the most important intervention in these patients, the OCD being treated also with SSRIs and psychotherapy (Darby 2011).

Again the same points can be made about the comonality of the polymorphisms mentioned above to both the bipolar illness and the anxiety and OCD components (Kontis 2011).

Another common co-morbidity with bipolar disorder is migraine,with a genetic overlap existing in the two conditions (Oedegaard 2010).

Some patients may have both the criteria for borderline personality disorder and bipolar disorder, with mood stabilisation therefore being an important part of treatment, while psychotherapy is necessary to treat the borderline symptoms. Ofter atypical antipsychotics turn out to be the most useful mood stabiliser in these patients (Elisei 2012).

Our group have recently discussed epilepsy as a comorbid condition in bipolar disorder (Holland 2012, 2013), and here we have raised numerous ways in which the neurobiology of these two conditions are intertwined.

We would also like to put on record a further important though unusual co-morbidity of Bipolar disorder; that with ADHD. These patients are, in our experience, often characterised by marked impulsivity related to the ADHD and serious suicide attempts. It has been suggested that sometimes. Patients with ADHD in childhood may develop into Bipolar disorder in Adulthood (Rozencweig 2013).

However one very important co-morbidity in bipolar disorder is polydrug and alcohol abuse. Very often difficult to treat patients with substance abuse problems in fact have underlying bipolar disorder, which first needs to be stabilised before the substance abuse can be got under control (Grech 2014).

DISCUSSION

Comorbidities in psychotic illness, especially if not assessed and treated adequately,can often be the explanation of patients not improving adequately and recovering, and can explain the presence of many patients being chronically involved in mental health services.

With failure to improve often comes increased risk of suicide and self harm or harm to others. It is therefore important that comorbidities in psychotic illness are adequately identified and treated.

However, we here present the argument that, given that there are often genetic commonalities which affect both conditions, then in Psychiatry, it is imprecise to describe many conditions as being ‘comorbid’.

While comorbidities in physical illness are clearly the coexistence of two independent illnesses, Comorbidities in Mental illness are the result of the polygenic nature of mental illnesses, especially in psychotic illness whether schizophrenia or bipolar disorder. As a consequence, often the comorbidities of psychiatric illness are caused by two conditions which have in common the presence of particular single nucleotide polymorphisms (snps), which regulate the metabolism of neurotransmitters or the presence of neurotrophic factors or other neuroactive compounds. Thus inevitably, many such comorbidities are inextricably linked. As a consequence, it can be expected that patients with such comorbidities as ‘Bipolar Disorder with OCD’are different phenotypes from those who only have ‘Bipolar Disorder’, and will always have a prognosis which is different, indeed often worse, than either of the conditions individually, since the interplay of the different polymorphisims involved can be expected to be the same whenever the patient relapses.

CONCLUSION

Thus, we suggest that conditions such as ‘Bipolar Disorder with OCD’, or ‘Bipolar Disorder with Anxiety’ or ‘Schizophrenia with obsessional features’ could be described as separate conditions with a different prognosis from Bipolar Disorder alone or Schizophrenia alone, since in the ‘comorbid‘ patients, there exist snps which directly affect such conditions as cathecolamine metabolism or neurogenesis so as to affect both conditions, so that their prognosis is always different from each condition separately. This supposition is supported by the recent publication by Wang et al. which identifies different polymorphisms involved in bipolar disorder with or without anxiety and their interactions (Wang 2014).

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