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ARE THERE DIFFERENT GENOTYPES IN BIPOLAR II AND BIPOLAR I DISORDER AND IF SO, WHY THEN DO WE TEND TO OBSERVE UNIPOLAR DEPRESSION CONVERTING TO BIPOLAR II AND THEN CONVERTING TO BIPOLAR I?

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SUMMARY

We review the recent literature in order to establish the importance of a spectrum for bipolar affective disorder, and that unipolar depression, bipolar II and bipolar I are discrete entities that may however evolve in sequence. We discuss clinical, genetic and neurobiological data which illustrate the differences between bipolar I and bipolar II. To fit the data we suggest a series of multiple mood disorder genotypes, some of which evolve into other conditions on the bipolar spectrum. Thence we discuss the nature of the bipolar spectrum and demonstrate how this concept can be used as the basis of a staging model for bipolar disorder.

Key words: *bipolar I disorder - bipolar II disorder - unipolar depression – genotypes - bipolar spectrum - epigenetics*

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INTRODUCTION

Drawing from both clinical observations and Kraeplin's original concept of manic depressive illness, the concept of a 'bipolar spectrum' as a collection of subtypes of bipolar disorder (BD) was first described by Akiskal and Pinto in 1999 (Akiskal 1999). More recently, Angst has proposed a continuum model for BD including depression and psychotic states (Angst 2007). Current DSM-V guidelines recognise bipolar I disorder (BD-I) and bipolar-II disorder (BD-II), with cyclothymic disorder also included within the bipolar spectrum disorders.

The concept of the bipolar spectrum was immediately controversial.

In 1995, Winokur et al. had argued against the concept of a bipolar spectrum after finding that patients with BD-I had a higher incidence of familial mania than seen in patients with unipolar depression (UPD), showing that these two conditions do not share familial risk factors and are therefore separate illnesses.

In contrast, Chiaroni et al. (2005) found that the incidence of a cyclothymic temperament in healthy relatives increased as the severity of a family history of BD increased, from the lowest rates of cyclothymic temperament in subjects with a negative family history of affective disorders to the highest in those with at least one first degree relative with BD-I. From this they concluded that a spectrum concept of BD was supported, with cyclothymic temperament acting as a behavioural endophenotype for BD. Later observations by Tavormina and Agius (2007) have supported the inclusion of UPD in the spectrum of bipolar disorders, as part of an attempt to define the criteria that must be fulfilled by diseases in order to be considered as part of a spectrum. BD and major depressive disorder (MDD) were analysed in terms of these criteria and it was found that a two dimensional spectrum fits BD and MDD in many respects (Rogers 2012).

Birmaher and Axelson (2006) reported that the longitudinal course of BD in children and adolescents is fluctuating, with rapid cycling between symptom polarities, and encompasses a spectrum of symptom severity. They noted the difficulties in diagnosing and treating children and adolescents with BD and hence argued the importance of utilising a bipolar spectrum model to facilitate early diagnosis and intervention in this group (Birmaher 2006).

Part of the difficulty in defining a bipolar disorder spectrum lies in the two interpretations of a 'spectrum'.

In the first type of spectrum, conditions which are allied or similar in many ways are seen to evolve, one into the other, as a matter of course. A spectrum of this sort describes the evolution or longitudinal course of a particular illness over time, with the progression between conditions determined by underlying biological processes. This form of spectrum is analogous to the staging of an illness, as seen in other conditions such as cancer (Edge et al. 2010).

A second form of spectrum is the situation in which a number of different conditions lie side by side and have similar characteristics or are analogous to each other, but are nevertheless discrete and cannot interconvert. The original and most obvious example of this is white light, being composed of a mixture of different wavelengths that can be split by a prism into a spectrum of colour. Since red, yellow and blue light are different in wavelength from each other, they cannot turn one into another, and each is therefore a separate condition (Newton 1704).

The issue therefore arises: given that a 'bipolar spectrum' has been described, which of these two types of spectrum is it? This is an important question, since underlying it is the issue as to whether bipolar illness is one condition in different stages of development, so that prognosis can be improved if dealt with at an early stage, or whether UPD, BD-I and BD-II disorder are different conditions, each with potentially different treatment and prognosis. We go on to review current evidence and knowledge in an attempt to answer this question.

Phenomenological differences between unipolar depression, bipolar II and bipolar I illness

Early in the development of the concept of the bipolar spectrum, it was reported that there were differences reported between UPD, BD-II and BD-I.

Angst (1995) reported on a 27 year prospective study of 186 patients with UPD and 220 patients with BD who met DSM-III criteria for major depression or mania. The patients were classified into bipolar disorders (including BD and bipolar schizoaffective disorder) and unipolar disorders (UPD and unipolar schizoaffective disorder). Differences were observed between bipolar and unipolar disorders: moving along the spectrum from UPD to BD, the age of onset decreased, with a greater number of shorter episodes and more periodicity.

In another study, 135 patients with BD-I were compared to 71 BP-II patients with similar demographic characteristics and ages of onset over 10 years (Judd et al. 2003). Several differences were noted between the groups: BD-II patients had a higher lifetime prevalence of anxiety disorders, particularly social and simple phobias. Their illness followed a more chronic course and had more major and minor depressive episodes and shorter inter-episode well intervals. However, first episodes of BD-I were more acutely severe.

In terms of character traits, Zaninotto et al. (2015) found that BD-I patients exhibited higher self-transcendence than was seen in BD-II and MDD. A similar temperament profile was seen in BD-II and MDD in this study, with high harm avoidance and low self-directedness. Shapero et al. (2015) found that there were distinct cognitive styles in BD and MDD. Joyce et al. (2004) reported that BD patients displayed higher rates of borderline, schizotypal and histrionic personality traits than MDD patients. Oedegaard et al. (2008) showed that dissociative experiences were more frequent in BD-II than in MDD patients.

Vieta et al. (1997) compared the course and suicidal behaviour of 38 patients with BD-I to 22 with BD-II, finding no significant difference with regards to suicidal behaviour variables and stating that there was little use in analysing suicide rates to distinguish between the two groups. BP-II patients had fewer hospitalisations and presented less frequently with psychotic symptoms, but a greater frequency of suicidal episodes than BP-I patients. It has also been suggested that while the prevalence of suicidal behaviour in BD-I and BD-II is similar, the risk factors for it may differ between the two conditions (Valtonen et al. 2005).

Benazzi (2003) discussed the possibility of a continuum between BD-II and MDD, studying 308 BD-II and 236 MDD outpatients who presented with a major depressive episode. Although there were significantly more atypical features and depressive mixed states in BD-II than in UPD, further analysis revealed a link between atypical and early onset UPD and BD-II. BD-II patients were not significantly different from those with atypical UPD with regards to age of onset, recurrences and BD-II family history, despite being significantly different from patients with typical UPD within these same parameters. BD-II patients were significantly different from late onset UPD, but notably not early onset UPD, regarding atypical features, recurrences and BD-II family history. From this, Benazzi concluded that there were no phenomenological differences between BD-II and atypical or early onset UPD, even going on to state that most of the observed differences seen with typical UPD disappeared when patients were matched for age of onset.

Mitchell et al. (2001) compared the clinical features of depression in 39 BD-I patients with depression in 39 matched MDD patients. Similarly to previous studies (Mitchell et al. 1992), they found little difference in severity of depression between the two groups. However, it was noted that BD-I patients were more likely to display psychomotor related and atypical depressive features, supporting Benazzi's proposed link between BD and atypical UPD.

Again looking at depression, Akiskal and Benazzi (2005) found a higher prevalence of BD-II (at 56.8%) than UPD in a cross section of patients presenting with depressive episodes. Compared with MDD, BD-II patients were significantly younger at the onset of their first major depressive episode and also differed on other clinical aspects, including having higher rates of atypical features and a stronger family history of BD.

Solomon et al. (2006), looking at depressive episodes in a large cohort of patients with BD and UPD, proposed a new screening instrument for BD (the Screening Assessment of Depression-Polarity – SAD-P). This was based on the three most common factors that distinguished between unipolar and bipolar major depression: the presence of delusions during the current episode, an increased number of prior episodes of major depression, and a family history of major depression or mania. An increased number of previous depressive episodes over a lifetime history has also been seen in elderly patients (Lee et al. 2014).

In a study similar to Solomon et al., Frankland et al. (2015) found that BD-I was distinguished from MDD with regards to greater psychomotor retardation and more psychotic features, while BD-II was more likely to show more mixed features.

Evidence from Leonpacher et al. (2015) also supports this. They found that out of 34 depression-related clinical features, the following were significantly more common in depression in BD-I than MDD: delusions, psychomotor retardation, incapacitation, greater number of mixed symptoms, greater number of episodes, shorter episode length and a history of experiencing a high after depression treatment. A higher number of mixed symptoms and feeling high after an antidepressant were the only two features to distinguish depression in BD-II from MDD.

In terms of trait characteristics in patients with a major depressive episode, Dervic et al. (2015) saw high lifetime impulsivity, aggression and hostility in B, with more impulsivity and lifetime aggression in BD-I than BD-II and greater hostility in BD-II than BD-I. BD patients were more likely to have an earlier illness onset and commencement of treatment than patients with UDP, as well as a stronger family history for mania, more previous affective episodes and more current psychotic and subsyndromal manic symptoms.

When comparing depressive episodes in BD-I and BD-II, Brugue et al. (2008) also found clinically significant distinguishing factors: major depression in BD-I was more likely to be associated with melancholia and preceded by history of psychotic symptoms, whereas depression in BD-II was more strongly linked with rapid cycling and having experienced atypical symptoms, similarly to what was seen by Benazzi and Mitchell et al.

BD-II has also been linked with a greater proportion of time spent in depressive states (a 40% increase when compared to BD-I) and a higher proportion of time spent ill generally (Mantere et al. 2008). This was found to be due to a higher frequency rather than a longer duration of depressive episodes, as may be expected if rapid cycling were more common in BD-II. In contrast to this, Pallaskorpi et al. (2015) concluded that there was little difference in proneness to depressive states in BD-I and BD-II: no difference in time spent in depressive states persisted once confounders were controlled for. 90% of BD patients had recurrences and most had multiple.

A spectrum of severity for depressive states in BD was supported by evidence from Moreno et al. (2011), who found that severity of depressive states was highest in BD-I, followed by BD-II and then MDD. This may have in turn led to an observed range of decreases in quality of life along the same spectrum. Severity was due not only to having both more types of depressive symptoms and a greater number of them, but also due to an increased presence of co-morbidities including personality disorders, substance abuse and anxiety disorders. In contrast to other studies, Moreno et al. found that BD-I patients experienced a higher number of lifetime major depressive episodes. Both BD-I and BD-II patients were seen to have experienced their first major depressive episode an average of ten 10 years earlier than in MDD.

Kiejna et al. (2006) assessed 246 patients who had been given a diagnosis of a recurrent unipolar affective disorder, looking at the frequency of BD traits and symptoms. In these patients, UPD was re-confirmed in only 32.9%: 19.5% had BD-I, 35% had BD-II and 12.6% had a bipolar disorder not otherwise specified. Having an onset of depression before 25 years of age increased the risk of all three types of BD. Patients with UPD were more likely to be professionally active, with a shorter duration of disorder and fewer depressive episodes.

Baek et al. (2011) concluded that there were sufficient differences between BD-I and BD-II to regard them as separate conditions, looking at various aspects of the patient's history. For example, more rapid cycling and seasonality and a higher frequency of depressive episodes were seen in BD-II. Regarding the depressive symptoms themselves, psychomotor agitation, excessive guilt and suicidal ideation were more common in BD-II. There was also a higher lifetime frequency of co-morbidities, especially phobias and eating disorders. Regarding mania, elated mood predominated in BD-II, while elated and irritable moods were seen equally in BD-I. Baek et al. did however make the point that the current clinical distinguishing factor between BD-I and BD-II (the presence of mania vs hypomania) is fairly arbitrary and ambiguous.

In this vein, Bega et al. (2012) identified multiple differences (other than mania vs hypomania) that distinguished BD-I and BD-II in a large cohort (935 BD-I and 494 BD-II patients). Predictors of BD-I included depressive symptoms (such as weight gain, fidgeting, feelings of worthlessness and difficulties with responsibilities), medications for depression, a history of suicide attempts, unemployment, specific phobias and Cluster C traits. Choi et al. (2011) studied seasonal and premenstrual changes in mood in BD-I, BD-II and controls and found that these changes were greater in patients with BD, linking this to a common biological mechanism for these cyclic conditions. The differences were greater (showing higher scores on the two screening tools used) in BD-II than BD-I for both seasonality and premenstrual syndrome severity. Again, this may link to the higher incidence of rapid cycling in BD.

The above literature describes differences in different aspects of the phenomenology of BD-I, BD-II and UPD, supporting a model of three different but related illnesses. However, we must now turn to the literature which suggests that it is possible for patients to convert from UPD to BD-II to BD-I.

Conversion between Unipolar Depression, Bipolar II Disorder and Bipolar I Disorder

From the beginning of the concept of the bipolar spectrum, it was reported that UPD could convert first to BD-II and then to BD-I. In some circles this began to be seen as proof of the bipolar spectrum concept.

In 1978, Angst et al. reported that 10% of the 159 cases of UPD admitted to the Psychiatric University Clinic of Zurich between 1959 and 1963 had a change of diagnosis to bipolar affective illness in the time period up to 1975. This change in diagnosis was particularly common in UPD patients who had three or more depressive episodes and, significantly, could not be wholly attributed to initial diagnostic error.

In another longitudinal study, Coryell et al. (1995) studied 932 patients with non-bipolar MDD or schizoaffective disorder, BD-I or BD-II over a course of 10 years. Of the initially non-bipolar patients, 5.2% developed mania (demonstrating a change to BD-I), with the highest risks in those with psychosis and a family history of mania. 5.0% developed hypomania, indicating a shift to BD-II. Risk factors for this switch were chronicity of the index episode and a younger age at intake and onset. Coryell et al. interpreted these figures as showing the stability of the initial diagnosis, arguing for the separation of non-bipolar disorders, BD-II and BD-I.

Looking at the factors which could predict a conversion from MDD to BD, Akiskal et al. (1995) studied 559 unipolar MDD patients over 11 years who completed self-report personality measures during MDD episodes at the start of the study. 3.9% of the MDD patients converted to BD-I over the 11 years, with the only factors differentiating these converting patients from those who stayed with a diagnosis of MDD being the presence of psychotic symptomatology and greater acuteness and severity of their MDD. 8.6% of MDD patients converted to BD-II over the same time, however there were many more differences between the converters and non-converters in this case. Their MDD began at an earlier age and had a more 'protracted and tempestuous' course, with shorter intervals of being well. Temperamental instability during MDD episodes was a predictor of conversion to BD-II, with a 91% sensitivity prediction of conversion possible using the three self-report factors mood lability, energy-activity and daydreaming. Akiskal et al. suggest that these temperamental differences may be better than the presence of hypomanic episodes as a method of defining BD-II.

It is of interest that this ‘classical’ description of conversion from UPD to BD-II or BD-I occurs only in a relatively small number of patients, and that distinct phenotypes are described for the three conditions.

Similarly to the Akiskal et al. study, a study of 80 children and adolescents with depression (Kochman et al. 2005) found that 35 (43%) could be diagnosed with BD at the end of a 2 year follow up, and that conversion to BD was more likely in those children with a cyclothymic temperament at the beginning of the study. In this study, the BD that resulted at the end of the two years was mostly characterised as having rapid mood shifts with associated conduct disorders, aggressiveness, psychotic symptoms and suicidality.

Another study in children and adolescents (Axelson et al. 2011) found that of 140 patients with BD-NOS (not otherwise specified), 31 (22%) progressed to BD-II and 32 (23%) progressed to BD-I (with 9 patients progressing from BD-NOS through BD-II to BD-I). Conversion was associated with a first or second degree family history of mania or hypomania. Follow up occurred for a mean of 5 years, but the median time from intake to conversion was only 58 weeks.

In an adult cohort of 57 subjects with initial cyclothymia or BD-NOS, 42.1% progressed to BD-II and 10.5% progressed to BD-I over a 4.5 year follow up (Alloy et al. 2012). 17.4% of 144 individuals with initial BD-II progressed to BD-I over the same time. This study looked at non-patient young adults who had high General Behaviour Inventory scores and 'soft' bipolar spectrum disorders diagnosed in childhood or adolescence. Early age of onset and high impulsivity predicted conversion to BD-I. It was also found that progression to BD-II was associated with a high BAS (behavioural approach system) sensitivity, supporting the bipolar spectrum concept. BAS is a model of BD that attributes the condition to hypersensitivity of a behavioural-motivational system. If, as was shown here, high BAS sensitivity is associated with a higher rate of progression to BD, then a spectral model of BD is supported.

Lower rates of conversion to BD were reported by Gilman et al. (2012): 4% of individuals transitioned to BD from MDD over three years. Here, neither age of onset nor the presence of atypical features were associated with conversion, while generalised anxiety disorder and social phobias were associated. Demographic factors associated with conversion to BD included black race/ethnicity, younger age and lower levels of education. Environmental factors included a history of child abuse and problems in the patient's social support group in the previous year.

Boschloo et al. (2014) found that 20.6% of patients with MDD developed manic symptoms (15.9%) or mania/hypomania (4.7%) over four years, again supporting the concept of a bipolar spectrum. Factors associated with this progression included initial isolated manic symptoms and co-morbid alcohol dependence. Low education was associated only with a development of manic symptoms, while the development to a manic or hypomanic episode was associated with male gender, childhood trauma and severity of depressive symptoms.

Woo et al. (2015) found that 18.4% of 250 MDD patients developed BD over five years. They looked at bipolar spectrum disorder diagnostic criteria (BPSD) and found that these criteria predicted conversion with a high sensitivity (0.870) and specificity (0.917). Other factors associated with conversion included a family history of BD, early onset of depression, brief major depressive episodes and factors associated with antidepressants (for example antidepressant induced mania or hypomania, wear-off of antidepressant effect, and resistance to antidepressants).

Looking at an international cohort of 61,392 patients, Merikangas et al. (2011) came to the conclusion that there was sufficient progression of clinical features in sub-threshold BD to BD-I to support the validity of a bipolar spectrum. For example, severity of symptoms (both manic and depressive) and suicidal behaviour increased from sub-threshold BD to BD-I. Some features, for example role impairment, were similar across different BD subtypes.

What is interesting in these accounts is that only a small proportion of patients are described as undergoing the progression from UPD to BD-II or BD-I. Also, certain characteristics that are associated with conversion are reproduced in each paper quite consistently. These characteristics include those that predict the change to each condition and the characteristics of depressed patients with each of the three illnesses. The consistency of these findings seems to suggest different phenotypes for unipolar (non converting) depression, BD-II and BD-I.

We now will describe what is known about the neurobiology and genetics of the bipolar spectrum.

Neurobiology of Bipolar Disorder

Cognitive changes

Schenkel et al. (2012) studied cognitive dysfunction in children with BD, and saw a progression of impairment from healthy controls to BD-II to BD-I. BD-I patients performed significantly worse than controls in all aspects of cognitive function, including attention, executive function, working memory, visual memory, and verbal learning and memory. BD-I patients also performed worse than BD-II in all the above aspects apart from working memory. BD-II patients had a level of cognitive dysfunction that was intermediate between healthy controls and BD-I, performing worse than controls only in verbal learning and memory. These findings support the concept of a bipolar spectrum.

In contrast, Pålsson et al. (2013) found that there was no difference between BD-I and BD-II with regards to cognitive impairment in adult patients (although both groups of BD patients performed worse than healthy controls). They did however find that current antipsychotic treatment was the strongest predictor of cognitive impairment, and suggested that this could account for findings such as those shown by Schenkel et al. (2012).

Neuroimaging

Loss of grey matter in BD, as seen on MRI scans, has been demonstrated by McDonald et al. (2006). Armone et al. (2009) further characterised this loss, finding reductions in whole brain and prefrontal lobe volume, as well as increases in both globus pallidus and lateral ventrical volume. Compared with schizophrenia (which also shows loss of grey matter), BD is associated with enlarged amygdalae and smaller lateral ventricle volume. BD has also been shown to be associated with reduced hippocampus volume, previous contrary evidence perhaps being explained by the neuroprotective effect of lithium (Hajek et al. 2012).

McGrath et al. (2004) performed a literature review looking at differences between BD-I and BD-II regarding both neuroimaging and metabolic differences. In both modalities, few differences were seen and those that were found were inconsistent between studies. They did however note that only a small number of studies compare BD-I and BD-II and that even these may not be adequately powered to detect small differences.

One more recent study that did support differences between BD-I and BD-II was by Ha et al. (2009) when comparing MRI scans of BD patients and healthy controls. They observed grey matter reductions in the ventromedial prefrontal regions (as well as perhaps the anterior limbic cortices, if less conservative statistical thresholds were used) in both BD subtypes when compared to controls. BD-I patients showed deficits that were not evident in BD-II in bilateral frontal, temporal, parietal and parahippocampal cortices. Ha et al. suggested that the different patterns of grey matter reductions could support different neurobiological characteristics of BD-I and BD-II.

White matter deficits have also been observed in BD. Liu et al. (2012), using diffusion tensor imaging, found differences between BD-I and BD-II that supported different underlying neuropathological substrates. Both BD-I and BD-II patients showed fibre impairments in the thalamus, anterior cingulate and inferior frontal areas, while only BD-II patients showed greater changes in the temporal and inferior prefrontal regions. In BD-I, fibre impairments were mostly right sided and related to cognitive dysfunction, while in BD-II changes were largely bilateral and were more strongly linked with emotional processing.

Fractional anisotropy (FA) values (indicating white matter bundle coherence) of the subgenual anterior cingulate cortices were correlated with working memory performance in both subtypes of BD, while executive function was correlated with FA values of the right inferior frontal area in BD-I, and the left middle temporal area in BD-II. In BD-II only, FA values of the left middle temporal area were correlated with scores of the YMRS (young mania rating scale) and FA values of inferior prefrontal areas were correlated with the number of hypomanic episodes.

Caseras et al. (2015) also found evidence to support different underlying neuropathological substrates for BD-I and BD-II, using behavioural, neurofunctional and neuroanatomical methods. During the presentaion of emotional distracters during an attention control task, both subtypes of BD displayed increased BOLD (blood oxygenation level dependent) responses in the amygdala, NA (nucleus accumbens) and dlPFC (dorsolateral prefrontal cortex) that were associated with increased emotional reactivity. However, functional connectivity between the dlPFC and amygdala was increased in BD-II, but decreased in BD-I. As the dlPFC acts to downregulate amygdala activity, this suggested that this mechanism of downregulation is enhanced in BD-II in order to compensate for an overactive amygdala, resulting in a normal reaction time in the task and no deficits in cognitive function compared to controls. In contrast, in BD-I, the inefficient downregulation of an overactive amygdala by the dlPFC means that reaction time is slowed, indicating a general working memory deficit. Higher cognitive resources are recruited in the parietal and prefrontal 'working memory areas' to try to compensate for this deficit. This evidence could be interpreted as supporting a bipolar spectrum, with amygdala hyperactivity acting as an initial step in BD-II, and dlPFC-amygdala connectivity degenerating and causing the progression from BD-II to BD-I.

An fMRI study that also supports a bipolar spectrum in terms of dlPFC activity and working memory was described by Dell'Osso et al. in 2015. During a working memory task, BD patients showed greater right dlPFC engagement than controls, regardless of the working memory load. This increased engagement was greatest in BD-I, with an intermediate level between controls and BD-I seen in BD-II. As with the Caseras study, the dlPFC hyperactivity suggests inefficient working memory processing. However, this study was not very large (15 BD-I patients and 13 BD-II) and differences were statistically significant only between BD-I and controls.

SPECT (single positron emission tomography) was used by Chou et al. (2010) to study differences in serotonin transporter (SERT) binding in euthymic BD-I and BD-II patients. SERT levels were significantly lower in the midbrain in BD-I than in BD-II and healthy controls, and this decrease was correlated with the duration of BD-I. This evidence supports distinct subtypes of BD, but provides little support for or against a bipolar spectrum.

Genetics

There have been many descriptions of differences between Bipolar I and Bipolar II at the level of interactions of different genetic single nucleotide polymorphisms.

For example, Lu et al. (2012) found that BD-I patients who had the long allele at 5-HTTLPR (the serotonin transporter gene-linked polymorphic region) had lower harm avoidance than BD-II patients, suggesting a gene-temperament interaction.

Further evidence for the genetic distinction of BD-I and BD-II comes from Lee et al. (2011). They looked at the COMT (catechol-O-methyltransferase) Val158Met polymorphism and the DRD3 (dopamine D3 receptor) Ser9Gly polymorphism in 711 individuals and found that while neither polymorphism, either individually or together, could predict BD-II, the Met/Met genotype of COMT and an interaction between Met/Met of COMT and Ser/Ser of DRD3 could both predict BD-I. The same group have also provided evidence that the Val/Val genotype of the BDNF (brain derived neurotrophic factor) Val66Met polymorphism, and an interaction of this genotype with Ser/Ser and Ser/Gly DRD3 genotypes, can predict BD-II but not BD-I (Lee et al. 2011). Also, an interaction between the Val/Val genotype of the BDNF polymorphism and the A1/A2 genotype of the DRD2/ANKK1 (dopamine D2 receptor/ankyrin repeat and kinase domain containing 1) Taq1A polymorphism was found in BD-II patients, but not BD-I patients or healthy controls (Huang et al. 2012). The fact that different polymorphisms have different predictive power for the presence of either BD-I or BD-II suggests that the two BD subtypes are genetically distinct.

Similar studies looking at BD-II with anxiety disorder (AD) (a common co-morbidity) have also provided evidence for the genetic distinction between BD-I and BD-II. Lee et al. (2013) found that BD-II without co-morbid AD (but not BD-II with AD, or BD-I) could be differentiated from controls on the basis of an interaction between the Val/Val genotype of the BDNF Val66Met polymorphism and the Val/Met and Met/Met genotypes of the COMT Val158Met polymorphism. Chang et al. (2013) found that the DRD3 polymorphism was associated with BD-II with co-morbid AD, and that the BDNF polymorphism was associated with BD-I with co-morbid AD. Also, an interaction between the Val/Val genotype of BDNF and the Gly/Gly genotype of DRD3 was seen in BD-II with AD, but not in BD-II without AD.

The progranulin (GRN) gene has been linked with BD and provides further evidence of genetic distinction between the subtypes (Galimberti et al. 2014). While plasma progranulin levels are significantly lower in both BD-I and BD-II patients than controls, a significantly decreased frequency of the rs5848T allele of GRN was seen only in BD-I. This suggests different pathological mechanisms behind the conditions.

Epigenetics

Apart from single nucleotide polymorphisms, epigenetic influences may be involved in the development of BD-II, mediating the onset or susceptibility to the condition.

D'Addario et al. (2012) looked at BDNF expression in BD, finding it to be reduced in BD-II compared to controls (due to hypermethylation of the BDNF promoter) but not in BD-I. In this study, BD-II patients

tended to have had a longer duration of illness, which may have contributed to the hypermethylation. However, the study provides important evidence that epigenetic mechanisms may be important in the development of BD-II, and that this development may be distinct from that of BD-I.

DISCUSSION

It has been seen in the above discussion that the ability of single nucleotide polymorphisms to predict BD-I or BD-II is supported by data both from neuroimaging and epigenetics to suggest that these conditions have different genotypes.

How then can it be, that one can observe progression from UPD, to BD-II and then BD-I?

It is important to note that none of the papers describing this progression report complete change of the whole observed sample, but rather a change in a proportion of the sample over time. It is also interesting that those patients who do make this progression seem in general to demonstrate a more unstable temperament, displaying anxiety symptoms and instability of mood as is also more commonly seen in BD-II.

Thus it seems likely that in any group of patients presenting initially with UPD due to mood disorder, there will be patients with a number of different genotypes. As a result of these genotypes, and despite the same initial presentation, some will convert to BD and some will not. Most of those who convert to BD will have a genotype consistent with BD-II, often with unstable mood and increased anxiety, and will stay at BD-II. Some, with a different genotype, will undergo further conversion to BD-I. An example of such a model is provided in Figure 1.

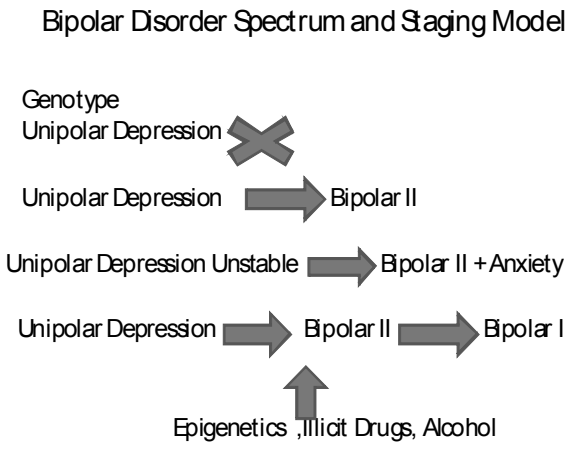

Figure 1. A staging model of bipolar disorder which also takes into account the bipolar spectrum. Different genotypes either do not develop into bipolar disorder or develop into either BD-II, or BD-II with co-morbid anxiety, or BD-I. Epigenetic influences affect all the pathways, as do illicit drugs and alcohol

The above description would explain the pattern of conversion that is seen in clinical practice. In this model, both types of spectra (as described in the introduction) occur: there are a series of distinct yet similar genotypes, but there is also possible conversion of illnesses according to the individual genotype of the patient. This conversion, from UPD to BP-II with or without anxiety, and in some cases on to BD-I, is also subject to epigenetic influences.

This review is only intended to describe the type of spectrum and hence the form of staging system which will describe the longitudinal development of bipolar disorder.

Much in molecular biology will be important in developing models of how the staging system will work and how the different conditions develop into each other, including research into areas that have not yet been able to discriminate between BD-I and BD-II and hence have not been discussed in this review. These include studies on mood stabilising neurons and their deterioration (Kato 2008), circadian rhythm dysregulation (Alloy 2015), early apoptosis (Fries 2014), Hypothalamic-Pituitary-Adrenal axis dysfunction, (Fries 2014) P2X7 receptors (Gubert 2014), BDNF and inflammatory markers (Bücker 2015), impaired endoplasmic reticulum stress responses (Pfaffenseller 2014), histone deacetylase activity and BDNF levels (Stertz 2014).

CONCLUSION

The above model emphasises the huge importance in the clinical evaluation of the patient and of taking a full longitudinal history of the patient, since it is only thus that it is possible to understand how the illness of any one particular patient has evolved. Such a longitudinal history is therefore important in deciding the diagnosis and hence the treatment of the patient.

This understanding of the illness can then be expressed as a staging system (Agius 2014, Grande 2014, Frank 2015), including the stages of First Depressive Episode, Recurrent Depressive Disorder, First Manic Episode, Bipolar II disorder and Bipolar I Disorder. Such a staging system should integrate genetic, epigenetic, neuroimaging and neurocognitive evidence with symptomatology to describe how the disease progresses over time.

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