Psychiatria Danubina, 2012; Vol. 24, Suppl. 1, pp 197–201 *Conference paper*

BIPOLAR II DISORDER AND BORDERLINE PERSONALITY DISORDER - CO-MORBIDITY OR SPECTRUM?

Mark Agius[1,2,3], Jean Lee[2] , Jenny Gardner[3,4] & David Wotherspoon

[1]Department of Psychiatry University of Cambridge, Cambridge, UK
[2]Clare College Cambridge, Cambridge, UK
[3]South Essex Partnership University Foundation Trust, UK
[4]Eastern Deanery, UK.

SUMMARY

We assess the number of patients who we have on the Database of a Community Mental Health Team in the UK who have Bipolar Disorder and Borderline Personality Disorder. We report how many of these have been seen as having both disorders. Hence we discuss the issue as to whether Borderline Personality disorder is to be placed within the bipolar spectrum. We note the difficulties regarding the use of phenomenology alone to decide this problem, and we note the similarities in genetics, neuroimaging observations and neurobiological mechanisms among the following conditions; Bipolar Disorder, Unipolar Depression, Post-traumatic Stress Disorder, and Borderline Personality Disorder. Ethiologies such as Trauma, Abuse, Childhood adversity and exposure to War appear to influence all these conditions via epigenetic mechanisms. Hence we argue that for a spectrum to be proposed, conditions in the spectrum need to be underpinned by similar or common Neuroimaging and neurobiological mechanisms.On this basis, it may be reasonable to include Borderline Personality Disorder within a broadly described bipolar spectrum. New details of the common Neurobiological mechanisms continue to emerge.

Key words: *bipolar disorder – borderline personality disorder - unipolar depression - post-traumatic stress disorder – trauma – abuse - childhood adversity - war exposure – neuroimaging – genetics – epigenetics - neurobiology*

* * * * *

INTRODUCTION

It has frequently been suggested that Bipolar II Disorder and Borderline Personality disorder could be seen as both being part of the bipolar spectrum, while many papers have been written to suggest that Borderline Personality disorder is often co-morbid with Bipolar II Affective disorder. Clearly, being part of a spectrum of disease implies a much closer relationship between the two entities than a comorbidity, which simply implies the co-existence of two diseases in the same patient but with no particular relationship between them (e.g. diabetes mellitus and depression occurring in the same patient). On the other hand, being part of a spectrum suggests that diseases may be very closely related, perhaps by being caused by similar sets of genes (Bipolar disorder and schizophrenia in the 'schizophrenia spectrum), by the possibility of one disease transmuting over time into another (Unipolar Depression, Cyclothymia, Bipolar II and Bipolar I Disorder), or at the very least the illnesses are very similar to each other phenominologically (Bipolar II and Bipolar I disorder).

We have attempted to determine from the database of the patients held within our team how many of our patients have Bipolar II disorder and Borderline Personality disorder coexisting.

Patients with Bipolar II disorder will have episodes of Hypomania, lasting 4 days at least, alternating with episodes of Depression which last for a longer period of time, often several weeks (DSM 4 1994). Patients with borderline personality disorder will have the following symptoms; Mood Instability, Suicidal Behaviour, Chronic feeling of emptiness, Relationship instability, fear of abandonment, chronic feeling of boredom, high emotional 'charge', short episodes of psychosis, Impulsiveness, disturbance of Image or Identity (Zaman 2000). None of these symptoms are pathognomonic of any condition; indeed, Suicidal Behaviour, Chronic feeling of emptiness, Relationship instability, fear of abandonment, and chronic feeling of boredom may be present in many patients with depression, and issues regarding identity can be present in other psychiatric illnesses. Patients with bipolar I disorder may have psychotic symptoms, and it is well known that patients with bipolar II and Bipolar I are also at high risk of suicide.

On the other hand, it is clear that Mood Instability is not the same thing as episodes of Hypomania, since mood instability can imply changes of mood from euthymic to depressed and back to euthymic again, while Hypomania is clearly defined by DSM4 as episodes of high mood lasting four days (although there can be shorter episodes of high mood, so that many patients with episodes of high mood are seen as subsyndromal). It has been argued that (Bradford Reich 2012) mood lability including anxiety, anger, discomfort and irritability characterises borderline patients, (Elisei 2012) while lability involving elation, as we have described, is more characteristic of bipolar patients (Bradford Reich 2012, Elisei 2012).

What we have done is apply the definition of hypomania as 4 days of elevated mood lasting at least 4

days to the patients with generic mood instability in the database of our patients, thus identifying patents who have hypomania, and thus have bipolar II disorder, and thus identifying how many patients who were previously thought of as 'Borderline' can also be interpreted on the basis of hypomania to have bipolar II. Those who have other symptoms of borderline Disorder as well as hypomania where then seen as having co-morbid borderline Disorder and Bipolar II Disorder.

RESULTS

Our Database contains records of all the patients who have been treated in Bedford East Community Mental Health Team since 2006. The total Number is 1175 patients. Of these 280 have been identified as having Bipolar Affective disorder, Borderline Personality Disorder or both conditions simultaneously. Of these 107 have Bipolar I Disorder. 88 had Bipolar II Affective Disorder. 75 patients were diagnosed with Borderline Personality Disorder.

8 Patients had Bipolar II Disorder co-morbid with Borderline Personality Disorder.1 Patient had Bipolar I Affective Disorder co-morbid with Borderline Personality Disorder, and two patients were reported as having Comorbid schizoaffective disorder (arguably very severe bipolar I disorder with psychosis) and Borderline Personality disorder.

Thus Co-morbid Bipolar Disorder and Borderline Personality Disorder represents a small but easily identifiable group of patients in our practice, representing 5.64 of all bipolar patients and 14.66 of borderline patients. Clearly more patients with borderline personality disorder can be argued to be bipolar than the other way round. Indeed there are two other factors operating here; one is that we have only began identifying bipolar patients with the strict criteria of clear hypomanic episodes over the last four years, and patients admitted to the database earlier would not have been diagnosed in the same way, so that patients, over the last four years will have definitely been diagnosed with Bipolar or Co-morbid Bipolar and Borderline based on clearly identified episodes of Hypomania. Previously the criteria would not have been so strict, and possibly mood instability and hypomania may have been confused, increasing the likelihood of patients being diagnosed as borderline disorder- by the same token, previously to four years ago, only patients with Bipolar I Diagnosis would have been identified as bipolar in our practice. The second issue is that doctors who were only temporarily attached to our team, such as registrars may not have identified patients as Bipolar II using the strict DSM criteria of bipolar which the permanent staff were using.

DISCUSSION

Akiskal has suggested that borderline personality disorder could be better understood as part of the bipolar affective spectrum (Akiskal 1985, Akiskal 1985). Jules Angst (2007) has argued for a bipolar spectrum in which patients with unipolar depression change to bipolar disorder at a regular rate over time suggested that borderline personality disorder may in some way relate to the bipolar spectrum, but left open the way in which Borderline patients should be related to the spectrum.

Since borderline disorder can often be comorbid with and share the same symptomathology with affective disorders, and this comorbidity is quite common (Elisei 2012), there is constant discussion about the relationship between borderline disorder and the bipolar spectrum including bipolar II disorder (Paris 2007, Elisei 2012). Our figure of 14.66% of patients with Borderline Personality Disorder also being co-morbid with bipolar disorder fits with the various studies which have reported that 12-23% of patients with BDII meet criteria for BPD as well (Paselow 1995, Vieta 1999, Benazzi 2000, Elisei 2012). It is, however lower than Chantal's report of from 35 to 51.5% (Chantal 2010, Elisei 2012).

In order to justify the inclusion of Borderline Personality Disorder in the Bipolar Spectrum, it has been suggested that that the overlap between BPD and mood disorders was caused by the item "affective instability" and that "impulsivity" could be its "essential feature" (Benazzi 2008). Hence it has been suggested that when attempting to find an association between hypomania symptoms and BPD traits, the only significant association was between 'The episodic impulsivity of hypomania and the trait impulsivity of BPD" (Benazzi 2008).

Alternatively, It has been suggested that Bipolar II Disorder be divided into two subtypes: one stable and functional between episodes and one unstable between episodes which is related to Borderline Personality Disorder (Benazzi 2000). This would enable most or all Borderline patients to be included in the Bipolar spectrum under the heading of the type of Bipolar II disorder which is unstable between episodes.

However, one relationship between bipolar disorder (Hajek 2012, Hajek 2012) and borderline personality disorder (Soloff 2008, Sato 2012, Driessen 2000, Brambilla 2004, Nunes 2009, Ruocco 2012) can be derived from Neuroimaging techniques. Both these conditions, together with Untreated Depression (MacMaster 2008, Sheline 2003) and Post Traumatic Stress Disorder (Admon 2012, Bremner 1995, Bremner 1999, Bremner 2006, Bremner 2007, Bremner 2006, Bremner 1997, Vythilingam 2002, Vermetten 2003) are conditions in which the Hippocampus is relatively small on MRI. The Amigdala are also involved (Saleh 2012). This may suggest that there are important biological similarities underlying these conditions. Indeed there is evidence that the size of the Hippocampus can be improved in all of these conditions by treatments (SSRIs, Lithium, Valproate) which promote neurogenesis.

Soloff described the anatomical changes in Borderline Personality Disorder as follows; Compared with Healthy Controls, Borderline Personality Disorder subjects had significant bilateral reductions in gray matter concentrations in ventral cingulate gyrus and several regions of the medial temporal lobe, including the hippocampus, amygdala, parahippocampal gyrus, and uncus (Soloff 2008). Borderline Personality Disorder women (and abused Borderline Personality Disorder women), but not Borderline Personality Disorder men, had significant reductions in medial temporal lobe, including the amygdale (Soloff 2008). Borderline Personality Disorder men, but not Borderline Personality Disorder women, showed diminished gray matter concentrations in the anterior cingulate gyrus compared with findings in Healthy Controls (Soloff 2008). Diminished gray matter in the prefrontal cortex and the medial temporal cortex may mediate the dysregulation of impulse and affect in Borderline personality disorder (Soloff 2008). This would explain Benazzi's concept of "affective instability" and "impulsivity" being related to and specifically distinguishing Borderline disorder (Benazzi 2008), and equally his description of a form of bipolar disorder which is unstable between episodes and related to Borderline Personality Disorder (Benazzi 2000).

Borderline patients also have smaller amigdala volumes (Driessen 2000, Nunes 2009), reported inreeased size of the Putamen has been attributed possibly to substance abuse which occurs in many of these patients (Brambilla 2004).

Sheline describes reduced Hippocampal Volume in patients with untreated depression (Sheline 2003). Longer durations during which depressive episodes went untreated with antidepressant medication were associated with reductions in hippocampal volume (Sheline 2003). Hippocampal volume decrease associated with illness burden is among the most replicated findings in unipolar depression. In Bipolar Disorder, until recently, this could not be demonstrated in bipolar illness/depression. Preserved hippocampal volumes in most studies of participants with bipolar disorder may reflect potential neuroprotective effects of lithium (Hajek 2012). Hajek has recently been able to compare patients with bipolar illness on lithium with those not on lithium and with controls (Hajek 2012). Both the left and right hippocampal volumes were significantly larger in the Li group than in controls or the non-Li group, which had smaller left and right hippocampal volumes than the control group (Hajek 2012). Imaging studies in posttraumatic stress disorder (PTSD) have found smaller volume of the hippocampus as measured with magnetic resonance imaging (MRI) in patients with PTSD related to both combat and childhood abuse (Bremner 2006). Brain areas implicated in the stress response include the amygdala, the hippocampus, and the prefrontal cortex (Bremner 2007), and the amydala and prefrontal cortex are also involved in Depression.

Equally, we have previously discussed how stress, working through the hypothalamo-pituitary axis, working through Cortisol levels and Glucocorticoid receptors, influences both the size of the hippocampus (Frodl 2012) and the balance between the trophic (BDNF, and, in Bipolar Disorder BCL-2 and BAG-1) and atrophic factors in the cells, thus producing a common mechanism in all conditions whereby stress is a causative factor in all of them (Goh 2010). From a genetic point of view, the principle that the major 'psychotic' mental illnesses are caused by many genes each of small effect (Craddock 2005) relates to all the illnesses we are considering, and some of these, such as the SERT gene, the COMT gene and the BDNF gene, with their polymorphisms, are clearly common to all the conditions under consideration. More genes are constantly being evaluated. Furthermore there is now evidence, that epigenetic regulation of genes can link depression, childhood adversity, and suicidality, all of which are linked with the conditions we are describing (Turecki 2012, Pregelj 2011, Labonte 2010, Autry2009, Klempan 2009).

It is worth noting also that recent studies of persons who have suffered abuse or 'childhood adversity,or even war trauma and who suffer from Depression and a propensity to depression, Post-Traumatic Stress Disorder, and Borderline Personality Disorder demonstrate similar findings in terms of neuroimaging – e.g. smaller Hippocampus- and pathophysiological responses to stress (Driessen 2000, Admon 2012, Bremner 1995, Bremner 1997, Vythilingam 2002, Everaerd 2012).

Hence, all of these conditions have substantially similar anatomical and Physiological correlates.

The heterogeneity of mood disorders indicates that its origin may lie in dysfunction of multiple brain regions (amygdala, nucleus accumbens, hippocampus, prefrontal cortex and cingulate cortex) (Crupi 2011).

Furthermore, Neurogenesis in the Hippocampus, promoted by SSRIs and Lithium, can help reverse the reduction in size of the Hippocampus in all of these conditions (Vermetten 2003, Hajek 2012, O'Leary 2012, Crupi 2011).

These last observations, demonstrating similar neuroscientific findings- that is comparable Neuroimaging and comparable relationship with neurogenesis, combined with the clinical observations above seem to us to be the best argument for including Borderline Personality Disorder in a spectrum of illness ranging from depression to Bipolar I Disorder. The controversy about this will doubtless continue for some years, but it seems that Borderline Personality Disorder should only be considered a separate diagnosis once patients have been properly assessed for Bipolar II Disorder and this diagnosis has been ruled out. However, having reviewed the literature, we can welcome the suggestion that Borderline Personality Disorder could be included into the bipolar spectrum, and indeed we would welcome in general the idea of a classification of mental illness based on the concept of spectra as being more rational

and describing better what we observe in practice, however, having reviewed the neurobiological mechanisms described above, we suggest that phenomenology without underpinning common neurobiological mechanisms are insufficient to demonstrate a spectrum of disease. Indeed we would propose a dictum; No spectrum without common or related neurobiological mechanisms.

Acknowledgements

The lead author wishes to thank Dr . Jean Lee and Dr .David Wotherspoon who developed with him the idea of looking for common neurobiological findings in mood disorders and producing several presentations about this issue when they were students in Cambridge. He also wishes to thank Dr Jenny Gardner for her support while he wrestled with the issue of whether Borderline Personality Disorder should be in the Bipolar Spectrum and the consequent audit of his team's patient list. Consequently he acknowledges them all three as co-authors. Unfortunately, work and personal necessities did not permit more close working together on the final text.
It was very helpful to have sight of Dr Elisei's manuscript while preparing this one, as it greatly facilitated and clarified the literature search.

Conflict of interest: None to declare.

REFERENCES

1. *Angst J. The bipolar spectrum. Br J Psychiatry 2007; 190:189-91.*
2. *Admon R, Leykin D, Lubin G, Engert V, Andrews J, Pruessner J, Hendler T. Stress-induced reduction in hippocampal volume and connectivity with the ventromedial prefrontal cortex are related to maladaptive responses to stressful military service. Hum Brain Mapp. 2012 Jul 17. doi: 10.1002/hbm.22100. [Epub ahead of print]*
3. *Akiskal HS. Borderline: An adjective in search of a noun. J Clin Psychiatry 1985; 46:41.*
4. *Akiskal HS. The nosologic status of borderline personality: Clinica and polysomnographic study. Am J Psychiatry 1985; 142:192-8.*
5. *American Psychiatric Association 1994. Diagnostic and Statistical Manual of Mental Disorders DSM IV.*
6. *Angst J. The bipolar spectrum.Br J Psychiatry. 2007 Mar;190:189-91.*
7. *Autry AE, Monteggia LM. Epigenetics in suicide and depression. Biol Psychiatry 2009; 66:812-3.*
8. *Benazzi F. BPD and bipolar II disorder in private practice depressed outpatients. Comprehensive Psychiatry 2000; 41:106-110.*
9. *Benazzi F: A relationship between bipolar II disorder and borderline personality disorder? Progress in Neuro-Psychopharmacology and Biological Psychiatry 2008; 32:1022-1029.*
10. *Bradford Reich D, Zanarini MC, Fitzmaurice G. Affective lability in bipolar disorder and borderline personality disorder 2012; 53:230-237.*
11. *Brambilla P, Soloff PH, Sala M, Nicoletti MA, Keshavan MS, Soares JC. Anatomical MRI study of borderline personality disorder patients. Psychiatry Res 2004; 131:125-33.*
12. *Bremner JD, Randall P, Scott TM, Bronen RA, Seibyl JP, Southwick SM, Delaney RC, McCarthy G, Charney DS, Innis RB. MRI-based measurement of hippocampal volume in patients with combat-related posttraumatic stress disorder. Am J Psychiatry 1995; 152:973-81.*
13. *Bremner JD. The relationship between cognitive and brain changes in posttraumatic stress disorder. Ann N Y Acad Sci 2006; 1071:80-6.*
14. *Bremner JD. Alterations in brain structure and function associated with post-traumatic stress disorder. Semin Clin Neuropsychiatry 1999; 4:249-55.*
15. *Bremner JD: Neuroimaging in posttraumatic stress disorder and other stress-related disorders. Neuroimaging Clin N Am 2007; 17:523-38.*
16. *Bremner JD. Stress and brain atrophy. CNS Neurol Disord Drug Targets 2006; 5:503-12.*
17. *Bremner JD, Randall P, Vermetten E, Staib L, Bronen RA, Mazure C, Capelli S, McCarthy G, Innis RB, Charney DS.Magnetic resonance imaging-based measurement of hippocampal volume in posttraumatic stress disorder related to childhood physical and sexual abuse--a preliminary report. Biol Psychiatry 1997; 41:23-32.*
18. *Chantal H. Personality Disorder and Mood Spectrum 2010.*
19. *Craddock N, Owen M. The beginning of the end for the Kraepelinian dichotomy BJP May 2005; 186:364-366.*
20. *Crupi R, Marino A, Cuzzocrea S New therapeutic strategy for mood disorders. Curr Med Chem 2011; 18:4284-98.*
21. *Driessen M, Herrmann J, Stahl K, Zwaan M, Meier S, Hill A, Osterheider M, Petersen D. Magnetic resonance imaging volumes of the hippocampus and the amygdala in women with borderline personality disorder and early traumatization. Arch Gen Psychiatry 2000; 57:1115-22.*
22. *Elisei S, Anastasi S, Verdolini N. The continuum between bipolar disorder and Borderline Personality Disorder. Psychiatria Danubina 2012; 24(Suppl. 1):46–49.*
23. *Everaerd D, Gerritsen L, Rijpkema M, Frodl T, van Oostrom I, Franke B, Fernández G, Tendolkar I. Sex modulates the interactive effect of the serotonin transporter gene polymorphism and childhood adversity on hippocampal volume. Neuropsychopharmacology 2012; 37:1848-55.*
24. *Frodl T, O'Keane V.How does the brain deal with cumulative stress? A review with focus on developmental stress, HPA axis function and hippocampal structure in humans. Neurobiol Dis 2012 Mar 9. [Epub ahead of print]*
25. *Goh C, Agius M.The stress-vulnerability model how does stress impact on mental illness at the level of the brain and what are theconsequences? Psychiatr Danub 2010; 22:198-202.*
26. *Hajek T, Cullis J, Novak T, Kopecek M, Höschl C, Blagdon R, O'Donovan C, Bauer M, Young LT, Macqueen G, Alda M. Hippocampal volumes in bipolar disorders: opposing effects of illness burden and lithium treatment. Bipolar Disord 2012; 14:261-70.*
27. *Hajek T, Kopecek M, Höschl C, Alda M. Smaller hippocampal volumes in patients with bipolar disorder are masked by exposure to lithium: a meta-analysis.J Psychiatry Neurosci 2012; 37:110143. doi: 10.1503/jpn.110143. [Epub ahead of print]*

28. *Hajek T, Bauer M, Pfennig A, Cullis J, Ploch J, O'Donovan C, Bohner G, Klingebiel R, Young LT, Macqueen GM, Alda M. Large positive effect of lithium on prefrontal cortex N-acetylaspartate in patients with bipolar disorder: 2-centre study J Psychiatry Neurosci 2012; 37:185-92.*
29. *Klempan TA, Ernst C, Deleva V, Labonte B, Turecki G. Characterization of QKI gene expression, genetics, and epigenetics in suicide victims with major depressive disorder. Biol Psychiatry 2009; 66:824-31.*
30. *Labonte B, Turecki G. The epigenetics of suicide: explainning the biological effects of early life environmental adversity. Arch Suicide Res 2010; 14:291-310.*
31. *MacMaster FP, Mirza Y, Szeszko PR, Kmiecik LE, Easter PC, Taormina SP, Lynch M, Rose M, Moore GJ, Rosenberg DR. Amygdala and hippocampal volumes in familial early onset major depressive disorder. Biol Psychiatry 2008; 63:385-90.*
32. *Nunes PM, Wenzel A, Borges KT, Porto CR, Caminha RM, de Oliveira IR. Volumes of the hippocampus and amygdala in patients with borderline personality disorder: a meta-analysis. J Pers Disord 2009; 23:333-45.*
33. *O'Leary OF, O'Connor RM, Cryan JF Lithium-induced effects on adult hippocampal neurogenesis are topographically segregated along the dorso-ventral axis of stressed mice. Neuropharmacology 2012; 62:247-55.*
34. *Paris J, Gunderson J, Weinberg I. The interface between borderline personality disorder and bipolar spectrum disorders. Comprehensive Psychiatry 2007; 48:145-154.*
35. *Paselow ED, Sanfilipo MP, Fieve RR. Relationship between hypomania and personality disorders before and after successful treatment. The American Journal of Psychiatry 1995; 152:232-238.*
36. *Pregelj P. Gene environment interactions in bipolar disorder. Psychiatr Danub. 2011; 23 Suppl 1:S91-3.*
37. *Ruocco AC, Amirthavasagam S, Zakzanis KK. Amygdala and hippocampal volume reductions as candidate endophenotypes for borderline personality disorder: a meta-analysis of magnetic resonance imaging studies. Psychiatry Res 2012; 201:245-52.*
38. *Saleh K, Carballedo A, Lisiecka D, Fagan A, Connolly G, Boyle G, Frodl T. Impact of family history and depression on amygdala volume. Psychiatry Res. 2012 Aug 3. [Epub ahead of print]*
39. *Sato JR, de Araujo Filho GM, de Araujo TB, Bressan RA, de Oliveira PP, Jackowski AP. Can neuroimaging be used as a support to diagnosis of borderline personality disorder? An approach based on computational neuroanatomy and machine learning. J Psychiatr Res. 2012; 46:1126-32.*
40. *Sheline YI, Gado MH, Kraemer HC. Untreated depression and hippocampal volume loss. Am J Psychiatry 2003; 160:1516-8.*
41. *Soloff P, Nutche J, Goradia D, Diwadkar V. Structural brain abnormalities in borderline personality disorder: a voxel-based morphometry study. Psychiatry Res 2008; 164:223-36.*
42. *Turecki G, Ernst C, Jollant F, Labonté B, Mechawar N. The neurodevelopmental origins of suicidal behavior. Trends Neurosci 2012; 35:14-23.*
43. *Vieta E, Colon F, Martinez-Aran A, Benabarre A, Gasto C. Personality disorders in bipolar II patients. The Journal of Nervous and Mental Disease 1999; 187:245-248.*
44. *Vermetten E, Vythilingam M, Southwick SM, Charney DS, Bremner JD. Long-term treatment with paroxetine increases verbal declarative memory and hippocampal volume in posttraumatic stress disorder. Biol Psychiatry 2003; 54:693-702.*
45. *Vythilingam M, Heim C, Newport J, Miller AH, Anderson E, Bronen R, Brummer M, Staib L, Vermetten E, Charney DS, Nemeroff CB, Bremner JD. Childhood trauma associated with smaller hippocampal volume in women with major depression. Am J Psychiatry 2002; 159:2072-80.*
46. *Zaman R, Makdum A Churchill's Pocketbook of Psychiatry Churchill-Livingstone 2000 p 95.*

Correspondence:
Mark Agius, MD
SEPT at Weller Wing, Bedford Hospital
Bedford, Bedfordshire, MK42 9DJ, UK
E-mail: ma393@cam.ac.uk