Psychiatria Danubina, 2014; Vol. 26, Suppl. 1, pp 336–339 *Conference paper*

CO-MORBIDITY PART 2 - NEUROBIOLOGY AND SUICIDE RISK; MODELLING THE CONSEQUENCES OF BIPOLAR AND ANXIETY CO-MORBIDITY

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SUMMARY

We review the evidence that Bipolar Disorder with Comorbid Anxiety, Rapid Cycling Bipolar Disorder, Mixed Affective states, are all related to each other and to Dopamine Transmission in Bipolar Disorder. All these states are related to the presence of particular polymorphisms of the genes of the D2 andD3 receptors. All these states increase the risk of suicidality. Substance and alcohol abuse comorbid with bipolar disorder increases the risk of both Rapid Cycling and Suicidality.We present a model which demonstrates these relationships.

Key words: *Bipolar Disorder with Comorbid Anxiety - Rapid Cycling Bipolar Disorder - Mixed Affective states - Dopamine Transmission - D2 receptor -D3 receptor - suicidality*

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INTRODUCTION

The co-morbidity of Bipolar Disorder and Anxiety is a common one.

For those with BPD this is a specific concern because there is up to 93% lifetime risk (McIntyre 2006) and 32% current risk (Otto 2006) of comorbid anxiety. Those individuals with BPD who are more at risk of a comorbid anxiety disorder are those with depressive tendencies (Henry 2003, Dilsaver 2003) and those for whom a depressive episode was the initial mood disturbance of their illness (Toniolo 2009). Those with comorbid generalised anxiety disorder or social phobia more likely to have worse outcomes than those with other anxiety disorders (Boylan 2004).

Having comorbid Bipolar Disorder and anxiety can adversely affect the patient's experience of BPD. It is related to a more challenging illness course, it is also related to an earlier age of onset of symptoms of both the BPD and anxiety disorder (McElroy 2001, Goodwin 2002). The patients experience a higher number of mood episodes (Toniolo 2009) and more rapid mood switching (MacKinnon 2003). Thus these patients are more likely to be Rapid Cycling. It is also associated with a longer time to remission of Bipolar Disorder (Frank 2002), as well as more severe psychopathology (Cassano 1999).

Generally a person with both Bipolar Disorder and anxiety will have lower functioning as scored on the Global Assessment of Functioning Scale (GAF) (Lee 2008) and diminished role functioning (Otto 2006).

It is particularly important that the risk of suicidality is recognised; there are higher levels of suicidal ideation in this population (Young 1993, Birmaher 2002, Kilbane 2009) and there is a "dose-response" relationship between the comorbid anxiety symptoms and suicide attempts (Dilsaver 2008).

The cocept of "mixity" (Pacchiarotti 2013) describes the type of psychopathology experienced by patients who suffer from Mixed Affective States. These patients suffer a higher rates of suicidal ideation, more mixed episodes, higher frequencies of antidepressant (AD) use, depressive predominant polarity and an anxious temperament. Thus Patients with mixed states are likely to also suffer from comorbid Bipolar Disorder and anxiety.

There is evdence that patients who suffer from Rapid Cycling may develop into having Mixed Affective states. It has been suggested that many patients who under ICD 10 are listed as mixed affective episodes, are likely to also be described as Rapid Cycling (Seshadri 2013). It also appears that one aetiological cause of rapid cycling disorder is the comorbid presence of Alcohol and Substance Abuse (Seshadri 2013).

DOPAMINE TRANSMISSION IN BIPOLAR DISORDER

Recently attention has been drawn to Dopamine as a transmission system in Bipolar Disorder (Cousins 2009, Kato 2008, Edmonds 2013).

There is much evidence for dopamine being an important neurotransmitter in mania and depression.

Among this evidence, antipsychotics effective against mania block dopamine neurotransmission, while psychostimulants, such as amphetamine, cause mania, by increasing dopamine neurotransmission (Cousins 2009, Kato 2008, Edmonds 2013).

Multiple lines of evidence, including data from pharmacological interventions and structural and functional magnetic resonance imaging studies, suggest that the dopaminergic system may play a central role in bipolar disorder (Cousins 2009, Kato 2008, Edmonds 2013).

In bipolar disorder, tricyclic antidepressants can precipitate a rapid 'switch' from depression into mania, but the SSRIs do not tend to cause this (Peet 1994, Kato 2008, Edmonds 2013). This is because tricyclic antidepressants block the noradrenaline and serotonin transporters, but have negligible effect on the dopamine transporter. However in the prefrontal cortex, dopamine transport uses the noradrenaline transporter, hence tricyclics can increase the concentration of dopamine in prefrontal cortex synapses,while SSRIs do not (Valentini 2004, Kato 2008, Edmonds 2013). There is evidence that dopamine in particular is an important neurotransmitter in bipolar disorder. Thus there is an important difference in terms of neurotransmitters between bipolar and unipolar depression (Kato 2008, Edmonds 2013).

What has recently transpired is that the D2 and D3 receptors are particularly important in neurotransmission in Bipolar disorder, and that they are also involved in the co-morbidity of Bipolar Disorder with anxiety. This evidence comes from a series of studies on different polymorphisms or these two receptors and their corralations with other polymorphisms and with the conditions of Bipolar Disorder with or without Anxiety.

Because of these studies, and previous knowledge that Bipolar Disorder with Anxiety is also related to Rapid Cycling as well as Affective Mixed States and that both these conditions are also related to increased suicidality, we have been able to model how the three conditions Bipolar Disorder with Anxiety, Rapid Cycling and Affective Mixed States are related to each other and also to increased suicidality as well.

It appears that Bipolar Disorder with Anxiety, Rapid Cycling and Affective Mixed States are consequential one on the other, and all lead to increased suicidality, however that all of these are related to the presence of the appropriate polymorphisms of the D2 and D3 Receptors in the Bipolar Patient.

GENE POLYMORPHISMS AND BIPOLAR DISORDER

A number of studies have been carried out in recent years on polymorphisms of COMT, and DR2 and DR3 genes in Bipolar Disorder.

The results are as follows:

- A statistically significant main effect for the Met/Met genotype of the COMT Val158Met polymorphism predicted bipolar I patients (Lee 2011). A significant interaction effect for the Met/Met genotype of the COMT Val158Met and Ser/Ser genotypes of the DRD3 Ser9Gly polymorphism predicted bipolar I patients (Lee 2011). There was no association between the COMT Val158Met or DRD3 Ser9Gly and bipolar II (Lee 2011). A significant interaction effect for the Val/Val genotypes of the BDNF Val66Met polymorphism and the COMsT Val158Met Val/Met and Met/Met genotypes (P=0.007, 0.048) discriminated between Bipolar-II without Anxiety patients and controls (Huang CC 2012). A significant main effect for the Val/Val genotype of the BDNF Val66Met polymorphism predicted BP-II patients (Huang 2012). The significant interaction effect for the Val/Val genotype of the BDNF Val66Met polymorphism and A1/A2 genotype of DRD2/ANKK1 Taq1A polymorphism was found only in BP-II patients (Huang 2012).
- These findings are very interesting. Bipolar I and Bipolar II disorder are usually understood to be on the same 'Bipolar Spectrum', and it is indeed suggested that Bipolar II disorder may in time develop into Bipolar I. However Lee commented 'The COMT Val158Met and DRD3 Ser9Gly genotypes interact in bipolar I and bipolar II disorders and that bipolar I and bipolar II are genetically distinct'(Lee 2011), while Huang commented 'We provide initial evidence that the BDNF Val66Me and DRD2/ANKK1 Taq1A polymorphisms interact only in BP-II disorder and that BP-I and BP-II are genetically distinct'. Further consideration needs to be given to the consequences of these observations for our models of how Bipolar Disorder develops.

D2 AND D3 RECEPTORS IN BIPOLAR DISORDER

A series of studies have recently been published relating the D2 and D3 Receptors to Bipolar Disorder. The findings are as follows;

The DRD3 Ser9Gly polymorphism was associated with BP-II comorbid with AD (BPII(+AD)), (Lee 2013). The BDNF Val66Met polymorphism was associated with BP-I comorbid with AD (BPI(+AD)) (Lee 2013). An interaction between the Val/Val genotype of the BDNF Val66Met and Gly/Gly polymorphism of the DRD3 Ser9Gly was found in BPII(+AD), (Lee 2013), An interaction between the Val/Val genotype of the BDNF Val66Met and Gly/Gly polymorphism of the DRD3 Ser9Gly was not found in BP-II not comorbid with AD (BPI(-AD)) (Lee SY 20130. The DRD3 Ser9Gly polymorphism was associated with BP-II comorbid with AD (BPII(+AD)) (Chang YH 2013).

The BDNF Val66Met polymorphism was associated with BP-I comorbid with AD (BPI(+AD)) (Chang 2013). An interaction between the Val/Val genotype of the BDNF Val66Met and Gly/Gly polymorphism of the DRD3 Ser9Gly was found in BPII(+AD), but not in BP-II not comorbid with AD (BPI(-AD)) (Chang 2013). A statistically significant association between DRD2 Taq-I A1/A2 genotype and BP-II with AD (Wang 2014). A significant interaction of the DRD2 Taq-I A1/A1 and the ALDH2*1*1 genotypes in BP-II without AD was revealed (Wang 2014).

Commenting on these findings, Lee stated 'A significant effect of the COMT and the BDNF polymorphisms in bipolar-II without AD. This shows the involvement of the dopaminergic pathway in the pathogenesis of bipolar-II (Lee 2013). Chang commented 'The involvement of the dopaminergic pathway in Anxiety Disorder was confirmed, particularly with BP-II rather than BP-I (Chang 2013). He suggested that because the Val/Val genotype of the BDNF Val66Met polymorphism, rather than the other two polymorphisms, has been associated with anxiety, it seems to affect BP-I comorbid with Anxiety Disorder without the involvement of the DRD3 Seg9Gly polymorphism, but it may modify the involvement of DRD3 Gly/Gly in BP-II comorbid with Anxiety Disorder (Chang 2013). Wang (2014) has stated 'Our findings support the hypothesis that a unique genetic distinction between Bipolar II Disorder with and without Anxiety Disorder. The findings suggest a novel association between DRD2 Taq-I A1/A2 genotype and Bipolar II Disorder with Anxiety Disorder' (Wang 2014). Hence it appears that there are two different genotypes; one for Bipolar II Disorder with Anxiety Disorder and the other for Bipolar II Disorder without Anxiety Disorder.

This data, as well as the previously given information about Bipolar Disorder with Anxiety, Rapid Cycling, Mixed Affective States and Suicidality has led us to model how these are related to the presence of the appropriate polymorphisms of the D2 and D3 receptors.

The model is shown below (Figure 1).

CONCLUSION

It appears from our Model that Bipolar Disorder with Anxiety, Rapid Cycling and Affective Mixed States are consequential one on the other, and all lead to increased suicidality, however that all of these are related to the presence of the appropriate polymorphisms of the D2 and D3 Receptors in the Bipolar Patient. It is necessary to reconsider our well accepted model of the Bipolar Spectrum in view of the evidence that Bipolar I Disorder, Bipolar II Disorder, Bipolar I Disorder with Anxiety and, Bipolar II Disorder without Anxiety are different genotypes. Furthermore Bipolar Disorder with Anxiety, Rapid Cycling and Affective Mixed States are all linked with increased suicidality, while the risk might increase as a patient moves from one of these states to another.

Acknowledgements: None.

Conflict of interest: None to declare.

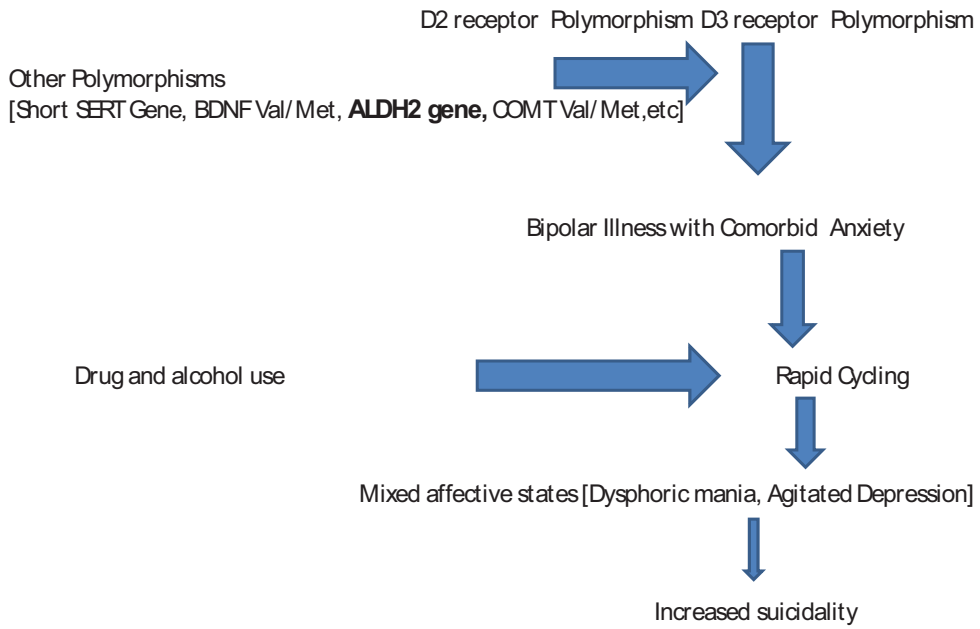

Figure 1. Model to show how dopamine receptor polymorphism translates into Bipolar Illness comorbid with anxiety (trait), increased suicidality, via the states of Rapid Cycling and Mixed Affective states

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