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THE COMORBIDITY OF BIPOLAR DISORDER AND CARDIOVASCULAR DISEASES FROM PHARMACOTHERAPY PERSPECTIVE

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SUMMARY

The heart and mind are intimately linked. Patients with severe mental disorders have increased mortality rates compared with the general population and the leading cause of premature death is cardiovascular disease (CVD). Despite their high prevalence and substantial medical impact, comorbidity between cardiac conditions and psychiatric illnesses frequently go undiagnosed and untreated. It is very interesting to investigate the impact of mental health on cardiac disease and what is the complex underlying mechanism that links theese two conditions.

Key words: *bipolar disorder - cardiovascular disease – commorbidity - effective treatment*

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INTRODUCTION

The heart and mind are intimately linked. Depression, anxiety disorders, schizophrenia and bipolar disorder (BD) have all been identified as risk factors for the onset and progression of cardiovascular disease (CVD) (Sowden **&** Huffman 2009). Unfortunately, despite their high prevalence and substantial medical impact, comorbidity between cardiac conditions and psychiatric illnesses frequently go undiagnosed and untreated. Clinically, the challenge lies in helping clinicians to identify psychiatric conditions in cardiac patients as well cardiac conditions in psychiatric patients and to initiate basic but critical treatments for these two disorders at the same time.

There is an accumulating evidence that patients with severe mental disorders have increased mortality rates compared with the general population. The leading cause of death for individuals with psychotic illnesses or bipolar disorder is CVD, which is often the result of patients' health problems associated with their psychiatric disorders, including, but not limited to, obesity, metabolic syndrome, and diabetes. Such problems occur more often, earlier and have worse outcomes in patients with serious mental illness than the general population because of a combination of factors such as inadequate access to quality care, poor lifestyle choices, and the association between some antipsychotic medications and weight gain (Mc Intyre et al. 2009).

Since CVD is one of foremost causes of morbidity and mortality worldwide and psychiatric ilnesess are asociated with premature onset of CVD, it is very interesting to investigate the impact of mental health on cardiac disease and what is the complex underlying mechanism that links theese two conditions. Antidepressants, antipsychotics, mood stabilizers and benzodiazepines are effective therapeutic interventions, and many are safe to use in cardiac populations. Some, such as selective serotonin reuptake inhibitors and atypical antipsychotics, may even improve cardiac outcomes in healthy individuals and patients with CVD, although more work is needed to confirm this hypothesis. Beside the impact of psychiatric medication on cardiac conditions, in this paper we will also explore possible behavioural and patophysiological mechanisms shared by both disorder.

BIPOLAR DISORDER MEDICATION AND CVD

Bipolar I disorder, which occurs in approximately 1% of the general population is significantly more prevalent in patients with cardiac disease (Baune et al. 2006). Individuals with BD

die younger than their peers, due largely to an increased prevalence of medical co-morbidities (Tsai et al. 2005) and much of this excess mortality stems from CVD (Carney et al. 2006). In fact, patients with BD are up to twice as likely to die from cardiovascular causes than their counterparts in the general population (Osby et al. 2001).

Lithium, the gold-standard treatment for acute and maintenance treatment of BD is associated with weight gain, which may impact cardiac health. Lithium may also affect cardiac conduction, frequently causing T wave flattening and inversion, and, more rarely, sinus node dysfunction, A-V block, and ventricular arrhythmias (Mitchel & Mackenzie 1992). Serious cardiac complications are rare, however, and, in general, lithium can be safely used in cardiac patients when psychiatric symptoms require its use.

Other effective treatments of bipolar disorder include anticonvulsant mood stabilizers, such as valproate, carbamazepine, and lamotrigine and atypical antipsychotics. Valproate has few effects on cardiac conduction (Limdi et al. 2007), but unlike the anticonvulsants carbamazepine (Akiskal et al. 2005) and lamotrigine (Isojarvi et al. 1998) has been associated with weight gain, insulin resistance, hyperlipidemia, and impaired glucose tolerance. Carbamazepine, like lithium, has been associated with arrhythmias and conduction delays (Kasarskis et al. 1992), however, these incidents are rare, and clinically significant cardiovascular toxicity is uncommon even in patients with toxic levels of carbamazepine. Lamotrigine appears safe to use in cardiac patients, without substantial effects on conduction, blood pressure or weight.

With appropriate monitoring, lithium and mood stabilizers are safe and effective treatments for bipolar disorder in cardiac populations, though there has been no significant study of their impact on the onset and progression of CVD.

Many of the atypical antipsychotics which are widely used in BD patients carry a significant risk of weight gain, diabetes, and hyperlipidemia (Baptista et al. 2002), central features of the metabolic syndrome. Some of these agents carry greater risk: olanzapine and clozapine are strongly associated with the metabolic syndrome, risperidone and quetiapine moderately so, and ziprasidone and aripiprazole only minimally (Newcomer 2005). The older typical antipsychotics (e.g., chlorpromazine, haloperidol) confer a moderate risk of weight gain and diabetes.

Other cardiovascular side effects of antipsychotics include orthostatic hypotension, seen frequently with risperidone, quetiapine, and lower-potency typical antipsychotics (e.g., chlorpromazine). Typical antipsychotics, especially thioridazine and intravenous haloperidol, have been associated with QT-interval prolongation and, rarely, torsade de pointes. Atypical antipsychotics confer less risk of arrhythmias, though ziprasidone may cause QT interval prolongation (Glassman 2005).

Despite these cardiac effects, mortality rates appear to be significantly lower in patients treated with antipsychotics than in untreated controls (Khan et al. 2007). This is largely due to decreased risk of suicide, but is also related to decreased risk of MI, even in subjects taking clozapine, which is strongly associated with the metabolic syndrome (Enger et al. 2004). Thus, it seems that while antipsychotics may increase some of the risk factors for CVD, such as weight gain, diabetes and hyperlipidemia, they may not increase the risk of severe cardiac events, and may in fact confer a protective effect.

Behavioral mechanisms

Among persons with psychiatric illness, there is a higher prevalence of unhealthy behaviors and known CVD risk factors, such as smoking, alcohol misuse, obesity, sedentary lifestyle, hypertension, diabetes, poor diet and poor treatment compliance. Individuals with mental illness are generally less likely to seek help and once help is sought, less likely to obtain adequate treatment for medical conditions (Birkenaes et al. 2006).

Pathophysiological mechanisms

Psychiatric illnesses are associated with changes in pathophysiology that can adversely impact the cardiovascular system. These changes include increased platelet reactivity, endothelial dysfunction, hypercortisolemia, autonomic dysfunction, decreased heart rate variability (HRV), and abnormal immune system activation. These pathophysiologic processes, commonly seen in patients with mental illness, promote heart disease via pro-atherogenic, pro-ischemic and pro-arrhythmic mechanisms. For example, elevated levels of proinflammatory markers and cytokines, such as IL-1, IL-6, C-reactive protein and tumor necrosis factor, are synthesized at high levels in atherosclerotic plaques and have been found to be

independent risk factors for post-MI reischemia and cardiac mortality (Saeddeddin et al. 2002). Platelet aggregation and endothelial dysfunction may also contribute to atherogenesis and have been found to be independently associated with cardiovascular events in patients with and without CVD (Pizzi et al. 2008). Further, hypercortisolemia that results from overstimulation of the hypothalamic-pituitary-adrenal axis promotes visceral obesity, a potent risk factor for CVD (Weber-Hamman et al. 2002) while low HRV, which reflects an increase in sympathetic tone and a decrease in parasympathetic tone, may put individuals at increased risk for myocardial ischemia, arrhythmias and sudden cardiac death (Carney et al. 2002). Alteration in autonomic control may also be one of the pathophysiologic mechanisms underlying the metabolic syndrome, contributing further to negative cardiac prognosis.

Homocysteine, recently extensively investigated as a new risk factor for CVD, is non-protein amino acid that occurs in human by the demetilation of nutritional methionine, catalyzed by methyltransferases (Reif et al. 2005)

Most cases of mild hyperhomocysteinemia are due to the nutritional folate and vitamin B12 deficiency and/or reduced glomerular filtration rat, while in severe cases mutations in key enzyme of homocysteine metabolism can be found.

Hyperhomocysteinemia has emerged as an independent and graded risk factor for the development of CVD which is, at the same time, the primary clinical outcome of the metabolic syndrome (Ninomiya et al. 2004). Elevated levels of serum homocysteine is a risk factor for several diseases of central nervous system (Herrman et al. 2007). Hyper homocysteinemia has been found in young male schizophrenia patients (Levine et al. 2005) and bipolar patients showing functional and cognitive deterioration (Dittmann et al. 2008). Our preliminary results showed strong association between MS (metabolic syndrome) and hyperhomocysteinemia (particularly elevated blood pressure and hyperhomocysteinemia) in bipolar disorder patients. Results of previous studies indicate the usfulness of including fasting homocysteinemia determination in diagnostic pannels of psychiatric patients in order to obtain a better assesements of their metabolic risk profile. This could be of significant clinical importance since most studies showed that vitamin B supplementation can lower homocysteine levels (Herrman et al. 2007) and consequently reduce a risk for the develpoment of CVD in bipolar patients.

CONCLUSIONS

Bipolar disorder is associated with increased prevalence of CVD. While treatments exist that are safe and effective at treating psychiatric symptoms in cardiac populations, these disorders commonly go undiagnosed and untreated. It is important to diagnose and treat these disorders, however, not only because symptom remission may improve quality of life, but also because there is evidence to suggest that treatment, both pharmacological and psychological, may improve cardiac prognosis. SSRIs and antipsychotic medications, especially, have both been associated with decreased mortality rates among cardiac patients. It is still unclear whether these effects are due to symptom remission, class-specific pharmacologic actions or a combination of both.

REFERENCES

1. *Akiskal HS, Fuller MA, Hirschfeld RM, Keck PE Jr., Ketter TA and Weisler RH. 2005. Reassessing carbamazepine in the treatment of bipolar disorder: clinical implications of new data, CNS Spectr 10 (6) suppl 1,11; discuss 12-3; quiz 14-5.*
2. *Baptista N, Kin M, Beaulieu S and Baptista EA. 2002. Obesity and related metabolic abnormalities during antipsychotic drug administration: mechanisms, management and research perspectives. Pharmacopsychiatry 35 (6) : pp. 205–219.*
3. *Baune BT, Adrian I , Arolt V and Berger K. 2006. Associations between major depression, bipolar disorders, dysthymia and cardiovascular diseases in the general adult population. Psychother Psychosom 75:319–326.*
4. *Birkenaes AB, Sogaard AJ, Engh JA et al.2006. Sociodemographic characteristics and cardiovascular risk factors in patients with severe mental disorders compared with the general population. J Clin Psychiatry 67 (3):pp. 425–433.*
5. *Carney CP and Jones LE. 2006. Medical comorbidity in women and men with bipolar disorders: a population-based controlled study, Psychosom Med 68 (5): pp. 684–691.*
6. *Dittmann S, Hennig-Fast K, Gerber S, Seemuller F, Riedel M, Emanulel SW, Langosch J, Engel RR , Moller HJ, Grunze HC.2008. Cognitive functioning in euthymic bipolar I and bipolar II patients. Bipolar Disord 10(8): 877-887.*

7. *Enger C, Weatherby L, Reynolds RF, Glasser DB and Walker AM. Serious cardiovascular events and mortality among patients with schizophrenia. J Nerv Ment Dis 2004; 192:19–27.*
8. *Glassman AH. 2005. Schizophrenia, antipsychotic drugs, and cardiovascular disease. J Clin Psychiatry 66: pp. 5–10 Suppl 6.*
9. *Hermann W, Lorenzl S, Obeid R.2007. Review of role of hyperhomocyteinemia and B-vitamin deficiency in neurological and psychiatric disorders-current evidence and preliminary recommendations. Fortschr Neurol Psychiatry 75 (9):515-27*
10. *Isojarvi JI, Rattya J, Myllyla VV et al.(1998). Valproate, lamotrigine, and insulin-mediated risks in women with epilepsy. Ann Neurol 43 (4) : pp. 446–451.*
11. *Kasarskis EJ, Kuo CS, Berger R and Nelson KR. 1992. Carbamazepine-induced cardiac dysfunction. Characterization of two distinct clinical syndromes, Arch Intern Med 152 (1): pp. 186–191.*
12. *Khan A, Schwartz K , Stern C et al. 2007. Mortality risk in patients with schizophrenia participating in premarketing atypical antipsychotic clinical trials. J Clin Psychiatry 68 (12) pp. 1828–1833.*
13. *Levine J, Sela BA, Osher Y, Belmaker RH.2005. High homocysteine levels in young male schizophrenia and bipolar patients and in an animal model. Prog Neuropsychopharmacol Biol Psychiatry 29(7):1181-91.*
14. *Limdi NA, Knowlton RK, Cofield S et al. 2007. Safety of rapid intravenous loading of valproate. Epilepsia 48 (3) pp. 478–483.*
15. *Mc Intyre RS.2009. Overview of managing medical comorbidities in patients with severe mental illness. Journal of Clin Psych 70(6).pp 17.*
16. *Mitchell JE and Mackenzie TB. 1982. Cardiac effects of lithium therapy in man: a review. J Clin Psychiatry 43:47–51.*
17. *Newcomer JW. 2005. Second-generation (atypical) antipsychotics and metabolic effects. CNS Drugs 19:1–93.*
18. *Ninomiya JK, Italien G, Criqui MH et al. 2004. Association of the metabolic syndrome with history of myocardial infarction and stroke in The Third National Health and Nutritional Examination Survey. Circulation 109:42-6.*
19. *Osby U, Brandt L, Correia, N, Ekbom A and Sparen P.2001. Excess mortality in bipolar and unipolar disorder in Sweden. Arch Gen Psychiatry 58 (9): pp. 844–850.*
20. *Pizzi C, Manzoli L, Mancini S and Costa GM. 2008. Analysis of potential predictors of depression among coronary heart disease risk factors including heart rate variability, markers of inflammation, and endothelial function. Eur Heart J 29:1110–1117.*
21. *Reif A, Pfuhlmann B and Lesch KP. 2005. Homocysteinemia as well as methylentetrahydro-folate reductase polymorphism are associated with affective psychoses. Progress in Neuropsychophar-macol Biological Psychiatry 1162-1168.*
22. *Saadeddin SM, Habbab MA and Ferns GA.2002. Markers of inflammation and coronary artery disease. Med Sci Monit 8 (1): pp. RA5–RA12.*
23. *Sowden GL and Huffman JC.2009. The impact of mental illness on cardiac outcomes: A review for the cardiologist. International Journal of Cardiology 132(1): p.p. 30-37.*
24. *Tsai SY, Lee CH, Kuo CJ and Chen C.2005. A retrospective analysis of risk and protective factors for natural death in bipolar disorder. J Clin Psychiatry 66 (12): pp. 1586–1591.*
25. *Weber-Hamann B, Hentschel F, Kniest A et al. 2002. Hypercortisolemic depression is associated with increased intra-abdominal fat. Psychosom Med 64 (2) :pp. 274–277.*

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