MEDICAL COMORBIDITY IN THE COURSE OF BIPOLAR DISORDER

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Bipolar disorder is a serious illness affecting approximately 2-4% of the population and is one of the world's leading causes of disability. In individuals with bipolar disorder, medical comorbidity associated with cardiovascular, respiratory and endocrine disorders is related to increased rates of mortality. Recent updates to multi-system inflammatory related conceptualizations of bipolar disorder focus on the unique power that medical illness and biological processes may play as factors associated with course and outcome in bipolar disorder. The current study examined medical comorbidity and its associations with various demographic and psychological variables in individuals with bipolar disorder, schizophrenia, and major depressive disorder with psychotic features followed for 10 years from their first hospital admission. When compared to an age, gender and race-matched control sample from the population, those with bipolar disorder had significantly higher medical comorbidity across a range of medical diagnoses both at 6 months and 10 years after first hospital admission. Ten years following initial hospitalization, individuals in all three diagnostic groups reported increased rates of diabetes (OR: 2.0 – 3.7), stroke (OR: 4.6 – 7.0) and asthma (OR: 1.9 - 3.1), and individuals with bipolar disorder reported increased rates of cancer (OR = 2.1). A number of psychological and demographic symptoms were examined for their ability to predict the development of medical illness across the assessment interval. Overall rates of medical illness were elevated both early in illness course and 10 years after diagnosis, suggesting that broad sequelae of multi-system inflammation are present early and progress over time.

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CHAPTER 1

INTRODUCTION

Bipolar Disorder: Diagnosis, Prevalence and Costs

Bipolar disorder is characterized by the recurrence of episodes of mania or hypomania, and often depression, with more severe courses being marked by increased intensity, duration and number of mood episodes (APA, 2013). The *DSM-5* identifies a number of diagnoses for individuals who experience difficulties associated with both abnormally low and abnormally high mood; these include bipolar I disorder, bipolar II disorder, cyclothymic disorder, in addition to medical and substance-related mood disturbances (APA, 2013). Bipolar I disorder is differentiated from bipolar II disorder by the presence of manic episodes, in which individuals have a distinct period of abnormally and persistently elevated, expansive or irritable mood and/or a very high level of energy for at least 7 days, or the symptoms become severe enough to warrant hospitalization. The current category of cyclothymic disorder applies for individuals who have both symptoms of depression and of hypomania but that do not meet full diagnostic criteria for either type of episode.

Bipolar disorder is a serious illness affecting approximately 2-4% of the population, and occurring equally across cultures (Kessler et al., 2005; Merikangas et al., 2011; Akiskal et al., 2000). Bipolar disorder is associated with high employee absenteeism, poor social functioning, and increased risk of suicide (Ruggero et al., 2007). Not surprisingly, bipolar disorder is one of the world's leading causes of disability (Mathers & Loncar, 2006; Murray & Lopez, 1997). It is estimated that costs associated with treating bipolar disorder are approximately $45 billion per year (Kleinman et al., 2003). A meta-analysis of 22 cost-of-illness studies in bipolar disorder reveals per capita costs ranging from $8,000 to $14,000 (Kleine-Budde et al., 2013). Treatments

for individuals with bipolar disorder vary widely and include inpatient hospitalization, outpatient treatment, medications, psychosocial treatment, vocational skills training, and drug and alcohol counseling (Malhi, Adams, Lampe, Paton, O'Connor, Newton et al., 2009; Geddes & Miklowitz, 2013).

Comorbidity is often the rule rather than the exception with bipolar disorder, both in terms of medical problems and other psychiatric disorders (Merikangas et al., 2007). In the National Comorbidity Survey-Replication, anxiety disorders were present in 86.7% of individuals with bipolar I disorder (BD I). Impulse control disorders were present in 71.2% of those with BD I, and substance use disorders were also prevalent, with 60.3% of the BD I sample having some form of substance use disorder. The vast majority of individuals with BD I are afflicted with multiple comorbidities (97% have one or more, 86% have 3 or more disorders). A similar pattern of comorbidity emerges when bipolar II (96% have one or more, 86% have 3 or more) and subthreshold bipolar disorder are examined (88% have one or more, 58% have 3 or more).

Medical Morbidity and Mental Illness

One particular focus in the field of mental health is in gaining further understanding into connections between mental and physical health. There is significant evidence to suggest that serious mental illnesses are associated with a host of negative health outcomes. Combinations of medical and mental illness are associated with significant morbidity over time. Recent attention has focused on the vast public health cost associated with interactions between physical and mental health problems (Whiteford, et al., 2013; Patel et al, 2015). A meta-analysis of over 8000 psychiatric patients revealed a number of physical symptoms and illnesses associated with having a mental disorder, as well as twice the death rates due to natural and unnatural causes

when compared to the general population (Felkner, Yazel & Short, 1996). Almost half of psychiatric patients included in this meta-analysis had known medical comorbidity, with over one third having undiagnosed medical conditions. Additionally, Felkner suggests that approximately 20% had medical problems that may have caused or exacerbated their psychiatric illness. A number of studies examining health-related outcomes in large community mental health systems have found rates of death between 2.4 and 3.0 times higher than the general population in individuals with mental disorders (Miller, Paschall & Svendsen, 2006; Berren, Hill, Merikle et al., 1994; Dickey, Normand & Weiss, 2002). Similar results were found in a large population-wide effort to survey individuals in Ohio's public mental health hospital (Miller, Paschall & Svendsen, 2006). Osborn et al. (2007) conducted a study examining the risk for cardiovascular disorder and cancer in individuals with serious mental illness and found that associations persisted even when accounting for smoking, psychiatric diagnosis, sex or antipsychotic medication exposure. The association between mental health problems and physical illness has been demonstrated across a wide variety of conditions and is associated with increased risk of death due to both natural (e.g. disease) and unnatural (e.g. suicide, accidents) causes (Felkner, Yazel & Short, 1996).

Medical Comorbidity in Bipolar Disorder

When examining medical comorbidity specific to bipolar disorder, it is important to remain aware of shared psychiatric comorbidity (i.e. Merikingas, 2007) and potential secondary and tertiary connections between specific mental health conditions and medical issues. Many comorbid conditions are shared among disorders. This study will focus on medical comorbidity specific to bipolar disorder, but it is likely at least a portion of risk factors are common to other disorders as well.

In individuals with bipolar disorder, medical comorbidity associated with cardiovascular, respiratory and endocrine disorders is related to increased rates of mortality. In a chart-review study of 1379 outpatients treated for bipolar disorder at Duke University Medical Center, Beyer and colleagues (2005) found high rates of comorbid endocrine and metabolic diseases (13.6%), circulatory illness (13.0%), and nervous and sensory disorders (10.7%). Common specific disorders include cardiovascular disease/hypertension (10.7%), chronic obstructive pulmonary disorder/asthma (6.1%), diabetes (4.3%), HIV (2.8%) and hepatitis C (1.9%). The mean age of the sample in the above study was 32.8 years (SD = 18.3 years). A more recent cross-national population-based study (McIntyre, Konarski, Soczynska, Wilkins, Panjwani et al., 2006) of medical comorbidity compared individuals who had experienced a manic episode (n = 938) to those who had not (n = 35,848). Similar results were found, with individuals experiencing a manic episode reporting higher rates of migraine (24.8%), asthma (15.9%), gastric ulcers (10.8%), hypertension (10.4%), chronic bronchitis (7.9%), and chronic fatigue (3.8%). Large population-based studies are complemented by a number of studies examining the prevalence of specific risk factors and illnesses in bipolar disorder.

The presence of medical comorbidity in those who suffer from bipolar disorder also appears to have a significant impact on psychological functioning and quality of life. Goldstein, Liu, Schaffer, Sala and Blanco (2012) examined data from subjects with bipolar disorder (n = 1600) who completed the National Epidemiological Survey on Alcohol and Related Conditions. They found that bipolar subjects who were obese (n = 506) were significantly more likely to have a major depressive episode, more likely to report suicide attempts. However, this association was not present after baseline demographic variables were accounted for, suggesting that other factors such as socioeconomic status, may explain links between depression and

obesity in bipolar individuals. Fenn, Bauer, Alshuler, Evans, Williford et al., (2005) also conducted a retrospective study of medical comorbidity and health-related quality of life in 330 veterans hospitalized for bipolar disorder and found that medical comorbidity was associated with lower physical health related quality of life, independent of age. As well, they found that younger bipolar individuals reported lower mental health related quality of life when compared to older individuals.

Cardiovascular Disease

A number of studies have examined the role that cardiovascular illness plays in contributing to the illness burden seen in bipolar disorder. Tsaung et al. (2011) found increased rates of cardiovascular-related deaths in females with bipolar disorder, though this effect was not seen in men (Standardized Mortality Ratio = 1.63). Rates of hypertension and cardiovascular disease vary drastically based on both individual and study factors (5 – 61%; Johannessen, Strudsholm, Foldager, & Munk-Jorgensen; Carey & Jones, 2006; Lin, Tsai & Lee, 2007); however, the majority of studies find evidence of an increased risk in individuals with bipolar disorder. A large 6-year retrospective study examining risk for developing cardiovascular events found two-fold higher rates of stroke in a patient group relative to healthy controls (Lin et al., 2007). As well, among individuals with bipolar disorder in a large population-based study, more time in depressive episodes was associated with increased risk for death due to cardiovascular events (Fiedorowicz, Jancic, Potash, Butcher & Coryell, 2014).

Pulmonary Disease

Rates of pulmonary illness are also elevated in bipolar disorder when compared to the general population. Individuals with bipolar disorder have increased incidence of conditions such as asthma, pulmonary embolism and chronic obstructive pulmonary disorder, at rates from 3% to

17% (Strudsholm, Johannessen, Foldager, & Munk-Jorgensen, 2005; McIntyre et al., 2006; Kilbourne, Cornelius, Han, et al., 2004; Calabrese, Hirschfeld, Reed, et al., 2003). Prevalence benchmarks for pulmonary issues in the general population in these studies were between 2% and 10%. A study of 1453 adolescents with asthma found higher incidence of major depression (2.8% vs. 1.1%) and bipolar disorder (1.0% vs 0.3%; Chen, Su, Chen Hsu et al., 2014) when compared to controls.

Gastrointestinal Disease

Three studies have shown higher rates of peptic ulcers in bipolar patients relative to healthy controls. Estimates of gastrointestinal disease incidence range from 0.9% to 10.8% in patients compared to 0.2% to 5.0% in control groups (Ghadarian & Engelsmann, 1985; Ewald, Mortensen and Mors, 2001; Kilbourne et al., 2004; McIntyre et al., 2006). Additionally, one study of an inpatient population found gastrointestinal disorders in 16.4% of inpatients with bipolar disorder, as compared to 10.9% of inpatients with schizophrenia (Oreski, Jakovljevic, Aukst-Margetic, Orlic, & Vuksan-Cusa, 2012).

Endocrine-Metabolic Disease

Metabolic disorders have been widely studied in bipolar disorder. A recent review by McIntyre et al (2010) found higher rates of metabolic syndrome in bipolar patients than in the general population across twelve countries. In the United States, rates ranged from 30% to 53% in patients compared to 32% in the general population. In one study that found similar rates compared to the general population, a number of metabolic markers still predicted outcome. Individuals with comorbid BD and metabolic syndrome had higher rates of suicide attempts than those without metabolic syndrome (Fagiolini et al., 2005). Age-related increases in metabolic syndrome were also noted. Cardenas et al. (2008) found a prevalence rate of 49% in a sample of

individuals treated at a VA clinic. Fiedorowicz et al. (2008) found 53% of a clinical sample of individuals with bipolar disorder met criteria for metabolic syndrome. A study comparing bipolar disorder and schizophrenia found relatively equivalent rates of metabolic syndrome (43.2% and 45.9%, respectively; Correll, Frederickson, Kane, & Manu, 2008). When fasting blood sugar requirements for metabolic syndrome were decreased from 110 to 100, rates in both patient groups increased 54%, suggesting that a number of patients are on the borderline of meeting criteria for metabolic syndrome and could be considered at risk. In countries where studies included general population comparison groups, rates ranged from 22% to 50% (McIntyre et al, 2010). Increased waist circumference was the most consistently reported abnormality across studies. Co-occurring metabolic syndrome and bipolar disorder was associated with a more complex illness presentation, less favorable response to treatment, adverse course and outcome. Treatment with atypical antipsychotics appears to be related to weight gain and metabolic problems in a number of studies (Correll et al., 2007). As well, individuals diagnosed with bipolar disorder appear to be at the same risk for developing metabolic syndrome as those diagnosed with schizophrenia (Correll, Frederickson, Kane and Manu, 2008).

Obesity

A number of studies exist examining the relationship between obesity and bipolar disorder, as well. In a sample of outpatients receiving treatment, McElroy, Frye, Suppes, Dhavale, et al. (2002) found that 58% of individuals with bipolar disorder were overweight, 21% were obese, and 5% were extremely obese. An additional study found rates as high as 75% for patients being overweight, and almost half were classified as obese (Fiedorowicz et al., 2008). A number of risk factors for obesity in bipolar disorder were identified: geographical location, gender, comorbid binge-eating disorder, age, income level, degree of exposure to weight-gain-

associated psychotropics, medical disorders associated with obesity and health habits. As well, Elmslie, Silverstone, Mann, Williams and Romans (2000) found higher rates of centrally distributed body fat in bipolar patients when compared to controls. Higher rates of obesity within the bipolar population were observed in patients treated with medications. One first episode study found that weight gain in the 6 months following a patient's first manic episode was associated with male gender and prescription of olanzapine or risperidone (Bond, Kauer-Sant'Anna, Lam, & Yatham, 2010).

Medical Comorbidity from a Multi-System Inflammation Perspective

Recently, researchers have sought to integrate markers of physical health into conceptualizations of mental health problems. Soreca, Frank and Kupfer (2009) have attempted to understand bipolar disorder from a multi-system approach that centers on the role of inflammation and its relationship to bipolar disorder. Recent updates to multi-system inflammatory-related conceptualizations of bipolar disorder focus on the unique roles that dysfunctional biological processes may play in influencing course and outcomes in bipolar disorder (Leboyer, Soreca, Scott, Frye, Henry, Tamouza & Kupfer, 2012).

A number of lines of evidence provide a rationale for viewing bipolar disorder as a multi-system inflammation-related condition. Rates of inflammatory diseases, as well as biological markers of inflammatory response, are elevated in individuals with bipolar disorder (Hamdani et al., 2012). This suggests that there may be shared relationship between the psychological symptoms of bipolar disorder and immune functioning. As well, auto-immune disorders, cardiac disease, infection with specific viruses, obesity, and the metabolic syndrome are all present in higher-than-expected frequencies in patients with bipolar disorder. Additionally, a number of both cardinal and ancillary symptoms of bipolar disorder are associated with increased levels of

inflammation (Fiedorowicz et al., 2009; Goldstein et al., 2009; Murray et al., 2009). Sleep dysfunction, depression, and stressful life events are all associated with increased levels of inflammation (Lange et al., 2010; Mullington et al., 2009; Leonard, 2010), and are often reported in individuals with bipolar disorder. Genetic and environmental risk factors, rather than being conceptualized as risks for psychological symptoms of bipolar disorder, are recognized for their contributions to brain and peripheral inflammation processes. Stressors such as negative life events, poor sleep quality, or the presence of pre-existing inflammation-related conditions then put an individual at greater risk for developing bipolar disorder, and a host of other associated inflammation-related conditions.

Rates of inflammatory diseases such as diabetes, the metabolic syndrome and hypertension, are increased in individuals with bipolar disorder, and are unique predictors of illness progression, even after health behaviors, psychosocial functioning and medication exposure are taken into account (Fiedorowicz et al., 2009; Goldstein et al., 2009; Murray et al., 2009). 70% of individuals with adolescent-onset bipolar disorder receive treatment for one or more co-occurring medical conditions (Evans-Lacko et al., 2009), and increased rates of medical issues are also observed in studies which predate medication treatment, suggesting that these effects cannot be entirely conceptualized in terms of health behaviors following illness development or side effects from medications. The following sections provide a framework for understanding the relationships between inflammation related dysfunction and bipolar disorder symptoms.

Inflammatory Markers, Medical Illness and Bipolar Disorder

Chronic mild inflammation is seen both in brain and peripheral systems in bipolar disorder (Hamdani et al., 2012) and chronic inflammation has been shown to promote

hypertension, diabetes, obesity and atherosclerosis (Drake et al., 2011). Specific cytokines that promote inflammatory response and are known to promote the formation of fatty deposits on blood vessel walls (e.g., interleukin-1, IL-2, IL-4, IL-6, TNF-a) are elevated during mania (Brietzke et al., 2009). In addition, high levels of C-reactive protein (CRP), a protein which acts as a tagging system for cells to be dismantled, are correlated with mania. CRP plays a similar role to the interleukin family in regards to being upregulated when inflammatory processes are active, and high levels of hsCRP are associated with adverse cardiovascular effects (Greenland et al., 2001). Leboyer et al. suggest that similar to findings in depression demonstrating a link between inflammation, oxidative stress, depression and cardiovascular disease (Maes, et al., 2011), hsCRP and other inflammatory cytokines may explain a portion of the comorbidity between medical and mental health pathology.

Pro-inflammatory cytokines can reduce the effectiveness of monoamine signaling pathways as well. Inflammation activates indoleamine 2-3 dioxygenase (IDO), an enzyme which breaks down tryptophan and serotonin *(*Mynt et al., 2007), reducing the availability of serotonin in the synapse. IL-1-b and TNF-a are known to activate serotonin transporters (Zhu, Blakely, & Hewlett, 2006). Mitogen activated protein kinases (MAPK), which are mobilized to restore physiological homeostasis in response to environmental insults, are known to down regulate dopaminergic signaling as well. Recent studies suggest that IL-6 may have utility in understanding the course of bipolar disorder, as levels were increased in the more pernicious late-stage classification (Grande et al., 2014).

Along with changes in serotonin- and dopamine-related protein expression, inflammation is associated with increases in oxidative stress, which have the potential to cause damage to a wide range of genes, proteins and enzymes. One study of later stage patients showed a greater

degree oxidative stress when compared to early-stage patients (Berk et al., 2011), which the author suggests may be associated with declines in cognitive performance.

Brain-derived neurotrophic factor (BDNF) is involved in the repair, creation, insulation and activation of neural pathways, and has been examined across a wide range of psychological conditions, most notably depression (Leonard, 2010). Low BDNF levels are thought to be associated with decreased neurogenesis and glutamatergic excitotoxicity, are correlated with mood state in bipolar disorder (Fernandes et al., 2010), and are associated with coronary heart disease (Lorgis et al, 2010).

Circadian and Sleep-related Contributions to Inflammation

Circadian influences are associated with both bipolar disorder and a variety of comorbid health risk factors or illnesses. Sleep disturbances represent an important avenue of exploration, as abnormalities in sleep are observed prior to first mood episodes, persist through illness phases, and are seen in recovered patients (Harvey, 2008). Aberrant sleep length, both long duration and short duration, is associated with an increased risk for coronary heart disease in women (Ayas et al., 2003). Sleep deprivation studies demonstrate a wide array of deleterious immune responses as a result of sleep loss, both in the short term and over prolonged periods (Lange et al., 2010; Mullington et al., 2009).

Autoimmune Dysfunction, Inflammation and Bipolar Disorder

Higher rates of autoimmune disorders, such as multiple sclerosis, thyrotoxicosis, ulcerative colitis, psoriasis and rheumatoid arthritis are seen in unaffected relatives of patients with bipolar disorder (Eaton et al., 2010), suggesting that a genetic or environmental susceptibility to autoimmune conditions may be a component of bipolar disorder. Genotypes associated with increased risk for autoimmune thyroiditis are found at increased frequency in

bipolar individuals and unaffected monozygotic twin siblings as well, supporting an inflammation-related genetic susceptibility hypothesis (Vonk et al., 2007). Abnormal response to gliandin, suggestive of risk for celiac disease, has also been observed in bipolar patients (Dickerson et al, 2011).

Viral Influences on Inflammatory Processes in Bipolar Disorder

Many have attempted to explain increased risk for affective disorders in children born to mothers pregnant during influenza periods in light of inflammation and retro-virus activation (Scott et al., 2006). Overexpression of RNA for human endogenous retro-virus (HERV-W), a protein associated with promoting a pro-inflammatory response, is also seen in brain samples taken postmortem from bipolar patients (Weis et al., 2007). Additionally, infection with herpes simplex virus type 1 was found to be associated with cognitive deficits in bipolar patients (Dickerson et al., 2004).

Influences of Stress on Inflammation in Bipolar Disorder

Some also view medical problems in bipolar disorder to be consequences of long-term maladaptive responses to physiological stress, i.e. allostatic load (McEwen & Stellar, 1993; Kapczinski, Vieta, Andreazza, Frey et al., 2008; Vieta, Popovic, Rosa, Sole et al., 2013). Leboyer et al. (2012) provided compelling evidence highlighting the importance of inflammatory processes in bipolar disorder; however, less attention was paid to how inflammation and stress are related to and interact with one another. McEwen and Stellar (1993) conceptualize and understand the relationship between stress and inflammation as a complex and interactional system, where stressors serve as a signal to prepare the body for insult, and the body responds through functional and adaptive changes. However, if the stress-response system is engaged too frequently, or too intensely, cumulative wear-and-tear can break down the previously functional

and adaptive stress-response reactions. This concept, termed allostatic load, is particularly useful as it provides a mechanism to understand how biological stress may result in not only mental health problems such as bipolar disorder, but also medical illness.

Allostatic load is a concept introduced by McEwen and Stellar (1993) and is used to understand the interactional effects of stress and physiological adaptation to stress. Ultimately, there is a cost to activating and engaging biological processes in response to stress, particularly if the response is extreme or inefficient. Over- or under-working systems involved in stress response can cause additional wear and tear in these systems and lead to disease manifestation. The metrics used to provide evidence for allostatic load are often associated with stress-related hormones, neurotransmitters, oxidative stress, immune functioning, and gene expression. There are a number of deleterious effects observed when stress-response systems break down or become inefficient, as evidenced by increases in all-cause mortality and declines in physical and cognitive performance as allostatic load increases (Karlamangla, Singer, Greendale & Teeman, 2005; Karlamanga, Singer, McEwen, Rowe & Seeman, 2005; Kauer-Sant'anna, Kapczinski, Andreazza, & Bond et al., 2009). Structural and functional changes in the brain resulting from increased levels of stress hormones (i.e. glucocorticoids) are well documented (McEwen, 2003), and include hippocampal atrophy, reduced neurogenesis in the dentate gyrus, and increased free radical generation (Dranovsky & Hen, 2006; Malberg, Eisch, Nestler & Duman, 2000; McEwen, 2003). Chronic stress is also associated with changes in the organization of the prefrontal cortex (Jay, Rocher, Hotte, Naudon et al., 2004; Moghaddam & Jackson, 2005) and amygdala (Vyas, Bernal, & Chattarji, 2003), systems intimately involved in psychological processes such as emotional perception, planning, and inhibition. The cost of over-engaging stress-response systems is an increase in oxidative stress—considered the primary biological process underlying

allostatic load. High levels of oxidative stress cause biological breakdown in the homeostatic systems involved in responding to stress in an adaptive manner.

Allostatic load is a multi-dimensional, interactional theory which can be used to understand how cognition, physical health and clinical and functional outcome may interact with one another. It is particularly useful in conceptualizing how risk factors and stressors associated with both bipolar disorder and high rates of inflammation may influence one another over time, leading to the eventual expression of both debilitating psychological symptoms and significant physical illness.

Allostasis is a concept that has been applied to bipolar disorder in the past. Kapczinski, Vieta, Andreazza, and Frey et al. (2008) and Vieta, Popovic, Rosa, and Sole et al. (2013) highlighted the importance of breakdowns in cognitive systems as a result of allostatic load. They suggested that allostasis may be particularly explanatory in conceptualizing clinical features and disease course in bipolar disorder.

A number of biological markers of cognitive decline in aging are also seen in bipolar disorder, and not surprisingly, are also associated with cognitive decline in bipolar-specific studies. Markers of oxidative stress, such as thiobarbituric acid reactive substances (TBARS), are increased in individuals with bipolar disorder. A marker associated with brain damage (S100B) was found to be associated with depressed and manic phases (Andreazza, Cassini, Rosa, Leite et al., 2007). Abnormalities that occur in dopamine systems during manic episodes are also suggested to cause increased oxidative burden (Kapczinkski et al., 2008), in part due to biological consequences of morphological differences in D1/D3 receptor balance observed in bipolar disorder and schizophrenia.

Brain-derived neurotrophic factor has been one of the most widely studied biological

markers of disease state in bipolar disorder. As discussed above, BDNF levels are decreased during manic and depressive episodes (Fernandes, 2010), and are inversely correlated with symptom expression (Machado-Viera, Dietrich, Leke, Cereser, et al., 2007). As well, a polymorphism in the BDNF gene is associated with impaired cognitive performance as well as increased risk for rapid cycling (Muller, De, Sicard, King, & Strauss, 2006). Vieta et al. (2013) suggest that structural brain changes seen in bipolar disorder in regions associated with signaling stressful events, i.e. enlarged amygdala and reduced prefrontal cortex and hippocampal volume, may represent a vulnerability factor for individuals with bipolar disorder causing increased susceptibility to consequences of allostatic load.

Significant overlap exists in the evidence base for both allostatic load theories and multi-system theories, i.e. BDNF levels, brain morphology, markers of immune function, and the impact of oxidative stress. It is not surprising that these theories overlap substantially. Allostatic load theories and multi-system inflammation-based conceptualizations of bipolar disorder place medical comorbidity and biological disturbance as core features of illness. From the frame of these theories, it is not surprising to see how medical illness may be a marker of or co-occurring factor in the expression of psychological disorders. However, there are equally compelling alternative explanations for the high rates of medical comorbidity in bipolar disorder.

Alternative Explanations

Medical comorbidity may be a primary characteristic of bipolar disorder; however, a number of additional explanations are plausible. Consequences of illness, such as lifestyle factors, risky health behaviors, and/or medication exposure, may drive the high rates of comorbidity seen in bipolar individuals. Though a large body of literature points toward dysfunctional immune responses in bipolar disorder, the majority of evidence provided in

support of allostatic load and inflammatory theories of bipolar disorder is cross-sectional. Thus, answering questions about whether medical illness expression is a primary component or comes as a consequence of diagnosis or treatment is difficult.

Lifestyle may be one potential route through which physical health problems manifest. Factors such as lack of exercise, unhealthy diet, deterioration in self-care, and poor self-awareness appear to contribute to rates of metabolic difficulties in bipolar patients (Morriss & Mohammed, 2005). High rates of cigarette smoking in individuals with BD are also presumed to contribute to increased rates of cardiovascular disease (Corvin, O'Mahony, O'Regan, Comerford et al., 2001). Additionally, alcohol and substance use are prevalent in bipolar disorder, with a recent study finding risk of developing alcohol dependence was 49% in bipolar men and 29% in bipolar women (Frye, Altshuler, McElroy et al., 2003). Strakowski et al., (1998) found a rate of alcohol abuse of 32% in first admission bipolar patients, with 76% meeting criteria for drug abuse, suggesting that exposure to drugs and alcohol is prevalent early on. Strakowski, Sax, Mcelroy, Hawkins and West (1998) suggest that cannabis use disorders may precede and contribute to the development of bipolar disorder, and approximately 60% of individuals with bipolar disorder develop substance abuse prior to bipolar disorder onset (Strakowski and DelBello, 2000). Childhood adversity, as well, is associated with increased rates of medical illness in bipolar disorder (McElroy, Keck, Nolen, Kupka, Grunze & Rowe, 2013). Early life adversity can cause significant structural changes in the brain, including decreased hippocampal glucocorticoid receptor density (McGowal et al., 2009), and increased risk for being overweight (Dube et al., 2009; Shonkoff & Garner, 2012). Early life stress and the deleterious biological responses that occur as a result may manifest in the form of medical illness later in life.

Medical illness may also develop as a result of poor health behaviors as well. Lack of

awareness, high levels of impulsivity or lack of behavioral controls, substance abuse, all which are considered psychological manifestations of bipolar disorder may be driving increased rates of poor health behaviors, and as a consequence, medical illness. In this model, medical illness is more distally related to a diagnosis of bipolar disorder, only emerging as a consequence after psychiatric symptoms are expressed.

Another potential secondary cause of medical comorbidity concerns treatment-emergent side effects. Complex polypharmacy has increased substantially in more recent years. Among individuals discharged from the NIMH Biological Psychiatry Branch, complex polypharmacy consisting of three or more psychotropics increased 13 times over the 22 years from 1974 to 1996 (Frye et al., 2000). In a separate study from 1996 to 2006, number of prescriptions increased by over 40% and the number of individuals on three or more psychotropic medications doubled (Mojtabai & Olfson, 2010).

Debate exists on the extent to which pharmacotherapy side effects for bipolar disorder play a role in driving high rates of medical comorbidity (Wantabe, 2005). Though few studies are designed in a manner to address casual links between medication use and development of medical problems, a large body of literature points toward treatment-emergent metabolic difficulties associated with antipsychotic medication treatment (McIntyre et al., 2003) and valproate (Bowden et al., 2000; Reynolds et al., 2007). Correll et al. (2008) suggest that individuals treated with second generation antipsychotics, regardless of a diagnosis of schizophrenia or bipolar disorder, have a shared susceptibility to antipsychotic-related metabolic abnormalities. A more recent study comparing individuals with bipolar disorder to those with schizophrenia found higher rates of obesity and higher serum lipid concentrations in those with bipolar diagnosis (Ventriglio, Gentile, Baldessarini et al., 2013) High rates of polypharmacy,

complex and understudied relationships between medications, and significant side effect profiles of many treatments, may be influencing rates of medical comorbidity in bipolar disorder.

Evidence from Longitudinal Studies

Despite acknowledgement of the important role that medical comorbidity plays in bipolar disorder, fewer studies have examined the longitudinal trajectory of medical issues in bipolar disorder. The majority of evidence reviewed above relies on cross-sectional study designs, which limit the ability to draw conclusions about how medical conditions develop and the extent to which they are related with course and outcome of psychiatric illness. Examining how medical illness unfolds across time in individuals with bipolar disorder, as well as understanding how it interacts with functional outcomes is an important avenue of exploration. Are there physical manifestations of mental health problems that may be used to inform treatment? If so, are they of prospective or prognostic use?

Though understanding the impact of medical comorbidity amid all of the other interacting biological, social and psychological processes is a difficult task, a number of prospective studies demonstrate the importance of taking medical comorbidity into account. Kemp, Gao, Chan, Ganocy et al. (2010) conducted a study examining the relationships between medical comorbidities and treatment outcomes in bipolar disorder: 225 individuals with rapid cycling bipolar I and II disorder were enrolled randomized open-label 36-week lithium and valproate treatment trails. They found significant relationships between endocrine and metabolic disorders and treatment outcome. Higher rates of baseline medical comorbidity were associated with higher ratings on bipolar-related psychiatric outcome measures. As well, endocrine and metabolic illnesses, such as metabolic syndrome and diabetes, were inversely correlated with remission from depression at the end of the trial. Additionally, this study replicated an often cited

relationship between higher levels of obesity and poor treatment outcome as measured by psychopathology, suicide attempts, relapse and re-hospitalization (Fagiolini, Kupfer, Houck, Novick & Frank, 2003; Calcin, van de Velde, Ruzickova, et al., 2009).

A prospective analysis of 306 randomized clinical trial participants in a VA hospital examined the impact of medical comorbidity on bipolar disorder outcome over 3 years (Pirraglia, Biswas, Kilbourne, Fenn & Bauer, 2009). Increased levels of physical illness at baseline predicted higher depression scores and less improvement in mental health-related quality of life. Participants with high medical comorbidity in the Pittsburg Maintenance Therapies in Bipolar Disorder (MTBD) study had longer duration of lifetime depression and inpatient depression treatment, higher baseline depression ratings, and higher likelihood of being treated for depression in the context of the study (Thompson, Kupfer, Fagiolini, Scott, & Frank, 2006). Most telling in light of the importance of medical comorbidity on treatment outcome, depressed and mixed/cycling patients with more severe baseline medical comorbidity had slower decreases in depression scores, even after accounting for baseline depression levels.

A recent article examined the relationship between medical comorbidity and outcomes in 264 individuals treated with adjunctive lithium for bipolar disorder and followed for six months (Kemp, Sylvia, Calabrese, Nierenberg, Thase, et al., 2014). Though baseline severity of mood symptoms did not differ between low and high medical comorbidity groups, which the authors suggest may be due to a relatively healthier sample, a number of interesting baseline characteristics were found. At study entry, high medical illness rates were associated with current depressive episodes and comorbid obsessive compulsive disorder. The high medical comorbidity group had on average of 15 more hypomanic or manic episodes and 10 more major depressive episodes prior to entering the study (mean age = 39.2 years). The average number of

previous mood episodes for the high medical comorbidity group was 66.5 as compared to 37.7 for the low medical comorbidity group, despite similar age at onset. At this stage in treatment, significant consequences appear to be accumulating alongside comorbid medical illness. As well, burden associated with physical comorbidity appears not only to be a marker associated with diagnosis, but also one associated with severity of symptoms.

Kilbourne, Perron, Mezuk, Welsh, Ilgen et al., (2009) examined relationships between medical comorbidity, substance use and health related quality of life in a sample of 334 individuals with bipolar disorder followed over a one year period. Drug use and medical comorbidity both independently predicted health related quality of life decreases over the course of the year, even after controlling for symptoms of bipolar disorder.

Malhotra, Kulhara, Chakrabarti and Grover (2013) conducted a 6 month study of 97 individuals with bipolar disorder to evaluate changes in metabolic syndrome over time. They found that 40% of patients with bipolar disorder had metabolic syndrome at the beginning of the study, as compared with 32% of patients in the study who were diagnosed with schizophrenia. At the six month follow up, an additional 8% of bipolar individuals developed metabolic syndrome. An additional 10-year nationwide population-based prospective study found increased risks of initiation of anti-diabetic (10.1% vs. 6.3%) and anti-hyperlipidemia medications (15.8% vs. 6.3%) in 367 patients with bipolar disorder when assessed at the 10-year time point (Bai, Su, Chen, Chen and Chang, 2013). The authors in this study controlled for age, gender, urbanization and income, and found that the relationship between increased rates of anti-diabetic and anti-hyperlipidemia medications and bipolar disorder persisted. Interestingly, the authors found similar findings in individuals with schizophrenia, but not in those with major depressive disorder.

Generally, as the majority of the evidence above may suggest, higher rates of medical illness are associated with worse outcome in terms of functioning or psychopathology level. Despite evidence suggesting the importance of biological factors in bipolar disorder, medical illness is often overlooked in large scale analysis of variables associated with diagnostic course or treatment outcome. Leboyer et al. (2012) noted the lack of studies which considered medical comorbidity as a variable in developmental models of bipolar disorder, citing relatively few prospective analyses in bipolar samples. The authors pointed out the importance of understanding different trajectories of medical burden in order to incorporate them into current models of bipolar disorder

Summary of Reviewed Literature

A number of cross-sectional studies support a conceptualization of bipolar disorder that takes medical comorbidity into account. Medical illnesses, across a variety of systems, are more prevalent in bipolar disorder (McIntyre, 2010; Hamdani et al., 2012). A number of systems associated with inflammation, both in the brain and in the periphery, are particularly affected in individuals with bipolar disorder (Leboyer et al., 2012), including increased levels of oxidative stress (Berk et al., 2011), dysfunctions in sleep (Harvey, 2008), high rates of auto-immune disorders (Eaton et al., 2010) and early-life viral insult (Scott et al., 2006). Additionally, biomarkers indicate a high level of allostatic load in individuals with bipolar disorder (Andreazza, Cassini, Rosa, Leite et al., 2007; Kapczinski et al., 2008; Fernandes, 2010). Despite the ample evidence for increased inflammation and medical comorbidity in bipolar disorder, a majority of the above studies did not take into account secondary factors that might explain the presence of high rates of medical illness in bipolar disorder. For example, lifestyle factors are known to exert a strong influence on a variety of outcomes in bipolar disorder; lack of exercise,

unhealthy diets, deterioration in self-care and poor self-awareness appear to contribute to rates of metabolic difficulties in bipolar patients, while high rates of smoking in bipolar disorder may underlie increased cardiovascular mortality (Morriss & Mohammed, 2005; Corvin, O'Mahony, O'Regan, Comerford et al., 2001).

As well, the presence of medical illness alongside bipolar disorder is associated with a host of deleterious long-term outcomes, in addition to interacting with treatment outcome. Individuals with bipolar disorder who have endocrine or metabolic disorders present with higher ratings on bipolar-related psychiatric outcome measures (Kemp, Gao, Chan, Ganocy et al., 2010). Rates of obesity in bipolar disorder are also related to poor treatment outcome, increased numbers of suicide attempts, higher rates of relapse and rehospitalization (Fagiolini, Kupfer, Houck, Novick & Frank, 2003; Calcin, van de Velde, Ruzickova, et al., 2009). Increased levels of baseline physical illness predict higher depression scores and less improvement in mental health-related quality of life in individuals being treated for bipolar disorder (Thompson, Kupfer, Faglioni, Scott & Frank, 2006). Recently, Kemp, Sylvia, Calabrese, Nierenberg, Thase, et al. (2014) found that when they split their sample into high and low medical comorbidity groups, the high medical comorbidity group had on average 15 more hypomanic or manic episodes and 10 more major depressive episodes prior to entering the study than the low medical comorbidity group did. While the low comorbidity group had 37.7 mood episodes, individuals with higher rates of medical comorbidity had significantly more mood episodes (66.5). As well, over long term treatment (approximately 10 years), individuals with bipolar disorder are significantly more likely to start anti-lipidemia or anti-diabetic medication treatment (Bai, Su, Chen, Chen and Chang, 2013).

Despite the variety of methods used to examine the impact and prevalence of medical comorbidity in bipolar disorder, the majority of studies have focused on a small set of medical illnesses and did not comprehensively assess across a wide range of medical diagnoses. There appear to be clear relationships between depressive symptoms and medical comorbidity in individuals with bipolar disorder, in addition to relationships between bipolar diagnosis and medical comorbidity independent of bipolar symptoms. However, a number of questions remain.

The relationship between symptoms of bipolar disorder and medical illness is likely complex and multifaceted. When examining specific symptoms associated with high rates of medical comorbidity in bipolar disorder, it is important to take note of previous literature which suggests depressive symptoms often drive the majority of associations between physical illness and psychological symptoms. Further complicating the matter, a number of studies have found specific risk factors or medical illnesses to be increased in bipolar disorder, even in reference to comparison populations with schizophrenia (Kilbourne et al., 2007; Oreski et al., 2012). A more full understanding of the specificity of relationships between medical and psychiatric diagnosis is necessary if medical comorbidity is to be incorporated into conceptualizations of course and outcome in bipolar disorder.

Current Study: Examining Patterns Across Time

The primary aim of the present study was to describe rates of medical illness in bipolar disorder across the first 10 years following initial hospitalization. The majority of studies of medical comorbidity in bipolar disorder are either cross-sectional, retrospective or in populations who have previously received treatment. Furthermore, this study examined how medical comorbidity unfolds in bipolar disorder by examining rates of medical illness, predictors of medical illness, and how medical illness relates to psychological and physical functioning in a

first-episode psychosis population tracked over 10 years.

There are a number of benefits to following individuals from early in their treatment. First episode studies offer a baseline measurement relatively free of long-term treatment-related side effects and confounds. The cumulative effects of illness burden (e.g. allostatic load) are low compared to populations diagnosed and treated for long periods of time. First episode populations also offer heterogeneity in presentation and prognosis, and thus unique insights into characteristics of early stage illness. Furthermore, the length of follow up allows for examination of transitions between illness stages. Additionally, there are very few longitudinal studies which report medical comorbidity rates in bipolar disorder, particularly over long durations. This 10-year examination of medical comorbidity in first episode bipolar disorder represents a temporally comprehensive effort to date to understand the nature and impact that physical comorbidity plays in the aftermath of diagnosis.

Prior studies in first episode mania have highlighted the importance that depressive symptoms play as a signal for predicting future psychosocial and functional recovery after an initial episode. Not only are major depressive episodes in bipolar disorder associated with lower psychosocial functioning and poor outcome, this relationship persists even when less severe, sub-syndromal depressive symptoms are taken into account. (Kauer-Sant'Anna, Bond, Lam & Yatham, 2009). In first episode patients, even sub-syndromal depression has implications for eventual outcome. In later stage treatment trials, high levels of medical comorbidity are most associated with depressive symptoms and total number of illness episodes. It was expected that in this sample, depressive symptoms would be strong contributors to medical burden over time.

Individuals from this sample diagnosed with schizophrenia and major depressive disorder served as comparison groups. In addition, individuals with bipolar disorder were compared to

age and gender matched controls from a national epidemiological study, the National Health and Nutrition Examination Survey (NHANES, 2000). Given that depressive symptomatology appears to be the most reliable psychological marker connecting bipolar disorder, medical comorbidity and outcome, we compared individuals diagnosed with bipolar disorder to those with major depressive disorder. As well, individuals with schizophrenia share similar medical morbidity, and thus were selected as an additional control group. Comparing medical comorbidity across diagnostic groups was done in order to help to identify whether the nature of medical issues are unique to any one specific disorder or shared risk factors common amongst a number of disorders. In addition to understanding the specificity of medical comorbidity in bipolar disorder, the current study aimed to examine predictors of medical illness and associations with functioning rates at baseline, 4 years, and 10 years following hospitalization.

Aims for Current Study

Aim 1: The study's first aim was to compare the rates of four common medical illnesses (i.e. metabolic, cardiovascular, obesity, and neurological/migraine) at baseline and 10 years later in patients with bipolar disorder relative to an age, gender, race and temporal catchmentmatched sample representative of the general population.

Hypothesis 1: At baseline, it was expected that individuals with bipolar disorder would have higher rates of cardiovascular disease when compared with National Health and Nutrition Examination Survey (NHANES, 2000) controls. No differences were expected to emerge between individuals with bipolar disorder and controls in metabolic, obesity, and neurological illnesses.

Hypothesis 2: At the 10 year time point, it was expected that individuals with bipolar disorder would have higher rates of cardiovascular disease, neurological

disorders/migraine, metabolic difficulties, and obesity when compared to NHANES controls.

Aim 2: The study's second aim was to compare the rates of the most common medical illnesses (i.e. metabolic, cardiovascular, obesity, and neurological/migraine) at baseline and across 10 years in patients with bipolar disorder relative to patients from the same sample, but with diagnoses of schizophrenia or major depressive disorder (MDD) with psychosis.

Hypothesis 3: At baseline, rates of medical illness would not be significantly different amongst diagnostic groups.

Hypothesis 4: At 10 years, it was hypothesized that individuals with bipolar disorder would have higher rates of cardiovascular disease when compared to individuals with major depressive disorder and schizophrenia. Rates of illness for other disorder were not expected to be significantly different.

Aim 3: The study's third aim was to test for clinical predictors (i.e. depressive, manic, negative, positive, and disorganized symptoms) of medical illness development by year 10 in individuals with bipolar disorder, while also examining the influence and controlling for lifestyle (i.e. smoking), treatment (i.e. medication) and demographic (i.e. socioeconomic status, age, gender) factors.

Hypothesis 5: It was expected that smoking, treatment and demographic factors would account for a significant portion of the comorbidity between medical illness and psychiatric diagnosis that developed by year 10. Specific demographic, treatment and lifestyle factors were chosen for their known associations with the development of medical illness, and it was expected that there would be associations between smoking status, age, medication class, and socioeconomic status at the 10 year time point. In

particular, we expected higher rates of medical illness at 10 years in individuals who were older in age, on anti-psychotic or anti-manic medications, and of low socioeconomic status.

Hypothesis 6: It was hypothesized that even after controlling for lifestyle, treatment and demographic factors, a significant portion of variability in the development of medical illness in individuals with bipolar disorder would be explained by psychological symptoms. Specifically, it was expected that depressive symptoms would be most strongly associated with development of medical illness in general, even after controlling for lifestyle, treatment and demographic factors (Thompson et al., 2006; Pirraglia et al., 2009; Kemp et al., 2010). Additionally, it was expected that individuals with higher levels of positive symptoms at baseline would be more likely to be diagnosed with a medical disorder, but that this relationship would no longer be significant after controlling for lifestyle, medication and demographic factors, (i.e. medication exposure). No significant effects were expected for manic symptoms, disorganized symptoms, or negative symptoms.

CHAPTER 2

METHODS

Participants

Archival data from a large-scale longitudinal study of outcomes in first episode psychosis was used for the present study. 628 individuals were originally recruited into the parent study between 1989 and 1995 and determined to be eligible for the study. A total of 470 of them were reassessed at the 10-year follow up. Forty-two individuals died prior to the 10 year assessment. If a medical illness was attributed to a participant's cause of death in participants who died during the 10 year follow up interval, the individual was included in the analysis. The remaining 116 who are not included in the sample declined to participate (n = 61), could not be contacted (n = 36), had uncooperative relatives (n = 10) or lacked the capacity the provide consent (n = 36).

Inclusion criteria for the study were as follows: first admission to a psychiatric hospital in the 6 months prior to enrollment, ages 15 to 60, capacity to provide consent, and clinical evidence of definite or possible psychosis. The analysis set included only individuals who provided baseline and 10 year medical information and excluded individuals who were diagnosed with drug-induced or undetermined psychosis. Individuals in the study were assessed at baseline and then again at 6 months, 4 years and 10 years. Measures from the 6 month and 10 year assessments were used for the present study.

The final sample included three diagnostic groups, including schizophrenia (n = 191), bipolar disorder (n = 93) or major depressive disorder with psychotic features (n = 55). The majority of individuals in the sample were male (55.6%). Sample demographics were predominately white (77.0%), with 13% African American, 7.7% Hispanic and 2.4% identifying

with other races or ethnicities. See table 1 for demographics by diagnostic category.

Measures

Demographic information was obtained (age, gender, marital status, education, ethnicity and socioeconomic status). In addition, a number of measures assessing medical, clinical, psychological and diagnostic status were administered. Hollingshead Four Factor Index of Social Position (Hollingshead, 1975) ratings were collected at baseline.

Diagnosis

The 10 year diagnosis was made based on the Structured Clinical Interview for DSM-IV Axis I Disorders (Frist, Spitzer, Gibbon & Williams, 1997) in addition to consensus clinical information and narrative accounts of symptoms experienced through the study. The process was completed by at least four psychiatrists in each instance. The SCID trainer observed 5-10% of interviews. Intraclass correlations for raters were 0.75 for psychotic symptoms and 0.78 for negative symptoms. Depressive symptoms had a kappa value of 0.73. At 10 years, agreement ratings were 0.81 for psychotic symptoms, 0.87 for negative symptoms and 0.79 for depressive symptoms.

Symptoms

Negative symptoms were assessed using the Scale for Assessment of Negative Symptoms (SANS; Andreasen, 1983), and psychotic symptoms were assessed based on 16 items on delusions and hallucinations from the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1983). Disorganized symptom scores were based on bizarre behavior and thought disorder sections of the SAPS. Depressive symptom scores were based on number of SCID past-month depressive symptoms. Mania was assessed using the Brief Psychiatric Rating Scale – Excitement subscale (BPRS-E; Woerner, 1988). Global Assessment of Functioning (GAF) was

rated for the best month in the year prior to the baseline assessment, and estimated at monthly intervals at each assessment through year 10.

Medication Use

During the first 48 months, detailed medication logs, including start and stop dates were collected. Medications were classified into three categories: antimanics, antipsychotics and antidepressants.

Quality of Life

The Quality of Life Scale (QOLS) is a 21-question semi-structured interview originally designed to assess deficits in general functioning in individuals with schizophrenia (Heinrichs, Hanlon & Carpenter, 1984). The QOLS measures functioning across a variety of domains related to psychosocial activity. The interview assesses school, work and family/social functioning (e.g. interest in recreational activities, capacity for empathy, anhedonia, sense of purpose, enjoyment in social activities with family, friends, and romantic interests).

Physical Health

Comprehensive analysis of physical illness was conducted using a scale designed to assess medical problems across a number of different systems of the body and was given at 6 months, 24 months, 48 months and 10 years following study entry. Individuals reported if they were diagnosed or received medical treatment for over 25 categories of illness, including a number of cardiovascular diseases (hypertension, high blood pressure, heart trouble, stroke), pulmonary diseases (asthma, bronchitis, chronic upper respiratory infections), neurological disorders (epilepsy, seizures), endocrine-metabolic disorders (diabetes, high blood sugar, thyroid disease), autoimmune disorders (e.g., chronic fatigue, Raynaud's, lupus) and gastrointestinal disease (ulcers, other GI disease). At 10-year follow up, individuals were asked to rate their

overall and comparative health and the impact of their physical health on daily life, in addition to reporting medical procedures, hospitalizations, and emergency room visits. Smoking was assessed with items from the National Household Survey on Drug Abuse interview (DHHS, 1988). A variable was created to determine if individuals in the Suffolk sample reported any cases of medical illness throughout the first 10 years. If an individual was diagnosed with an illness at 6 months and failed to report the illness across the interval, they were counted as having the illness. Prevalence variables were computed for any illness that an individual reported across the assessment interval.

Analytic Strategy

Frequencies of cardiovascular illness, obesity, metabolic illness and neurological illness/migraine were reported in individuals with bipolar disorder, major depressive disorder and schizophrenia at baseline and 10 years after study entry. Odds ratios were used to compare groups at each time point. Age and gender matched controls from the 1999-2000 NHANES dataset were used to determine if rates of medical illness are higher than would be expected in the general population.

The study also used multiple logistic regression to predict factors associated with the development of any medical illness at year 10. Analysis was repeated for each of the four key illnesses of interest as the dependent variable (i.e., cardiovascular disease, metabolic disorder/diabetes, neurological disorders and migraine). Three blocks of predictor variables were used. The first block controlled for pre-existing illness at baseline. The second block included variables which are known to exert influence on medical illness rates both in the general population and in individuals with bipolar disorder (socioeconomic status, GAF, smoking status,

age, medication class). The third block contained psychological symptoms which showed significant bivariate associations with a specific illness.

CHAPTER 3

RESULTS

Comparing rates of illness to a matched control sample

Tables 2 - 9 include odds ratios and confidence intervals for each illness reported in the study sample and the NHANES sample. The NHANES sample was matched on temporal catchment, age, gender and ethnicity. At 6 months, those with bipolar disorder had significantly increased risk of diabetes (OR = 3.71) and asthma (OR =3.07) compared to controls, but no difference for stroke, thyroid disorder, cancer, arthritis, or hypertension. Comparable rates of cardiovascular disease were not available in the NHANES sample due to illness prevalence being evaluated in a disparate manner between datasets. Contrary to our hypothesis, there was substantial risk for incidence of medical illness, specifically diabetes and asthma, 6 months after hospitalization.

Similar analysis was repeated using information gathered at a 10 year follow up interview and is included in the second panel of Tables 2 - 9. At 10 years, individuals with bipolar disorder had significantly increased odds of diabetes (OR = 2.03), stroke (OR = 6.98), asthma (OR = 2.06), and cancer (OR = 2.16), but no difference for hypertension, thyroid disorder, or arthritis. Comparable rates of cardiovascular disease were again not available in the NHANES sample due to illness prevalence being evaluated in a disparate manner between datasets.

Comparing Frequencies of Medical Illness Between Diagnostic Groupings

Next, OR were calculated to compare medical illness among the three patient groups. There were no significant differences in rates of any medical illness examined when comparing individuals with bipolar and schizophrenia diagnoses at 6 months or at 10 years. Failure to detect significant findings may be due in part to either the relatively low prevalence rate of medical

illness, or to due to an insufficient sample size. We found no evidence to suggest higher rates of cardiovascular disease in individuals with bipolar disorder when compared to those with major depressive disorder with psychotic features or schizophrenia.

Predictors of Medical Illness 10 Years after First Hospitalization: Bivariate Associations

Any Medical Illness

Table 10 reports odds ratios between the development of any medical illness and psychological and demographic variables at 6 months and 10 years. Among demographic and 6 month variables, only age (OR = 1.44) appeared to increase risk of any medical illness at year 10, whereas male gender decreased odds (OR = .27). Among treatment variables, antidepressant use at six months decreased odds (OR = .46) whereas baseline to four year antidepressant use increased odds (OR = 1.61).

Diabetes

Table 11 reports odds ratios between the development of diabetes and psychological and demographic variables at 6 months and 10 years. Among baseline demographics and six month predictors of diabetes, age (OR = 1.70), six month BMI (OR = 1.70), SANS-A (OR = 1.48), percentage of time on antidepressant and antipsychotic medications from baseline to four years increased odds of developing diabetes (OR = 1.32, OR = 1.38 respectively). Higher social functioning scores at six months were associated with reduced odds of diabetes (OR = .76). Of the 10 year predictor variables assessed, BMI (OR = 1.46), SANS-A (OR = 1.40), and employment status (OR = 2.27) increased odds for diabetes, while social functioning and better global functioning reduced risk for diabetes (OR = 0.67 and OR = 0.59, respectively)

Headache

Table 12 reports odds ratios between the development of headache and psychological and demographic variables at 6 months and 10 years. Prevalence of headaches was positively associated with female gender (OR = .54) and anti-depressant use from baseline to year four (OR = 1.24), and were negatively associated with 6 month negative symptoms (OR = .78). Of the 10 year variables, depressive symptoms increased odds of reporting new headaches (OR = 1.46), while antidepressant use reduced risk of headaches (OR = .63).

Hypertension

Table 13 reports odds ratios between the development of headache and psychological and demographic variables at 6 months and 10 years. Specific predictors which increased odds of developing hypertension from the demographic and six month variables were percentage time on antidepressant medications (OR = 1.36), 6 month BMI (OR = 1.44), age (OR = 1.95), and percent time on antidepressants and antipsychotic medications from baseline to four years (OR = 1.32, OR = 1.38). Male gender (OR = .57), higher 10 year BMI and 10 year depressive symptom scores increased odds for hypertension as well (OR = 1.71 and 1.26 respectively).

Body Mass Index

BMI at 6 months was associated with age (r = .142, p < .01), SES (r = .162, p < .01), 6 month negative symptoms (r = .142, p = 0.2), and 6 month depression scores (r = .153, p < .01). BMI at 10 years was associated with SES (r = .185, p < .01) and being on an antipsychotic at the 10 year follow up (r = .186, p < .01). 6 month BMI was strongly correlated with 10 year BMI (r = .608, p < .01).

Predictors of Medical Illness 10 Years after First Hospitalization: Hierarchical Regression

Multiple hierarchical logistic regression was conducted to determine the relative unique influences of demographic factors (age, gender, ethnicity, SES), BMI (6 months and 10 years),

medications (0 – 4 year, 10 year), and psychological symptoms (positive symptoms, negative symptoms, disorganized symptoms, depression and mania; 6 month and 10 year for all predictors) on medical illnesses incidence between baseline and year 10. Specific predictors were selected for each analysis if bivariate associations suggested a relationship between predictor and illness development at either 6 months or 10 years. In this case, both 6 month and 10 year variables were entered if associations between predictors and illness development were significant at either time point. An analogous hierarchal linear regression was conducted to determine contributions of the same set of individual predictors on 10 year body mass index (BMI at 10 years was excluded from the predictor set).

One or More Medical Illness

Table 14 includes an examination of contributions of individual predictors and corresponding confidence interval ranges. The first logistic regression model was conducted according to the three steps described above. Of the predictor variables in the final model, female gender was negatively associated with development of any medical illness (OR = .22) and percentage of time on antidepressant medications from baseline to year four was positively associated with development of any medical illness (OR = 1.57).

Diabetes

Table 15 includes an examination of contributions of individual predictors and corresponding confidence interval ranges for the development of diabetes. Of the predictor variables in the final model, age (OR = 1.73), 6 month BMI (OR = 2.01) remained significant baseline predictors of 10 year illness, and employment status was the only 10 year variable which was significant (OR = 1.62). See Table 5 for an examination of contributions of individual predictors and corresponding confidence interval ranges.

Headache

Table 16 includes an examination of contributions of individual predictors and corresponding confidence interval ranges for the development of headache at 10 years. When demographic factors, anti-depressant usage, negative symptoms, BMI and 10 year medication class were included with pre-existing illness and psychological symptoms, the overall model was significant. The only significant predictor of headache development in the final model was 10 year depressive symptoms (OR = 1.61).

Cardiovascular

Table 17 includes an examination of contributions of individual predictors and corresponding confidence interval ranges for the development of cardiovascular disease at 10 years. The final logistic regression model was conducted according to the three steps described above. Of the predictor variables in the final model, age (OR = 1.76), 6 month BMI (OR = 1.5) and percent time on antidepressant medication from baseline to year four remained as significant positive predictors (OR = 1.56).

Body Mass Index

Table 18 includes an examination of contributions of individual predictors and corresponding confidence interval ranges for BMI at 10 years. A three step hierarchical linear regression was conducted with similar predictors as described above. Demographics and medications explained a significant portion of variability in BMI over and above 6 month BMI (block 1). The addition of psychological symptoms to the model did not result in a significant increase in the proportion of variability explained by the model. In the final model, 10 year BMI was most strongly associated with 6 month BMI, followed by antipsychotic use at 10 years and mood stabilizer use at 10 years.

CHAPTER 4

DISCUSSION

Brief Summary of Results

A number of important findings emerged from this examination of medical illness in a sample of individuals with first episode psychosis. The relationship between mental health problems and medical problems is complex and likely involves interactions among underlying inflammation related pathology, treatment effects and psychological sequalae of illness, which may result in increased medical risk factors and the eventual self-report of medical pathology. When comparing individuals in the patient sample to age, gender and ethnicity-matched controls, there were substantial elevations of a number of medical illnesses associated with both chronic stress and chronic inflammation. Two of these diagnoses (diabetes and asthma) were present in higher than expected levels at baseline, suggesting metabolic and inflammation related abnormalities occurring early in psychiatric illness course. Ten years after first hospitalization, individuals expressed substantial risk for an additional set of aging related illnesses (i.e. cancer and stroke) over and above what would be expected based on baseline illness rates and 10 year general population controls. Diabetes and asthma rates remained elevated relative to controls at the 10 year time point. Factors associated with illness development were both demographic (e.g. age and body mass index) and psychological (e.g. depressive symptoms and/or anti-depressant treatment) and will be discussed below.

Examining Medical Illness Rates over Time

Differences in rates of medical illness in bipolar disorder were present at a time point earlier than hypothesized. At only 6 months after initial hospitalization for psychosis, there were substantially greater odds of individuals with bipolar disorder having diabetes when compared to a nationally representative age, gender and ethnicity matched sample. Prior evidence suggests an

increased risk of type 2 diabetes in older individuals (age 50 – 74) with schizoaffective disorder and bipolar I disorder, which remained independent of medication usage. Additionally, a recent meta-analysis conducted by Vancampfort et al. (2013) of 81 studies examining bipolar disorder and metabolic abnormalities revealed high overall rates of metabolic syndrome in individuals diagnosed with bipolar disorder (37.3%), with approximately 2.0 increased odds of having metabolic syndrome in studies which had a general population comparison group. Among bipolar individuals with metabolic syndrome, anti-psychotic medication usage was associated with approximately 1.7 times the odds of developing metabolic abnormalities. This study is consistent with evidence suggesting that there may be active metabolic abnormalities in individuals with bipolar disorder that confer risk for diabetes, and adds to the literature by demonstrating these abnormalities at an early time point in illness progression; these abnormalities are detectable only 6 months after initial hospitalization. When compared to a nationally representative sample, individuals in the patient sample had approximately 3.7 times the odds of having diabetes, indicating a substantial risk profile early in the course of illness. Interestingly, the increased risk of diabetes at 6 months was not seen in schizophrenia diagnosis, which is contrary to what might be expected (Cohen & DeHart, 2011; Ryan, Collins & Thakore, 2003), however, a relatively similar risk profile was seen in major depressive disorder with psychosis. Factors associated with diabetes risk at 6 months independent of diagnosis were age (OR = 2.17), employment status (OR = 4.25), and BPRS-Excitement subscale (OR = 1.58).

The link between asthma and psychiatric diagnosis has been demonstrated across a wide range of conditions, and is most well studied in anxiety and major depressive conditions. Bender (2007) found that high schoolers with asthma report higher rates of depressive symptoms (sadness and hopelessness 45.3% vs 29.3%) and considered suicide at a higher rate (31% vs

16.2%) than peers without asthma, along with attempting suicide at twice the national rate. A number of authors have suggested mechanisms which may explain this comorbidity. Increased levels of systemic inflammation characterized by Th2 lympocyte production, which is also seen in animal models of chronic stress, are suggested as a potential pathway to understand the comorbidity between mood and asthma symptoms (Lu et al., 2015). Treatment effects may be particularly important as well; Brown et al. (2007) examined psychiatric symptoms in individuals who were administered chronic prednosone therapy, a common therapy for asthma symptoms, and noted an increase in manic symptoms after four years of treatment when compared to baseline scores. Solis et al. (2006) attempted to understand the temporal relationship between asthma and mood disorder, and found through retrospective report that asthma preceded depression diagnosis in 62% of patients, depression preceded asthma in 24% of patients, and they presented at the same time in 14% of patients. This study adds to the body of literature implicating relationships between immune functioning, chronic inflammation-based medical disorders, and symptoms of mood disorders. The majority of previous studies have examined the relationship between anxiety and depressive symptoms and asthma, and fewer studies have examined the relationship between asthma and bipolar disorder or bipolar symptoms. There was approximately a 3 fold increase in odds of asthma in individuals diagnosed with bipolar disorder only 6 months after hospitalization. Consistent with Solis, et al. (2006), this study demonstrates a high co-occurrence in the early phase of bipolar illness. A similar magnitude relationship was also seen in major depressive disorder, and a somewhat attenuated risk profile was seen in individuals diagnosed with schizophrenia (OR = 1.97), suggesting that these results may not be specific to bipolar disorder. Factors associated with increased risk for

asthma development were depressive symptoms as well as socioeconomic status and 6 month BMI.

It was suspected that illnesses in the patient sample would more closely mirror a national sample early on in treatment course, although perhaps with increased cardiovascular difficulties early in life. This study helps to place an increased emphasis on understanding underlying biological pathologies which may be active in the early phases of a psychotic disorder. Though increased rates of cardiovascular difficulties were not observed at the six month assessment, there are a number of implications which stem from the disorders which were present only six months following initial hospitalization. The presence of diabetes, a metabolic and neuroendocrine disorder, and asthma, a chronic inflammatory condition, early in the phase of illness progression suggest that metabolic and inflammatory pathway abnormalities may be occurring alongside or perhaps even preceding the onset of an initial psychotic disorder. These results are consistent with a number of other studies which have called for increased examination and understanding of both metabolic and neuroendocrine and chronic inflammatory processes occurring in bipolar disorder (Merikangas, 2007).

One benefit of this current examination of medical comorbidity in bipolar disorder is the long follow up period, spanning the first 10 years of illness course after initial hospitalization. In addition to increased baseline prevalence of a number of medical illnesses, there were additional illnesses which were present at higher than expected rates at the end of the ten year follow up period. Individuals with bipolar disorder had approximately two-fold increased odds of having diabetes, asthma, and cancer when compared to age, gender and ethnicity matched controls from a nationally representative sample. Most surprisingly, individuals with bipolar disorder had

approximately 7 times increased risk of suffering from a stroke 10 years after hospitalization when compared to matched controls.

Individuals with bipolar disorder had the least odds of developing diabetes out of the three diagnostic groups examined, with individuals with MDD and schizophrenia demonstrating substantially increased risk profiles of over three times the risk (OR ~2.0 for bipolar vs. ~3.7 for MDD and schizophrenia). Consistent with literature on metabolic changes following anti-psychotic treatment (Pramyothin and Khaodhiar, 2010), the risk profile shifted from negligible risk for diabetes at 6 months in individuals with schizophrenia to a substantially greater risk profile at 10 years. A number of predictors appeared to indicate increased odds of developing diabetes across the entire sample. Six month and ten year negative symptoms, global functioning, and social functioning were significant predictors of diabetes risk, along with baseline to four year antipsychotic and antidepressant exposure.

While diabetes profiles diverged somewhat based on diagnostic groups, the prevalence rate of asthma appeared to remain high, stable, and relatively equivalent across diagnostic groups throughout the assessment period, with between two to three times increased odds of having asthma when compared to the general population at both 6 month and 10 year assessment intervals. There were relatively few predictors of asthma risk, with only 10 year depressive symptoms, 6 month BMI and high SES predicting increased rates of asthma at 10 years.

Rates of cancer and stroke, which did not significantly differ from the general population at the six month assessment, appeared in higher prevalence than would be expected at the 10 year follow up. Rates of stroke were substantially increased at the 10 year follow up period, with between 4.5 and 7.0 times the odds of having a stroke, depending on which diagnostic group was being compared with the matched control sample. Though the odds found in the patient sample

may be inflated by low sample sizes, the overall finding is consistent with a recent meta-analysis examining stroke and myocardial infarction in bipolar disorder which found increased risk of stroke (RR = 1.74; Prieto et al., 2014), but no increased risk of myocardial infarction. Unfortunately, a matched sample was not able to be created for cardiovascular illness due to heterogeneity in assessment methods between the control and patient samples.

Along with increased rates of stroke, cancer rates appeared to be increased over what would be expected based on the control sample, however, this finding was restricted specifically to individuals with bipolar disorder. Cancer rate appeared to be the only specific medical illness which was increased in bipolar disorder but not in MDD or schizophrenia, and thus may be a more specific marker. However, given the relatively low number of individuals in the bipolar sample who had been diagnosed with cancer, and a catch-all category which includes all self-reported cancer diagnoses, it is difficult to resolve this finding within the context of the literature. There is some evidence to suggest that there are increased risks of certain specific cancers in bipolar disorder (Hung et al., 2014), however this study also found an even greater risk of cancer in major depression when compared with bipolar disorder. It should be noted that this sample used a psychosis specifier for major depressive disorder and bipolar disorder, thus comparisons between the results of these two studies should be tempered.

Medical illness appears to be prevalent early on in the course of a psychotic disorder, and over time, new disorders increase in prevalence and overall medical burden increases substantially. It is difficult to draw firm conclusions regarding relationships amongst psychiatric illness and sometimes distally related medical illnesses; however, the overall pattern of increased medical burden across a number of systems, in a variety of types of psychotic disorders, is

consistent with previous literature highlighting increased medical pathology over time across a range of psychopathologies (Weeke and Vaeth, 1986; Osby et al., 2001; Tsai et al., 2005).

Despite increased risk compared to the general population across a wide range of medical conditions at 10 years, there do not appear to be large or specific differences which might serve to differentiate diagnostic groupings. No differences in rates of medical illnesses were detected when comparing individuals with bipolar disorder to those with schizophrenia. There are a number of potential explanations for this null finding. Within the relatively larger context of individuals with bipolar disorder, this sample was selected for having bipolar disorder with psychotic features. The sample of individuals may differ from a more broad range of individuals with bipolar disorder both with and without psychotic symptoms. There has been significant debate as to whether or not bipolar disorder is more related to thought disorders such as schizophrenia than it is to traditional mood disorders (van Os, 2009; Kotov, Ruggero, Kreuger, Watson, Yuan and Zimmerman, 2011), and a number of genetic and family studies point towards shared biological etiology amongst these two particular disorders. The comparison group of individuals with schizophrenia may be more similar in terms of predispositions towards specific medical illnesses due to shared biological pathology or etiology. In fact, some authors suggest that bipolar I disorder with psychotic features is more closely related to schizophrenia than other forms of bipolar disorder, such as cyclothymia or bipolar II disorder. It may be that a lack of significant findings when comparing individuals with bipolar disorder to those with schizophrenia within this sample was due greater diagnostic homogeneity than might be expected if our sample was representative of a broader bipolar disorder diagnostic group. When viewed through the lens of psychiatric symptoms, there is evidence to suggest a similarity

between bipolar disorder and schizophrenia, and this may be the case in this instance, at a level of analysis examining biological expressions of physical illness.

However, bipolar disorder and schizophrenia are treated differently in clinical settings, and one might expect that treatments and side-effect burden would accumulate over 10 years in a differential pattern based on whether participants were diagnosed with bipolar disorder or schizophrenia. Given the substantial literature on treatment-associated side effects of both mood stabilizer and antipsychotic medications, it was surprising to find that there were no specific differences in medical illness rates when comparing the two groups in this sample.

Alternatively, this study may not have had adequate power to detect differences between individuals with bipolar disorder and those with schizophrenia. There were sample size concerns with the relatively fewer number of individuals who had any particular medical illness within the patient group. This is likely due to the wide range and large variance in prevalence rates of each specific condition. Comparisons which utilized the larger sample size afforded by the National Health and Nutrition Examination Survey were able to detect significance at approximately 2.0 OR.

Factors Associated with Medical Illness Development

A more nuanced examination of correlates of medical illness was conducted as well. We attempted to determine if there were specific demographic, psychological or functionally-based predictors of illness development, and to determine their relative contribution to illness burden, that is, to answer the question: are there specific markers which may shed light on associations between psychological symptoms or demographic difference, which might help to explain the development of particular medical illnesses across the 10 year period following hospitalization?

Significant predictors were entered into regression equations to determine the relative contribution of demographic and psychological functioning variables, in addition to 10 year psychological functioning. Across a wide range of conditions, and with a number of potential explanatory variables included, a somewhat consistent pattern emerged. Demographic and medication variables appeared to exert the strongest influence of the development of any medical illness, with gender and percent time on antidepressant medications from baseline to four years explaining small portions of variability in overall medical burden. Among psychological symptoms, depressive cluster symptoms, or treatment with anti-depressant medications, appeared to be the most reliable predictors of the development of two of four of the illnesses of interest: headache and cardiovascular problems. The finding of an association between depressive symptoms and headache has been demonstrated on a number of occasions, and may be the driving factor in increased rates of headache seen in each diagnostic grouping (Pine, Cohen and Brook, 1996; Breslau et al., 2000). It should be noted that there was significant collinearity observed between antidepressant medication exposure and depression symptoms, as would be expected based on the clinical and psychopharmacological needs of individuals in this sample with significant depressive symptoms, thus it is difficult to disentangle the predictive power of either depressive symptoms or depression medication treatment. Regardless, the endorsement of depressive symptoms and their subsequent treatment is a frequent clinical occurrence, and was found to be a significant predictor of headache and hypertension symptoms in individuals in this examination. As well, a substantial literature (reviewed in Bradley and Rumsfeld et al., 2015) has demonstrated strong associations between depressive disorders and cardiovascular disease, and this examination provides confirmation of this widely-replicated association.

Limitations

There are a number of limitations to this study, in addition to those highlighted in each section above. Most importantly, the diagnosis of medical illness was ascertained via self-report. There are a number of issues with this method of assessment which might lead to a misestimating true medical illness prevalence rate. First, the study requires that individuals be aware that there is an underlying medical illness present. Access to general medical care, sufficient enough to warrant a diagnosis of a physical illness, is likely to have influenced the rates at which individuals are even simply aware of, nonetheless able to self-report at a later time. All other contributors being equal, individuals with higher SES may be more able to seek healthcare and receive diagnoses, artificially inflating their rate of illness reporting.

Unfortunately, a thorough baseline assessment of self-reported medical pathology was not conducted until approximately six months after discharge from a psychiatric hospital, which limits this study and its ability to draw firm conclusions about the very-early course of first episode psychosis. To more fully understand potential developmental and immune-system dysfunction-based psychopathological etiologies, assessment of medical pathology at the point of hospitalization would need to be conducted. Even better, tracking individuals who may be at risk for developing psychotic disorders, prior to an initial hospitalization, may offer a greater insight into how inflammation, physical stress, and mental health symptoms influence one another.

Additionally, this study was not initially proposed to be an examination of the biological systems underlying both physical and mental illness, rather it was designed to be an epidemiologically valid examination of continuously enrolled community sample living in one county in the northeastern region of the United States. Medical information was gathered

throughout the course of the study; however the study was not designed to answer fine-grained questions concerning the biological course of a number of these illnesses.

Medication treatments are thought to be a contributor to medical burden in individuals with psychological illness, and specific medications, even within the same class of medications, can often have drastically different side effect profiles (Üçok & Wolfgang, 2008). Unfortunately, this study utilized a class-based system for analyzing medication use, and did not examine for the effects of any particular medication. Further studies in this area may be strengthened by analyzing for medication-specific effects, i.e. are there differences in medical illnesses between those with first episode psychosis who begin to take aripiprazole or olanzapine, for example.

Conclusions

The examination of medical pathology across a range of diagnostically similar individuals is a difficult and complex task. There were a number of design factors which limited the study in its ability to answer questions regarding temporal associations and relationships amongst demographic, biological, psychological variables. Nonetheless, the current examination provides a number of important pieces of information to the literature on comorbidities between medical illness and bipolar disorder.

First, medical comorbidity is high in individuals suffering from bipolar disorder with psychotic features, and this burden is present not only after the long-term accumulation of illness burden, but early on in the course of illness. We found evidence which may hint at an emergence of physical illness alongside psychological illness, as was evidenced by the higher than expected rates of asthma and diabetes, both chronic conditions and progressive conditions, early in the course of bipolar disorder. Secondly, there do not seem to be a specific set of psychological or demographic predictors which have utility across a wide range of medical illnesses. As is the

case in the literature on these specific medical conditions, the predictive factors vary drastically from illness to illness. Among psychological symptoms, depressive symptoms appear to be the most strongly related to pathologies which result in headache and hypertension. Third, there do not seem to be a substantial number of medical illnesses which serve to differentiate individuals with bipolar disorder from those with closely related diagnoses of schizophrenia or major depressive disorder with psychosis. Fourth, and finally, the relationships between symptom-level psychological functioning the end result of a medical illness are weak. Quantitative markers of biological health, such as blood pressure, fasting blood sugar, and measures of immune functioning may be necessary to more fully understand processes underlying medical comorbidity in bipolar disorder.

Table 1.
Demographics

		SCZ (*n* = 191)	BD (*n* = 93)	MDD (*n* = 55)
Age		28.5 (8.3)	29.1 (10.0)	31.1 (11.2)
Gender	Female	69 (36.1%)	49 (52.7%)	36 (65.5%)
	Male	122(63.9%)	44 (47.3%)	19 (34.5%)
Race	Black	35 (18.3%)	4 (4.3%)	5 (9.1%)
	Hispanic	16 (8.4%)	3 (3.2%)	7 (12.7%)
	White	134 (70.2%)	84 (90.3%)	43 (78.2%)
	American Indian	1 (0.5%)	1 (1.1%)	-
	Asian	5 (2.6%)	1 (1.1%)	-
Marital Status (% never married)		126 (72%)	32 (35.6%)	11 (25.0%)

Table 2

Odds ratios comparing diabetes prevalence in psychosis groups vs. NHANES controls

	6 Month			10 Year		
Diabetes	% (n)	OR	95% CI	% (n)	OR	95% CI
NHANES[a]	1.5% (18)	--	--	5.3% (117)	--	--
Schizophrenia (*n*=191)	1.6% (3)	1.04	0.3 - 3.57	19.3% (31)	3.67*	2.40 - 5.63
Bipolar (*n*=93)	5.6% (5)	3.71*	1.34 - 10.22	10.7% (9)	2.03*	1.00 - 4.14
MDD (*n*=55)	5.8% (3)	3.76*	1.07 - 13.18	19.6% (9)	3.71*	1.77 - 7.76

Note. a. n_{6mo} = 1192, n_{10yr} = 2336 ; * $p < .05$.

Table 3

Odds ratios comparing arthritis prevalence in psychosis groups vs. NHANES controls

	6 Month			10 Year		
Arthritis	% (n)	OR	95% CI	% (n)	OR	95% CI
NHANES[a]	5.4% (61)	--	--	18.7% (370)	--	--
Schizophrenia (*n*=191)	2.7% (5)	0.50	0.20 - 1.26	15.8% (26)	0.84	0.55 - 1.30
Bipolar (*n*=93)	5.7% (5)	1.06	0.41 - 2.69	22.4% (17)	1.20	0.70 - 2.05
MDD (*n*=55)	5.8% (3)	1.07	0.33 - 3.53	34.1% (14)	1.83	.99 - 3.39

Note. a. n_{6mo} = 1192, n_{10yr} = 2352 ; * $p < .05$.

Table 4

Odds ratios comparing stroke prevalence in psychosis groups vs. NHANES controls

		6 Month			10 Year	
Stroke	% (n)	OR	95% CI	% (n)	OR	95% CI
NHANES[a]	0.3% (4)	--	--	0.8% (19)	--	--
Schizophrenia (*n*=191)	0.0% (0)	--	--	4.4% (8)	5.37**	2.32 - 12.43
Bipolar (*n*=93)	1.1% (1)	3.23	0.36 - 29.23	5.7% (5)	6.98	2.55 - 19.11
MDD (*n*=55)	0.0% (0)	--	--	3.8% (2)	4.63	1.05 - 20.40

Note. a. n_{6mo} = 1192, n_{10yr} = 2352 ; * $p < .05$.

Table 5

Odds ratios comparing asthma prevalence in psychosis groups vs. NHANES controls

		6 Month			10 Year	
Asthma	% (n)	OR	95% CI	% (n)	OR	95% CI
NHANES[a]	7.3% (81)	--	--	15.9% (323)	--	--
Schizophrenia (*n*=191)	14.4% (24)	1.97*	1.22 - 3.20	30.8% (45)	1.94*	1.36 - 2.76
Bipolar (*n*=93)	22.4% (17)	3.07*	1.73 - 5.45	32.9% (23)	2.06*	1.27 - 3.35
MDD (*n*=55)	22.2% (10)	3.05*	1.48 - 6.28	48.6% (18)	3.06*	1.72 - 5.43

Note.a. n_{6mo} = 1192, n_{10yr} = 2352 ; * $p < .05$.

Table 6

Odds ratios comparing thyroid disorder prevalence in psychosis groups vs. NHANES controls

		6 Month			10 Year	
Thyroid	% (n)	OR	95% CI	% (n)	OR	95% CI
NHANES[a]	2% (23)	--	--	6.1% (136)	--	--
Schizophrenia (*n*=191)	3.8% (7)	1.94	0.82 - 4.58	9.1% (16)	1.49	0.87 - 2.56
Bipolar (*n*=93)	1.1% (1)	0.55	0.07 - 4.14	10.7% (9)	1.75	0.86 - 3.55
MDD (*n*=55)	7.8% (4)	3.99*	1.33 - 11.97	12.2% (6)	2.00	0.84 - 4.74

Note.a. n_{6mo} = 1192, n_{10yr} = 2352 ; * $p < .05$.

Table 7

Odds ratios comparing cancer prevalence in psychosis groups vs. NHANES controls

	6 Month			10 Year		
Cancer	% (n)	OR	95% CI	% (n)	OR	95% CI
NHANES[a]	1.4% (17)	--	--	4.3% (98)	--	--
Schizophrenia (*n*=191)	0.5% (1)	0.36	0.05 - 2.75	4.9% (9)	1.14	0.57 - 2.29
Bipolar (*n*=93)	2.2% (2)	1.52	0.35 - 6.69	9.4% (8)	2.16*	1.02 - 4.59
MDD (*n*=55)	0.0% (0)	--	--	5.8% (3)	1.33	0.41 - 4.32

Note.a. n_{6mo} = 1192, n_{10yr} = 2352 ; * $p < .05$.

Table 8

Odds ratios comparing hypertension prevalence in psychosis groups vs. NHANES controls

		6 Month			10 Year	
Hypertension	% (n)	OR	95% CI	% (n)	OR	95% CI
NHANES[a]	13.2% (137)	--	--	25.8% (482)	--	--
Schizophrenia (*n*=191)	5.5% (10)	0.42	0.22 - 0.81	23.2% (36)	0.90	0.62 - 1.31
Bipolar (*n*=93)	8.1% (7)	0.61	0.28 - 1.36	25.7% (19)	1.00	0.60 - 1.67
MDD (*n*=55)	17.0% (8)	1.29	0.60 - 2.78	41% (16)	1.59	0.88 - 2.87

Note.a. n_{6mo} = 1192, n_{10yr} = 2352 ; * $p < .05$.

Table 9
Bivariate Association of Predictors with Any Illness

	6 Month			10 Year		
		95 %CI			95 %CI	
Any Illness	OR	low	high	OR	low	high
Age	1.61**	1.31	1.97	1.44*	1.07	1.93
Gender	0.52**	0.35	0.75	0.27**	0.14	0.50
Ethnicity (black)	0.44*	0.20	0.94	0.19*	0.04	0.89
Ethnicity (white)	1.00	0.53	1.87	0.23*	0.05	1.00
SES	1.03	0.86	1.24	1.10	0.85	1.43
GAF 6 mo	1.32**	1.09	1.59	1.15	0.86	1.53
Employment	0.64*	0.44	0.92	0.59	0.34	1.04
Social function 6 mo	1.15	0.96	1.38	1.01	0.76	1.35
BMI 6 mo	1.06	0.88	1.28	1.19	0.87	1.62
SAPS-P 6mo	0.98	0.82	1.19	0.97	0.73	1.29
SAPS-D 6mo	0.88	0.71	1.07	0.86	0.67	1.09
SANS-A 6mo	0.84	0.69	1.01	0.98	0.73	1.30
SANS-E 6mo	0.75**	0.62	0.91	0.86	0.65	1.13
SANS-total 6mo	0.75**	0.62	0.91	0.89	0.67	1.17
DEP 6mo	1.13	0.93	1.37	1.01	0.76	1.34
AD 6 mo	0.76	0.51	1.11	0.46*	0.24	0.87
AP 6 mo	1.65*	1.08	2.52	1.08	0.61	1.90
MS 6 mo	0.84	0.55	1.29	0.78	0.41	1.47
BPRS-E 6 mo	1.04	0.86	1.26	1.16	0.82	1.64
% time AD 0 - 4 yr	1.17	0.98	1.39	1.61**	1.16	2.24
% time MS 0 - 4 yr	1.05	0.88	1.25	1.24	0.94	1.65
% time AP 0 - 4 yr	0.86	0.72	1.03	0.96	0.75	1.24
smoke 6mo	0.96	0.80	1.15	1.01	0.76	1.35
smoke 48mo	0.77*	0.62	0.97	0.84	0.61	1.16
BMI 10 yr	-	-	-	1.44*	1.06	1.95
AD 10 yr	-	-	-	0.60	0.34	1.07
AP 10 yr	-	-	-	1.06	0.63	1.79
MS 10 yr	-	-	-	0.44*	0.22	0.90
SAPS-P 10yr	-	-	-	0.91	0.72	1.15
SAPS-D 10yr	-	-	-	0.91	0.70	1.19
SANS-A 10yr	-	-	-	1.00	0.77	1.30
SANS-E 10yr	-	-	-	0.89	0.67	1.18
SANS 10yr	-	-	-	0.98	0.72	1.33
DEP 10 yr	-	-	-	1.34	0.96	1.86
YMRS tradition	-	-	-	0.86	0.68	1.10
YMRS refine	-	-	-	0.88	0.69	1.12
BPRS-E 10 yr	-	-	-	0.83	0.66	1.05
GAF 10 yr	-	-	-	1.00	0.77	1.30
Employment 10 yr	-	-	-	1.19	0.71	2.00
Social function 10 yr	-	-	-	1.00	0.77	1.31

Note. * $p < .05$., ** $p < .01$

Table 10
Bivariate Association of Predictors with Diabetes

	6 Month			10 Year		
		95 %CI			95 %CI	
Diabetes	OR	low	high	OR	low	high
Age	2.17**	1.38	3.43	1.70**	1.33	2.17
Gender	1.41	0.47	4.19	0.67	0.40	1.13
Ethnicity (black)	0.66	0.04	10.85	0.52	0.20	1.31
Ethnicity (white)	1.65	0.21	12.93	0.47*	0.23	0.97
SES	1.50	0.90	2.49	1.04	0.81	1.35
GAF 6 mo	0.79	0.46	1.36	0.64*	0.48	0.87
Employment	4.25*	1.18	15.25	1.61	0.93	2.80
Social function 6 mo	0.73	0.43	1.22	0.65**	0.49	0.87
BMI 6 mo	1.16	0.70	1.94	1.7**	1.31	2.20
SAPS-P 6mo	0.69	0.28	1.67	0.87	0.62	1.24
SAPS-D 6mo	1.32	0.88	1.98	0.98	0.72	1.32
SANS-A 6mo	1.38	0.83	2.27	1.48**	1.13	1.96
SANS-E 6mo	1.07	0.64	1.79	1.10	0.83	1.46
SANS-total 6mo	1.24	0.76	2.04	1.30	0.99	1.71
DEP 6mo	1.24	0.76	2.00	1.22	0.93	1.59
AD 6 mo	1.41	0.44	4.49	0.63	0.37	1.07
AP 6 mo	0.43	0.09	1.92	0.77	0.42	1.40
MS 6 mo	0.86	0.27	2.77	1.15	0.62	2.15
BPRS-E 6 mo	1.58**	1.14	2.18	1.08	0.83	1.41
% time AD 0 - 4 yr	1.15	0.74	1.80	1.32**	1.06	1.66
% time MS 0 - 4 yr	0.98	0.59	1.61	0.95	0.73	1.23
% time AP 0 - 4 yr	1.43	0.85	2.41	1.38**	1.07	1.79
smoke 6mo	1.18	0.72	1.93	1.11	0.84	1.46
smoke 48mo	0.91	0.50	1.67	0.95	0.70	1.29
BMI 10 yr	-	-	-	1.46**	1.12	1.89
AD 10 yr	-	-	-	0.63	0.36	1.10
AP 10 yr	-	-	-	0.73	0.41	1.29
MS 10 yr	-	-	-	0.91	0.49	1.68
SAPS-P 10yr	-	-	-	1.04	0.80	1.35
SAPS-D 10yr	-	-	-	0.96	0.71	1.30
SANS-A 10yr	-	-	-	1.4*	1.08	1.82
SANS-E 10yr	-	-	-	1.23	0.94	1.61
SANS 10yr	-	-	-	1.45**	1.10	1.91
DEP 10 yr	-	-	-	1.14	0.88	1.47
YMRS tradition	-	-	-	0.99	0.75	1.31
YMRS refine	-	-	-	0.98	0.74	1.30
BPRS-E 10 yr	-	-	-	1.02	0.78	1.35
GAF 10 yr	-	-	-	0.59**	0.43	0.81
Employment 10 yr	-	-	-	2.27**	1.30	3.95
Social function 10 yr	-	-	-	0.67**	0.50	0.89

Note. * $p < .05$., ** $p < .01$

Table 11

Bivariate Association of Predictors with Headache

	6 Month			10 Year		
	95 %CI			95 %CI		
Headache	OR	low	high	OR	low	high
Age	1.19	0.91	1.57	1.07	0.87	1.30
Gender	0.4**	0.22	0.71	0.54**	0.36	0.81
Ethnicity (black)	0.16**	0.04	0.63	0.63	0.29	1.38
Ethnicity (white)	0.45*	0.21	0.98	0.63	0.34	1.18
SES	0.94	0.71	1.24	1.15	0.94	1.40
GAF 6 mo	0.93	0.70	1.25	0.98	0.79	1.21
Employment	0.83	0.47	1.48	0.87	0.57	1.32
Social function 6 mo	1.00	0.75	1.34	1.14	0.92	1.41
BMI 6 mo	1.17	0.89	1.54	1.06	0.86	1.32
SAPS-P 6mo	1.20	0.95	1.52	1.20	0.99	1.46
SAPS-D 6mo	0.96	0.69	1.34	0.99	0.80	1.23
SANS-A 6mo	1.11	0.83	1.48	0.96	0.77	1.19
SANS-E 6mo	0.54**	0.35	0.83	0.68**	0.52	0.88
SANS-total 6mo	0.79	0.57	1.09	0.78*	0.61	0.98
DEP 6mo	1.48**	1.14	1.92	1.26*	1.03	1.55
AD 6 mo	0.74	0.41	1.33	0.67	0.44	1.02
AP 6 mo	1.85*	1.02	3.36	1.24	0.80	1.91
MS 6 mo	1.24	0.61	2.49	1.15	0.71	1.86
BPRS-E 6 mo	1.24	0.98	1.58	1.20	0.99	1.45
% time AD 0 - 4 yr	1.26	0.99	1.61	1.24*	1.03	1.49
% time MS 0 - 4 yr	1.02	0.78	1.34	1.02	0.84	1.24
% time AP 0 - 4 yr	0.79	0.59	1.05	0.93	0.76	1.14
smoke 6mo	1.08	0.83	1.41	1.05	0.85	1.28
smoke 48mo	0.94	0.67	1.33	0.92	0.72	1.17
BMI 10 yr	-	-	-	1.02	0.81	1.27
AD 10 yr	-	-	-	0.63*	0.40	0.98
AP 10 yr	-	-	-	0.94	0.60	1.47
MS 10 yr	-	-	-	1.17	0.70	1.95
SAPS-P 10yr	-	-	-	1.00	0.80	1.25
SAPS-D 10yr	-	-	-	0.98	0.77	1.24
SANS-A 10yr	-	-	-	1.00	0.80	1.25
SANS-E 10yr	-	-	-	1.00	0.79	1.27
SANS 10yr	-	-	-	1.09	0.86	1.38
DEP 10 yr	-	-	-	1.46**	1.19	1.79
YMRS tradition	-	-	-	0.92	0.73	1.16
YMRS refine	-	-	-	0.92	0.72	1.16
BPRS-E 10 yr	-	-	-	1.00	0.79	1.25
GAF 10 yr	-	-	-	0.98	0.78	1.22
Employment 10 yr	-	-	-	0.89	0.58	1.38
Social function 10 yr	-	-	-	1.04	0.83	1.30

Note. * $p < .05$., ** $p < .01$

Table 12
Bivariate Association of Predictors with Hypertension

	6 Month			10 Year		
		95 %CI			95 %CI	
Hypertension	OR	low	high	OR	low	high
Age	2.12**	1.53	2.92	1.95**	1.58	2.40
Gender	0.68	0.34	1.36	0.57**	0.38	0.87
Ethnicity (black)	0.15	0.02	1.43	0.87	0.40	1.90
Ethnicity (white)	0.90	0.30	2.69	0.64	0.33	1.23
SES	1.44*	1.02	2.04	1.14	0.93	1.41
GAF 6 mo	1.16	0.82	1.66	0.95	0.75	1.19
Employment	0.90	0.45	1.81	0.86	0.55	1.35
Social function 6 mo	1.12	0.79	1.58	0.97	0.77	1.21
BMI 6 mo	1.55**	1.14	2.10	1.44*	1.16	1.80
SAPS-P 6mo	1.03	0.74	1.45	1.03	0.82	1.29
SAPS-D 6mo	0.92	0.60	1.41	0.90	0.69	1.17
SANS-A 6mo	0.91	0.63	1.32	1.15	0.92	1.45
SANS-E 6mo	0.81	0.54	1.21	0.98	0.78	1.25
SANS-total 6mo	0.83	0.57	1.22	1.06	0.84	1.34
DEP 6mo	1.24	0.90	1.72	1.11	0.89	1.40
AD 6 mo	0.80	0.39	1.65	0.65	0.42	1.00
AP 6 mo	1.60	0.77	3.34	1.32	0.84	2.06
MS 6 mo	1.03	0.45	2.34	1.06	0.64	1.73
BPRS-E 6 mo	0.77	0.46	1.29	0.86	0.65	1.13
% time AD 0 - 4 yr	1.45**	1.09	1.93	1.36**	1.13	1.64
% time MS 0 - 4 yr	0.93	0.66	1.32	1.08	0.89	1.31
% time AP 0 - 4 yr	1.09	0.77	1.54	0.98	0.80	1.21
smoke 6mo	0.96	0.68	1.34	0.93	0.74	1.17
smoke 48mo	0.71	0.45	1.12	0.92	0.71	1.19
BMI 10 yr	-	-	-	1.71**	1.36	2.15
AD 10 yr	-	-	-	0.83	0.52	1.32
AP 10 yr	-	-	-	1.16	0.74	1.83
MS 10 yr	-	-	-	1.38	0.80	2.36
SAPS-P 10yr	-	-	-	0.75	0.55	1.02
SAPS-D 10yr	-	-	-	0.86	0.66	1.12
SANS-A 10yr	-	-	-	1.06	0.85	1.32
SANS-E 10yr	-	-	-	1.13	0.89	1.43
SANS 10yr	-	-	-	1.20	0.95	1.53
DEP 10 yr	-	-	-	1.26*	1.02	1.55
YMRS tradition	-	-	-	0.93	0.73	1.18
YMRS refine	-	-	-	0.91	0.72	1.16
BPRS-E 10 yr	-	-	-	0.94	0.74	1.20
GAF 10 yr	-	-	-	0.95	0.76	1.19
Employment 10 yr	-	-	-	1.01	0.65	1.58
Social function 10 yr	-	-	-	0.83	0.66	1.05

Note. * $p < .05$., ** $p < .01$

Table 13

Logistic Regression Predicting Any Illnesses Incidence at 10 Year

Any Illness	OR	95% CI	R^2
6 month prevalence	0.6	0.31 - 1.17	0.11
Age	1.29	0.87 - 1.91	
Gender	0.23*	0.10 - 0.56	
Ethnicity Black	0.49	0.09 - 2.67	
Ethnicity White	0.26	0.06 - 1.20	
10 year diagnosis sz sa ssf	0.74	0.29 - 1.88	
10 year diagnosis bp	0.73	0.23 - 2.31	
10 year diagnosis depr	1.88	0.34 - 10.4	
Smoking 6 mo	0.97	0.69 - 1.38	
BMI 6 mo	1.16	0.79 - 1.69	
% time on AD 0 - 4 yr	1.51*	1.02 - 2.25	
% time on MS 0 - 4 yr	1.19	0.85 - 1.67	

Note. * $p < .05$.

Table 14

Logistic Regression Predicting Diabetes Incidence at 10 Year

Diabetes	OR	95% CI	R^2
Age	1.73	1.07 - 2.78	0.17
Gender	0.48	0.18 - 1.26	
Ethnicity black	0.42	0.11 - 1.65	
Ethnicity white	0.24*	0.07 - 0.78	
Smoking 6 mo	0.92	0.58 - 1.48	
BMI 6 mo	2.01*	1.23 - 3.28	
SANS-A 6mo	0.68	0.33 - 1.37	
GAF 6 mo	0.45*	0.21 - 0.96	
Employment 6 mo	0.58	0.20 - 1.70	
Social functioning 6 mo	0.56	0.27 - 1.19	
% time on AD 0 - 4 yr	0.92	0.59 - 1.42	
% time on AP 0 - 4 yr	1.27	0.65 - 2.48	
BMI 10 yr	1.01	0.63 - 1.62	
SANS-A 10yr	1.02	0.40 - 2.61	
GAF 10 yr	1.5	0.62 - 3.65	
Employment 10 yr	5.26*	1.62 - 17.1	
Social functioning 10 yr	0.74	0.31 - 1.78	
AD 10 yr	0.7	0.25 - 1.96	
AP 10 yr	2.68	0.66 - 11.0	

Note. * $p < .05$.

Table 15

Logistic Regression Predicting Headache Incidence at 10 Year

Headache	OR	95% CI	R^2
Age	0.96	0.64 - 1.46	0.08
Gender	0.53	0.25 - 1.09	
Ethnicity black	1.36	0.37 - 5.05	
Ethnicity white	0.69	0.22 - 2.24	
Smoking 6 mo	0.85	0.58 - 1.25	
BMI 6 mo	0.86	0.58 - 1.27	
% time on AD 0 - 4 yr	0.91	0.61 - 1.36	
SANS-E 6mo	0.69	0.45 - 1.08	
AD 10 yr	0.66	0.29 - 1.48	
DEP 10 yr	1.61*	1.12 - 2.31	
SANS-E 10 yr	1.33	0.91 - 1.94	

Note. * $p < .05$.

Table 16

Logistic Regression Predicting Hypertension Incidence at 10 Year

Hypertension	OR	95% CI	R^2
Age	2.15*	1.42 - 3.25	0.16
Gender	1.25	0.60 - 2.61	
Ethnicity black	1.51	0.45 - 5.04	
Ethnicity white	0.37	0.13 - 1.06	
Smoking 6 mo	0.95	0.66 - 1.37	
BMI 6 mo	0.95	0.62 - 1.47	
Dep 6 mo	0.79	0.53 - 1.16	
% time on AD 0 - 4 yr	1.53*	1.08 - 2.17	
BMI 10 yr	2.22*	1.42 - 3.45	
DEP 10 yr	1.04	0.70 - 1.55	
AD 10 yr	0.84	0.35 - 1.98	

Note. * $p < .05$.

Table 17
Linear Regression of Prediction of 10 year BMI

	Std. B	t	Sig.	R^2
Constant		1.75	.08	
BMI 6 mo	.57**	10.28	.00	.40
Age	-.06	-1.14	.25	
Gender	.04	.70	.49	
Ethnicity	.04	.72	.47	
SES	.07	1.24	.22	
AD 10 yr	-.02	-.36	.72	
AP 10 yr	.14*	2.26	.02	
MS 10 yr	.13*	2.31	.02	
SAPS-P 10 yr	-.07	-.98	.33	
SAPS-D 10 yr	.02	.23	.82	
SANS 10 yr	.05	.72	.47	
SCID Dep 10 yr	-.06	-.93	.35	
YMRS	-.04	-.45	.65	

Note. * $p < .0$

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