CIRCADIAN RHYTHM AND BIPOLAR DISORDER

IMPACT OF CIRCADIAN RHYTHM DISTURBANCES IN BIPOLAR DISORDER

By LAUREN CUDNEY, B.Sc.

A Thesis Submitted to the School of Graduate Studies in Partial Fulfillment of the

Requirements for the Degree Master of Science

McMaster University MASTER OF SCIENCE (2013) Hamilton, Ontario (Neuroscience)

TITLE: Impact of Circadian rhythm disturbances on bipolar disorder AUTHOR: Lauren Cudney, B.Sc. (McMaster University) SUPERVISORS: Dr. Benicio N. Frey and Dr. Roberto B. Sassi NUMBER OF PAGES: ix, 52

Abstract

This thesis presents research examining the impact circadian rhythm disturbances experienced in bipolar disorder (BD) have at two levels of investigation. First, circadian rhythm disturbance is studied with regard to quality of life in individuals with BD. The results of an analysis investigating the impact of self-reported circadian rhythm disturbance on quality of life (QOL) show circadian rhythm is strongly associated with poor QOL in patients with BD, independent of severity of depressive symptoms, sleep disturbance and use of sleep medications. Next, the impact of circadian rhythm disturbance on oxidative stress was studied. Oxidative stress has previously been implicated in BD, yet no studies have investigated the relationship between these systems in the context of the disorder. We demonstrate that circadian rhythm disturbance is related to increased lipid peroxidation in BD patients, which is not seen in controls. This study provides a basis for further investigation of the links between oxidative stress and circadian rhythms in the pathophysiology of BD. Taken together, these results provide evidence that circadian rhythms have a widespread impact on two separate aspects of BD: personal sense of well being and a biological marker of oxidative stress. These novel findings contribute to the mounting evidence indicating circadian rhythm disturbance as one of the core features of BD, and an important target for treatment.

Acknowledgements

Table Of Contents

List of Tables

List of Figures

List of Abbreviations

AIC	Akaike Information Criterion
BD	Bipolar disorder
BRIAN	Biological Rhythm Interview of Assessment in Neuropsychiatry
CAT	Catalase
DLMO	Dim Light Melatonin Onset
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders -IV
DTI	Diffusor Tensor Imaging
ELISA	Enzyme-Linked Immunosorbent Assay
GSH	Glutathione
IPSRT	Interpersonal Social Rhythm Therapy
MADRS	Montgomery Åsberg Depression Rating Scale
MDA	Malondialdehyde
MDA-TBA	Malondialdehyde-thiobarbituric
PSQI	Pittsburgh Sleep Quality Index
ROS	Reactive Oxygen Species
SCID-I	Structured Clinical Interview for the DSM-IV
SCN	Superchiasmatic Nuclei
SOD	Superoxide Dismutase
TBARS	Thiobarbituric Acid Reactive Substance
WHOQOL	World Health Organization Quality of Life
QOL	Quality of life

Declaration of Academic Achievement

This thesis consists of 4 chapters: Chapter 1 provides background on bipolar disorder and circadian rhythms; Chapters 2 and 3 are manuscripts currently under review in peer-reviewed journals; Chapter 4 discusses the results and future directions of these articles. Data collection of clinical scales and biomarkers took place between June 2011- July 2013 at the Mood Disorders Program and Women's Health Concerns Clinic at St. Joseph's Healthcare Hamilton. These studies were conceived and designed by Dr. Benicio Frey, Dr. Roberto Sassi and myself. I oversaw all aspects of the research including study coordination, data collection and data management. Participant recruitment was carried out by research assistants Sarah Begin, Amy Bustamam and Melanie Cochrane, and myself. Ms. Helen Begin, RN, CCRA, CCRC, CPMHN(c), Dr. Luciano Minuzzi and myself, assisted in the clinical screening of participants. I performed statistical analysis with the assistance of Dr. David Streiner and Dr. Luciano Minuzzi. Portions of this work were presented at the 2013 Society of Biological Psychiatry annual conference in San Francisco, CA and the International Conference on Bipolar Disorders 2013 in Miami, FL. The paper in Chapter 2 (Circadian rhythm is independently associated with quality of life in bipolar disorder) is submitted to the *Journal of Affective Disorders* as of August 2013. The paper in Chapter 3 (Alterations in circadian rhythms are associated with increased lipid peroxidation in females with bipolar disorder) was submitted to the *International Journal of Neuropsychopharmacology* as of August 2013.

CHAPTER 1

General Introduction

Understanding the neurobiology of psychiatric illness is critical to developing better treatments of such complex disorders as bipolar disorder (BD). There are many theories of the pathophysiology of BD, one of which is focused on disruptions of the sleep and circadian rhythms. There is a growing body of literature that shows sleep and circadian rhythm disturbance are intimately linked to mood disorders, based on several lines of evidence (psychosocial cues, genetic and molecular studies). The primary aim of this thesis is to investigate the relationships of disrupted circadian rhythms in BD on two levels of analysis: subjective ratings of quality of life (QOL) and a biological marker of oxidative stress. To begin, Chapter 1 provides a general background on BD, circadian rhythms and evidence of disrupted circadian rhythms in BD, followed by an outline of aims and hypotheses. The impact of circadian rhythm disturbance on overall quality of life in BD is presented in Chapter 2. Next, results of the impact of circadian rhythm disturbance on a marker of lipid peroxidation are presented in Chapter 3, as a means of exploring the possible relationship between the circadian clock and oxidative stress in BD. Finally, results are summarized and discussed in the context of future directions of study in Chapter 4.

Bipolar disorder: Description and biological theories

BD is a chronic, debilitating psychiatric illness characterized by elevated mood, over activity and impaired judgment (APA, 2000; Belmaker, 2004). There is an estimated

prevalence of 4% of bipolar spectrum disorder, or approximately 30 million people worldwide (Merikangas et al., 2007). In reports on the global burden of disease by cause, BD is considered one of the most disabling illnesses of all psychiatric and medical conditions (Murray & Lopez, 1997).

The debilitating nature of BD is two-fold; not only do the mood episodes cause a great deal of social and occupational problems, but comorbid conditions are often the rule rather than the exception for patients. BD is most frequently comorbid with anxiety disorders and substance use disorders (Merikangas et al., 2007). Risk of suicide in BD was found to be the highest of all psychiatric illnesses for males and second highest for females, as shown in a 30-year prospective study on a national cohort (Nordentoft, Mortensen, & Pedersen, 2011). In fact, close to 50% of adults with BD attempt suicide at least once in their lifetimes (Hawton, Sutton, Haw, Sinclair, & Harriss, 2005). It has also been shown that patients with BD have increased premature mortality and morbidity in general, even when suicide is taken into account (Kupfer, 2005). This is likely because patients with are at a much greater risk of certain medical conditions, such as obesity and cardiovascular disease, and this risk seems to be higher than in other psychiatric disorders (Weiner, Warren, & Fiedorowicz, 2011). The clinical evidence for the progressive and debilitating nature of BD is substantial, however the underlying neurobiology remains unclear. There are many pathways currently under investigation in the neurobiology of BD, including neurotrophic factors, inflammation and oxidative stress (Berk et al., 2011).

Circadian Rhythms: Definition and molecular functioning

Rhythmic changes that occur in a nearly 24-hour period are referred to as circadian rhythms, from the Latin phrase for 'circa diem', meaning 'about a day'. There are three main components of the circadian clock: cues from the environment influence the endogenous clock, the clock itself which maintains a rhythm regardless of environmental cues, and an output pathway to synchronize the peripheral organs and tissues (Reppert et al., 2002). The master circadian clock is in the superchiasmatic nuclei (SCN), which orchestrates the timing of rhythms in the rest of the body endogenously also receive input from hormones and peptides from the periphery, as well as from the environment. Integration of the autonomous clock in the SCN and environmental cues, such as light-dark cycles, control the rhythms of the organism around a circadian rhythm of 24-hours. Light-dark and sleep-wake cycles are particularly important for entraining the endogenous clock to the appropriate phase since the SCN receives direct input from the retina (Cermakian & Sassone-Corsi, 2002). Environmental events that influence the circadian rhythm are known as "zeitgebers" (Ehlers, Frank, & Kupfer, 1988). Zeitgebers can be either physical stimuli (e.g., light), or social events such as timing of general activities or meals. Thus, proper functioning of these systems leads to synchronization of the internal and external environments. Coordinated expression of biochemical, physiological and behavioural rhythms is thought to be adaptive, in that it prepares the body for environmental changes important for survival of the species. Desynchronized rhythms have been shown to have many adverse effects in humans and compromises overall metabolism, autophagy and DNA repair (Kondratova & Kondratova, 2012).

Circadian rhythm disruption in bipolar disorder

In a substantial proportion of patients with BD, erratic schedules can be very detrimental and will often put them at increased risk of relapse (Frank et al., 2008; Giglio et al., 2010). Sleep disturbance is one of the most commonly reported prodromes of affective episodes and is a core symptom of both mania and depression (Jackson et al., 2003). Sleep-wake cycles are the most observable cue of circadian rhythm, and therefore one of the best clues as to whether circadian rhythms are disrupted. Studies based on subjective measures of sleep disturbance show that remitted BD patients have many of the same characteristics as patients with insomnia, such as decreased sleep efficiency, elevated sleep-related anxiety (Harvey et al., 2005) and more daytime sleepiness (St-Amand, Provencher, Bélanger, & Morin, 2013)

The influence of external cues on the circadian system makes it an excellent target for therapeutic interventions in BD. Ehlers et al. (1988) was the first to propose the social zeitgeber theory that BD patients are at increased vulnerability to circadian rhythm and sleep disturbance based on changes in their routines. There is now considerable evidence that stressful life events which disrupt routines, social rhythms and sleep, put individuals with BD at risk for a mood episode (Shen, Alloy, Abramson, & Sylvia, 2008). Strong social rhythms are associated with improved sleep quality and decreased risk of a mood episode. This is the theory behind the interpersonal and social rhythm therapy (IPSRT), which is effective in acute and maintenance treatment of BD when practiced in combination with pharmacotherapy (Frank et al., 2005; Miklowitz et al., 2007). Despite

the evidence for circadian rhythm disturbance in BD, the effects these disturbances have on the course of illness remains understudied.

Aims and Hypotheses

The overall objective of this study is to examine how disruptions in circadian rhythms, as reported with the biological rhythm interview of assessment in neuropsychiatry (BRIAN), impact various aspects of BD. First, we examined how quality of life (QOL) is influenced by circadian rhythm disturbance within a sample of depressed and euthymic BD patients. QOL is known to be lower in individuals with BD and impairments are also associated with decreased sleep quality. However, no study to date has investigated how circadian rhythm is related to QOL in BD. It is hypothesized that circadian rhythm disruption will be independently associated with impaired QOL in BD patients. This study is presented in Chapter 2 in the form of a manuscript submitted to the *Journal of Affective Disorders*, entitled "Circadian rhythm is independently associated with quality of life in bipolar disorder".

Next, we investigated whether greater circadian rhythm disruptions may influence BD patients at the molecular level, by looking at whether circadian rhythm disturbance was associated with lipid peroxidation in females with BD. Oxidative stress has been implicated in the pathophysiology of BD based on biochemical, pharmacological and postmortem studies (Steckert, Valvassori, Moretti, Dal-Pizzol, & Quevedo, 2010). Many elements of redox metabolism, especially antioxidant defense mechanisms, have been shown to follow a circadian rhythm. Both circadian rhythm disturbance and oxidative

stress have been shown to be involved in the pathophysiology of BD. However the relationship between these two systems remains unclear in the context of BD. The aim of this study is to examine the impact of circadian rhythm disturbance on lipid peroxidation in BD and healthy controls, while controlling for depressive symptom severity, age and psychotropic medication use. It is hypothesized that greater circadian rhythm disruption will be associated with increased lipid peroxidation. This is explored in Chapter 3 in a manuscript submitted to the *International Journal of Neuropsychopharmacology*, entitled "Alterations in circadian rhythms are associated with increased lipid peroxidation in females with bipolar disorder".

Chapter 2

Circadian rhythm is independently associated with quality of life in bipolar disorder

Lauren E. Cudney[1,2], Benicio N. Frey, M.D., M.Sc., Ph.D.[1,2,3,*], David L. Streiner, Ph.D.[3,4], Luciano Minuzzi, M.D., Ph.D.[1,2,3], Roberto B. Sassi, M.D., Ph.D.[1,3,*]

[1] Mood Disorders Program and [2] Women's Health Concerns Clinic, St. Joseph's Healthcare Hamilton, ON, Canada; [3] Department of Psychiatry and Behavioural Neurosciences, McMaster University, Hamilton, ON; [4] Department of Psychiatry, University of Toronto, ON, Canada

*Both authors contributed equally as senior authors

Abstract

Background: Evidence suggests patients with bipolar disorder (BD) experience circadian rhythm disturbances, however no studies have examined the impact of this disruption on quality of life (QOL). The aim of this study is to investigate the influence of circadian rhythm, depressive symptoms, sleep quality and sleep medication use on QOL in BD.

Methods: Eighty BD subjects (44 depressed and 36 euthymic) completed questionnaires assessing QOL (WHOQOL-BREF), circadian rhythm (BRIAN), depressive symptoms (MADRS) and sleep quality (PSQI). The impact of circadian rhythm, depressive symptoms severity, sleep quality and sleep medication use on QOL was determined with multiple regression analyses.

Results: Linear regression results indicated that BRIAN, MADRS, PSQI and sleep medication use explained 45.4% of the variance in QOL ($F_{4,75}$= 17.45; $p<0.0001$). In this model, BRIAN (β=-0.29, t=-2.50, $p<0.05$), MADRS (β=-0.33, t=-3.14, $p<0.01$) and sleep medication use (β=-0.42, t=-2.19, $p<0.05$) were the only predictors of QOL. 45.3% of the variance in QOL was still explained by the model when PSQI was removed ($F_{3,76}$= 20.9; $p<0.0001$), indicating circadian rhythm disruption (β=-0.35, t=-3.43, $p<0.01$), severity of depressive symptoms (β=-0.36, t=-3.40, $p<0.01$) and sleep medication use (β=-0.44, t=-2.32, $p<0.05$) were independent predictors of QOL.

Limitations: The cross-sectional assessment and the lack of objective measures of circadian rhythm.

Conclusion: Disruption in circadian rhythm is associated with poor QOL in BD, independent of sleep disturbance, use of sleep medication and severity of depression. Treatment strategies targeting regulation of circadian rhythms, such as sleep/wake, eating patterns, activities and social rhythms, are likely to improve QOL in this population.

Keywords: Bipolar disorder; Circadian Rhythm; Quality of life; Sleep

Introduction

Bipolar disorder (BD) is a complex and debilitating disorder that affects about 4% of the general population (Merikangas et al., 2007). BD was previously considered a cyclic disorder, consisting of alterations between depressive or manic episodes and periods of euthymia. More recently there has been a reconceptualization of BD as chronic and multisystemic disorder, given that a substantial proportion of symptoms of BD do not completely remit even when patients are not experiencing a manic or depressive episode (Leboyer & Kupfer, 2010). Cognitive impairments, difficulties in relationships, social and occupational functioning often persist beyond clinical remission from acute mood episodes (Giglio, Magalhães, Kapczinski, Walz, & Kapczinski, 2010). Therefore, it is critical to understand the mechanisms that may contribute to the inter-episodic dysfunction of BD. In this regard, some of the most common problems observed during periods of remission are sleep and circadian rhythm disturbances (Harvey, Schmidt, Scarnà, Semler, & Goodwin, 2005). Studies based on subjective measures of sleep quality showed that remitted BD patients report many of the same disturbances as patients with primary insomnia, such as decreased sleep efficiency, elevated sleep-related anxiety (Harvey et al., 2005) and more daytime sleepiness (St-Amand, Provencher, Bélanger, & Morin, 2013). Perhaps more importantly, sleep disturbance is the most commonly reported prodromal symptom of mania and the sixth most prominent for depression (Jackson, Cavanagh, & Scott, 2003).

Sleep-wake cycles are the most recognizable behavioural manifestation of circadian rhythm functioning, but other time cues (referred to as zeitgebers) such as social

10

activities, timing of meals and exercise are able to entrain biological rhythms along a nearly 24-hour period (Ehlers, Frank, & Kupfer, 1988). Ehlers et al. (1988) was the first to propose the social zeitgeber theory, in which individuals with BD are more vulnerable to social routine and sleep disturbances that may predispose them to onset of mood episodes. There is now substantial evidence that stressful life events, which disrupt routines and social rhythms, put individuals with BD at risk for a mood episode (Shen, Alloy, Abramson, & Sylvia, 2008). Besides subjective measures of sleep quality, more objective measures of sleep/wakefulness and activities that follow circadian timing are also altered in BD. Actigraphic assessment of euthymic BD patients showed greater variability in circadian activity compared to controls (Jones, Hare, & Evershed, 2005), variability of sleep duration (Millar, Espie, & Scott, 2004) and lower daily activity levels (Salvatore et al., 2008). Measurement of melatonin secretion, the primary hormone for circadian rhythm synchronization, also indicates differences in circadian rhythms of BD patients (Nathan, Burrows, & Norman, 1999), Taken together, these clinical studies show that disturbances in sleep and circadian rhythm are seen throughout the course of the disorder, suggesting this disturbance can be seen as both state and trait markers of BD.

Quality of life (QOL) is a subjective measure of satisfaction with many aspects of life including physical and psychological health, social relationships and environment (The WHOQOL Group, 1995), and has consistently been shown to be decreased in BD patients. Many of these domains overlap with aspects of social rhythms, and circadian rhythm. For instance, Giglio et al. (2008) found that euthymic BD patients with symptoms of insomnia had lower QOL than those without sleep disturbance. It has been

suggested that sleep alterations may contribute to impaired QOL in BD possibly due to the effects of poor sleep quality on concentration, cognition and memory (Giglio et al., 2008). Depressive symptoms have also been shown to be a strong predictor of poor QOL (Amini & Sharifi, 2012; Yatham et al., 2004). In fact, depressed BD patients experience more impairment in QOL than unipolar depressed patients, even when severity of depression was taken into account (Berlim et al., 2004). It is also possible that acute depressive symptoms have a strong negative impact on subjective ratings of QOL due to cognitive distortions experienced during depression (Michalak, Yatham, & Lam, 2005).

As disturbances in sleep and circadian rhythm are prominent features of BD, a better understanding of how these symptoms relate to overall sense of well-being and QOL is required. To the best of our knowledge, the interplay of depressive symptoms, sleep quality and circadian rhythm on QOL has not been studied in euthymic and depressed BD subjects. In addition, many psychotropic drugs used in the treatment of BD affect sleep, but it is still unclear how these drugs may impact of sleep and circadian rhythm on QOL. The objective of the present study is to examine the impact of sleep, circadian rhythm, sleep medication use and severity of depression on QOL in a well-characterized sample of euthymic and depressed BD subjects. We hypothesize that abnormalities in circadian rhythm will be independently associated with poor QOL in individuals with BD.

Methods

Participants

Eighty patients with BD type I (n=58), BD type II (n=21) or NOS (n=1) were recruited from the Mood Disorders Program and Women's Health Concerns Clinic at St. Joseph's Healthcare Hamilton, Ontario. All subjects gave written informed consent to take part in the study, as approved by the ethics committees of St. Joseph's Healthcare Hamilton and Hamilton Health Sciences. The diagnosis of BD was confirmed with the Structured Clinical Interview for the DSM-IV (SCID-I). Patients with BD were included in the study if they either met criteria for a current major depressive episode (n=44) or if they did not meet criteria for a current mood episode (n=36) according to the SCID-I. Patients were excluded if they met criteria for a hypomanic, manic or mixed episode.

Clinical Instruments

QOL was measured using the World Health Organization Quality of Life assessment (WHOQOL-BREF-TR), which covers four domains of QOL: physical health, psychological, social relationships and environment in 24 questions, with greater scores indicating better QOL (Group, 1995). This scale has been validated and widely used in BD research. The Montgomery-Åsberg Depression Rating Scale (MADRS) was employed to measure depressive symptom severity (Montgomery & Asberg, 1979). Degree of circadian rhythm disruption was measured with the Biological Rhythm Interview of Assessment in Neuropsychiatry (BRIAN). The BRIAN consists of 18-items

measuring sleep, overall activities, social rhythm and eating behaviour scored from 1 (no difficulties) to 4 (serious difficulties), with greater scores indicating more circadian rhythm disruption. This scale has been validated in BD patients in its ability to discriminate euthymic BD and controls (Giglio et al., 2009). The BRIAN scale has previously been used in conjunction with measures of cognitive functioning in euthymic BD patients and showed that circadian rhythm disruption was a predictor of poorer functioning (Giglio et al., 2010). Pittsburgh Sleep Quality Index (PSQI) was used to measure subjective sleep quality (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989). The PSQI is a standardized self-rating questionnaire which evaluates 7 components of sleep quality, including subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. To more closely examine the use of sleep medications on QOL, a separate factor was included based on the answer to "use of sleep medication" (component 6). Sleep medication status was categorized as 'yes' if participants reported using sleep medications either ' a week' or 'more than three times per week' on component 6 of the PSQI. This answer was cross-referenced with medications recorded for each participant during the clinical assessments (including bedtime use of benzodiazepines, zopiclone, quetiapine or over-the-counter compounds such as melatonin).

Statistical analysis

All analyses were performed with R (Version 2.14.2, R Development Core Team, 2012). Multiple regression analysis was performed using MADRS, PSQI, BRIAN and sleep

medication status as predictors, and WHOQOL as the dependent variable. Backward stepwise selection was performed with variable selection made by comparing Akaike information criterion (AIC) in order to find the most suitable model for predicting QOL outcomes in BD subjects. Assumptions of linear regression were tested with Shapiro-Wilk test (normality), a partial residuals plot (linearity), Durbin-Watson test (independence of errors), non-constant error variance (homoscedasticity) and variance inflation factor test (multicollinearity). Both models met all of the regression assumptions, including colinearity. To avoid colinearity between PSQI and sleep medication factor, the PSQI subscale for "use of medication" (component 6) was dropped from the total PSQI score, as previously done by Giglio et al. (2010).

Results

Demographic and clinical data are displayed in Table 1. In patients with BD, lower QOL was correlated with increased depressive symptoms (r_P=-0.59, 95% CI [-0.72, -0.43], $p<0.001$), greater circadian rhythm disruption (r_P=-0.57, 95% CI [-0.70, -0.40], $p<0.001$) and poorer sleep quality (r_P=-0.51, 95% CI [-0.65, -0.32], $p<0.001$), as shown in Figure 1. Results from the regression analyses are reported in Table 2. Multiple regression analyses indicated that BRIAN, MADRS, PSQI and sleep medication use explained 45.4% of the variance in QOL scores ($F_{4,75}$= 17.45; $p<0.0001$). In this model, BRIAN (β=-0.29, t=-2.50, $p<0.05$), MADRS scores (β=-0.33, t=-3.14, $p<0.01$) and sleep medication use (β=-0.40, t=-2.19, $p<0.05$) were significant predictors of QOL, whereas PSQI scores were not associated with poor QOL ($p>0.05$). When PSQI was removed from the model, the model

still explained 45.3% of the variance in QOL ($F_{3,76}$= 22.81; $p<0.0001$), indicating that BRIAN (β=-0.35, t=-3.51, $p<0.01$), MADRS scores (β=-0.35, t=-3.42, $p<0.01$) and sleep medication use (β=-0.42, t=-2.33, $p<0.05$) were all independent predictors of QOL.

Discussion

This is the first study to investigate the relationship between circadian rhythm and QOL in individuals with BD. The novel finding of this study is that disruption in circadian rhythm is strongly associated with poor QOL in patients with BD, independent of severity of depressive symptoms, sleep disturbance and use of sleep medications. Results of Model 1 (Table 2) show that despite a significant correlation between WHOQOL and PSQI scores, subjective sleep quality is not a significant predictor for QOL when depression severity, circadian rhythm disruption and sleep medication status are taken into account. Considering that circadian rhythm disturbance predicted decreased QOL better than sleep quality alone, this suggests that other factors associated with circadian rhythms like eating patterns, activities and social rhythms also play an important role in overall QOL. The BRIAN scale contains five questions that measure sleep disturbance as it contributes to circadian rhythm disruption. It is likely that these sleep questions are enough to account for the impact of sleep quality on QOL variation in patients with BD. These findings are also consistent with previous findings showing that although sleep and circadian rhythm systems interact with each other, circadian rhythm is influenced by more than just sleep/wake patterns (Harvey, 2008). Previous research has implicated circadian rhythm disturbance in various domains of functioning that are

directly or indirectly related to QOL. For instance, Giglio et al. (2010) found that overall

functioning (including measures of autonomy, work, cognition, financial and

interpersonal issues) was best predicted by circadian rhythm as measured by BRIAN in

euthymic BD subjects. Another study found that even in periods of euthymia BD subjects

tend to report a later daily first social and work contact as compared to matched controls

(Jones et al., 2005). Similarly, occupational functioning was more quickly improved in

BD patients after therapy focused on regulation of social rhythms (interpersonal social

rhythm therapy; IPSRT) compared to a psychoeducational therapy (Frank et al., 2008).

Our results suggest that therapies targeting the regulation of circadian rhythms such as

IPSRT, exercise, psychoeducation, light therapy, sleep hygiene, etc. may have a direct

impact in improving QOL along with symptom recovery in BD.

We also found that use of sleep medications was associated with poor QOL in BD

(Table 2). Previous studies found an association between sleep medication use and

impaired physical, but not psychological QOL in individuals with and without insomnia

(Sasai et al., 2010). This may be a valid comparison to our sample of BD subjects, since

sleep disturbances commonly observed in periods of euthymia in BD are comparable to

those seen in individuals with primary insomnia (Harvey et al., 2005). Therefore it is

possible that the use of sleep medications is associated with poor QOL in BD because

more severe forms of BD have greater sleep disturbances. This would, in turn, increase

the need for use of sleep aids. Side effects of sleep aids, such as sedation, fatigue and

dizziness may also play a role in decreasing QOL. Notably, preclinical studies found that

mood stabilizers such as lithium and valproate, can regulate the expression of circadian

rhythm genes (Johansson, Brask, Owe-Larsson, Hetta, & Lundkvist, 2011). This is consistent with human studies showing that these mood stabilizers reduce the melatonin light sensitivity in healthy volunteers (Hallam, Olver, & Norman, 2005a; Hallam, Olver, Horgan, McGrath, & Norman, 2005b). Our study, however, cannot distinguish whether the effects of sleep aids on QOL are associated with changes in the expression of circadian rhythm genes or melatonin.

Finally, we replicated previous findings that the severity of depressive symptoms is an independent predictor of poor QOL (Michalak et al., 2005). Yatham et al. (2004) previously showed QOL was inversely correlated with severity of depression in both unipolar and bipolar depression. However, it is worth mentioning that QOL is not merely an inverse measure of depression, since QOL improvements typically lag after remission of depressive symptoms (Murray & Michalak, 2012). A study on the treatment of BD depression with quetiapine found that improvement in QOL was positively correlated with improvement in depressive and anxiety symptoms and sleep quality, and that this relationship increased over time (Endicott, Paulsson, Gustafsson, Schiöler, & Hassan, 2008). We are not aware of any study reporting investigation of the impact of circadian rhythm improvement on QOL.

One limitation of the present study is that objective measures of circadian rhythm disturbance such as actigraphy were not employed. Sleep and circadian assessment with dim light melatonin onset (DLMO) and actigraphy have recently been studied in youth with mood symptoms, which showed that disturbances in rhythms of melatonin and sleep quality differed in early stages of mood disorder (Naismith et al., 2012). DLMO was not

associated with severity of depression or sleep quality rating scales. Future studies are needed to evaluate whether objective measures of circadian rhythms such as melatonin/DLMO are related to self-report measures such as the BRIAN. Another limitation is that BD subjects experiencing manic, hypomanic or mixed episodes were excluded. Recent studies found that reports of QOL during manic and hypomanic episodes tend to be less impaired than during depressive or mixed states (Jansen et al., 2013; Michalak, Torres, Bond, Lam, & Yatham, 2013). As disturbance of circadian rhythms have also been associated with onset of manic episodes (Jackson et al., 2003), studies on the impact of circadian rhythm disruption on QOL in manic/hypomanic subjects are warranted.

In conclusion, circadian rhythm was strongly associated with QOL, independent on severity of depressive symptoms, sleep quality and use of sleeping aids in a sample of well-characterized euthymic and depressed BD subjects. Our results suggest that circadian rhythm may have a direct impact on QOL, which highlights the importance of interventions that target circadian rhythm in combination with pharmacotherapy in BD. Further studies investigating the neurobiology behind circadian rhythm disturbance in BD, and how pharmacological and non-pharmacological interventions interact with these systems are encouraged.

Figures

Figure 1: Correlations of QOL with: **a)** depressive symptom severity (r_P=-0.59, 95% CI [-0.72, -0.43], p<0.001) **b)** circadian rhythm disturbance (r_P=-0.57, 95% CI [-0.70, -0.40], p<0.001 **c)** sleep quality (r_P=-0.51, 95% CI [-0.65, -0.32], p<0.001).

a)
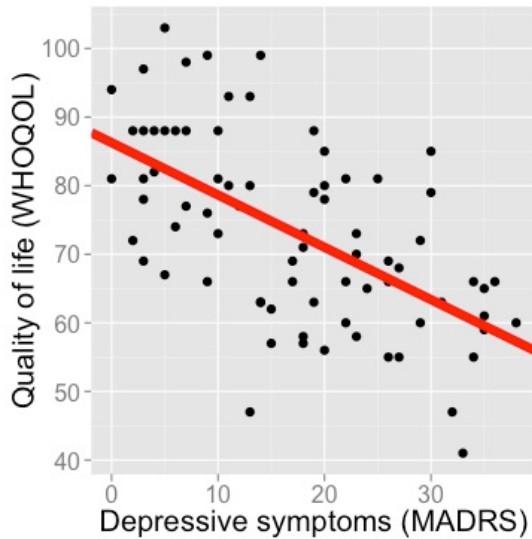
b)
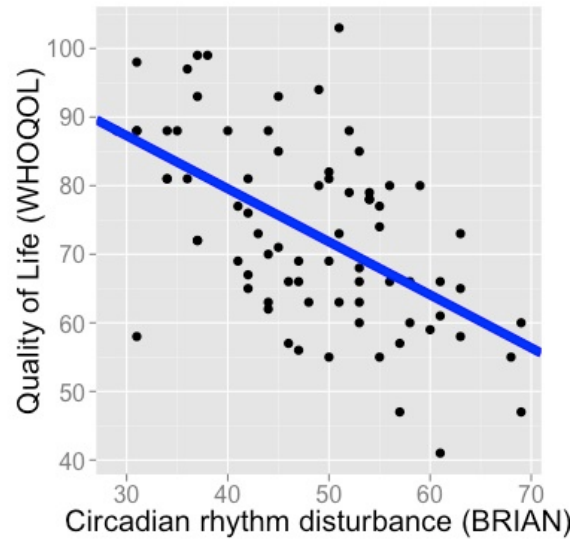
c)
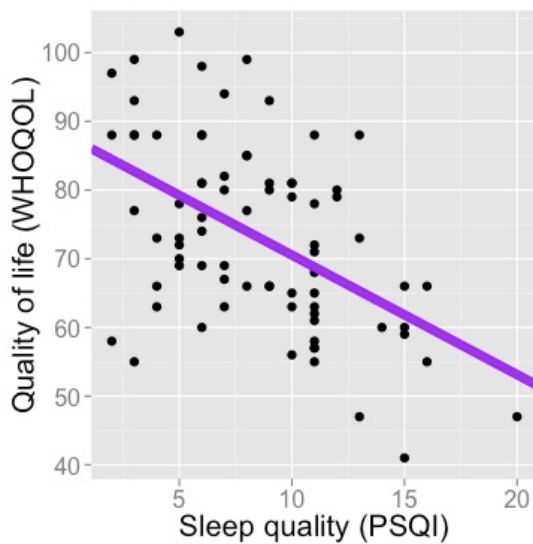
Tables

Table 1: Demographic and clinical characteristics of study participants

Variable	Bipolar sample (n=80)
Mean Age, years (S.D.)	42.62 (12.88)
Range	20-66
Sex	
Female	64 (80.0%)
Male	16 (20.0%)
Occupation status	
Employed	38 (47.5%)
Unemployed	38 (47.5%)
Missing data	4 (5.0%)
Education, years (S.D.)	15.24 (3.11)
Current psychiatric comorbidities, n (%)	
Alcohol/Substance abuse	11 (13.8%)
Eating Disorders	2 (2.5%)
Generalized Anxiety Disorder	11 (13.8%)
Obsessive Compulsive Disorder	4 (5.0%)
Panic Disorder	7 (8.8%)
Post Traumatic Stress Disorder	10 (12.5%)
Social Phobia	12 (15.0%)
Specific Phobia	3 (3.8%)
Psychiatric medications, n (%)	
Mood Stabilizers	47 (58.8%)
Antipsychotics	40 (50.0%)
Antidepressants	44 (55.0%)
Anxiolytics	40 (50.0%)
Sleep Medication use	
Yes	54 (67.5%)
No	26 (32.5%)
Mean WHOQOL (S.D.)	74.05 (13.90)
Range	41-103
Mean MADRS (S.D)	16.76 (10.55)
Range	0-38
Mean BRIAN (S.D.)	47.69 (10.06)
Range	29-69
Mean PSQI (without Component 6) (S.D.)	8.35 (3.88)
Range	2-20

Table 2: Multiple Regression Analysis Predicting Quality of Life in BD patients

Model 1.
Summary of multiple linear regression analysis including all predictors for QOL

Predictors	Standardized coefficients (β)	Unstandardized coefficients (b)	Standard Error	t-value	Pearson's r
MADRS	-0.33**	-0.43**	0.14	-3.14	-0.59**
BRIAN	-0.29*	-0.40*	0.16	-2.50	-0.57**
PSQI (without C6)	-0.12	-0.44	0.40	-1.10	-0.51**
Sleep medication use	-0.40*	-5.53*	2.52	-2.19	N/A

Model significance: Adj. R^2= 0.454; F= 17.45; df= 4,75; p<0.0001. AIC=377.45
*p<0.05, **p<0.01

Model 2.
Summary of model of best fit based on stepwise variable selection of QOL predictors

Predictor	Standardized coefficients (β)	Unstandardized coefficients (b)	Standard Error	t-value	Pearson's r
MADRS	-0.35**	-0.46**	0.14	-3.42	-0.59**
BRIAN	-0.35**	-0.49**	0.14	-3.51	-0.57**
Sleep medication use	-0.42*	-5.85*	2.51	-2.32	N/A

Model significance: Adj. R^2= 0.453; F= 22.81; df= 3,76; p<0.0001. AIC=376.72
*p<0.05, **p<0.01

References

Amini, H., Sharifi, V., 2012. Quality of life in bipolar type I disorder in a one-year followup. Depression Research and Treatment 2012, 1–11.

Berlim, M.T., Pargendler, J., Caldieraro, M.A., Almeida, E.A., Fleck, M.P.A., Joiner, T.E., 2004. Quality of life in unipolar and bipolar depression. The Journal of Nervous and Mental Disease 192, 792–795.

Buysse, D.J., Reynolds, C.F., Monk, T.H., Berman, S.R., Kupfer, D.J., 1989. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Research 28, 193–213.

Ehlers, C.L., Frank, E., Kupfer, D.J., 1988. Social zeitgebers and biological rhythms. A unified approach to understanding the etiology of depression. Archives of General Psychiatry 45, 948–952.

Endicott, J., Paulsson, B., Gustafsson, U., Schiöler, H., Hassan, M., 2008. Quetiapine monotherapy in the treatment of depressive episodes of bipolar I and II disorder: Improvements in quality of life and quality of sleep. Journal of Affective Disorders 111, 306–319.

Frank, E., Soreca, I., Swartz, H.A., Fagiolini, A.M., Mallinger, A.G., Thase, M.E., Grochocinski, V.J., Houck, P.R., Kupfer, D.J., 2008. The role of interpersonal and social rhythm therapy in improving occupational functioning in patients with bipolar I disorder. American Journal of Psychiatry 165, 1559–1565.

Giglio, L.M., Magalhães, P.V.S., Kapczinski, N.S., Walz, J.C., Kapczinski, F., 2010. Functional impact of biological rhythm disturbance in bipolar disorder. Journal of Psychiatric Research 44, 220–223.

Giglio, L.M.F., Andreazza, A.C., Andersen, M., Ceresér, K.M., Walz, J.C., Sterz, L., Kapczinski, F., 2008. Sleep in bipolar patients. Sleep Breath 13, 169–173.

Giglio, L.M.F., da Silva Magalhães, P.V., Andreazza, A.C., Walz, J.C., Jakobson, L., Rucci, P., Rosa, A.R., Hidalgo, M.P., Vieta, E., Kapczinski, F., 2009. Development and use of a biological rhythm interview. Journal of Affective Disorders 118, 161–165.

Hallam, K.T., Olver, J.S., Horgan, J.E., McGrath, C., Norman, T.R., 2005a. Low doses of lithium carbonate reduce melatonin light sensitivity in healthy volunteers. International Journal of Neuropsychopharmacology 8, 255–259.

Hallam, K.T., Olver, J.S., Norman, T.R., 2005b. Effect of sodium valproate on nocturnal melatonin sensitivity to light in healthy volunteers. Neuropsychopharmacology 30,

1400–1404.

Harvey, A.G., 2008. Sleep and circadian rhythms in bipolar disorder: seeking synchrony, harmony, and regulation. American Journal of Psychiatry 165, 820–829.

Harvey, A.G., Schmidt, D.A., Scarnà, A., Semler, C.N., Goodwin, G.M., 2005. Sleep-Related Functioning in Euthymic Patients With Bipolar Disorder, Patients With Insomnia, and Subjects Without Sleep Problems. American Journal of Psychiatry 162, 50–57.

Jackson, A., Cavanagh, J., Scott, J., 2003. A systematic review of manic and depressive prodromes. Journal of Affective Disorders 74, 209–217.

Jansen, K., Campos Mondin, T., Azevedo Cardoso, T. de, Costa Ores, L.D., de Mattos Souza, L.D., Tavares Pinheiro, R., da Silva Magalhães, P.V., da Silva, R.A., 2013. Quality of life and mood disorder episodes: Community sample. Journal of Affective Disorders 147, 123–127.

Johansson, A.S., Brask, J., Owe-Larsson, B., Hetta, J., Lundkvist, G.B., 2011. Valproic acid phase shifts the rhythmic expression of Period2:: Luciferase. Journal of Biological Rhythms 26, 541–551.

Jones, S.H., Hare, D.J., Evershed, K., 2005. Actigraphic assessment of circadian activity and sleep patterns in bipolar disorder. Bipolar Disorders 7, 176–186.

Leboyer, M., Kupfer, D.J., 2010. Bipolar disorder: new perspectives in health care and prevention. Journal of Clinical Psychiatry 71, 1689–1695.

Merikangas, K.R., Akiskal, H.S., Angst, J., Greenberg, P.E., Hirschfeld, R.M.A., Petukhova, M., Kessler, R.C., 2007. Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication. Archives of General Psychiatry 64, 543–552.

Michalak, E.E., Torres, I.J., Bond, D.J., Lam, R.W., Yatham, L.N., 2013. The relationship between clinical outcomes and quality of life in first-episode mania: a longitudinal analysis. Bipolar Disorders 15, 188–198.

Michalak, E.E., Yatham, L.N., Lam, R.W., 2005. Quality of life in bipolar disorder: a review of the literature. Health and Quality of Life Outcomes 3, 72.

Millar, A., Espie, C.A., Scott, J., 2004. The sleep of remitted bipolar outpatients: a controlled naturalistic study using actigraphy. Journal of Affective Disorders 80, 145–153.

Montgomery, S.A., Asberg, M., 1979. A new depression scale designed to be sensitive to change. The British Journal of Psychiatry 134, 382–389.

Murray, G., Michalak, E.E., 2012. The quality of life construct in bipolar disorder

research and practice: past, present, and possible futures. Bipolar Disorders 14, 793–796.

Naismith, S.L., Hermens, D.F., Ip, T.K.C., Bolitho, S., Scott, E., Rogers, N.L., Hickie, I.B., 2012. Circadian profiles in young people during the early stages of affective disorder. Translational Psychiatry 2, e123.

Nathan, P.J., Burrows, G.D., Norman, T.R., 1999. Melatonin sensitivity to dim white light in affective disorders. Neuropsychopharmacology 21, 408–413.

Robb, J.C., Cooke, R.G., Devins, G.M., Young, L.T., Joffe, R.T., 1997. Quality of life and lifestyle disruption in euthymic bipolar disorder. Journal of Psychiatric Research 31, 509–517.

Salvatore, P., Ghidini, S., Zita, G., De Panfilis, C., Lambertino, S., Maggini, C., Baldessarini, R.J., 2008. Circadian activity rhythm abnormalities in ill and recovered bipolar I disorder patients. Bipolar Disorders 10, 256–265.

Sasai, T., Inoue, Y., Komada, Y., Nomura, T., Matsuura, M., Matsushima, E., 2010. Effects of insomnia and sleep medication on health-related quality of life. Sleep Medicine 11, 452–457.

Shen, G.H.C., Alloy, L.B., Abramson, L.Y., Sylvia, L.G., 2008. Social rhythm regularity and the onset of affective episodes in bipolar spectrum individuals. Bipolar Disorders 10, 520–529.

St-Amand, J., Provencher, M.D., Bélanger, L., Morin, C.M., 2013. Sleep disturbances in bipolar disorder during remission. J Affective Disorders 146, 112–119.

The WHOQOL Group, 1995. The World Health Organization Quality of Life assessment (WHOQOL): position paper from the World Health Organization. Social Science & Medicine 41, 1403–1409.

Yatham, L.N., Lecrubier, Y., Fieve, R.R., Davis, K.H., Harris, S.D., Krishnan, A.A., 2004. Quality of life in patients with bipolar I depression: data from 920 patients. Bipolar Disorders 6, 379–385.

Yin, L., Wang, J., Klein, P.S., Lazar, M.A., 2006. Nuclear receptor Rev-erb {alpha} is a critical lithium-sensitive component of the circadian clock. Science 311, 1002.

Chapter 3

Alterations in circadian rhythms are associated with increased lipid peroxidation in females with bipolar disorder

Lauren E. Cudney [1,2]; Roberto B. Sassi, M.D., Ph.D. [1,3,*]; Guilherme A. Behr, M.Sc. Ph.D. [2, 5]; David L. Streiner, Ph.D. [3,4]; Luciano Minuzzi, M.D., Ph.D. [1,2,3]; Jose C. F. Moreira, Ph.D. [5]; Benicio N. Frey, M.D., M.Sc., Ph.D. [1,2,3,*]

* These authors contributed equally as senior authors.

[1] Mood Disorders Program and [2] Women's Health Concerns Clinic, St. Joseph's Healthcare Hamilton, ON, Canada; [3] Department of Psychiatry and Behavioural Neurosciences, McMaster University, Hamilton, ON; [4] Department of Psychiatry, University of Toronto, ON, Canada; [5] Center of Oxidative Stress Research, Professor Tuiskon Dick Department of Biochemistry, Institute of Health Basic Sciences, Federal University of Rio Grande do Sul (UFRGS), Porto Alegre, RS, Brazil

Abstract

Disturbances in both circadian rhythms and oxidative stress systems have been implicated in the pathophysiology of bipolar disorder (BD), yet no studies have investigated the relationship between these systems in BD. We studied the impact of circadian rhythm disruption on lipid damage in 52 depressed or euthymic BD females, while controlling for age, severity of depressive symptoms and number of psychotropic medications, compared to 30 healthy controls. Circadian rhythm disruption was determined by a self-report measure (Biological Rhythm Interview of Assessment in Neuropsychiatry; BRIAN), which measures behaviours such as sleep, eating patterns, social rhythms and general activity. Results of a multiple linear regression showed that circadian rhythm disturbance was associated with increased lipid peroxidation in females with BD ($p<0.05$). Circadian rhythms were not associated with damage to lipids in healthy controls, where aging was the only significant predictor. These results suggest an interaction between the circadian system and redox metabolism, in that greater disruption in daily rhythms was associated with increased lipid peroxidation in BD only. Antioxidant enzymes have been shown to follow a circadian pattern of expression, and it is possible that disturbance of sleep and daily rhythms experienced in BD may result in decreased antioxidant defense and therefore increased lipid peroxidation. This study provides a basis for further investigation of the links between oxidative stress and circadian rhythms in the neurobiology of BD.

Introduction

Bipolar Disorder (BD) is a chronic illness consisting of episodes of mania and depression, affecting nearly 4% of the population (Merikangas et al., 2007). Abnormalities in circadian rhythms, such as sleep, daily activity, social rhythms and eating behaviour are commonly observed not only during mood episodes but also during periods of euthymia (Harvey et al., 2005). There is a growing body of evidence suggesting complex associations between BD and circadian activity (McClung, 2013). Disruptions in sleep/wake cycle are well known triggers of affective episodes in patients with BD (Proudfoot et al., 2011), and indeed one of the most effective psychotherapy interventions in BD targets the maintenance of stable biological rhythms as one of its core goals (Frank et al., 2007). In fact, virtually all treatments for mood disorders have an influence on circadian rhythms, in particular chronotherapeutics such as light therapy, sleep deprivation and sleep phase advancement (Wehr et al., 1979; Benedetti, 2012). From a molecular perspective, there are several lines of evidence supporting that circadian rhythms are sensitive to disruption in BD patients, such as abnormalities in circadian genes and circadian endocrine markers (Milhiet et al., 2011; McClung, 2013).

Circadian rhythm disruption has been shown to have negative consequences in numerous biological systems in healthy subjects, in particular, immune, inflammatory and oxidative stress systems (Faraut et al., 2012). Multiple mechanisms have been proposed to explain the correlation between sleep and oxidative stress, including sleep-related changes in transcriptional responses of genes involved in oxidative stress in peripheral

28

tissues (Anafi et al., 2013). The endogenous timekeeper in mammals is the

suprachiasmatic nuclei (SCN) in the hypothalamus, which regulates biological rhythms of

endocrine secretion, body temperature, sleep/wake cycles and other behaviours including

cognition (Kyriacou and Hastings, 2010) in a period close to 24-hours (Reppert and

Weaver, 2002). Almost all peripheral tissues exhibit circadian oscillations that are

synchronized by the SCN (Cermakian and Boivin, 2009). The molecular mechanisms of

circadian rhythm are tightly linked with transcription - translation feedback loops of

circadian genes such as *CLOCK* and *BMAL1* in the SCN, which activate transcription of

other regulatory circadian genes (Reppert and Weaver, 2002). Notably, many of these

genes (e.g. *PER, CRY, REV-ERBα* and *GSK3β*) have been considered among the top

candidate genes for BD and some have been implicated in treatment response (Etain et al.,

2011). Animal models of mania also implicate circadian rhythm and sleep disruptions in

BD, in that *CLOCK* mutations and sleep deprived mice demonstrate a manic-like

behavioural profile (McClung, 2007).

Melatonin is the primary circadian signaling molecule, which has increased

secretion in the dark and is inhibited in the light (Nölte et al., 2009). Several studies

suggest BD patients have irregular melatonin secretion. For example, the inhibition of

melatonin synthesis in light has been shown to be impaired in BD patients compared to

controls (Nathan et al., 1999). In addition, lower nocturnal melatonin levels have been

observed during depression and euthymia (Kennedy et al., 1996). A recent study showed

that patients with depression have an increased number of melatonin receptors in the SCN

(Wu et al., 2013). An increase in melatonin receptors may be a compensatory mechanism

for the reduced melatonin levels in patients with mood disorders, and these receptors have been recently suggested as targets of novel antidepressant agents (Fornaro et al., 2013). Therefore, circadian rhythm differences in mood disorders are observable at molecular and behavioural levels, but how these changes emerge is still unknown.

Besides its role in circadian rhythm control, melatonin has antioxidant properties, acting as an electron donor in scavenging free radicals to protect against oxidative damage to lipids, proteins and DNA (Reiter et al., 1995). Oxidative damage occurs when there is a disturbance in the oxidant-antioxidant balance, as a result of an overproduction of reactive oxygen species (ROS) and/or insufficient antioxidant defense (Halliwell, 2012). Melatonin is more effective at neutralizing ROS than other intracellular antioxidants such as glutathione (GSH) and also stimulates antioxidant enzyme activity (Reiter et al., 1995; Wang et al., 2013). Evidence has shown that oxidative stress may be important in the pathophysiology of BD, particularly with respect to lipid peroxidation. A meta-analysis of studies on peripheral markers of oxidative stress showed that lipid peroxidation was significantly increased in BD (Andreazza et al., 2008), as indicated by increased thiobarbituric acid reactive substances (TBARS) (Draper and Hadley, 1990). Lipid peroxidation has been found to be increased across all mood states, and has been considered a trait marker of BD (Andreazza et al., 2008). Several recent studies also show an increase in end-products of lipid peroxidation in BD peripheral blood (Versace et al., 2013) and in postmortem brain tissue in BD (Andreazza et al., 2013). Together, these results suggest an imbalance toward a pro-oxidant state in BD, however the factors leading to an altered redox metabolism remain unknown.

The above-mentioned studies indicate there are disturbances in both circadian rhythms and oxidative stress systems in BD, yet it remains unclear whether there is any relationship between these systems within the disorder. Thus, the aim of the present study is to determine whether disruptions in circadian rhythms have an impact on levels of lipid peroxidation in depressed and euthymic subjects with BD, as compared to matched controls. Because sex differences have been reported in a number of circadian rhythm measures (Mong et al., 2011; Kuljis et al., 2013), we have restricted this initial study to the female population. Other variables that may impact oxidative stress levels such as age, severity of depression and psychotropic medications in BD were also investigated. We hypothesized that circadian rhythm disturbances would negatively affect lipid peroxidation levels in individuals with BD.

Methods

Participants and study design

Fifty-two females with BD (37 BD type I and 15 BD type II) and 30 age-matched healthy controls were recruited from the Mood Disorders Program and the Women's Health Concerns Clinic, St. Joseph's Healthcare Hamilton, Ontario. All subjects gave written informed consent to take part in the study, as approved by the ethics committees of St. Joseph's Healthcare Hamilton and Hamilton Health Sciences. The diagnosis of BD was confirmed with the Structured Clinical Interview for the DSM-IV (SCID-I). Patients with BD were included in the study if they either met criteria for a current major depressive episode (n=44) or if they did not meet criteria for any current mood episode

(n=32) according to the SCID-I. Participants were excluded if they met criteria for a hypomanic, manic or mixed episode. Control participants were excluded if they met criteria for current or lifetime history of any psychiatric illness according to the SCID-I. Severity of depressive symptoms was measured with the Montgomery-Åsberg Depression Rating Scale (MADRS). Circadian rhythms were measured with the Biological Rhythm Interview of Assessment in Neuropsychiatry (BRIAN), a self-report questionnaire composed of 18-items measuring sleep, general activities, social rhythm and eating behaviour scored from 1 (no difficulties) to 4 (serious difficulties), with greater scores indicating greater circadian rhythms disruption. This scale has been validated in BD subjects in its ability to discriminate euthymic BD and controls (Giglio et al., 2009). Psychiatric medications were recorded for each participant and are listed in Table 3. Only psychotropic medications including mood stabilizers, antidepressants, antipsychotics and anxiolytic medications were included in the total number of medications participants were taking.

Laboratory assays

Participants provided blood samples collected by venipuncture. We obtained serum by centrifugation at 3000g for 15 minutes and kept samples frozen at -80°C until biochemical assays were performed. Malondialdehyde (MDA) levels were obtained as a measure of lipid peroxidation, with higher MDA levels representing greater lipid oxidative damage. Specifically, lipid peroxidation was measured via colorimetric detection of the malondialdehyde- thiobarbituric (MDA-TBA) adduct with TBARS assay

kit (Cayman Chem, Ann Arbor, MI, USA). Plates were read at the kit specified

wavelength of 535 nm using an automated reader (Spectra Max Plus 384, Molecular

Devices, Plate Reader).

Statistical analyses

All analyses were performed with *R* (Version 2.14.2, R Development Core Team,

2012). In the BD sample, multiple linear regression analysis was performed using BRIAN,

MADRS, age and number of psychiatric medications as predictors, and MDA as the

dependent variable. A multiple linear regression was also performed in the healthy

control sample with only age and BRIAN as predictors and MDA as the dependent

variable, since depression severity and psychiatric medications were not relevant to this

population. Assumptions of linear regression were tested with Shapiro-Wilk test

(normality), a partial residuals plot (linearity), Durbin-Watson test (independence of

errors), non-constant error variance (homoscedasticity) and variance inflation factor test

(multicollinearity). MDA levels were square root transformed to lead to a normal

distribution. Both models met all of the regression assumptions. A *p* value of <0.05 was

used to indicate statistical significance.

Results

Demographic and clinical data for BD and control subjects are displayed in Table

3. As expected, MADRS and BRIAN scores were significantly higher in BD patients than

controls. In the BD group, higher levels of lipid oxidative damage were correlated with

increased circadian rhythm disruption (BRIAN, r_P=0.33, 95% CI [0.06, 0.56], p<0.05) and greater number of psychiatric medications (r_P=0.29, 95% CI [0.02, 0.52], p<0.05) as shown in Figure 2, but not related to depression severity (r_P=0.08, 95% CI [-0.20, 0.34], p=0.59), or age (r_P=0.15, CI[-0.12, 0.41], p=0.28) (Figure 3b). In the multiple linear regression model, circadian rhythms disruption (β=0.46, t=2.56, p<0.05) and number of psychiatric medications (β=0.28, t=2.10, p<0.05) were independent predictors of lipid damage in the BD sample ($F_{4, 47}$= 3.54; p<0.05). In order to investigate whether these results were due to circadian fluctuations of MDA levels, we correlated MDA with time of blood draw in the BD sample and found no significant relationship (r_P=0.01, 95% CI [-0.26, 0.29], p=0.92). There was no difference in the timing of blood draws between BD and control subjects (Table 3). In healthy controls, higher MDA levels were correlated with age only (r_P=0.40, 95% CI [0.05, 0.67], p<0.05) (Figure 3a), but not with BRIAN. In the multiple linear regression model, age (β= 0.004, t=2.50, p<0.05) was the only significant predictor of lipid peroxidation ($F_{2, 27}$= 3.93, p<0.05) in healthy controls. Results from the regression analyses for BD subjects and healthy controls are reported in Tables 4a and 4b, respectively.

Discussion

Lipid peroxidation levels are influenced by circadian rhythms in BD

The main finding of the present study is that severity of circadian rhythm disruption in BD is associated with increased lipid oxidative damage independent of age, severity of depressive symptoms and use of psychotropic medications. Formation of lipid

peroxidation (i.e. MDA, TBARS) is an indicator of an imbalance favouring the formation of ROS and leading to lipid damage. Cellular defense against ROS depends on non-enzymatic antioxidants (i.e. GSH and vitamins) and protective enzymes, such as superoxide dismutase (SOD) and catalase (CAT) (Halliwell, 2012). Notably, there is evidence that many of these antioxidant defense mechanisms follow circadian rhythms in various organisms and tissues (Kondratova and Kondratova, 2012). For instance, circadian fluctuations of SOD have been observed in animal tissues and human blood plasma (Hardeland et al., 2003). It has been suggested that circadian timing of these protective enzymes is to compensate for times of increased ROS formation (Hardeland et al., 2003). Therefore, it is conceivable that a disruption in the circadian expression of antioxidant enzymes may result in a redox imbalance leading to increased formation of oxidative molecules (i.e. MDA, TBARS) in BD patients with greater rhythm disruptions. Future studies measuring a wider range of markers of oxidative stress at various time points during the 24-hours are needed to investigate this hypothesis.

Sleep is a major component of circadian rhythm regulation and has been hypothesized to neutralize ROS produced during the wake cycle (Brown and Naidoo, 2010). Recent animal studies indicate that sleep deprivation results in decreased antioxidant enzymes and increased oxidative stress in certain brain areas such as the hippocampus, thalamus and hypothalamus (Alzoubi et al., 2012). Lungato et al. (2013) showed that CAT was reduced and total SOD activity was increased after sleep deprivation in rats, suggesting that an imbalance of antioxidant enzymes occurs after sleep disturbance. However, the levels of MDA were not associated with sleep

deprivation in this latter study (Lungato et al., 2013). A recent study looking at the impact

of sleep on whole blood transcriptomes in humans, found that insufficient sleep resulted

in a decrease in the expression of a number of circadian rhythm genes (Möller-Levet et al.,

2013). Interestingly, this study found that while certain circadian rhythm genes (*PER2,*

PER3 and *TIMELESS*) were downregulated after sleep deprivation, some oxidative stress

genes (*PRDX2* and *PRDX5*) were upregulated. Together these studies indicate that sleep

loss may lead to dysregulation of the circadian clock and increased oxidative stress

(Möller-Levet et al., 2013). Sleep disturbance/insomnia is one of the core symptoms of

BD, so it is possible that sleep disturbance may contribute to increased oxidative stress in

BD. Future studies should investigate this possibility.

  We also observed that the number of psychotropic medications was positively

associated with lipid damage in BD patients. Based on this association it seems that

polypharmacy may have some influence on oxidative stress and this finding may be

particularly relevant in BD because it is well known that polypharmacy is the rule rather

than the exception in BD (Lin et al., 2006; Greil et al., 2012). However, we do not know

if this association is a direct effect of psychotropic agents on oxidative stress or a result of

greater illness severity or comorbid conditions (Correll et al., 2007). In addition, our

study cannot distinguish which medications individually impact lipid damage, since the

majority of patients included in the study are on more than one medication. There is

evidence suggesting that the mood stabilizers lithium and valproate exert neuroprotective

effects against increased oxidative stress in a rodent model *in vivo* (Frey et al., 2006).

Similarly, increased TBARS seen in untreated mania was significantly decreased after

treatment with lithium, further corroborating lithium's potential antioxidant effects (Machado-Vieira et al., 2007). Several studies have also shown that treatment with antidepressants can reverse the increased oxidative stress in individuals with major depressive disorder (Behr et al., 2012). Furthermore, many of the antipsychotics used by our study participants have been shown to have effects on different components of antioxidant enzymes in animal studies (Parikh et al., 2003). Future studies are needed to better discriminate the impact of individual and combination treatments on oxidative stress in humans.

We also found that age was the only significant predictor of lipid damage (MDA levels) in healthy controls, but not in BD subjects. This result is consistent with many previous studies showing that lipid peroxidation increases with healthy aging (Di Massimo et al., 2006; Voss and Siems, 2006). While studies of lipid peroxidation have shown that aging resulted in an increase in TBARS levels in different species, the daily rhythms of TBARS seem to be conserved across different age groups (Manikonda and Jagota, 2012). Together, these studies suggest that, within normal healthy aging, the daily rhythms of redox metabolism remains intact but there is an increase in the amount of lipid peroxidation over time. We believe that we did not observe a correlation between MDA levels and aging in the BD subgroup because the circadian disturbances and medication effects overshadowed the effects of aging on lipid peroxidation.

Limitations and Conclusions

To our knowledge, this is the first study to investigate the relationship between circadian rhythm disruption and lipid peroxidation levels in individuals with BD. We found that circadian rhythm disruption as measured by BRIAN has a negative impact on MDA in females with BD. These results suggest an interaction between the circadian system and redox metabolism in BD, in which a measure of daily rhythm disturbances was indicative of increased lipid peroxidation in BD. One of the limitations of our study is the lack of objective measures of circadian rhythm disturbances. Future studies should employ the use of actigraphy or dim light melatonin onset to assess the impact of objective measure of circadian rhythm and lipid peroxidation in BD. The finding of an association between the number of psychiatric medications and increased levels of lipid peroxidation in our BD sample deserves further investigation. It is notorious in the mood disorders literature that medication effects are often difficult to evaluate/interpret, and are potentially confounded by severity of symptoms, dosage and comorbid conditions (Ranjekar et al., 2003). Future investigation on the impact of individual and combination of medications on lipid peroxidation in BD are warranted. Finally, we also found that lipid peroxidation levels seem to be influenced by different variables in BD compared to healthy controls, where only age was a significant predictor. This study provides a basis for further investigation of the links between oxidative stress and circadian rhythms in the pathophysiology of BD.

Figures

Figure 2: Correlations of lipid peroxidation in BD with: **a)** circadian rhythm disturbance (r_P=0.33, 95% CI [0.06, 0.56], $p<0.05$); **b)** number of psychotropic medications (r_P=0.29, 95% CI [0.02, 0.52], $p<0.05$).

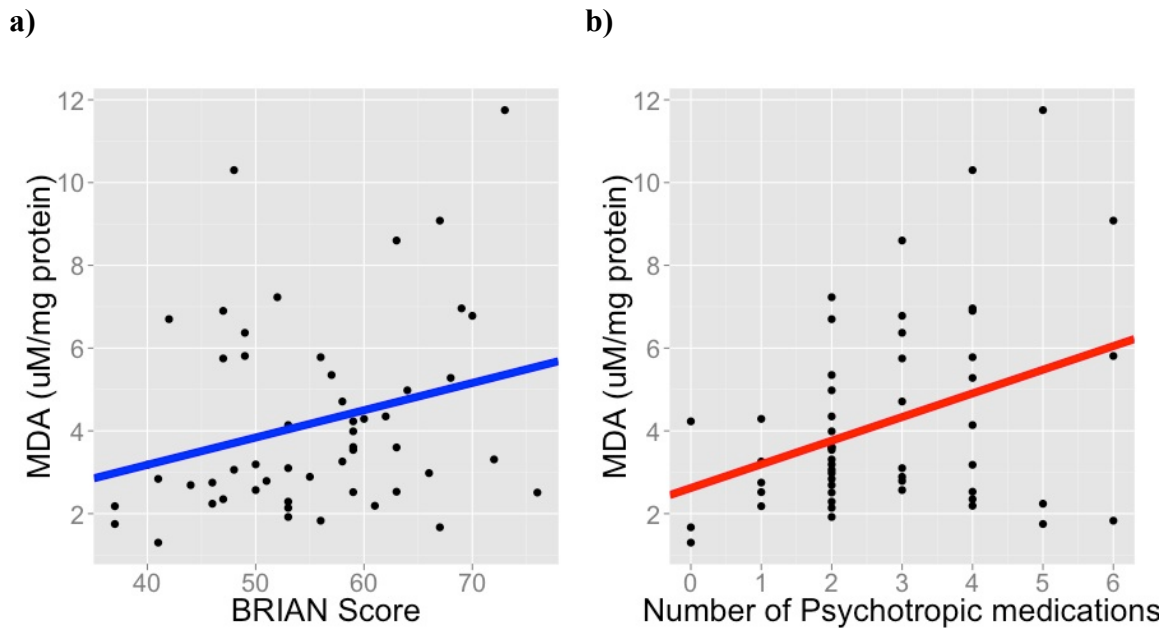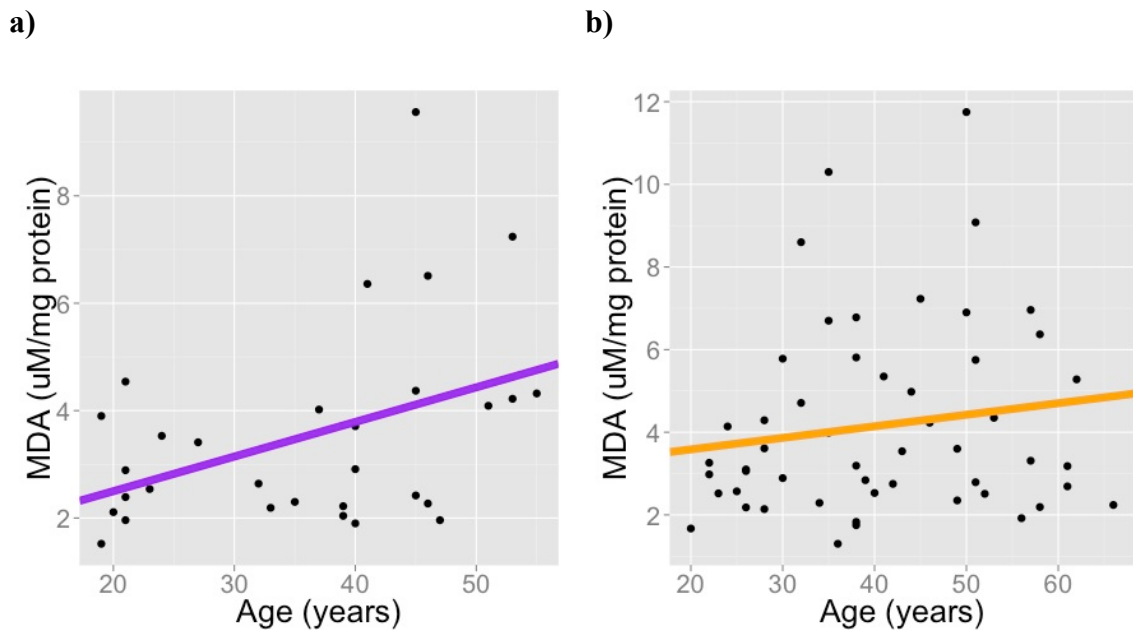**a)**   **b)**

Figure 3: Correlation of lipid peroxidation with age in **a)** controls (r_P=0.40, 95% CI [0.05, 0.67], $p<0.05$); **b)** BD (r_P=0.15, 95% CI [-0.12, 0.41], p=0.28)

a)   **b)**

Tables

Table 3: Demographic and clinical data

Variable	Bipolar Disorder	Healthy Controls	t-test, p-value
	N=52	N=30	
	Mean ± SD	Mean ± SD	
Age, years	40.75 ± 12.48	35.93 ± 11.71	t(63.87)=1.75, p=0.08
BMI	29.33 ± 8.01	28.40 ± 7.08	t(45.77)= 0.49, p=0.63
BRIAN	49.81 ± 9.39	26.90 ± 7.76	t(67.56)=11.12, p<0.01
MADRS	17.33 ± 11.04	1.53 ± 1.81	t(55.67)=10.08, p<0.01
Time of Blood draw	12:07 ± 2:08	12:01 ± 2:16	t(48.87)=0.11, p=0.91
Lipid damage (TBARS, μM MDA/mg protein)	4.19 ± 2.32	3.53 ± 1.84	t(72.14)=1.42, p=0.16
Duration of illness, years	25.98 ± 15.14	N/A	
Lithium	n= 15	N/A	
Mood stabilizers	n= 26	N/A	
Antipsychotics	n= 27	N/A	
Antidepressants	n= 31	N/A	
Anxiolytics	n= 25	N/A	
Average # of psychotropic medications	2.75 ± 1.48	N/A	

Table 4*a*: Predictors of lipid oxidative damage in BD subjects

Predictor	Standardized coefficients (β)	Unstandardized coefficients (B)	Standard Error	t-value	Pearson's r
Age	0.1029	0.0011	0.0015	0.494	0.15
MADRS	-0.2347	-0.0028	0.0019	-1.288	0.08
BRIAN	0.4568*	0.0064*	0.0022	2.563	0.33*
# of psychotropic medications	0.2799*	0.0249*	0.0121	2.099	0.29*

Adj. R^2=0.165; F=3.53; df=4,47; p<0.05

*p<0.05

Table 4*b*: Predictors of lipid oxidative damage in healthy controls

Predictor	Standardized coefficients (β)	Unstandardized coefficients (b)	Standard Error	t-value	Pearson's r
Age	0.0044*	0.0018*	0.0018	2.499	0.40*
BRIAN	-0.0039	0.0027	0.0027	-1.464	-0.21

Adj. R^2=0.168; F=3.92; df=2,27; p<0.05

*p<0.05

References

Alzoubi KH, Khabour OF, Salah HA, Abu Rashid BE (2012) The Combined Effect of Sleep Deprivation and Western Diet on Spatial Learning and Memory: Role of BDNF and Oxidative Stress. J Mol Neurosci 50:124–133.

Anafi RC, Pellegrino R, Shockley KR, Romer M, Tufik S, Pack AI (2013) Sleep is not just for the brain: transcriptional responses to sleep in peripheral tissues. BMC Genomics 14:362.

Andreazza AC, Kauer-Sant'Anna M, Frey BN, Bond DJ, Kapczinski F, Young LT, Yatham LN (2008) Oxidative stress markers in bipolar disorder: A meta-analysis. J Affect Disord 111:135–144.

Andreazza AC, Wang JF, Salmasi F, Shao L, Young LT (2013) Specific subcellular changes in oxidative stress in prefrontal cortex from patients with bipolar disorder. J Neurochemistry (In press).

Behr GA, Moreira JCF, Frey BN (2012) Preclinical and clinical evidence of antioxidant effects of antidepressant agents: implications for the pathophysiology of major depressive disorder. Oxi Med Cell Longev 2012:609421.

Benedetti F (2012) Antidepressant chronotherapeutics for bipolar depression. Dialogues in Clin Neurosci 14:401–411.

Brown MK, Naidoo N (2010) The UPR and the anti-oxidant response: relevance to sleep and sleep loss. Mol Neurobiol 42:103–113.

Cermakian N, Boivin DB (2009) The regulation of central and peripheral circadian clocks in humans. Obes Rev 10 Suppl 2:25–36.

Correll CU, Frederickson AM, Kane JM, Manu P (2007) Does antipsychotic polypharmacy increase the risk for metabolic syndrome? Schizophr Res 89:91–100.

Di Massimo C, Scarpelli P, Lorenzo ND, Caimi G, Orio FD, Ciancarelli MGT (2006) Impaired plasma nitric oxide availability and extracellular superoxide dismutase activity in healthy humans with advancing age. Life Sci 78:1163–1167.

Draper HH, Hadley M (1990) Malondialdehyde determination as index of lipid peroxidation. Meth Enzymol 186:421–431.

Etain B, Milhiet V, Bellivier F, Leboyer M (2011) Genetics of circadian rhythms and mood spectrum disorders. Eur Neuropsychopharmacol 21:S676–S682.

Faraut B, Boudjeltia KZ, Vanhamme L, Kerkhofs M (2012) Immune, inflammatory and cardiovascular consequences of sleep restriction and recovery. Sleep Med Rev 16:137–149.

Fornaro M, McCarthy MJ, De Berardis D, De Pasquale C, Tabaton M, Martino M, Colicchio S, Cattaneo CI, D'Angelo E, Fornaro P (2013) Adjunctive agomelatine therapy in the treatment of acute bipolar II depression: a preliminary open label study. Neuropsychiatr Dis Treat 9:243–251.

Frank E, Swartz HA, Boland E (2007) Interpersonal and social rhythm therapy: an intervention addressing rhythm dysregulation in bipolar disorder. Dialogues in Clin Neurosci 9:325–332.

Frey BN, Valvassori SS, Réus GZ, Martins MR, Petronilho FC, Bardini K, Dal-Pizzol F, Kapczinski F, Quevedo J (2006) Effects of lithium and valproate on amphetamine-induced oxidative stress generation in an animal model of mania. J Psychiatr Neurosci 31:326.

Giglio LMF, da Silva Magalhães PV, Andreazza AC, Walz JC, Jakobson L, Rucci P, Rosa AR, Hidalgo MP, Vieta E, Kapczinski F (2009) Development and use of a biological rhythm interview. J Affect Disord 118:161–165.

Greil W, Häberle A, Haueis P, Grohmann R, Russmann S (2012) Pharmacotherapeutic trends in 2231 psychiatric inpatients with bipolar depression from the International AMSP Project between 1994 and 2009. J Affect Disord 136:534–542.

Halliwell B (2012) Free radicals and antioxidants: updating a personal view. Nutr Rev 70:257–265.

Hardeland R, Coto-Montes A, Poeggeler B (2003) Circadian rhythms, oxidative stress, and antioxidative defense mechanisms. Chronobiol Int 20:921–962.

Harvey AG, Schmidt DA, Scarnà A, Semler CN, Goodwin GM (2005) Sleep-related functioning in euthymic patients with bipolar disorder, patients with insomnia, and subjects without sleep problems. Am J Psychiatry 162:50–57

Kennedy SH, Kutcher SP, Ralevski E, Brown GM (1996) Nocturnal melatonin and 24-hour 6-sulphatoxymelatonin levels in various phases of bipolar affective disorder. Psychiatry Res 63:219–222.

Kondratova AA, Kondratov RV (2012) The circadian clock and pathology of the ageing brain. Nature 13:325–335.

Kuljis DA, Loh DH, Truong D, Vosko AM, Ong ML, McClusky R, Arnold AP, Colwell CS (2013) Gonadal- and Sex-Chromosome-Dependent Sex Differences in the Circadian System. Endocrinology 154:1501–1512.

Kyriacou CP, Hastings MH (2010) Circadian clocks: genes, sleep, and cognition. Trends Cogn Sci (Regul Ed) 14:259–267.

Lin D, Mok H, Yatham LN (2006) Polytherapy in bipolar disorder. CNS drugs 20:29–42.

Lungato L, Marques MS, Pereira VG, Hix S, Gazarini ML, Tufik S, D'Almeida V (2013) Sleep deprivation alters gene expression and antioxidant enzyme activity in mice splenocytes. Scand J Immunol 77:195–199.

Machado-Vieira R, Andreazza AC, Viale CI, Zanatto V, Cereser V Jr., Vargas RDS, Kapczinski F, Portela LV, Souza DO, Salvador M, Gentil V (2007) Oxidative stress parameters in unmedicated and treated bipolar subjects during initial manic episode: A possible role for lithium antioxidant effects. Neurosci Lett 421:33–36.

Manikonda PK, Jagota A (2012) Melatonin administration differentially affects age-induced alterations in daily rhythms of lipid peroxidation and antioxidant enzymes in male rat liver. Biogerontology 13:511–524.

McClung CA (2007) Circadian genes, rhythms and the biology of mood disorders. Pharmacol Ther 114:222–232.

McClung CA (2013) How might circadian rhythms control mood? Let me count the ways... Biol Psychiatry 74:242–249.

Merikangas KR, Akiskal HS, Angst J, Greenberg PE, Hirschfeld RMA, Petukhova M, Kessler RC (2007) Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication. Arch Gen Psychiatry 64:543–552.

Milhiet V, Etain B, Boudebesse C, Bellivier F (2011) Circadian biomarkers, circadian genes and bipolar disorders. J Physiol Paris 105:183–189.

Mong JA, Baker FC, Mahoney MM, Paul KN, Schwartz MD, Semba K, Silver R (2011) Sleep, rhythms, and the endocrine brain: Influence of sex and gonadal hormones. J Neurosci 31:16107–16116.

Möller-Levet CS, Archer SN, Bucca G, Laing EE, Slak A, Kabiljo R, Lo JC, Santhi N, Schantz von M, Smith CP (2013) Effects of insufficient sleep on circadian rhythmicity and expression amplitude of the human blood transcriptome. Proc Nat Acad Sci 110:E1132-E1141.

Nathan PJ, Burrows GD, Norman TR (1999) Melatonin sensitivity to dim white light in affective disorders. Neuropsychopharmacology 21:408–413.

Nölte I, Lütkhoff A-T, Stuck BA, Lemmer B, Schredl M, Findeisen P, Groden C (2009) Pineal volume and circadian melatonin profile in healthy volunteers: An interdisciplinary approach. J Magn Reson Imaging 30:499–505.

Parikh V, Khan MM, Mahadik SP (2003) Differential effects of antipsychotics on expression of antioxidant enzymes and membrane lipid peroxidation in rat brain. J Psychiatr Res 37:43–51.

Proudfoot J, Doran J, Manicavasagar V, Parker G (2011) The precipitants of

manic/hypomanic episodes in the context of bipolar disorder: a review. J Affect Disord 133:381–387.

Ranjekar PK, Hinge A, Hegde MV, Ghate M, Kale A, Sitasawad S, Wagh UV, Debsikdar VB, Mahadik SP (2003) Decreased antioxidant enzymes and membrane essential polyunsaturated fatty acids in schizophrenic and bipolar mood disorder patients. Psychiatry Res 121:109–122.

Reiter RJ, Melchiorri D, Sewerynek E, Poeggeler B, Barlow-Walden L, Chuang J, Ortiz GG, Acuña-Castroviejo D (1995) A review of the evidence supporting melatonin's role as an antioxidant. J Pineal Res 18:1–11.

Reppert SM, Weaver DR (2002) Coordination of circadian timing in mammals. Nature 418:935–941.

Versace A, Andreazza AC, Young LT, Fournier JC, Almeida J, Stiffler RS, Lockovich JC, Aslam HA, Pollock MH, Park H (2013) Elevated serum measures of lipid peroxidation and abnormal prefrontal white matter in euthymic bipolar adults: toward peripheral biomarkers of bipolar disorder. Mol Psychiatry (In press).

Voss P, Siems W (2006) Clinical oxidation parameters of aging. Free Radic Res 40:1339–1349.

Wang F-W, Wang Z, Zhang Y-M, Du Z-X, Zhang X-L, Liu Q, Guo Y-J, Li X-G, Hao A-J (2013) Protective effect of melatonin on bone marrow mesenchymal stem cells against hydrogen peroxide-induced apoptosis in vitro. J Cell Biochem (In press).

Wehr TA, Wirz-Justice A, Goodwin FK, Duncan W, Gillin JC (1979) Phase advance of the circadian sleep-wake cycle as an antidepressant. Science 206:710–713.

Wu Y-H, Ursinus J, Zhou J-N, Scheer FAJL, Ai-MinBao, Jockers R, van Heerikhuize J, Swaab DF (2013) Alterations of melatonin receptors MT1 and MT2 in the hypothalamic suprachiasmatic nucleus during depression. J Affect Disord 148:357–367.

CHAPTER 4

General Discussion

In the present study, we aimed to investigate the impact of disrupted circadian rhythms in BD. This was accomplished in two separate ways: by examining the relationship with overall QOL, and by examining whether there is an association with the oxidative stress system in BD patients.

The first research question (in Chapter 2) addressed whether self-reported disruptions to circadian rhythms had an impact on QOL in a sample of depressed and euthymic BD patients, while also accounting for depressive symptom severity, sleep quality and sleep medication use. Analysis showed that sleep quality was not a significant predictor when the model included depressive symptoms, circadian rhythms disturbance and sleep medication. This suggests that components of daily rhythm other than sleep, such as social rhythms, eating patterns and general activities, are important contributors to QOL in BD. Many concepts included in QOL such as satisfaction with social relationships, sleep, daily living activities and work, are under the influence of circadian control in that they are generally experienced at certain times during a 24-hour cycle. Thus, it is logical that disturbances in the daily rhythms of these components would result in poorer subjective ratings of satisfaction in these areas. This has implications for the importance of targeting regulation of daily routines for BD patients, as is done in IPSRT.

This study provides further support for the social rhythms theory, in that with improved daily routines/social rhythms, there is an improvement in QOL. Clinical trials

of olanzapine and quetiapine treatment for BD have shown a lag between when mood symptoms are remitted and QOL is improved (Endicott, Paulsson, Gustafsson, Schiöler, & Hassan, 2008;Shi et al., 2002). Therefore, longitudinal research is necessary to further elucidate how changes in circadian rhythms, as targeted by IPSRT or other chronotherapeutics, impact QOL across mood symptom remission. Studying the temporal relationship of circadian rhythm regulation and QOL will provide insight into this delay between symptom recovery and subjective well-being improvement.

Results of the study in Chapter 3 showed that increased circadian rhythm disturbance have a negative impact on lipid peroxidation levels in females with BD. These results suggest an interaction between the circadian system and redox metabolism in BD, in which a measure of daily rhythm disturbances was indicative of increased lipid peroxidation. There are several implications for these results that necessitate future studies. Longitudinal studies of the effects of therapies on circadian disturbance, while also measuring oxidative stress markers are necessary to further explain the relationship between these systems. An important next step is to determine the relationship between oxidative stress measures and objective measures of circadian rhythms, such as DLMO and actigraphy in BD as well as controls.

A recent study found that white matter integrity as measured by diffusor tensor imaging (DTI) was correlated with lipid peroxidation in individuals with BD (Versace et al., 2013). White matter integrity has been shown to be abnormal in BD (Emsell et al., 2013), and damage to lipids may be a contributing factor due to the high lipid content of myelin sheaths (Versace et al., 2013). As lipid peroxidation was associated with circadian

rhythm disturbance, our study provides a basis for future investigation of impact of circadian rhythm disturbance on white matter integrity in BD. Integrating neuroimaging, peripheral markers of oxidative stress and measurements of circadian rhythms may provide a better understanding of etiology and treatment targets of BD.

A limitation mentioned in Chapter 2 and 3, is that the BRIAN is a subjective measure of circadian rhythm disruption. It was developed to provide a clinically interpretable scale of circadian rhythm disturbance and was first validated in euthymic BD and healthy controls (Giglio et al., 2009). The factors measured by the BRIAN are taken as proxies of underlying biological rhythm disruptions in sleep-wake cycles, temperature, melatonin and cortisol (Grandin et al., 2006). However, an important follow-up is to determine the relationship of the BRIAN with gold standard objective measures of biological rhythm. Considering a self-report measure such as the BRIAN was strongly associated with both a subjective measure like QOL and a biological marker of oxidative stress in BD, it is highly likely that objective measures will corroborate our results.

Conclusions

The main objective of this thesis was to examine the impact that circadian rhythm disturbance has on BD. The results presented above provide evidence that self-reported circadian rhythm disruption is independently associated with QOL in BD patients, regardless of depression severity. This suggests that addressing circadian disturbances may improve QOL in these individuals. We also examined the relationship between the self-reported circadian disturbance and redox metabolism and found that disturbances was

48

indicative of increased lipid peroxidation in BD. Elucidating the links between the circadian system and oxidative stress may clarify how these two processes are disrupted in BD and investigation of the neural networks impacted is an important future direction. To conclude, the results presented provide evidence that circadian rhythms are disturbed in BD patients, and have a widespread impact on two separate aspects of BD: overall personal accounts of well-being and a biological marker of oxidative stress. These novel findings contribute to the mounting evidence indicating circadian rhythm disturbance as a core feature of BD, and an important target for treatment.

Additional References

American Psychiatric Association. (2000). Diagnostic and statistical manual of mental disorders (4th ed., text rev.). Arlington, VA: Author

Belmaker, R. H. (2004). Bipolar disorder. *The New England Journal of Medicine, 351*(5), 476–486.

Berk, M., Kapczinski, F., Andreazza, A. C., Dean, O. M., Giorlando, F., Maes, M., et al. (2011). Pathways underlying neuroprogression in bipolar disorder: Focus on inflammation, oxidative stress and neurotrophic factors. Neuroscience & Biobehavioral Reviews, 35(3), 804–817.

Cermakian, N., & Sassone-Corsi, P. (2002). Environmental stimulus perception and control of circadian clocks. *Current Opinion in Neurobiology, 12*(4), 359–365.

Ehlers, C. L., Frank, E., & Kupfer, D. J. (1988). Social zeitgebers and biological rhythms. A unified approach to understanding the etiology of depression. *Archives of General Psychiatry, 45*(10), 948–952.

Emsell, L., Langan, C., Van Hecke, W., Barker, G. J., Leemans, A., Sunaert, S., et al. (2013). White matter differences in euthymic bipolar I disorder: a combined magnetic resonance imaging and diffusion tensor imaging voxel-based study. *Bipolar Disorders, 15*(4), 365–376.

Endicott, J., Paulsson, B., Gustafsson, U., Schiöler, H., & Hassan, M. (2008). Quetiapine monotherapy in the treatment of depressive episodes of bipolar I and II disorder: Improvements in quality of life and quality of sleep. *Journal of Affective Disorders*, *111*(2-3), 306–319.

Frank, E., Kupfer, D. J., Thase, M. E., Mallinger, A. G., Swartz, H. A., Fagiolini, A. M., et al. (2005). Two-year outcomes for interpersonal and social rhythm therapy in individuals with bipolar I disorder. *Archives of General Psychiatry, 62*(9), 996–1004.

Frank, E., Soreca, I., Swartz, H. A., Fagiolini, A. M., Mallinger, A. G., Thase, M. E., et al. (2008). The role of interpersonal and social rhythm therapy in improving occupational functioning in patients with bipolar I disorder. *American Journal of Psychiatry, 165*(12), 1559–1565.

Frey, B. N., Andreazza, A. C., Houenou, J., Jamain, S., Goldstein, B. I., Frye, M. A., et al. (2013). Biomarkers in bipolar disorder: A positional paper from the International Society for Bipolar Disorders Biomarkers Task Force. *Australian & New Zealand Journal of Psychiatry, 47*(4), 321–332.

Giglio, L. M. F., da Silva Magalhães, P. V., Andreazza, A. C., Walz, J. C., Jakobson, L.,

Rucci, P., et al. (2009). Development and use of a biological rhythm interview. *Journal of Affective Disorders*, *118*(1-3), 161–165.

Giglio, L. M., Magalhães, P. V. S., Kapczinski, N. S., Walz, J. C., & Kapczinski, F. (2010). Functional impact of biological rhythm disturbance in bipolar disorder. *Journal of Psychiatric Research, 44*(4), 220–223.

Grandin, L. D., Alloy, L. B., & Abramson, L. Y. (2006). The social zeitgeber theory, circadian rhythms, and mood disorders: Review and evaluation. *Clinical Psychology Review*, *26*(6), 679–694.

Harvey, A. G., Schmidt, D. A., Scarnà, A., Semler, C. N., & Goodwin, G. M. (2005). Sleep-related functioning in euthymic patients with bipolar disorder, patients with insomnia, and subjects without sleep problems. *American Journal of Psychiatry, 162*(1), 50–57.

Hawton, K., Sutton, L., Haw, C., Sinclair, J., & Harriss, L. (2005). Suicide and attempted suicide in bipolar disorder: a systematic review of risk factors. *Journal of Clinical Psychiatry, 66*(6), 693–704.

Jackson, A., Cavanagh, J., & Scott, J. (2003). A systematic review of manic and depressive prodromes. *Journal of Affective Disorders, 74*(3), 209–217.

Kondratova, A. A., & Kondratov, R. V. (2012). The circadian clock and pathology of the ageing brain. *Nature Publishing Group, 13*(5), 325–335.

Kupfer, D. J. (2005). The increasing medical burden in bipolar disorder. *JAMA: The Journal of the American Medical Association, 293*(20), 2528–2530.

Merikangas, K. R., Akiskal, H. S., Angst, J., Greenberg, P. E., Hirschfeld, R. M. A., Petukhova, M., & Kessler, R. C. (2007). Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication. *Archives of general psychiatry, 64*(5), 543–552.

Miklowitz, D. J., Otto, M. W., Frank, E., Reilly-Harrington, N. A., Wisniewski, S. R., Kogan, J. N., et al. (2007). Psychosocial treatments for bipolar depression: a 1-year randomized trial from the Systematic Treatment Enhancement Program. *Archives of general psychiatry, 64*(4), 419–426.

Murray, C., & Lopez, A. D. (1997). Alternative projections of mortality and disability by cause 1990–2020: Global Burden of Disease Study. *The Lancet*.

Nordentoft, M., Mortensen, P. B., & Pedersen, C. B. (2011). Absolute risk of suicide after first hospital contact in mental disorder. *Archives of general psychiatry, 68*(10), 1058–1064.

Reppert, S. M., & Weaver, D. R. (2002). Coordination of circadian timing in mammals.

Nature, 418(6901), 935–941.

Shen, G. H. C., Alloy, L. B., Abramson, L. Y., & Sylvia, L. G. (2008). Social rhythm regularity and the onset of affective episodes in bipolar spectrum individuals. *Bipolar Disorders, 10*(4), 520–529.

Shi, L., Namjoshi, M. A., Zhang, F., Gandhi, G., Edgell, E. T., Tohen, M., et al. (2002). Olanzapine versus haloperidol in the treatment of acute mania: clinical outcomes, health-related quality of life and work status. *International Clinical Psychopharmacology*, *17*(5), 227.

St-Amand, J., Provencher, M. D., Bélanger, L., & Morin, C. M. (2013). Sleep disturbances in bipolar disorder during remission. *Journal of Affective Disorders, 146*(1), 112–119.

Steckert, A. V., Valvassori, S. S., Moretti, M., Dal-Pizzol, F., & Quevedo, J. (2010). Role of oxidative stress in the pathophysiology of bipolar disorder. *Neurochemical Research, 35*(9), 1295–1301.

Versace, A., Andreazza, A. C., Young, L. T., Fournier, J. C., Almeida, J. R. C., Stiffler, R. S., et al. (2013). Elevated serum measures of lipid peroxidation and abnormal prefrontal white matter in euthymic bipolar adults: toward peripheral biomarkers of bipolar disorder. *Molecular Psychiatry* (In press).

Weiner, M., Warren, L., & Fiedorowicz, J. G. (2011). Cardiovascular morbidity and mortality in bipolar disorder. *Annals of clinical psychiatry, 23*(1), 40–47.