BIOLOGICAL RHYTHMS DISRUPTIONS AND THE MENSTRUAL CYCLE

INVESTIGATING BIOLOGICAL RHYTHMS DISRUPTIONS ACROSS THE MENSTRUAL CYCLE IN WOMEN WITH COMORBID BIPOLAR DISORDER AND PREMENSTRUAL DYSPHORIC DISORDER

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TITLE: Investigating Biological Rhythms Disruptions Across the Menstrual Cycle in Women with Comorbid Bipolar Disorder and Premenstrual Dysphoric Disorder

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Lay Abstract

Sleep disruptions are common in women diagnosed with Bipolar Disorder and in those diagnosed with Premenstrual Dysphoric Disorder. Illness burden has been shown to be greater in women diagnosed with a comorbidity of the above disorders in terms of clinical variables such as number of comorbidities, episode relapse, rapid cycling and mixed mood states. This thesis aims to investigate whether women diagnosed with Bipolar and comorbid Premenstrual Dysphoric Disorder have greater biological rhythms disruptions than women diagnosed with either disorder. Biological rhythms will be evaluated at both the follicular and late-luteal stages. The overall goal of this work is to add to the currently scant literature on the clinical presentation of a Bipolar and Premenstrual Dysphoric Disorder comorbidity.

Abstract

Introduction: Sleep and biological rhythms have not been investigated in women with comorbid Bipolar and Premenstrual Dysphoric Disorder in the context of the menstrual cycle. We explored whether menstrual cycle phase causes increased disturbances in sleep, biological rhythms and mood symptoms. Additionally, we explored whether these women have worse illness outcome than women diagnosed with either Bipolar or Premenstrual Dysphoric Disorder, and healthy women.

Methods: In this post-hoc analysis, participants were split into four groups: those with a Bipolar and comorbid Premenstrual Dysphoric Disorder diagnosis (n = 17, BDPMDD), those with a Bipolar Disorder diagnosis (n = 16, BD), those with a Premenstrual Dysphoric Disorder diagnosis (n = 19, PMDD), and women with no history of psychiatric diagnosis (n = 25, HC). The primary outcome variable was biological rhythm disruption as measured by the Biological Rhythms Interview and Assessment in Neuropsychiatry (BRIAN). The secondary outcome variables were depressive symptoms (Montgomery-Asberg Depression Scale, MADRS; Hamilton Depression Rating Scale, HAMD), manic symptoms (Young Mania Rating Scale, YMRS), and sleep quality (Pittsburgh Sleep Quality Index, PSQI). All variables were collected at both mid-follicular and late-luteal stages of the menstrual cycle.

Results: The BDPMDD group did not have significantly higher disruptions in biological rhythms than the BD or PMDD groups at the luteal phase; however, there were significant disruptions and mood symptoms in comparison to the HC group, especially at the follicular stage, which point to markedly higher disruptions in these areas that seem to persist beyond the symptomatic luteal phase.

Conclusion and Future Directions: Women diagnosed with a BD and PMDD comorbidity experience a higher illness burden then women diagnosed with either BD or PMDD. A relatively small sample size, not excluding for participants who were taking medications that affect sleep and relying solely on subjective measures of biological rhythms may explain some of the null results. Future studies should employ objective measures of sleep such as actigraphy to complement subjective measures like the BRIAN, as well as recruit a larger sample of participants. More importantly, more studies surrounding this topic must be done in order to create a robust body of evidence that can be used to compare results across studies and identify specific biological rhythms domains that can be targets for treatment.

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List of Abbreviations

AAO	Age at onset
BD	Bipolar Disorder
BDNF	brain-derived neurotrophic factor
BMI	body mass index
BRIAN	Biological Rhythms Interview of Assessment in Neuropsychiatry
CBT	Cognitive behavioural therapy
CD	Cyclothymic Disorder
DRSP	Daily Record of Severity of Problems
DRSP	Daily Record of Severity of Symptoms
DSM	Diagnostics and Statistical Manual of Mental Disorders
ESR1	Estrogen receptor alpha
FSH	follicle-stimulating hormone
GnRH	gonadotropin-releasing hormone
HAMD	Hamilton Depression Rating Scale
HPA	hypothalamic-pituitary-adrenal
HPO	hypothalamic-pituitary-ovarian
IPSRT	interpersonal and social rhythm therapy
LH	luteinizing hormone
MADRS	Montgomery-Asberg Depression Rating Scale
MDD	Major Depressive Disorder
OC	oral contraceptive
PMDD	Premenstrual Dysphoric Disorder
PNAS	poor neonatal adaptation syndrome
PSQI	Pittsburgh Sleep Quality Index
SAS	Social Adjustment Scale
SCN	suprachiasmatic nucleus
STAI	State-Trait Anxiety Inventory
VLPO	ventrolateral preoptic nucleus
YMRS	Young Mania Rating Scale

Declaration of Academic Achievement

Dr. Benicio Frey and Dr. Luciano Minuzzi were responsible for creating the research question associated with the original study. Sabrina Syan was responsible for screening and recruiting participants, data collection, as well as all administerial duties related to the study.

I was responsible for creating the database that included all clinical and biological rhythms data. Dr. Benicio Frey and Dr. Luciano Minuzzi were involved with helping to develop the research question for this post-hoc analysis and with data interpretation. I was responsible for performing all the statistical analyses, which will be discussed in this thesis.

I express my sincere gratitude to everyone involved with this study as their collective work facilitated my ability to perform this analysis.

CHAPTER 1 – Bipolar Disorder

1.1 – Overview

One of the earliest documentations of Bipolar Disorder (BD) was in 1851 by French psychiatrist Jeane-Pierre Falret who coined the term "la folie circulaire", which translates to circular insanity, in his observations of individuals who had been experiencing bouts of mania and depression separated by symptom-free periods (Angst et al., 2000). To add to this spectrum of symptoms that defined the early conceptions of BD, Emil Kraepelin described the existence of "mixed states" in the late 19th century, which combined manic and depressive elements and were thought to be a more severe form of BD (Swann et al., 2013). Kraepelin then further developed these ideas to explore and unify a spectrum of symptoms that he collectively called "manic depressive insanity" (Mason et al., 2016). In the first edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM), published in 1952, these characteristics were combined under the term "manic depressive reactions" with a predominant focus on the cycling between manic and depressed episodes, while the mixed state was considered as a separate type of disease presentation; it was not until the third iteration of the DSM, published in 1980, that we saw a closer description of what we now consider as bipolar disorder, termed as such, with an emphasis on specific diagnostic criteria that we continue to use today (Mason et al., 2016).

1.2 – Diagnostic Criteria

Presently, the DSM-5 employs bipolar disorder as an umbrella term that encompasses several diagnostic criteria, which include: 1) BD Type I (with or without catatonia), 2) BD Type II (with or without catatonia), 3) Cyclothymic Disorder, 4) Substance/Medication-Induced Bipolar and Related Disorder, 5) Bipolar and Related Disorder due to another medical condition, 6) Other Specified Bipolar and Related Disorder, and finally 7) Unspecified Bipolar and Related

Disorder, along with several specifiers for Bipolar and Related Disorders (e.g. with rapid cycling, with melancholic cycling, with catatonia, with peripartum onset, with seasonal onset, with anxious distress, with mixed features, with atypical features, and with psychotic features) (Kaltenboeck et al., 2016).

1.2.1 – BD Type I and Type II

The diagnosis of BD Type I is confirmed when an individual has experienced a manic episode lasting 1 week (or any duration if it leads to hospitalization), which includes 1) a persistently elevated or irritable mood, and 2) increased goal-directed behavior; additionally, the presence of at least 3 out of 7 other symptoms (e.g. inflated self-esteem, decreased need for sleep, more talkative, racing thoughts, high distractibility, increase in goal-directed behavior or psychomotor agitation, and involvement in high risk situations) is required to confirm the diagnosis (American Psychiatric Association, 2013; Kaltenboeck et al., 2016). On the other hand, the diagnosis of BD Type II is confirmed when an individual has experienced at least 1 hypomanic and 1 depressive episode in their lifetime; a hypomanic episode is confirmed when an individual exhibits 3 out of the 7 above-mentioned symptoms, but the episode lasts for at least 4 days without a severe impairment in occupational or social functioning (American Psychiatric Association, 2013; Kaltenboeck et al., 2016).

1.2.2 – Cyclothymic Disorder

If an individual has experienced recurrent cycling between low-grade depressive and hypomanic symptoms for a period of at least 24 months, where these symptoms do not meet full criteria for hypomania or depression and where the individual does not experience an absence of mood disturbances for longer than 2 months at a time, they would be diagnosed with cyclothymic disorder (CD) (Van Meter et al., 2012). One of the challenges of diagnosing a

patient with CD is that its presentation can be similar to personality disorders, such as borderline personality disorder; therefore, clinicians usually look for a change in behavior that accompanies the mood disturbances in order to confirm the CD diagnosis (Kaltenboeck et al., 2016; Van Meter et al., 2012). Unfortunately, the research on CD is limited and several groups are pushing for increased attention on this diagnostic category considering that epidemiological studies have found its prevalence to be more than double that of BD type I (Van Meter et al., 2012).

1.2.3 – Other Categories

Finally, the "Other Specified Bipolar and Related Disorder" and "Unspecified Bipolar and Related Disorder" categories are similar in that, they account for individuals who experience bipolar symptoms but do not meet full criteria for the previous categories; the only difference is that, in the former, the clinician must outline why the individual did not meet full criteria for any of the other categories, whereas in the latter, this specification is not required (Kaltenboeck et al., 2016). These additions to the DSM-5 have been praised as a solution to the "bipolar disorder not otherwise specified" problem present in the DSM-IV as it acknowledges a wider subset of BD presentation, such as short-duration hypomanic episodes and short-duration cyclothymia, without lumping individuals into a vague category (American Psychiatric Association, 2013; Kaltenboeck et al., 2016).

1.3 – Prevalence and Impact

Presently, BD is estimated to be prevalent in 1-5% of the world's population, affecting men and women equally (Miller & Black, 2020). At the societal level, the cost of BD on the world economy is considerably large, with a majority of these costs being a result of the indirect financial consequences associated with this disorder due to factors such as loss of work productivity and insufficient treatment (Fagiolini et al., 2013). While exact data on the global

financial burden of BD is not available, it is of significance to point out available data from countries such as the United States and Australia, where BD annually costs these economies a substantial $US 151 billion and $AUS 1.59 billion, respectively (Fagiolini et al., 2013). Interestingly, BD patients who have been diagnosed with comorbidities use a significantly higher number of health resources, thereby adding to the economic cost of this disorder disproportionately more than patients who have been diagnosed with BD alone (Fagiolini et al., 2013).

At the individual level, the recurrent course of BD leaves patients with residual symptoms that contribute to psychosocial impairment, cognitive deficits, and a decreased quality of life (Post et al., 2018). BD also hinders occupational functioning for individuals who are employed, contributing to higher absenteeism and decreased productivity than individuals without the disorder; studies have also found that a significant number of people diagnosed with BD are either unemployed or underemployed, making them more likely to receive disability payments (McMorris et al., 2010; F. Post et al., 2018). Altogether, these findings reinforce the conception of BD as being one of the world's leading causes of disability and loss of work productivity (Alonso et al., 2011).

1.4 – Characteristics and Risk Factors

1.4.1 – Age at Onset and Clinical Implications

The mean age at onset (AAO) of BD type I is around 18 years of age, whereas the onset of BD type II typically occurs later, averaging at somewhere in the mid-20s; similarly, CD usually presents on the cusp of early adulthood, although patients who are diagnosed with CD are at a 15-50% higher risk of eventually developing BD type I or II (American Psychiatric Association, 2013). Interestingly, AAO has become a significant factor in BD research in the

attempt to understand how it contributes to disease presentation and whether similar AAOs reflect more homogenous subgroups of BD (Joslyn et al., 2016). Although there are varying reports of which specific clinical characteristics accompany an earlier AAO, a review of the literature by Joslyn et al. (2016) found that the most prevalent characteristics include psychiatric comorbidities, specifically anxiety disorders and substance use, as well as a higher severity of depression and risk of suicide. In a more thorough examination of the clinical characteristics that accompany early onset BD, Connor et al. (2017) compared a sample of young BD patients to age-matched depression patients and found that bipolar patients were more likely to engage in high risk and aggressive behaviours, to be involved in systems of care such as foster care and inpatient psychiatry, and to receive a significantly higher number of pharmacotherapies, all of which can contribute to poorer outcomes.

1.4.2 – Heritability and Age at Onset

Considering that BD has high heritability estimates, several studies now focus on specific clinical characteristics to identify whether these traits are precipitated by certain genetic variants; interestingly, AAO has been investigated as a possible marker of genetically homogenous BD subgroups. In one study that examined families having at least one individual with BD type I, it was found that the siblings of individuals with early onset BD were four times more likely to also experience an earlier onset of this disorder, as well as be at a higher risk of experiencing psychiatric disturbances, which included substance abuse and suicidality (Lin et al., 2006). To take things a step further and see what may actually contribute to an earlier AAO in BD, Post et al. (2016) found that BD patients with parents and grandparents who have experienced psychiatric difficulties are at a higher risk of earlier AAO of BD. Of course, this can be due to an increased exposure to psychosocial stressors that is common for children with parents who

experience psychiatric difficulties, as well as the epigenetic changes that occur due to these experiences (Post et al., 2016). Overall, AAO can be used as a variable that may elucidate emerging disease pathology and identify risk factors that can be taken into account to curtail disease prognosis, specifically for high-risk youth. Given that recent research has established that changes in neural structures and the ensuing functional deficits succeed the onset of BD, common clinical characteristics can be targets of emerging treatment plans in the effort to lessen the burden of illness for these individuals (Duffy et al., 2019).

1.4.3 – Exposures as Risk Factors

Several studies have investigated whether specific exposures in early life can possibly confer a greater risk to developing BD. For example, prenatal exposures such as maternal influenza infection, smoking, and significant stressors like exposure to war significantly increased the risk of BD development in offspring (Marangoni et al., 2018). Additionally, exposure to drugs of abuse, such as cannabis, opioids, cocaine and sedatives, increased risk of BD anywhere from two to five times (Marangoni et al., 2018). Finally, exposure to significant stressors in early life, such as physical or sexual abuse, or loss of a parent, confer a greater risk of developing BD (Marangoni et al., 2018). However, given that exposure to stressors can increase the risk of developing many mood disorders, these risk factors may not individual to BD alone (Marangoni et al., 2018).

1.5 – Treatments

1.5.1 – Overview

Treatments for BD vary but most are pharmacological in nature; the overall goal of treatment is twofold: to establish mood stability and to maintain these euthymic states by reducing subthreshold symptoms and improving functioning (Geddes & Miklowitz, 2013).

Considering that BD is typically a cyclical disorder, defined by irregular fluctuations between hypomania/mania and depression, there lies a challenge in the pharmacological treatment of individuals as the same treatments that focus on alleviating mania can cause depression, and vice versa.

1.5.2 – Pharmacological Treatment

Lithium continues to be the most reliable pharmacological treatment for BD, having the ability to decrease episode relapse while also reducing risk of suicidality by more than 50%; unfortunately, it does have its limitations, as evidenced by its many potential side effects and its low therapeutic index (Geddes & Miklowitz, 2013). When it comes to treating mania, antipsychotic drugs such as olanzapine and risperidone have been found to be more efficacious than anticonvulsants in the short-term treatment of this mood state; however, they are usually switched out for lithium for long-term pharmacological treatment (Geddes & Miklowitz, 2013). In terms of bipolar depression, it presents a different and more extensive set of challenges than unipolar depression, where uncertainty about the efficacy of possible medications has made it difficult to decide on a gold-standard treatment. Nevertheless, several meta-analyses have identified certain types of antipsychotics (e.g. olanzapine and quetiapine), anti-convulsants (lamotrigine), and anti-depressants as being adequately effective for the treatment of bipolar depression (Harrison et al., 2016). Given the limitations of monotherapies for bipolar depression, combination therapies have been investigated, especially for the added benefit of combining pharmacotherapies that possess different and beneficial mechanisms of action; for example, Geddes at al. (2016) investigated the administration of both quetiapine and lamotrigine in BD treatment and found that patients who received the combination had better outcomes than those who received either pharmacotherapy alone.

Aside from managing symptoms related to mood episodes, BD treatment involves maintenance therapy in the effort to decrease episode recurrence and consequently improve patient outcomes. However, choosing pharmacotherapies for long-term BD treatment can be just as indiscernible as in the short-term considering the multitude of options, each of which has its strengths and limitations (Thase, 2008).

1.5.3 – Adjunctive Treatments

In addition to pharmacotherapies, other forms of adjunctive treatments have been investigated in the context of maintenance therapy. Miklowitz et al. (2007) found that intensive psychotherapy, in the form of either cognitive behavioral therapy, interpersonal and social rhythm therapy, or family-focused therapy, yielded shorter time to recovery from a depressive episode and higher rates of recovery overall, when compared to brief psychotherapy. Alternatively, psychoeducation has been shown to decrease episode relapse and improve medication adherence, the latter of which poses as a significant challenge in the long-term treatment of BD (Bond & Anderson, 2015). Currently, there continues to be a push for more options of adjunctive treatments that can supplement pharmacotherapies and provide patients with a more well-rounded therapeutic plan in the effort to improve their outcomes.

1.6 – Gender-specific Characteristics and Implications for Treatment

1.6.1 – Overview

BD seems to present itself differently in males and females given the gender-specific characteristics that have been observed in the study of this disorder. Consequently, these differences add a layer of complexity to the treatment and management decisions that must be made, especially in the pursuit of offering options to patients that are tailored to their individual needs.

1.6.2 – Gender-specific characteristics

To start, Bipolar I disorder has been reported to be equally prevalent amongst males and females, whereas Bipolar II disorder is more likely to affect females (Dodd et al., 2005; Parial, 2015). More specific characteristics have been identified, such as Bipolar I disorder with predominantly manic episodes presenting more often in males, whereas Bipolar II disorder with predominantly depressive episodes presenting more often in females (Dodd et al., 2005). In a systematic review investigating the rapid cycling course of BD, Tondo et al. (1998) observed that 72% of cases occurred in females, with the female gender being a risk factor for developing this illness course. These results were replicated in a more recent study by Altshuler et al. (2010), who found that the increased rates of rapid cycling as well as the greater proportion of anxiety comorbidities that were exhibited by female participants contributed to them spending significantly more time in depressive states as compared to male participants. Females diagnosed with BD have also been found to experience mood episodes with mixed features more often than bipolar males do, as shown in a study involving over 3,000 adult bipolar participants (Tondo et al., 2018). Therefore, bipolar females can experience more severe mood instabilities and a higher number of mood shifts.

Overall, bipolar women have also been observed to experience a higher number of medical and psychiatric comorbidities, which are thought to significantly hinder their recovery from manic episodes; common psychiatric comorbidities include anxiety, eating disorders and borderline personality disorder, while common medical comorbidities include obesity, thyroid disease and migraines (Arnold, 2003; McElroy, 2004; Parial, 2015). On the other hand, male bipolar patients are more likely to develop a substance abuse comorbidity than are their female counterparts (Parial, 2015).

1.6.3 – Treatment Considerations for Female Bipolar Patients

Treatment choices for female BD patients must be made with the above observations in mind. Currently, the use of anti-depressants in BD treatment is highly contended but many clinicians still opt for their use, which can disproportionately affect females given that they are more likely to experience a depressive bipolar diathesis than bipolar males; therefore, this puts female patients at a higher risk of developing a more severe illness course considering the known side effects associated with the administration of anti-depressants. Antidepressant medications have been observed to increase chances of rapid cycling and females are more likely to experience antidepressant-induced mania; as such, there has been a call to decrease the use of anti-depressant medications and increase the use of mood stabilizers in the treatment of female BD patients since they are more prone to developing the rapid cycling illness course (Burt & Rasgon, 2004; Leibenluft, 1997; Tondo & Baldessarini, 1998). Although a historically reliable treatment for BD, the use of lithium in cases of rapid cycling and mixed states has also been discouraged due to its inadequate effect on the former and a lack of evidence for its efficacy in treating the latter; however, in regards to mixed states, recent reports are pushing for lithium use to be reconsidered given its high efficacy as a mood stabilizer (Dodd et al., 2005; Sani & Fiorillo, 2019).

Aside from the gender-specific characteristics exhibited by BD patients, there also exist gender-specific side effects to some BD medications that clinicians must take into account, specifically in the treatment of female patients. For example, valproate has been found to cause menstrual abnormalities and hyperandrogenism in bipolar females as compared to those taking lithium; interestingly, valproate has also been implicated in the occurrence of menstrual disturbances, hyperandrogenism, and polycystic ovaries in women being treated for epilepsy,

especially in those who had the drug administered before the age of 20 (Isojarvi et al., 1993; McIntyre et al., 2003).

Should women with BD become pregnant, their pharmacological treatment must also be closely monitored during the perinatal period as some medications can confer teratogenic risks and neonatal complications; considering that bipolar women are at an increased risk of experiencing postpartum psychosis, the risks and benefits of treatment must be weighed so that the safety of both mother and developing fetus is maintained (Jones & Jones, 2017). Firstly, antipsychotics have been found to increase the chance of gestational diabetes, impact the metabolism of expectant mothers, as well as affect the fertility of women who wish to become pregnant; antipsychotics, especially first generation ones, can also impact fetal outcomes by increasing the chance of cardiac malformations, premature delivery, low birth weight and the incidence of poor neonatal adaptation syndrome (PNAS; Jones & Jones, 2017). Lithium has also been implicated in increasing risk of cardiac malformations and PNAS; in fact, lithium administration is typically paused prior to delivery to decrease the fetus' exposure to its increased toxicity around that time (Jones & Jones, 2017). Finally, mood stabilizers are considered as a third-line of treatment that is used only if antipsychotics are not efficacious in preventing episode relapse, due to their strong association with teratogenic risks and neurodevelopmental delay; this can complicate BD treatment considering that mood stabilizers are routinely used in maintenance therapy, which is credited with decreasing episode relapse and significantly improving patient outcomes (Jones & Jones, 2017).

1.7 – Female Reproductive Life Event and Mood Worsening

Mood exacerbations that occur in parallel with female reproductive life events have become of interest in the research surrounding BD considering that they elucidate an important

target for further research and potential new treatments, namely the hormonal fluctuations that occur during these periods. In a study by Perich et al. (2017), it was found that bipolar women who experienced mood worsening around reproductive life events, such as the premenstrual, postnatal, and perimenopausal periods, were more likely to experience a severe illness course characterized by a higher number of comorbidities, increased incidence of rapid cycling and mixed mood episodes, and an earlier onset of the disorder. This evidence supports the notion of a sensitivity to hormonal fluctuations that can lead to increased mood disruptions, particularly in the BD population, considering that women diagnosed with BD have been found to be more likely to experience mood instability around the premenstrual period (Perich et al., 2017). Moreover, risk of relapse was found to be significantly higher during the premenstrual and postpartum periods, whereas the perimenopausal period is associated with an increased risk of depressive episode development (Frey & Dias, 2014).

Given the burgeoning evidence linking hormonal fluctuations and mood instability in this population, the influence of female reproductive hormones (primarily estrogen and progesterone) on cellular processes that could lead to eventual mood disturbances continues to be investigated. Increased oxidative stress and inflammatory biomarkers, which are hallmarks of BD presentation, were found to be attenuated by estrogen and progesterone; additionally, estrogen was found to upregulate the expression of brain-derived neurotrophic factor (BDNF), which is a molecule involved in enhancing synaptic signalling (Frey & Dias, 2014). Estrogen has been linked to a number of neurotransmitter systems, such as dopamine, serotonin and norepinephrine, and brain structures involved in mood regulation, culminating in a widespread influence on cognition and affect (Amin et al., 2005; Frey & Dias, 2014). These findings provide a molecular basis that can be further investigated to understand how hormonal fluctuations during

reproductive life events lead to an increased occurrence of mood instability in some bipolar women.

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Chapter 2 – Premenstrual Dysphoric Disorder

2.1 – Overview

For some women, the fluctuating pattern of hormones during the menstrual cycle contributes to considerable mood and behavioral changes, specifically prior to the onset of menstruation, amounting to a significant disruption to their functioning and quality of life. Documentations of what we now identify as premenstrual dysphoric disorder (PMDD) have gone as far back into history as the time of the Ancient Greeks, yet this disorder was not officially recognized until its inclusion in the revised version of the DSM-III in 1987, originally identified as "late luteal phase dysphoric disorder" (Endicott, 2000). The inclusion of PMDD as a diagnostic category in the DSM-5 has been highly criticized by some; however, one cannot deny the added benefits of legitimizing this diagnostic label, especially that it catapults necessary research to be done to improve the well-being of this proportion of women (Browne, 2015; Hartlage et al., 2014).

2.2 – The Menstrual Cycle

The menstrual cycle is governed by the cyclical fluctuation of hormones, mainly estrogen and progesterone, whose release is driven by the overarching influence of the hypothalamic-pituitary-ovarian (HPO) axis; estrogen and progesterone signal back to the hypothalamus and anterior pituitary in positive or negative feedback loops, depending on the phase of the menstrual cycle, to regulate the levels of circulating hormones (Arrais & Dib, 2006).

Menarche typically occurs between the ages of 12 – 15 years and menstrual cycles persist up until menopause, which usually occurs between the ages of 45 – 55 years (Schuiling & Likis, 2013). Menstrual cycle length can vary between 21 – 35 days and menstrual flow lasts between 6 – 8 days, although lengths as little as 2 days or as long as 8 days are considered within the

normal range (Schuiling & Likis, 2013). The onset of menses signals the beginning of a menstrual cycle, where the endometrium begins to shed; the follicular stage of the menstrual cycle includes menstruation and lasts until ovulation, which typically occurs around day 14 of the cycle (Farage et al., 2009). After ovulation, the luteal phase begins and lasts about 14 days as well. After menstruation ends, which is sometime during the first week of the follicular stage, the endometrium begins thickening again and continues to do so up until the start of the next menstrual cycle. Due to the fluctuation of hormones during the luteal phase, specifically in the week prior to menstruation, this period is of primary interest in the investigation of menstrual cycle-mediated mood disturbances.

Levels of estrogen and progesterone are at their lowest during the first week of the menstrual cycle. GnRH is the primary hormone that drives the regulatory mechanisms required for eventual production and secretion of estrogen and progesterone, and is produced by the hypothalamus (Arrais & Dib, 2006). Once secreted by the hypothalamus, GnRH reaches the anterior pituitary to signal luteinizing hormone (LH) and follicle-stimulating hormone (FSH) release, both of which contribute to the development of several primary follicles in the ovaries; these follicles and the endometrium release estrogen into the bloodstream until estrogen reaches its first peak during the menstrual cycle right before ovulation, then sharply declines (Arrais & Dib, 2006; Farage et al., 2009). At ovulation, LH and FSH levels peak and an egg is released from one of the maturing follicles; the mass of cells that remains after the egg is released forms the corpus luteum, which begins to produce progesterone (Farage et al., 2009). Levels of estrogen and progesterone steadily increase until they peak then decline approximately 5 – 7 days before the next menstrual cycle; endometrial breakdown and the initiation of the next cycle begin once levels of the two hormones reach their lowest (Farage et al., 2009).

Estrogen and progesterone can positively or negatively feed back to the anterior pituitary gland in order to control LH and FSH secretion; the type of feedback is determined by how long the pituitary is exposed to these hormones or how concentrated their levels are in the bloodstream (Arrais & Dib, 2006). Oral contraceptives (OCs) maintain consistent levels of both estrogen and progesterone using synthetic hormones and prevent the peak in estrogen that is typically the signal for ovulation to occur (Farage et al., 2009).

2.3 – Diagnostic Criteria

The DSM-5 outlines a list of symptoms that usually accompany PMDD patients, of which at least five must be met to confirm the diagnosis; these symptoms peak in severity in the week prior to menstruation, dissipate sometime after the start of menstruation, then disappear or become minimal in the week that follows, and must occur for most menstrual cycles in the past year (American Psychiatric Association, 2013). These symptoms are mostly affective in nature, where women may experience mood swings, irritability, anxiety or depression, which can be accompanied by shifts in their behavior, as evidenced by a decreased interest in activities, difficulty concentrating, lack of energy, appetite changes, sleep pattern changes, feeling overwhelmed, and variable physical symptoms (American Psychiatric Association, 2013). To confirm a PMDD diagnosis, prospective daily ratings of affective and somatic symptoms must be done for a minimal period of 2 months, through the use of self-report assessments such as the Daily Record of Severity of Problems (DRSP); tools like the DRSP also confirm the timing of symptoms throughout the cycle to eliminate for those that may be a result of other medical conditions (Biggs & Demuth, 2011).

2.4 – Prevalence and Impact

Approximately 3 – 8% of women meet the diagnostic criteria for PMDD, which is a rate that has been found to be consistent across many countries and cultures (Appleton, 2018). Although symptoms only occur during the latter half of the menstrual cycle, they can still cause significant disruptions to patients' lives that reflect in their personal, home and work lives. Yonkers et al. (1997) utilized the Social Adjustment Scale (SAS) to quantify functional impairment in domains related to interpersonal relationships and role function in a group of women diagnosed with PMDD in their investigation of using sertraline for symptomatic treatment of this patient population. It was found that baseline functional impairment during the late-luteal phase was comparable to that of a population with acute Major Depressive Disorder (MDD) in domains such as social and leisure activities, marital relationships, extended family relationships, and parental activities (Yonkers, 1997). Overall, women with moderate-to-severe premenstrual symptoms have also been found to experience decreased work productivity and increased absenteeism, as well as a decreased quality of life, prior to menses (Heinemann et al., 2010; T. B. Pearlstein et al., 2000). Despite the plethora of evidence that supports the notion of PMDD causing disability and impaired health, there have yet to be any studies investigating the exact economic burden that this disorder has on society as a whole; these metrics are necessary as they can further legitimize and actualize the impact of this disorder on individual and society (Rapkin & Winer, 2009).

2.5 – Risk Factors and Comorbidities

Several studies have identified similar risk factors to developing PMDD, which include older age, exposure to traumatic events (especially physical threats, sexual abuse, and severe accidents), pregnancy, baseline anxiety disorders, previous history of depression, and a family

history of psychiatric disorder (de Carvalho et al., 2018; Perkonigg et al., 2004; Skrzypulec-Plinta et al., 2010; Wittchen et al., 2002). Additionally, certain lifestyle factors, such as nicotine dependence, lack of exercise, and abuse of alcohol and illicit drugs, have been found to confer a greater risk for developing this disorder (de Carvalho et al., 2018; Perkonigg et al., 2004). Interestingly, studies investigating the heritability of premenstrual symptoms found that daughters of women who have reported experiencing severe PMS were more likely to experience those symptoms themselves, as compared to daughters of women who have not reported experiencing PMS (Miller et al., 2010). In line with these findings, other studies have found that a family history of either PMDD or MDD increases the likelihood of developing this disorder (Freeman & Sondheimer, 2003). Heritability estimates for severe premenstrual symptoms were calculated to be as high as 43%, which further supports the genetic links associated with premenstrual exacerbation of mood and somatic symptoms, and accordingly, PMDD (Miller et al., 2010).

Women diagnosed with PMDD are more likely to have at least one psychiatric comorbidity as opposed to women without PMDD; some of these comorbidities include major depressive disorder, anxiety disorders (especially specific phobia, social anxiety and PTSD), substance abuse, and somatoform disorder (Cohen et al., 2002; Hong et al., 2012). The prevalence of insomnia is also markedly high in this patient population, as well as the risk for suicidal ideation, plans and attempts (Hong et al., 2012)

2.6 – Etiology

Similar to other psychiatric disorders, the pathophysiology of PMDD is multifactorial and multiple avenues are currently being investigated on the biological, neurochemical and psychosocial fronts in order to elucidate the pathogenesis of this disorder. Given the window of

symptom onset and offset in women with PMDD, hormonal fluctuations have repeatedly been implicated in the etiology of this disorder. Interestingly, women with PMDD do not show significantly different sex hormone profiles than asymptomatic women, but rather, an increased sensitivity to the fluctuation of these hormones (Hantsoo & Epperson, 2015; Schmidt & Rubinow, 1998).

2.6.1 – Progesterone and Allopregnanolone

Progesterone and its metabolite allopregnanolone, which is a neuroactive steroid, have been implicated in the pathogenesis of PMDD because of the temporal relationship between levels of progesterone and mood symptoms that arise during the late luteal phase (Hantsoo & Epperson, 2015). Allopregnanolone also modifies $GABA_A$ receptor activity and typically induces anxiolytic effects through its activity on this receptor, similar to the activity induced by the action of benzodiazepines and barbiturates; however, in PMDD, the expression of $GABA_A$-R subunits may be altered, thereby affecting the sensitivity of this receptor to modulation by neurosteroids such as allopregnanolone (Sundström Poromaa et al., 2003). Additionally, the chronic surge of progesterone in the premenstruum followed by its plummet after menses has also been implicated in the alteration of $GABA_A$-R activity, which has been found to increase anxiety-like behavior, social withdrawal, and anhedonia in animal models of PMDD (Hantsoo & Epperson, 2015). Collectively, these patterns align with the view that women with PMDD have an increased sensitivity to hormone fluctuations, which can precipitate affective symptoms that are typical of this disorder.

2.6.2 – Estrogen

Another hormone that has been implicated in the etiology of PMDD is estrogen, which follows a course that is opposite to that of progesterone; estrogen typically decreases during the

premenstrual period and reaches a minimum prior to menstruation, then begins to rise again a few days later (Payne, 2003). Estrogen has been cited as promoting serotonergic function, similar to the action of antidepressants, as well as having an effect on other neurotransmitter systems that are involved in regulating mood, sleep, and executive functions, which are typically disrupted during the premenstruum in women diagnosed with PMDD (Hantsoo & Epperson, 2015; Payne, 2003). Specific genetic variants of estrogen receptor alpha (ESR1) were found to occur significantly more in PMDD patients as compared to control subjects; ESR1 is involved in the same neurotransmitter systems that have been investigated in PMDD pathogenesis, therefore, this finding might elucidate a link between PMDD patients' differential reaction to hormonal fluctuations and the underlying physiology that contributes to this trait (Huo et al., 2007).

2.6.3 – Stress and Trauma Exposure

Excessive exposure to stress has also been investigated in the context of PMDD etiology; as previously mentioned, a significant portion of women who had a history of trauma also had a PMDD diagnosis, while women with a history of exposure to physical and emotional abuse were more likely to experience moderate to severe PMS (Hantsoo & Epperson, 2015). PMDD patients have also been found to have a blunted stress response, which has been cited as a result of the decreased influence of allopregnanolone on the GABAergic system in these women, which can affect downstream mechanisms associated with allopregnanolone such as the activation of the hypothalamic-pituitary-adrenal (HPA) axis in the maintenance of stress responses (Lanza di Scalea & Pearlstein, 2017). Additionally, PMDD women were found to exhibit a heightened acoustic startle response during the luteal phase of their menstrual cycles when compared to their follicular phase; this is a reflex that has been conserved across many species and is modulated by some of the same neuroendocrine systems that have been investigated in PMDD (Epperson et al.,

2007). These findings actualize the link that has been postulated between neuroendocrine systems and emergent PMDD symptoms, especially that these women exhibit differential responses to neuroactive hormone fluctuations relative to controls (Epperson et al., 2007).

2.6.4 – Sleep and Circadian Rhythms

Finally, sleep disruptions and circadian rhythms constitute another avenue that is being explored in trying to understand PMDD pathophysiology. Women with PMDD have been observed to experience more stage 2 and less REM sleep during the luteal phase compared to healthy women, amounting to an overall lower quality of sleep (Parry, 2001). Other studies have found these differences to be consistent across the menstrual cycle as opposed to being isolated to the luteal phase; therefore, there still are inconsistencies in the sleep traits and patterns that are observed in the PMDD population (Shechter & Boivin, 2010). Moreover, PMDD patients were found to exhibit delayed responses to morning bright light, which acts as an environmental cue employed by circadian clock mechanisms to synchronize internal clocks with the environment; a delayed response by this population indicates impairment in internal timing functions, underscoring the circadian rhythm disturbance trait in the PMDD population (Parry, 2001). Overall, the interplay between the menstrual cycle, hormonal fluctuations and circadian rhythms is evident considering that sleep disturbances are a hallmark symptom of PMDD, which emphasizes the need for further research to be done in this field. These interactions will be explored in further detail in Chapter 3.

2.7 – Treatment

2.7.1 – Lifestyle Modifications

Lifestyle modifications that include dietary changes and exercise have been suggested in the treatment of PMDD; however, given the severity of the illness, studies have emphasized that

these be used in conjunction with other interventions to ensure better patient outcomes and a more well-rounded approach to tackling the disorder (Steiner et al., 2006). To begin, PMDD patients are encouraged to decrease their consumption of salt, refined sugar, caffeine and alcohol; consumption of the latter two can increase experiences of irritability and tension, which are already heightened in the premenstruum (Freeman & Sondheimer, 2003; Pearlstein & Steiner, 2008).

On the other hand, increasing the intake of complex carbohydrates has been encouraged since it has the potential to decrease food cravings as well as increase the availability of tryptophan in the body; tryptophan is an amino acid that is essential for serotonin production and given that PMDD women were found to experience a deficiency in whole blood tryptophan and serotonin levels, dietary supplementation of this amino acid may incur an added benefit (Hantsoo & Epperson, 2015; Pearlstein & Steiner, 2008). Calcium supplementation has also been cited as beneficial for the alleviation of emotional and somatic symptoms associated with the premenstrual period in PMDD, except for fatigue and insomnia (T. Pearlstein & Steiner, 2008). Women suffering from PMDD have also been encouraged to engage in physical exercise, whether aerobic or nonaerobic, as it can decrease fluid retention during the premenstrual period and also improve some mood symptoms (T. Pearlstein & Steiner, 2008)

2.7.2 – Pharmacologic Interventions

The American College of Obstetrics and Gynecology cites selective serotonin reuptake inhibitors (SSRIs) as the gold standard treatment for PMDD given their rapid therapeutic action, contrary to their slow therapeutic effect in other mood disorders (Hantsoo & Epperson, 2015). These medications can alleviate both mood and somatic symptoms associated with PMDD, and their rapid efficacy has been postulated to be due to their ability to quickly promote the

production of allopregnanolone and the action of $GABA_A$-R in the nervous system, both of which have been implicated in the etiology of PMDD (Hantsoo & Epperson, 2015; Pearlstein & Steiner, 2008).

One of these SSRIs is fluoxetine, which has shown good efficacy in alleviating a broad range of PMDD symptoms, as well as improving functioning during the luteal phase of the menstrual cycle (Freeman & Sondheimer, 2003). Typically, SSRI dosage for the treatment of PMDD is lower than dosages for the treatment of other mood disorders, such as MDD (Freeman & Sondheimer, 2003). The dosing pattern of serotonergic pharmacotherapy can take shape in one of four forms: 1) continuous, 2) intermittent, 3) semi-intermittent, and 4) symptom-onset dosing (Appleton, 2018). Continuous pharmacotherapy involves an individual taking their medication every day, and is usually best suited for those who have a comorbid mood disorder that can be addressed with the same pharmacotherapy prescribed for PMDD; semi-intermittent dosing is similar to continuous, in that, the medication is taken daily but dosing is increased in the last two weeks of the menstrual cycle to account for the occurrence of PMDD symptoms during that period (Appleton, 2018). On the other hand, intermittent dosing (also termed as luteal phase dosing) involves taking the pharmacotherapy during the last two weeks of the menstrual cycle, whereas symptom-onset dosing initiates pharmacotherapy when symptoms arise for the individual and terminates at the start of menstruation (Appleton, 2018).

Although beneficial for PMDD patients, SSRIs can cause certain side effects such as nausea, insomnia, headaches, and sexual dysfunction; therefore, specific dosing patterns are usually chosen to limit these side effects while optimizing patient outcomes (Hantsoo & Epperson, 2015). Moreover, approximately 40% of PMDD patients have been found to not respond to SSRI administration in a review that assessed treatment vs. placebo responders of

serotonergic treatments (Halbreich, 2008). Additionally, long term compliance for use of these medications has been shown to be relatively low, at a rate of about 50% (Wyatt et al., 2004). Therefore, more research is required to broaden our understanding of SSRI efficacy in treating women with PMDD and to investigate whether combinations of treatment modalities could be superior to this "gold standard".

2.7.3 – Hormonal Interventions

The goal of hormonal interventions is to override the effect of hormonal fluctuations, specifically at the onset of ovulation, that has been postulated to be a driving force of PMDD symptomatology. One option is the use of OCs in a continuous pattern on a 24/4 regimen (where the individual takes active pills for 24 days followed by inactive pills for 4 days); this extended form of hormonal dosing has shown better results in mediating PMDD symptoms than the typical 21/7 regimen of OC administration as it is postulated to contribute to a more stable hormonal environment that is lacking in PMDD women (T. Pearlstein & Steiner, 2008; Yonkers et al., 2005). However, investigations of the efficacy of OCs in PMDD treatment have found a large placebo response given that rates of response to placebo were close to rates of response to treatments, which puts into question the actual benefits of these treatments in mediating premenstrual symptoms (Eisenlohr-Moul et al., 2017; Halbreich, 2008). Interestingly, continuous OC administration was found to be efficacious as an adjunctive treatment for depressed women who were experiencing premenstrual exacerbation of their symptoms despite their use of antidepressants (Reid & Soares, 2018).

Ovulation suppression is another target of hormonal treatment for PMDD that involves medications such as gonadotropin-releasing hormone (GnRH) agonists and danazol. To start, GnRH agonists bind to GnRH receptors in the hypothalamus and prevent the action of this

hormone, thereby suppressing the downstream release of estrogen and progesterone in the ovaries and preventing their oscillatory behaviour close to menses (Pearlstein & Steiner, 2008). While the administration of GnRH agonists has benefited many women with PMDD by alleviating some of the physical and emotional symptoms they experience in the premenstruum, it is important to point out that women who experienced severe premenstrual depression did not experience an alleviation of these emotional symptoms (Appleton, 2018). Moreover, GnRH agonist therapy promotes a hypoestrogenic state, similar to that during menopause, which can severely impact bone and cardiac health if exposure is prolonged (Rapkin & Lewis, 2013). Add-back therapy has been proposed as a solution to the undesirable side effects associated with the hypoestrogenic state, where low levels of estrogen and/or progesterone are readministered to the patient to offset the effect of anovulation. While add-back therapy has been shown to not alter the efficacy of GnRH agonists in the mediation of PMDD symptoms, there is a risk for some women to experience a re-emergence of mood and somatic symptoms (Rapkin & Lewis, 2013; Wyatt et al., 2004). On the other hand, danazol is a synthetic androgen used for the same purpose as GnRH agonists and produces similar downstream effects; therefore, it possesses the same side effects associated with GnRH agonists by creating a hypoestrogenic state, but can additionally cause acne, hirsutism, weight gain, and teratogenicity (Appleton, 2018). As such, ovulation suppression is considered as a third-line therapy for PMDD due to its many side effects and the availability of medications like SSRIs and OCs which confer less harmful effects.

2.7.4 – Psychotherapy

Cognitive behavioural therapy (CBT) is a form of psychotherapy where negative thoughts are identified and mediated in the effort to improve coping skills. In a randomized control trial (RCT) of an 8-week internet-based CBT program for women with PMDD, Weise et

al. (2019) found that the program effectively reduced functional impairment and the effect of premenstrual symptoms, while also improving participants' coping mechanisms and stress management. CBT has also been cited as an effective adjunctive treatment to SSRIs that promotes long-term improvement of PMDD symptoms; however, there remains a debate as to the added benefit of CBT to SSRI therapy as other accounts refute the added efficacy of this combination (Rapkin & Lewis, 2013; Reid & Soares, 2018). Nevertheless, CBT has shown promise in the long-term maintenance and mediation of PMDD symptoms, possibly due to the shift it causes towards forming biopsychosocial attributions in order to promote better coping mechanisms (Hunter et al., 2002).

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3 – Biological Rhythms

3.1 – Overview

Biological rhythms are comprised of any bodily process or function that follows a regular cycle. Those entrained to a 24-hour period are termed circadian rhythms, which exert their control on both biological and behavioural processes such as sleep-wake cycles, hormone secretion, body temperature, motor activity and cognition (Lanfumey et al., 2013). For a biological rhythm to be considered circadian, it must meet the following three criteria: 1) they must have a period of 24 hours, 2) they can be entrained by external cues, and 3) their period length persists across a wide range of physiological temperature (Eban-Rothschild & Bloch, 2012). Biological rhythms also include eating, social and activity patterns, which contribute to the entrainment of the body's internal clock (Mondin et al., 2017). Disruptions in biological rhythms have been implicated in the etiology of several mood disorders, such as depression, seasonal affective disorder and BD (Lanfumey et al., 2013).

3.2 – The Molecular Basis of Circadian Rhythms

The path to understanding circadian rhythmicity in humans begins with the suprachiasmatic nucleus (SCN), which consists of paired nuclei situated atop the optic chiasm that collectively function as the master circadian clock in the body (Reppert & Weaver, 2001). Each nucleus of the SCN is made up of 10,000 neurons that work in synchrony to decode photic (from the retina) and non-photic (from other parts of the brain) inputs to consequently produce outputs that will entrain the clocks of cells throughout the body (Grandin et al., 2006; Welsh et al., 2010). The SCN does not produce a singular output, but rather, different oscillations of rhythms depending on the target tissue (Welsh et al., 2010). As we delve further into our

understanding of circadian rhythmicity, the pervasive influence of these processes becomes clearer and clearer.

An interplay between positive and negative feedback loops of transcribed genes and their respective proteins drive the rhythmic functions of the circadian pacemaker cells. Heterodimers composed of CLOCK and BMAL1 function as transcription factors that promote the transcription of *Period* and *Cryptochrome* genes; this produces PER and CRY proteins that form multimeric complexes, which are then translocated to the nucleus of the cell (Reppert & Weaver, 2001; Welsh et al., 2010). On one hand, CRY proteins negatively regulate CLOCK:BMAL1 heterodimers in the nucleus, and on the other hand, specific PER proteins promote *Bmal1* gene transcription; as *Bmal1* genes are transcribed to form BMAL1 proteins, and the levels of this protein rise, it begins to promote CLOCK and BMAL1 dimerization, which begins the positive feedback arm of this process again (Reppert & Weaver, 2001).

At the start of the circadian day (hour 0), *Period* and *Cryptochrome* RNA levels begin to rise, mainly driven by CLOCK and BMAL1 heterodimers; different *Period* RNA species peak at different times, ranging from hour 4 to hour 10 of the circadian day (Reppert & Weaver, 2001). By hour 12, PER and CRY proteins peak and simultaneously inhibit transcription of CLOCK and BMAL1; however, one of the PER protein types translocates into the nucleus to activate *Bmal1* gene transcription, which eventually leads BMAL1 protein levels to peak between hours 15 and 18 (Reppert & Weaver, 2001). It is presumed that increased levels of BMAL1 towards the end of the circadian day are what drives the heterodimerization with CLOCK proteins, which restarts the cycle of transcription and translation; therefore, BMAL1 levels are considered the rate limiting component of these feedback loops within the SCN (Reppert & Weaver, 2001).

3.3 – Sleep-Wake Cycles, Cortisol, Melatonin and Body Temperature

Circadian rhythms govern sleep-wake cycles and sleep architecture, and are driven by signals from the SCN, which entrains sleep rhythms to information it receives regarding light and dark from the environment (Shechter & Boivin, 2010). The SCN regulates these processes through its projections to several arousal and sleep-initiation areas in the brain. The tuberomammillary nucleus, locus coeruleus, and raphe nucleus are the main arousal centres that the SCN communicates with, and are each mainly driven by a specific neurotransmitter system: the histaminergic, noradrenergic and serotonergic systems, respectively (Shechter & Boivin, 2010). Meanwhile, the ventrolateral preoptic nucleus (VLPO) in the hypothalamus functions as the main sleep-initiation centre (Shechter & Boivin, 2010). When the VLPO is inhibited by the action of the histaminergic, noradrenergic and serotonergic systems, wakefulness is promoted, whereas when VLPO activity dominates, sleep is promoted (Shechter & Boivin, 2010).

Melatonin and cortisol are hormones that are influenced by environmental factors; they have opposing cycles and can each be used to determine circadian phase (Shechter & Boivin, 2010). Melatonin is produced from tryptophan, the precursor to serotonin, and is secreted by the pineal gland in rhythms determined by the SCN; levels of melatonin peak during the night then decrease to reach a minimum sometime in the morning (Claustrat & Leston, 2015). Melatonin receptors have been found both in the brain and in peripheral organs; this hormone contributes to the regulation of sleep-wake cycles through its action on receptors found in the SCN (Lanfumey et al., 2013). Melatonin is also involved in thermoregulatory processes related to sleep: the increase in melatonin levels during the evening promotes blood flow to the extremities of the body, which decreases overall body temperature and contributes to sleep initiation (Shechter & Boivin, 2010). In fact, body temperature is also governed by SCN activity and follows the

pattern of the sleep-wake cycle; in other words, body temperature is highest when an individual is at peak wakefulness, then gradually decreases to a minimum during sleep (Szymusiak, 2018). These thermoregulatory oscillations, specifically prior to sleep, are considered to be important contributors to sleep quality (Szymusiak, 2018).

Alternatively, cortisol begins to increase close to the morning and peaks a few hours after an individual wakes up, then progressively decreases throughout the day until levels reach a minimum around bedtime (Adam et al., 2017). Cortisol has far-reaching regulatory effects, namely in energy, metabolism, arousal, mood and the immune system; this hormone has been found to be greatly sensitive to stress and good proxy by which to predict health outcomes (Adam et al., 2017). For example, cortisol fluctuations with lower amplitudes were found to be greatly associated with poor physical and mental health outcomes, including, but not limited to, cancer, obesity, depression and mortality (Adam et al., 2017).

3.4 – Biological Rhythms and Mood Disorders

3.4.1 – The Social Zeitgeber Theory

Although photic cues are the most powerful zeitgebers, or "time givers", of the circadian system, nonphotic cues can still cause phase shifts in circadian rhythms that significantly affect the individual (Alloy et al., 2015). This forms the foundation of the Social Zeitgeber Theory, which has been implicated in the etiology of several mood disorders, and postulates that life events that impact sleep/wake times, mealtimes, work schedules, or other regularly occurring activities have the ability to cause disturbances in the circadian rhythm of individuals; in individuals diagnosed with mood disorders, such as depression and BD, these disturbances can precipitate mood episodes (Alloy et al., 2015). In fact, daily social zeitgebers have been proven

to entrain circadian rhythms even under complete darkness, further supporting this theory (Grandin et al., 2006).

3.4.2 – Biological Rhythms in Bipolar Disorder

Disturbances in circadian rhythms have been identified as a core feature of BD presentation. To start, sleep disturbances have been identified as the most common prodrome of mania in this population; additionally, women diagnosed with BD have been found to report poorer sleep quality than men, which was linked to worse mood outcomes for these females (Jackson et al., 2003; Saunders et al., 2015). Overall, biological rhythms disruptions in areas such as sleep, activity, and eating seem to persist even during euthymia, as evidenced through a study by Mondin et al. (2017) that compared BD participants with healthy controls; even higher disruptions were exhibited by BD participants who possessed an eveningness chronotype. In terms of the fluctuation of cortisol and melatonin, it has been suggested that their oscillations in BD are phase delayed in comparison to healthy individuals; researchers have gone as far as to postulate that bipolar patients have a permanently abnormal circadian pacemaker that contributes to a significantly different biological rhythms profile than individuals without a history of psychiatric illness (Grandin et al., 2006; Melo et al., 2017).

Individuals diagnosed with BD have also been found to have lower social rhythm regularity (Grandin et al., 2006). Given these observations, interpersonal and social rhythm therapy (IPSRT) was developed based off the tenets of the social zeitgeber theory, in order to help affected individuals maintain consistent daily rhythms and identify any potential disruptions (Grandin et al., 2006). Although some studies have not found this form of therapy to significantly improve outcomes for BD patients, other studies have credited it for decreasing BD symptomatology, improving functioning, and ameliorating response to mood-stabilizers

(Grandin et al., 2006; Steardo et al., 2020). Interestingly, the mood stabilizer lithium has been found to stabilize circadian rhythms, which might explain one facet of its success in treating a large number of BD patients (Grandin et al., 2006).

3.4.3 – Biological Rhythms in Premenstrual Dysphoric Disorder

As mentioned in Chapter 2, sleep disturbances are a common symptom of PMDD and usually occur in the late-luteal phase of the menstrual cycle. Women diagnosed with PMDD exhibited more non-REM and less REM sleep than their healthy counterparts, which contributes to a decreased quality of sleep for this population (Shechter & Boivin, 2010). Additionally, the delayed response of PMDD patients to morning bright light highlights an inherent dysfunction in their circadian clock that can disturb their sleep-wake cycles (Parry, Udell, et al., 1997).

Other circadian rhythms have been investigated in this population, specifically regarding melatonin and cortisol. In a study comparing PMDD participants to healthy controls, melatonin was collected intravenously at four different timepoints in the menstrual cycle; PMDD participants exhibited a later onset of melatonin secretion during the luteal phase of the menstrual cycle, as well as a shorter duration of secretion and lower mean levels (Parry, Berga, et al., 1997). These changes in melatonin secretion patterns across the menstrual cycle were not exhibited by the healthy controls, which points to a dysregulated circadian rhythm in the PMDD population (Parry, Berga, et al., 1997). Given the alterations to melatonin rhythm and its relation to controlling body temperature, studies have also found that significant changes to body temperature rhythms occur in the PMDD population during the luteal phase (Parry, LeVeau, et al., 1997). PMDD participants were found to exhibit a dampened body temperature amplitude, which can contribute to later sleep onset and an overall decreased quality of sleep; the lower amplitude might also signal weakened action of the internal pacemaker (Parry, LeVeau, et al.,

1997). Interestingly, treatments that target these lower amplitudes, such as sleep deprivation, have been found to improve mood in women diagnosed with PMDD (Jehan et al., 2017; Parry, LeVeau, et al., 1997). Finally, cortisol rhythms appear to be different in women diagnosed with PMDD in comparison to those who have not been diagnosed with the disorder. In a study by Parry et al. (2000), it was found that healthy women exhibit delayed cortisol secretion during the late-luteal phase of their menstrual cycles, that was not exhibited by PMDD participants; this may point to a blunted reaction to hormonal fluctuations that occur during the premenstruum in women diagnosed with PMDD (Parry et al., 2000). Altogether, these observations point to a significantly different circadian rhythms profile in the PMDD population, which can contribute to a propensity for mood disruptions that is further exacerbated by the sensitivity to hormonal fluctuations experienced by these women.

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Chapter 4 – Methodology and Materials

4.1 – Rationale

Thus far, I have discussed the characteristics of BD and how female reproductive life events can worsen BD illness course. Additionally, we explored the presentation of PMDD, which seems to be rooted in a sensitivity to hormonal fluctuations that drives symptoms during the late-luteal phase. One of the common features between these disorders is sleep disturbance. Interestingly, the Social Zeitgeber Theory postulates that events which disrupt regularly occurring activities (such as sleep/wake times and mealtimes) can precipitate mood worsening by means of throwing off the circadian rhythms of individuals diagnosed with mood disorders.

Considering that women diagnosed with comorbid BD and PMDD have been found to experience a worse illness course than women diagnosed with BD alone, we seek to add to these findings from a biological rhythms perspective. Specifically, I aim to investigate whether the convergence of mood disruptions, sleep disturbances and sensitivity to hormonal fluctuations in a BD and PMDD comorbidity leads to an increased illness burden for this population.

4.2 – Objectives

4.2.1 – Primary Objective

The primary objective was to determine whether biological rhythms disruptions will be particularly higher for women diagnosed with comorbid BD and PMDD during the *late luteal phase* of the menstrual cycle, as measured by the BRIAN, compared to the BD, PMDD and HC groups.

4.2.2 – Secondary Objective

The secondary objectives were (1) to determine whether women diagnosed with comorbid BDPMDD women will have greater disruptions to their biological rhythms, *across the*

menstrual cycle, compared to the BD, PMDD and HC groups; (2) to determine whether BDPMDD women have a higher number of depressive and manic/hypomanic symptoms, and disrupted sleep quality, as measured by the MADRS HAMD, YMRS and PSQI, during the *late luteal phase* of the menstrual cycle; and (3) to determine whether mood symptoms and sleep disruptions would be particularly exacerbated *across the menstrual cycle* for BDPMDD women.

4.3 – Hypotheses

Our primary hypothesis is that biological rhythms disruptions will be particularly higher for the comorbid group in comparison to the BD, PMDD and HC groups at the late-luteal phase. Our secondary hypotheses are as follows: 1) biological rhythms disruptions will be higher for the comorbid group during the follicular phase of the menstrual cycle as well, in comparison to the three other groups, 2) mood disturbances and sleep quality will be worse for the comorbid group during the late-luteal phase, and finally, 3) mood disturbances and sleep quality will also be worse for the comorbid group during the follicular phase as compared to the three other groups.

4.4 – Design

This is a secondary analysis of a recently published study from our group (Syan et al., 2018) where we sought to investigate whether biological rhythms disruptions are influenced by menstrual cycle phase, specifically in women diagnosed with comorbid Bipolar Disorder and Premenstrual Dysphoric Disorders; this group was compared to three others: 1) women with no history of psychiatric illness (control group), 2) women diagnosed with Premenstrual Dysphoric Disorder, and 3) women diagnosed with Bipolar Disorder. The original study investigated neural correlates associated with a diagnosis of comorbid Bipolar and Premenstrual Dysphoric Disorders and was approved by the Hamilton Integrated Research Ethics Board (HiREB).

4.5 – Participants

Study participants were females between the ages of 16 and 45, with regular menstrual cycles (25-32 days). In the current study, a total of seventy-seven participants were included from the original sample based on the availability of biological rhythms data, and were split into four groups: 1) healthy controls who had no history of psychiatric illness (HC), 2) women diagnosed with PMDD and no other psychiatric conditions (PMDD), 3) women diagnosed with BD and no history of PMDD, and 4) women diagnosed with comorbid BD and PMDD (BDPMDD).

General exclusion criteria included: 1) use of systemic hormonal treatment in the past 3 months, 2) pregnancy, 3) MRI contraindications, 4) history of head trauma with loss of consciousness, 5) neurological disorders, 6) alcohol or drug abuse or dependence in the past 6 months, and 7) unstable general health conditions.

4.6 – Determining Group Status

As described in the original study, all participants underwent two main assessments at screening that would then specify their group status: the SCID-I and the Daily Record of Severity of Symptoms (DRSP; Syan et al., 2018). Firstly, the SCID-I was administered to determine their psychiatric history (First et al., 2002). Secondly, the DRSP was used for at least 2 months of prospective symptoms charting by all participants to determine a PMDD diagnosis; the DRSP is a 21-item self-assessment of severity of symptoms that participants filled out every day of the 2-month period, and is based on PMDD criteria listed in the DSM-5 (Endicott et al., 2006). Levels of severity are as follows: 1 – Not at all, 2 – Minimal, 3 – Mild, 4 – Moderate, 5 – Severe, and 6 – Extreme (Endicott et al., 2006). Using these records, PMDD diagnosis was

subsequently confirmed by two independent psychiatrists who were blinded about participants' group status.

Healthy controls were excluded if i) they had a lifetime history of any psychiatric disorder according to the SCID-I assessment, or ii) if they displayed a difference greater than 30% in the four core symptoms of PMDD when comparing their late luteal and mid-follicular phases, according to the DRSP (Endicott et al., 2006).

Bipolar participants of both the BD and BDPMDD groups were included in the study based on the following criteria: 1) a diagnosis of BD according to the SCID-I, 2) no current mood episodes according to the SCID-I, 3) euthymic for at least 2 months prior to the start of the study, and 4) no changes in psychotropic medications for at least 2 months prior to the start of the study. Women in the BD group also did not display a difference greater than 30% when comparing the four core symptoms of PMDD at the late luteal and mid-follicular phases, according to the DRSP. BD and BDPMDD participants with lifetime, but not current, comorbidities with other psychiatric disorders were included in the study. Given that PMDD patients also present with comorbidities, a lifetime history of one depressive episode, a history of generalized anxiety disorder, and a past diagnosis of posttraumatic stress disorder were allowed as long as participants had not experienced any symptoms 6 months prior to starting the study.

4.7 – Study Visits

The study consisted of three visits to St. Joseph's Healthcare Hamilton. The primary visit was the screening visit, where informed consent was first obtained; to follow, the SCID-I was administered, as well as a psychiatric and gynecological history. The second and third visits were carried out during the mid-follicular and late luteal phases of the menstrual cycle, which were confirmed using prospective charting and hormonal analysis. The mid-follicular phase visit was

typically between days 5-10 of the menstrual cycle, while the late luteal phase visit was carried out during the week prior to the beginning of the following menstrual cycle. These two visits also included MRI scans, blood sample collection, hormonal analysis, and the completion of validated clinical questionnaires. Overall, about half of the participants had their first visit during the mid-follicular phase of their menstrual cycles, while the other half had their visit during the late luteal phase.

4.8 – Clinical Questionnaires

Depressive symptoms were assessed using the Montgomery-Åsberg Depression Rating Scale (MADRS) and the Hamilton Depression Rating Scale (HAMD), while manic/hypomanic symptoms were assessed using the Young Mania Rating Scale (YMRS; Hamilton, 1960; Montgomery & Åsberg, 1979; Young et al., 1978). Subjective measures were used to assess sleep quality (Pittsburgh Sleep Quality Index – PSQI) and disruptions in several domains of biological rhythms (Biological Rhythms Interview of Assessment in Neuropsychiatry – BRIAN) (Buysse et al., 1989; Giglio et al., 2009). Finally, the State-Trait Anxiety Inventory (STAI) was used to assess state and trait anxiety (Spielberger et al., 1983).

4.9 – Hormonal Analysis

As per the original study, whole blood samples were collected after the completion of the MRI scans at the mid-follicular and late-luteal visits (Syan et al., 2018). In total, 10 mL were collected, clotted at room temperature for 45 minutes, then centrifuged for 15 minutes at 20ºC and 3,000 rpm; four serum samples were then collected from the centrifuged tubes and frozen at -80ºC, up until they were assayed. Each serum sample was used to probe for an individual hormone; four hormones were assayed for in total: progesterone, 17-ß-estradiol, DHEAS, and allopregnanolone. The first three were assayed for using enzyme-linked immunosorbent assay

(ELISA) kits from ALPCO Diagnostics, Salem, NH, USA, and allopregnanolone was assayed for using ELISA kits from Kiamiya Biomedical Company, Seattle, WA, USA. Finally, hormone level data was interpreted by a licensed gynecologist to confirm that levels were within the accepted physiological range of the mid-follicular and late-luteal phases.

4.10 – Outcomes

4.10.1 – Primary Outcome

Biological rhythms were assessed using the BRIAN, which is an 18-item self-report questionnaire that investigates biological rhythms disruptions in four domains: sleep, activity, social and eating (Giglio et al., 2009). The rating scale ranges from "1 – Not at all" to "4 – Often", yielding a maximum score of 72, where a higher score indicates greater overall disruption in biological rhythms. The BRIAN questionnaire is the first of its kind to unify and assess several domains of biological rhythms, and total BRIAN scores were found to be highly correlated with total PSQI scores (Giglio et al., 2009). Moreover, the BRIAN measures these disruptions in the context of 15 days prior to assessment, in comparison to the PSQI which retrospectively measures sleep quality and sleep patterns for up to a month prior to assessment; therefore, use of the BRIAN decreases the rate of error that is commonly associated with recall bias given the shorter time span that it assesses. The BRIAN is a relatively novel subjective assessment of biological rhythms and, therefore, does not yet have agreed-upon cut offs to demarcate mild, moderate, and severe disruption; however, it was originally validated in a sample of both bipolar and healthy control participants, and was found to have had high reliability, validity and internal consistency in finding significant differences amongst the two groups (Giglio et al., 2009). The BRIAN was subsequently validated by our group against objective measures of sleep and circadian rhythms (Allega et al, 2018). To investigate the

primary objective, average total scores of the four BRIAN subdomains will be compared across all four groups to investigate whether BDPMDD have higher disruptions in the late luteal phase.

4.10.2 – Secondary Outcomes

Depressive symptoms were measured using two clinical questionnaires, the MADRS and the HAMD. The MADRS is a 10-item interviewer administered questionnaire that is used to assess the severity of depressive symptoms in the following domains: apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulty, lassitude, inability to feel, pessimistic thoughts and suicidal thoughts (Davidson et al., 1986). The scale ranges from 0 to 6 in each of those domains, adding up to a maximum score of 60, where higher scores denote increasing depressive symptoms. The accepted cut-offs for the MADRS are as follows: euthymic – 0 to 6, mild – 7 to 19, moderate – 20 to 34, and severe – 35 to 60 (Snaith et al., 1986). The HAMD is a 17-item interviewer administrated questionnaire that assesses the severity of depressive symptoms across the following domains: depressed mood, feelings of guilt, suicide, initial insomnia, insomnia during the night, delayed insomnia, work and interests, retardation, agitation, psychiatric anxiety, somatic anxiety, gastrointestinal somatic symptoms, general somatic symptoms, genital symptoms, hypochondriasis, weight loss, and insomnia (Hamilton, 1960). The scale in each of those domains is either from 0 – 2 or 0 – 4, where higher scores indicate a more depressive mood. The HAMD has the following cut-offs in the overall assessment of depression: euthymic – 0 to 7, mild – 8 to 16, moderate – 17 to 23, and severe – greater than or equal to 24 (Zimmerman et al., 2013). The final mood assessment employed was the YMRS, which is an 11-item clinician administered assessment of hypomanic/manic symptoms in the following domains: mood, energy, sexual interest, sleep, irritability, speech, language-thought disorder, content, disruptive – aggressive disorder, appearance, and insight

(Young et al., 1978). Seven items are graded on a 0 – 4 scale and the remaining four items are double weighted to have a 0 – 8 scale, in order to compensate for a lack of cooperation from severely manic patients; the maximum score is 60, with higher scores indicating increased manic symptoms. Finally, the PSQI was employed to assess subjective sleep quality across seven components (subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medications, and daytime dysfunction) which are tabulated from the 19-item questionnaire to produce a global sleep quality score; global scores can range from 0 to 21, with higher scores indicating worse sleep quality (Buysse et al., 1989).

For the secondary objectives, we compared average BRIAN subdomain scores between the different groups across the two timepoints. This was done to investigate whether these disruptions of biological rhythms in BDPMDD women carry throughout the menstrual cycle. We also compared MADRS, HAMD, YMRS and PSQI scores of the four different groups at both timepoints to determine whether the late-luteal phase is accompanied by worse mood and sleep patterns, particularly for the comorbid group. Finally, we investigated using the above-mentioned assessments to observe scores at both timepoints and determine whether disrupted mood and sleep quality carry throughout the menstrual cycle, particularly for the BDPMDD group. Collectively, these secondary objectives will help us determine whether women with comorbid BD and PMDD have a higher illness burden than women with either BD or PMDD alone.

4.11 – Statistical Analyses

Statistical analyses of clinical variables were carried out using R statistical software (Version 3.5.1). First, missing data was imputed using the “MICE” package. Descriptive statistics were then calculated using the “psych” package in R. For the descriptive data and clinical questionnaire scores, the normality of each measure was investigated using the Shapiro-

Wilks test. All variables were non-parametric; therefore, the Kruskal-Wallis rank sum test was used to evaluate the score means in each group and determine whether there were any significant differences between groups.

If results from the Kruskal-Wallis test were significant for the *descriptive data*, multiple comparisons of groups were performed using the Kruskal multiple comparisons test, which is found in the "pgirmess" package. If results from the Kruskal-Wallis test were significant for the *clinical questionnaires data*, Dunn's Test for multiple comparisons (using the Sidak method) was then employed to identify which pairs of groups had significant differences in their means; this test is part of the "dunn.test" package in R. Effect size was then calculated using the *multiVDA* function in the "rcompanion" package. Cliff's delta was reported from this output, with the following parameters as guides: 0.11 to < 0.28 – small, 0.28 to < 0.43 – medium, and ≥ 0.43 – large effect size (Mangiafico, 2016). Finally, a p-value of < 0.05 was considered significant for the comparisons.

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Chapter 5 – Results

5.1 – Demographic data

A total of seventy-seven women were included in this analysis from the original sample of participants. Overall, there were no differences in mean age of each group ($p = 0.056$); mean age was 27.44 (SD = 7.74) in the HC group, 32.21 (SD = 7.29) in the PMDD group, 30.44 (SD = 7.78) in the BD group, and finally, 33.41 (SD = 7.97) in the BDPMDD group (Table 1). Body mass index (BMI) was significantly higher ($p = 0.0003$) in the comorbid group (M = 29.54, SD = 4.30) compared to the HC (M = 23.24, SD = 3.29), PMDD (M = 24.41, SD = 4.26), and BD (M = 25.24, SD = 5.88) groups. Participants in the comorbid group appeared to have a lower mean number of years of education (M = 15.35, SD = 2.10); however, this was not found to be significantly lower than the mean numbers of years of education for the HC (M = 16.94, SD = 2.64), PMDD (M = 16.97, SD = 3.19), and BD (M = 16.44, SD = 3.33) groups ($p = 0.302$). Finally, mean age at menarche was relatively higher in the comorbid group (M = 12.47, SD = 1.12), but not significantly different ($p = 0.278$) than that of the HC (M = 11.76, SD = 1.51), PMDD (M = 11.63, SD = 1.16), and BD (M = 11.94, SD = 0.85) groups.

In terms of the clinical characteristics investigated in the BD and BDPMDD groups, mean age of bipolar onset (BD: M = 18.50, SD = 8.14; BDPMDD: M = 16.65, SD = 5.33) and mean number of comorbidities (BD: M = 1.06, SD = 1.29; BDPMDD: M = 1.41, SD = 1.80) were not found to be statistically different between the two groups, although the comorbid group did exhibit a younger age of bipolar onset and a slightly higher number of comorbidities. In terms of mean number of psychiatric medications taken by participants, the BDPMDD group did have a slightly higher average (M = 1.76, SD = 1.52) than the BD group (M = 1.69, SD = 1.20),

but again, this difference was not found to be statistically significant between the two groups ($p = 0.941$).

5.2 – Primary Outcome

5.2.1 – Biological Rhythms Disruptions during the Late-luteal Phase

The primary objective was to investigate whether biological rhythms disruptions, as measured by the BRIAN, were higher in the BDPMDD group compared to all three other groups during the late-luteal phase. In terms of sleep, disruptions were significantly higher in the comorbid group (M = 13.35, SD = 4.27, $p < 0.001$, Cliff's $d = 0.630$) when it was compared to the HC group (M = 8.76, SD = 2.4) alone; the PMDD (M = 11.95, SD = 4.06, $p = 0.012$, Cliff's $d = 0.486$) and BD (M = 12.31, SD = 3.32, $p = 0.005$, Cliff's $d = 0.660$) also experienced greater sleep disruptions when they were each compared to the HC group (Table 2). A similar pattern was observed in the activity domain, where each of the BDPMDD (M = 12.41, SD = 3.34, $p < 0.001$, Cliff's $d = 0.788$), PMDD (M = 11.53, SD = 3.27, $p < 0.001$, Cliff's $d = 0.768$), and BD (M = 10.88, SD = 3.83, $p = 0.002$, Cliff's $d = 0.642$) groups had significantly higher disruptions in this domain compared to the HC group (M = 6.64, SD = 2.87). The social domain was significantly disrupted during the luteal phase for the BDPMDD (M = 9.65, SD = 2.89, $p < 0.001$, Cliff's $d = 0.814$) and PMDD (M = 8.21, SD = 3.15, $p = 0.005$, Cliff's $d = 0.538$) groups in comparison to the HC (M = 5.4, SD = 1.55) group. And finally, the BDPMDD group (M = 10.53, SD = 3.1, $p = 0.002$, Cliff's $d = 0.592$) experienced significantly higher disruptions in the eating domain of the BRIAN in comparison to the HC group (M = 6.92, SD = 3.37).

5.3 – Secondary Outcomes

5.3.1 – Biological Rhythms Disruptions across the Menstrual Cycle

Sleep disruptions were significantly higher for the BDPMDD group (M = 12.65, SD = 3.41, $p = 0.001$, Cliff's $d = 0.636$) at the follicular phase when compared to the HC group (M = 8.82, SD = 2.9); sleep domain scores were not significantly higher in the BD and PMDD groups compared to the HC group, as they were in the luteal phase. Disruptions in the activity domain were higher in the BDPMDD (M = 11.88, SD = 3.64, $p < 0.001$, Cliff's $d = 0.835$), PMDD (M = 10.05, SD = 4.22, p = 0.004, Cliff's d = 0.590) and BD (M = 11.06, SD = 3.26, $p < 0.001$, Cliff's $d = 0.815$) groups when each was compared to the HC group (M = 6.6, SD = 1.78); this pattern was similar to the pattern of disruptions of the activity domain observed amongst the groups during the luteal phase. At the follicular phase, the social domain was significantly higher for the comorbid group alone (M = 9.53, SD = 2.98, $p < 0.001$, Cliff's $d = 0.782$) in its comparison with the HC group (M = 5.14, SD =) 1.78; the comorbid group did have significantly higher disruptions in the social domain when compared to the HC group during the luteal phase, but the PMDD group also exhibited a marked difference from the controls at that timepoint. Finally, the eating domain was significantly disrupted in the BDPMDD (M = 10.59, SD = 3.18, $p < 0.001$, Cliff's $d = 0.758$) and BD (M = 7.53, SD = 2.82, $p = 0.013$, Cliff's $d = 0.504$) when compared to the HC group (M = 6.24, SD = 2.2); disruptions in this domain were also significantly higher in the BDPMDD group when it was compared to the PMDD group (M = 7.53, SD = 2.82, $p = 0.017$, Cliff's $d = 0.558$). During the luteal phase, disruptions in the eating domain were only observed to be higher in the BDPMDD group in comparison to the HC group.

5.3.2 – Mood Disturbances and Sleep Quality during the Late-luteal Phase

BDPMDD women (M = 14.12, SD = 8.09, $p < 0.001$, Cliff's $d = 0.752$) experienced significantly more depressive symptoms than the HC group (M = 2.16, SD = 2.9) as measured by the MADRS; the PMDD (M = 14.68, SD = 7.8, $p < 0.001$, Cliff's $d = 0.848$) and BD (M = 9.62, SD = 6.6, $p = 0.012$, Cliff's $d = 0.630$) groups also had markedly higher MADRS groups in comparison to the HC group during the premenstruum (Table 3). Depressive scores from the HAMD questionnaire exhibited the same pattern as MADRS scores as the BDPMDD (M = 9.12, SD = 4.54, $p < 0.001$, Cliff's $d = 0.861$), PMDD (M = 9.37, SD = 5.12, $p < 0.001$, Cliff's $d = 0.853$), and BD (M = 6.5, SD = 3.79. $p = 0.003$, Cliff's $d = 0.720$) groups each experienced more depressive symptoms than the HC group (M = 1.2, SD = 1.58) according to this questionnaire. In terms of YMRS scores, each of the BDPMDD (M = 2.53, SD = 1.74, $p < 0.001$, Cliff's $d = 0.638$) and BD (M = 1.89, SD = 1.56, $p = 0.017$, Cliff's $d = 0.488$) groups had significantly higher scores than the HC group (M = 0.6, SD = 1.15) during the late-luteal phase. Finally, sleep quality was significantly worse for the BDPMDD (M = 8.06, SD = 3.27, $p = 0.004$, Cliff's $d = 0.604$) and BD (M = 8.12, SD = 4.63, $p = 0.013$, Cliff's $d = 0.496$) groups in comparison to the HC group (M = 4.4, SD = 3.25), as measured by the PSQI.

5.3.3 - Mood Disturbances and Sleep Quality across the Menstrual Cycle

MADRS scores revealed that only the BDPMDD group (M = 10.29, SD = 5.65, $p < 0.001$, Cliff's $d = 0.720$) had significantly higher depressive symptoms when compared to the HC group (M = 2.9, SD = 2.99) at the follicular phase; as mentioned in the previous section (5.3.2), the BDPMDD, PMDD and BD groups all had significantly higher MADRS scores when compared to the HC group at the late-luteal phase. HAMD scores corroborated these results, as BDPMDD participants (M= 5.71, SD = 3.82, $p < 0.001$, Cliff's $d = 0.658$) again had higher

scores than HC participants (M = 1.44, SD = 1.69); however, BD participants (M = 4.69, SD = 3.77, $p = 0.011$, Cliff's $d = 0.520$) also experienced significantly higher depressive symptoms compared to the HC group, as measured by the HAMD. In respect to HAMD results during the late-luteal phase, the PMDD, BD and BDPMDD groups all had significantly higher scores than the HC group. In regard to YMRS scores at the follicular phase, the only comparison that yielded a significant difference in scores was that between the BD (M = 1.62, SD = 1.36, $p = 0.012$, Cliff's $d = 0.490$) and HC group (M = 0.48, SD = 1); this was not similar to results in the late-luteal phase, since the BDPMDD and PMDD groups were found to have significantly higher scores in comparison to the HC group. Finally, the sole comparison of sleep quality to yield a difference in scores was between the BDPMDD (M = 7.24, SD = 3.67, $p = 0.023$, Cliff's $d = 0.470$) and HC (M = 4.28, SD = 2.42) groups; at the luteal phase, both the BDPMDD and BD groups had significantly higher sleep quality disruptions compared to the HC group.

Table 1 – Descriptive data

	HC N (%) Mean ± SD	PMDD N (%) Mean ± SD	BD N (%) Mean ± SD	BDPMDD N (%) Mean ± SD	*p*-value	Multiple Comparison
Participants	25 (32)	19 (25)	16 (21)	17 (22)	$p = 0.469$	
Age	27.44 ± 7.74	32.21 ± 7.29	30.44 ± 7.78	33.41 ± 7.97	$p = 0.056$	
BMI	23.24 ± 3.29	24.41 ± 4.26	25.24 ± 5.88	29.54 ± 4.30	$p = 0.0003$	BDPMDD > PMDD BDPMDD > BD BDPMDD > HC
Years of education	16.94 ± 2.64	16.97 ± 3.19	16.44 ± 3.33	15.35 ± 2.10	$p = 0.302$	
Age of BD onset	NA	NA	18.50 ± 8.14	16.65 ± 5.33	$p = 0.785$	
Age at menarche	11.76 ± 1.51	11.63 ± 1.16	11.94 ± 0.85	12.47 ± 1.12	$p = 0.278$	
Average number of comorbidities	NA	NA	1.06 ± 1.29	1.41 ± 1.80	$p = 0.770$	
Psychiatric Medications						
Lithium			2	1		
Mood stabilizers			4	7		
Antipsychotics			7	8		
Anxiolytics			4	7		
Antidepressants			7	7		
Sleep aids			2	2		
Mean number of psychiatric medications			1.69 ± 1.20	1.76 ± 1.52	$p = 0.941$	

Table 2 – Biological Rhythms Data

	HC Mean ± SD	PMDD Mean ± SD	BD Mean ± SD	BDPMDD Mean ± SD	Multiple Comparisons	*p*-value
BRIAN – Sleep (Follicular)	8.82 ± 2.9	10.11 ± 3.2	11.5 ± 3.79	12.65 ± 3.41	BDPMDD > HC	$p = 0.001$
BRIAN – Sleep (Luteal)	8.76 ± 2.4	11.95 ± 4.06	12.31 ± 3.32	13.35 ± 4.27	PMDD > HC BD > HC BDPMDD > HC	$p = 0.012$ $p = 0.005$ $p < 0.001$
BRIAN – Activity (Follicular)	6.6 ± 1.78	10.05 ± 4.22	11.06 ± 3.26	11.88 ± 3.64	PMDD > HC BD > HC BDPMDD > HC	$p = 0.004$ $p < 0.001$ $p < 0.001$
BRIAN – Activity (Luteal)	6.64 ± 2.87	11.53 ± 3.27	10.88 ± 3.83	12.41 ± 3.34	PMDD > HC BD > HC BDPMDD > HC	$p < 0.001$ $p = 0.002$ $p < 0.001$
BRIAN – Social (Follicular)	5.14 ± 1.78	7.26 ± 3.38	7.25 ± 3.26	9.53 ± 2.98	BDPMDD > HC	$p < 0.001$
BRIAN – Social (Luteal)	5.4 ± 1.55	8.21 ± 3.15	7.56 ± 3.18	9.65 ± 2.89	PMDD > HC BDPMDD > HC	$p = 0.005$ $p < 0.001$
BRIAN – Eating (Follicular)	6.24 ± 2.2	7.53 ± 2.82	9 ± 3.18	10.59 ± 3.18	BD > HC BDPMDD > HC BDPMDD > PMDD	$p = 0.013$ $p < 0.001$ $p = 0.017$
BRIAN – Eating (Luteal)	6.92 ± 3.37	8.79 ± 3.31	9.12 ± 2.78	10.53 ± 3.1	BDPMDD > HC	$p = 0.002$

Table 3 – Clinical Questionnaires Data

	HC Mean ± SD	PMDD Mean ± SD	BD Mean ± SD	BDPMDD Mean ± SD	Multiple Comparisons	*p*-value
MADRS (Follicular)	2.6 ± 2.99	6.42 ± 5.96	5.75 ± 5.12	10.29 ± 5.65	BDPMDD > HC	$p < 0.001$
MADRS (Luteal)	2.16 ± 2.9	14.68 ± 7.8	9.62 ± 6.6	14.12 ± 8.09	PMDD > HC BD > HC BDPMDD > HC	$p < 0.001$ $p = 0.012$ $p < 0.001$
HAMD (Follicular)	1.44 ± 1.69	3.84 ± 3.55	4.69 ± 3.77	5.71 ± 3.82	BD > HC BDPMDD > HC	$p = 0.011$ $p < 0.001$
HAMD (Luteal)	1.2 ± 1.58	9.37 ± 5.12	6.5 ± 3.79	9.12 ± 4.54	PMDD > HC BD > HC BDPMDD > HC	$p < 0.001$ $p = 0.003$ $p < 0.001$
YMRS (Follicular)	0.48 ± 1	1 ± 1.33	1.62 ± 1.36	1.24 ± 1.6	BD > HC	$p = 0.012$
YMRS (Luteal)	0.6 ± 1.15	1.89 ± 1.56	1.38 ± 1.41	2.53 ± 1.74	PMDD > HC BDPMDD > HC	$p = 0.017$ $p < 0.001$
PSQI (Follicular)	4.28 ± 2.42	4.95 ± 3.01	6.5 ± 3.03	7.24 ± 3.67	BDPMDD > HC	$p = 0.023$
PSQI (Luteal)	4.4 ± 3.25	6.21 ± 3.43	8.12 ± 4.63	8.06 ± 3.27	BD > HC BDPMDD > HC	$p = 0.013$ $p = 0.004$

Chapter 6 – Discussion and Conclusion

6.1 – Discussion

To our knowledge, this is the first study to examine biological rhythms disruptions within the context of the menstrual cycle in women diagnosed with comorbid BD and PMDD, as compared to women diagnosed with either BD or PMDD alone, and healthy women.

In terms of the characteristics of the sample, specifically in regard to the BD and BDPMDD comparison, age at bipolar onset was earlier in the comorbid group but this difference was not found to be significant; this is contrary to reports investigating the illness burden of the BD and PMDD comorbidity, which found that women diagnosed with both BD and PMDD had a significantly earlier onset of bipolar than women diagnosed with BD alone (Slyepchenko et al., 2017). Additionally, average years of education were non-significantly lower in the comorbid group compared to the three other groups; again, this contradicts previous findings that indicated a significantly lower education level in women with BD and comorbid PMDD as compared to women diagnosed with BD alone (Slyepchenko et al., 2017). As mentioned in Chapter 1, AAO is an important clinical variable, especially in its ability to inform about patient outcomes and heterogeneity in the presentation of bipolar disorder; earlier AAO has been associated with higher risk of anxiety comorbidities, severe depressive episodes, substance use and suicide attempts (Joslyn et al., 2016; Nowrouzi et al., 2016).

We expected the comorbid group to have significantly higher disruptions, specifically at the late-luteal stage, in all four subdomains of the BRIAN compared to the BD, PMDD and HC groups. However, aside from the BDPMDD – HC comparisons, the comorbid group only had a higher disruption than the PMDD group in the eating domain of the BRIAN at the follicular phase. Interestingly, in the sleep and social domains, the only group to have significantly higher

disruption during the follicular phase than the HC group was the BDPMDD group; given that BD – HC and PMDD – HC comparisons were not significantly different, these results support the notion that increased impairment in these domains persists throughout the menstrual cycle for BDPMDD women, thereby increasing the illness burden of a BD and PMDD comorbidity, compared to that of a sole BD or PMDD diagnosis. Social and functional impairment in PMDD women, in areas such as work productivity, family and relationship dynamics, and social activities, have been investigated and found to persist through the non-symptomatic follicular phase; although not reaching full impairment levels at this stage, they were found to be significantly higher than women not diagnosed with PMDD (Chawla et al., 2002; Halbreich et al., 2003). These results were not replicated in this analysis, specifically in the social domain scores of PMDD women, but they did reflect the results of the BDPMDD group which points to a worse illness course for women with BD and comorbid PMDD. Finally, the BD, PMDD and BDPMDD groups all experienced worse disruptions in the activity domain compared to the HC group, at both phases of the menstrual cycle; these disruptions reveal impairment in this particular domain for all three groups, albeit not influenced by menstrual cycle phase.

Depressive symptoms also persisted in the follicular phase for BDPMDD women, as evidenced through the significantly higher MADRS and HAMD scores of the BDPMDD group compared to the HC group. Surprisingly, the BD group also had significantly higher HAMD scores at the follicular phase in comparison to the HC group. At the late-luteal stage, the BD, PMDD and BDPMDD groups all experienced significantly more depressive symptoms than the HC group, reflected through both MADRS and HAMD scores. This was expected for the PMDD and BDPMDD groups; however, the fact that the BD group also exhibited these symptoms could point to a menstrual cycle-mediated effect on mood in these women as well. Finally, sleep

quality was significantly worse for BDPMDD women as compared to HC women, at both follicular and late-luteal stages. Sleep quality was not significantly impacted in the PMDD group during the late-luteal stage, but it was for the BD group. These results did not entirely reflect those of the BRIAN sleep domain at the luteal stage, as the PMDD group also had higher disruptions in this domain along with the BD and BDPMDD groups. Sleep disruptions have been investigated in BD where bipolar women have been found to report poorer sleep quality than bipolar men, and sleep disruptions have been linked to a poorer illness course in this disorder; therefore, sleep disruptions during the luteal phase of the menstrual cycle can contribute to making this period even more sensitive to episode relapse, especially in women with BD and comorbid PMDD (Saunders et al., 2015).

As this is the first study to examine sleep and mood disturbances across the menstrual for either of the BDPMDD, BD or PMDD populations, one of the challenges is that we are unable to compare most of our results to other studies. Overall, we cannot conclude that biological rhythms disruptions, mood disturbances and sleep quality are worse during the luteal phase for women diagnosed with BD and comorbid PMDD, as compared to BD and PMDD women. However, these clinical variables revealed disruptions that persisted throughout the menstrual cycle and contribute to the body of evidence that a BD and PMDD comorbidity results in a worse illness course than BD or PMDD alone. Although a PMDD diagnosis requires the follicular phase to be an asymptomatic period, there may be residual symptoms that persist and worsen the clinical outcomes of these women. Considering that women diagnosed with PMDD are often administered treatments at the start of the luteal phase, which are terminated at the beginning of menses, data confirming the presence of residual symptoms can inform treatment choices so that these residual symptoms can be targeted as well. As such, studies similar to this analysis, that

monitor changes in mood and biological rhythms across the menstrual cycle, can expand our understanding of the clinical profile of PMDD, in order to further understand how it impacts patients' lives during the premenstrual period and outside of it as well.

6.2 – Strengths and Limitations

One of the strengths of this study is the design employed to confirm menstrual cycle phase, namely through hormonal analysis, and to confirm the diagnosis of participants. The recruitment process was quite involved and required prospective charting 2 months prior to study entry, which made recruitment challenging. Diagnosis was confirmed through a clinical interview, and PMDD status was confirmed by two psychiatrists who independently evaluated DRSP charts. Additionally, all bipolar participants were euthymic for at least 2 months prior to study entry. Altogether, it achieved a relatively clean sample of participants and allowed for the study of impairment that might persist despite a clinically stable bipolar status in the BD and BDPMDD groups. Moreover, including both a BD and PMDD group provided great reference points to which BDPMDD data was compared, in order to examine several clinical variables amongst the three participant groups and expand on all three clinical profiles. As previously mentioned, this was the first study to examine whether menstrual cycle phase can impact biological rhythms, and the inclusion of the three clinical groups provided a more comprehensive view of how the menstrual cycle can impact each.

Another strength was the use of the BRIAN, which is the first assessment of its kind to evaluate disruptions across several biological rhythms domains. By identifying which domains are most affected, it would be possible to both better understand the impact of a BD diagnosis with comorbid PMDD and also better target those disruptions with tailored treatments. The use of clinician-administered mood questionnaires, namely the MADRS, HAMD and YMRS, also

contributed to investigating how the clinical status of women with BD and comorbid PMDD compares to BD, PMDD and healthy women at both phases of the menstrual cycle. Although biological rhythms disruptions have been thoroughly investigated in the BD population, they have never been investigated within the scope of the menstrual cycle; therefore, this study contributes to the literature investigating the influence of reproductive life events on mood worsening in BD women.

Considering that this is a post-hoc analysis, there are also several limitations to discuss. Firstly, the sample size of the study was relatively small although the effect size of the results was large (Cliff's $d \geq 0.43$) across all comparisons; however, a smaller sample size does limit our ability to generalize these results to the greater population. A larger sample size would have also allowed us to divide up participants into age ranges. We know that PMDD illness course worsens with age, specifically in the perimenopause period, so dividing participants based on age ranges and comparing the clinical variables across the groups and age brackets can add an extra layer of specificity in terms of data interpretation (Hassan et al., 2004).

BMI was also found to be significantly higher in the BDPMDD group in comparison to the three other groups. Due to the limitations of R programming and there being no code that can perform a non-parametric alternative to an ANCOVA across four groups, we could not control for this variable. Higher BMI can be indicative of obesity, which has been found to be quite common in the bipolar population at large and to cause a worse illness course defined by higher psychiatric comorbidities, mood episodes and cognitive dysfunction (Pisanu et al., 2019). On the other hand, some psychiatric medications can contribute to weight gain, and accordingly, a higher BMI. Therefore, knowing the dosages of medications that participants were taking can help in investigating whether certain medications or higher dosages were contributing this

significantly higher BMI. In regard to this analysis, average BMI for the comorbid group (M = 29.54, SD = 4.30) was in the overweight range as opposed to the obese one; however, the fact that it was significantly higher than the three other groups may confer an effect for which we were not able to control.

Additionally, there were no exclusion criteria for conditions such as insomnia or for participants who were taking medications that could alter sleep, such as antidepressants and anxiolytics. The impact on sleep by these medications has been well documented, especially in their use for remedying insomnia, and they can cause side effects such as daytime sleepiness and cognitive dysfunction (Xie et al., 2017), Specific to antidepressants, these pharmacotherapies can directly affect REM sleep, sleep initiation and sleep maintenance, all of which contribute to worse sleep quality and thereby influence biological rhythms (Wilson & Argyropoulos, 2005). Nevertheless, recruiting bipolar patients who are clinically stable while not receiving any form of pharmacotherapy can be incredibly challenging, and pharmacotherapy continues to be a confounding variable in many clinical studies. In relation to the issue of medications as a whole, medication load data was also not collected during the original study. It would have been interesting to add medication load as a factor in this investigation, to see the relation between increased medication dosages and biological rhythms disruptions in the BD, PMDD and BDPMDD groups.

Our primary outcome was measured using the BRIAN, which is a self-report questionnaire for evaluating biological rhythms disruptions; studies investigating subjective and objective measures of sleep found many discrepancies between the two types of measures, which puts into question the extent to which biological rhythms in general can be assessed solely using a subjective measure like the BRIAN (Zhang & Zhao, 2007). Additionally, the BRIAN does not

have agreed upon cut-offs that identify mild, moderate and severe impairment; therefore, our relying on significant differences amongst group means to explore disturbances was the only option available, albeit not a refined approach.

6.3 – Future Directions

The primary objective of the original study was not geared towards investigating biological rhythms disruptions in women diagnosed with BD and comorbid PMDD. As described above, this led to several limitations which had to be taken into account in the interpretation of the data. Future studies should lead with the objective of investigating biological rhythms and recruit participants who are not experiencing any sleep disorders and taking pharmacotherapies that do not affect sleep rhythms. Moreover, a larger sample size can increase the reliability of the results and potentially reveal effects that were not elucidated in this study.

In addition, objective biological rhythms measures must also be employed in conjunction with subjective measures in order to achieve a more well-rounded view of the disruptions experienced by women diagnosed with BD and comorbid PMDD. Given that the premenstrual period can be sensitive to mood episode relapses, the convergence of a sensitivity to hormonal fluctuations and disruptions in circadian rhythms, which seem to drive PMDD symptomatology in affected females, might increasingly predispose them to BD episode relapse. Data from actigraphy can better visualize possible disruptions to sleep rhythms in this population and identify when they are most likely to occur. In fact, the circadian system as a whole has been implicated in BD etiology, and the added effect of sensitivity to hormonal changes in women with comorbid PMDD can explain, in part, the added illness burden of this comorbidity (Sigitova et al., 2017).

6.4 – Conclusion

In this post-hoc analysis, we could not prove that the late-luteal stage is marked by significant disruptions in biological rhythms in women with BD and comorbid PMDD, in comparison to women with BD or PMDD alone; however, we did identify disruptions in sleep, social, activity and mood symptom domains that persisted in the follicular phase of the menstrual cycle. Therefore, women with a BD and PMDD comorbidity have a higher illness burden than woman diagnosed with either BD or PMDD.

The generalisability of these results is limited by the relatively small sample size of the study and confounding variables such as BMI and medication use. Nevertheless, this is the first study of its kind to investigate biological rhythms disruptions in women with comorbid BD and PMDD, and among BD and PMDD women as well. The lack of data surrounding this topic made it difficult for us to compare our results with other studies; however, it is a catalyst for further research to be done in order to explore premenstrual mood worsening in vulnerable populations like that of women with comorbid BD and PMDD. The hope is to identify novel treatment targets or tailor ones already in use to better serve these patients, in order to improve patient mental health outcomes and quality of life.

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