SLEEP ARCHITECTURE IN DEPRESSED PATIENTS TREATED WITH DESVENLAFAXINE

by

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Abstract

Objective: The primary objective of this study is to investigate the effects of desvenlafaxine, a serotonin-norepinephrine reuptake inhibitor, on sleep architecture in depressed patients, with a focus on changes in slow wave sleep (SWS), rapid eye movement (REM) sleep, and sleep efficiency. Secondarily, subjective changes in sleep quality and illness severity are assessed.

Methods: This was a prospective, double-blind, randomized, placebo-controlled study. Patients with major depressive disorder were randomized to receive a placebo or 50mg once daily of desvenlafaxine. Sleep architecture, subjective sleep quality, and illness severity were measured at baseline, after 3-5 days of treatment, and after 28-31 days of treatment. Sleep architecture was assessed using overnight, ambulatory polysomnography. Subjective sleep quality was evaluated using the self-reported Epworth Sleepiness Scale (ESS), Pittsburgh Sleep Quality Index (PSQI), and a visual analogue scale (VAS). Illness severity was measured using the Hamilton Depression Rating Scale (HDRS), Montgomery Asberg Depression Rating Scale (MADRS), Hamilton Anxiety Rating Scale (HARS), and the Clinical Global Impression-Severity (CGI-S) scale.

Results: Nine patients (two males and seven females), aged 19 to 48 years old, participated. There were no significant differences between the placebo and desvenlafaxine-treated groups on any sociodemographic measures. At baseline, there were no significant differences in sleep architecture or clinical measures between the two groups. At day 3-5, latency to REM sleep was significantly increased for the desvenlafaxine-treated group compared to placebo, and although this measure was still increased at day 28-31, the difference was no longer significant. No differences were found between the two groups at day 3-5 or day 28-31 on measures of sleep continuity or time spent in each sleep stage. Treatment with desvenlafaxine significantly decreased scores on the PSQI, HDRS, MADRS, HARS, and the CGI-S.
Conclusion: Treatment of depressed patients with desvenlafaxine decreased illness severity and improved subjective sleep quality. Minimal changes to sleep architecture were observed, with an acute increase in REM sleep latency being the only significant effect. These results suggest that desvenlafaxine may be capable of improving sleep quality in depressed patients, though further research with a larger sample size is needed to confirm and expand on these findings.
Co-Authorship

Participant recruitment, data collection, statistical analysis, and preparation of this document were completed by Tori-Rose Javinsky. Dr. Roumen Milev of the Department of Psychiatry, Queen’s University contributed to the design, participant recruitment, and physician-required portions of this study as well as to the preparation of this document.
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# Table of Contents

Abstract ............................................................................................................................. ii
Co-Authorship ................................................................................................................ iv
Acknowledgements ....................................................................................................... v
List of Figures .............................................................................................................. viii
List of Tables ............................................................................................................... ix

Chapter 1 : General Introduction .............................................................................. 1

Chapter 2 : Literature Review .................................................................................. 6
  2.1 Major Depressive Disorder ............................................................................... 6
     2.1.1 Clinical Characteristics .......................................................................... 6
     2.1.2 Epidemiology .......................................................................................... 8
     2.1.3 Pathophysiology .................................................................................... 11
  2.2 Sleep .................................................................................................................... 17
     2.2.1 Normal Sleep Architecture ..................................................................... 18
     2.2.2 Physiology of Sleep ................................................................................ 21
     2.2.3 Relationship between Sleep Disturbances and Depression ..................... 23
     2.2.4 Sleep Architecture in Depression ............................................................ 25
     2.2.5 Physiology of Sleep Disturbances in Depression .................................... 26
  2.3 Pharmacological Treatments of Depression ....................................................... 27
     2.3.1 Antidepressants and their Effects on Sleep .............................................. 27
     2.3.2 Desvenlafaxine ...................................................................................... 34

Chapter 3 : Methods .................................................................................................. 36
  3.1 Participants .......................................................................................................... 36
  3.2 Medication .......................................................................................................... 37
  3.3 Clinical Measures ............................................................................................... 38
  3.4 Polysomnographic Recordings .......................................................................... 38
  3.5 Statistical Analysis .............................................................................................. 40

Chapter 4 : Results .................................................................................................... 42
  4.1 Sociodemographic Characteristics ................................................................... 42
  4.2 Clinical Measures ............................................................................................... 42
     4.2.1 Illness Severity ........................................................................................ 42
     4.2.2 Subjective Sleep Quality ........................................................................ 46
  4.3 Polysomnographic Measures ............................................................................ 48
List of Figures

Figure 1. Participant Selection and Randomization into the Placebo and Treatment Groups. .............. 41
Figure 2. Subjective Sleep Quality ........................................................................................................ 47
Figure 3. Sleep Efficiency.......................................................................................................................... 50
Figure 4. Rapid Eye Movement Sleep....................................................................................................... 51
List of Tables

Table 1. Sociodemographic Characteristics................................................................................................................. 43
Table 2. Clinical Measures at Baseline................................................................................................................................. 44
Table 3. Clinical Measures at Day 3-5................................................................................................................................. 44
Table 4. Clinical Measures at Day 28-31............................................................................................................................. 45
Table 5. Polysomnographic Measures at Baseline............................................................................................................... 52
Table 6. Polysomnographic Measures at Day 3-5 .................................................................................................................. 53
Table 7. Polysomnographic Measures at Day 28-31 .............................................................................................................. 54
Chapter 1: General Introduction

Major depressive disorder (MDD) is a psychiatric mood disorder characterized by persistent low mood and/or anhedonia, accompanied by a number of other symptoms, and lasts for a period of at least two weeks (DSM-5, American Psychiatric Association, 2013). Not only is MDD a prevalent mood disorder, with one study reporting a lifetime prevalence rate of 9.9% in Canada (Patten et al., 2015), but it is also associated with several functional impairments, resulting in a high global disease burden (Mathers et al., 2008). Though there are numerous pathophysiological mechanisms underlying the illness, one of the most consistently reported is deficiency in the neurotransmission of serotonin, norepinephrine, and dopamine (Delgado, 2000).

Sleep disturbances are one of the most common symptoms associated with MDD, with up to 90% of patients reporting reduced sleep quality (Tsuno, Besset, & Ritchie, 2005). Indeed, sleep disturbances are included as one of the diagnostic criteria for MDD in the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2013). Insomnia is the most frequently experienced sleep disorder, with about 66% of depressed patients reporting significant difficulties falling asleep, frequent nighttime awakenings, and/or early-morning awakening (Perlis et al., 1997). Interestingly, there appears to be a bi-directional relationship between sleep disturbances and MDD. Not only are non-depressed individuals with insomnia more likely to develop MDD at some point in the future compared to those with no sleep difficulties (Baglioni et al., 2011) but insomnia has been demonstrated to be a prodromal symptom in recurrent MDD (Perlis, Giles, Buysse, Tu, & Kupfer, 1997). Furthermore, sleep disturbances in MDD correlate strongly with depression severity and treatment response (Buysse et al.,
1999; Dew et al., 1997; Liu et al., 2007), while improvements in sleep quality have been associated with lower recurrence rates of depression (Buysse et al., 1996). Improvements in sleep quality should therefore represent a key focus for enhancing the outcomes of treatment for MDD.

Sleep is made up of two distinct phases that cycle throughout the night – non-rapid eye movement (NREM) sleep, which can be further separated into stages 1, 2, 3, and 4, and rapid eye movement (REM) sleep. Stages 3 and 4 are the deepest stages of sleep and are frequently referred to as slow-wave sleep (SWS) (Markov & Goldman, 2006). Memory consolidation and tissue repair are important processes that occur during SWS, meaning that sleep deprivation and poor quality of sleep can have detrimental effects on health and cognition (Holl, Hartman, Veldhuis, Taylor, & Thorner, 1991; Walker & Stickgold, 2004). During the first third of the night, each sleep cycle consists predominately of SWS, while REM sleep dominates in the last third of the night (Markov & Goldman, 2006). Wakefulness, sleep onset, and the cyclical transitions between NREM and REM sleep throughout the night are regulated in part by a balance in the transmission of acetylcholine, norepinephrine, and serotonin between various brain regions (España & Scammell, 2011).

Several polysomnographic studies have demonstrated that sleep architecture is altered in MDD due to insufficient suppression of REM sleep, resulting in an increase in time spent in REM sleep, a shortened REM sleep onset latency, and decreased time spent in SWS. Additionally, changes in the temporal distributions of SWS and REM sleep and sleep fragmentation are commonly reported. These abnormalities can also be seen in never-depressed relatives of individuals with MDD, suggesting the presence of a genetic
component (Pillai et al., 2011). Both monoamine deficiency and elevated levels of acetylcholine have been observed in MDD (Drevets, Price, & Furey, 2008), resulting in an imbalance in the key neurotransmitters that regulate sleep. Thus, deficient monoaminergic neurotransmission likely contributes to both sleep disturbances and mood dysregulation in those with MDD.

Various antidepressants have been shown to ameliorate the sleep abnormalities associated with MDD. Due to their inhibition of the serotonin transporter (SERT), which results in increased serotonergic neurotransmission, selective serotonin reuptake inhibitors (SSRIs) such as sertraline, fluoxetine, and paroxetine have been demonstrated to suppress REM sleep, increasing its onset latency and decreasing the percentage of time spent in this stage. Their effects on SWS and sleep continuity, however, are less consistent (Hicks et al., 2002; Jindal et al., 2003; Trivedi et al., 1999). Tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) increase the neurotransmission of both serotonin and norepinephrine. The mechanism of action of TCAs involves inhibition of the serotonin and norepinephrine transporters while MAOIs work by preventing the monoamine oxidase family of enzymes from breaking down the monoamines. These antidepressants similarly suppress REM sleep with varying effects on other sleep parameters, though their potential for significant side effects makes them less favourable treatment options (Gillin et al., 1978; Kupfer et al., 1979; Kupfer et al., 1989; Landolt et al., 2001; Monti et al., 1990).

Desvenlafaxine is a relatively novel serotonin-norepinephrine reuptake inhibitor (SNRI) that is the synthetic form of the major active metabolite of venlafaxine. As an SNRI, desvenlafaxine inhibits the activity of the norepinephrine transporter (NET) in
addition to that of the SERT, increasing the activity of both norepinephrine and serotonin in the synapse. It has demonstrated a higher affinity for the SERT, being approximately 10-times more potent at inhibiting serotonin reuptake than that of norepinephrine (Deecher et al., 2006). Desvenlafaxine has been demonstrated to be a safe and efficacious treatment for MDD (DeMartinis, Yeung, Entsuah, & Manley, 2007; Liebowitz, Yeung, & Entsuah, 2007; Septien-Velez et al., 2007). Though polysomnographic studies have investigated the impact of both duloxetine and venlafaxine, two other SNRIs, on depressed sleep, no such studies to date have been conducted with desvenlafaxine. The only studies reporting on changes in sleep following treatment with desvenlafaxine have been those conducted in menopausal women, which have reported that desvenlafaxine reduces the number of nighttime awakenings due to hot flushes (Speroff, Gass, Constantine, & Olivier, 2008; Archer, Seidman, Constantine, Pickar, & Olivier, 2009). Given that its administration results in an increase in the neurotransmission of serotonin and norepinephrine, desvenlafaxine has the potential to improve the dysfunctional regulation of sleep and thus to enhance the treatment of MDD.

The primary aim of this study was to assess the objective changes in sleep quality before and after the introduction of desvenlafaxine treatment in patients with MDD using polysomnography, as compared to placebo-treated controls. While all aspects of sleep architecture were examined, particular attention is paid to REM sleep, SWS, and sleep efficiency. Secondarily, subjective changes in sleep quality and depressive symptomology before and after the introduction of desvenlafaxine were examined using self-report questionnaires. All variables were measured before the commencement of desvenlafaxine as well as after acute and chronic treatment.
It is hypothesized that compared to controls, subjects treated with desvenlafaxine will show a deterioration in objective sleep measures following 3 to 5 days of treatment due to the initial surge in noradrenergic neurotransmission. Conversely, after treatment for 28 to 31 days, it is hypothesized that desvenlafaxine-treated subjects will show an improvement in these measures compared to controls as the CNS adjusts to the increase in noradrenergic signaling. Specifically, it is expected that treatment with desvenlafaxine will increase REM onset latency, time spent in SWS, and sleep efficiency, and will decrease the duration of REM sleep and sleep onset latency. It is also anticipated that at the chronic measurement, desvenlafaxine treatment will improve measures of illness severity and subjective sleep quality.

Given the importance of managing sleep disturbances in the treatment of MDD, the results of this study will provide a better understanding of how desvenlafaxine treatment influences sleep architecture, which is bi-directionally correlated with depressive symptomology, in patients with MDD.
Chapter 2: Literature Review

2.1 Major Depressive Disorder

2.1.1 Clinical Characteristics

Major depressive disorder is defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) as a psychiatric mood disorder that is characterized by one or more discrete major depressive episodes (MDE) that last at least two weeks in length. These episodes consist of a persistent low mood and/or anhedonia, present most of the day nearly every day, accompanied by a range of other functional or cognitive symptoms. Specifically, the DSM-5 describes MDEs as consisting of five or more of the following symptoms: 1) depressed mood most of the day, 2) diminished pleasure or interest in most or all activities, 3) significant weight loss or changes in appetite, 4) insomnia or hypersomnia, 5) psychomotor agitation or retardation, 6) fatigue, 7) feelings of worthlessness or excessive or inappropriate guilt, 8) difficulties with concentration or indecisiveness, and 9) recurrent thoughts of death, suicidal ideation, or suicide attempts. These symptoms must be present in a significant manner, such that they persist and cause distress or functional impairment, and must not be attributable to the physiological effects of a substance or another medical condition (DSM-5, American Psychiatric Association, 2013).

While MDD can occur with just one MDE, it more commonly consists of recurring episodes. Indeed, not only do more than half of those who experience one MDE experience a recurrent episode, but the number of previous episodes is highly predictive of future episodes (Spaner et al., 1994). The frequency and length of MDEs vary greatly among individuals. A MDE can last for weeks, months, or years, with one study reporting
the average duration ranged from 25.3 to 31.7 weeks in developed countries and 23.1 to 33.8 weeks in developing countries (Kessler et al., 2010).

Major depressive disorder can be further described by a number of DSM-5 recognized subtypes, called specifiers, that define a unique cluster of characteristics or symptoms. These specifiers include depression with atypical features, melancholic features, psychotic features, catatonia, with a seasonal pattern, or with peripartum onset. Atypical depression is characterized by mood reactivity, where the patient’s mood brightens in response to positive events, and the presence of two or more of the following symptoms: 1) significant weight gain or increased appetite, 2) hypersomnia, 3) a heavy feeling in the limbs referred to as leaden paralysis, and 4) significant social impairment as a result of an enduring pattern of hypersensitivity to interpersonal rejection. Melancholic depression involves a lack of pleasure in nearly all activities and lack of mood reactivity in addition to three or more of the following: 1) a quality of depressed mood characterized by profound hopelessness, despair, or melancholy, 2) depression that is worse in the morning, 3) early morning awakening, 4) marked psychomotor agitation or retardation, 5) significant weight loss, and 6) excessive or inappropriate guilt. Depression with psychotic features is characterized by the presence of delusions or hallucinations in addition to meeting the criteria for a MDE. Depression with catatonia occurs when catatonic features, described as marked psychomotor disturbances such as decreased motor activity or catalepsy, are present during most of a MDE. If there is a temporal distribution of depressive episodes such that their onset occurs during a consistent time of the year with full remission being reached at all other times, then depression with a seasonal pattern, also called seasonal affective disorder, can be diagnosed. Lastly,
postpartum depression, now referred to as depression with peripartum onset in the DSM-5, occurs when the onset of MDD is during pregnancy or within 4 weeks of giving birth (American Psychiatric Association, 2013).

Although MDD is perhaps the best known mood disorder, it may be misdiagnosed as bipolar disorder or dysthymia. Major depressive disorder can be distinguished from bipolar I or II disorder given the absence of manic or hypomanic episodes that are the hallmark features of bipolar I and II, respectively. These episodes are defined as discreet periods of abnormally and persistently elevated or irritable mood accompanied by symptoms such as grandiosity, a decreased need for sleep, or an increase in risk taking behaviour (American Psychiatric Association, 2013). As well, episodes of depression associated with bipolar disorder tend to be more frequent and of shorter duration (Angst & Preisig, 1995). Major depressive disorder also differs from persistent depressive disorder, also called dysthymia, due to differences in their diagnostic criteria. Specifically, dysthymia must be diagnosed after a minimum duration of two years of depressed mood and requires the presence of fewer additional symptoms (American Psychiatric Association, 2013).

2.1.2 Epidemiology

Many epidemiological studies have been conducted to investigate the prevalence, age of onset, risk factors, comorbidity, and disease burden of MDD in populations around the world. There has been wide variability in reported prevalence estimates from different countries. For instance, one of the first epidemiological studies of MDD, conducted by Weissman et al. (1996), included data from investigators in 10 different countries. Annual rates of MDD ranged from 0.8% in Taiwan to 5.8% in New Zealand and lifetime
rates ranged from 1.5% in Taiwan to 19% in Beirut. This large variability is likely due in part to differences in study design and data collection methods (Ferrari et al., 2013). In an attempt to control for differences in methodology, the World Health Organization (WHO) World Mental Health Survey Initiative conducted a series of studies using a common protocol to more accurately estimate prevalence rates in 10 developed and 8 developing countries across the world (Kessler & Üstün, 2008). Data from 89,036 adult respondents showed that the estimated 12-month prevalence of MDEs was 5.5% in developed countries (varying from 2.2% in Japan to 8.3% in the United States) and 5.9% in developing countries (varying from 3.8% in China to 10.4% in Brazil). It was found that this prevalence varied significantly among age groups for developed countries but less so for developing countries (Kessler et al., 2010). The estimated lifetime prevalence of MDEs was reported to be 14.6% in developed countries and 11.1% in developing countries (Bromet et al., 2011).

A report by Patten et al. (2015) based on the 2012 Canadian Community Health Survey – Mental Health from Statistics Canada found that MDD accounted for the majority of cases of mood disorders, with lifetime and 12-month prevalence rates of 9.9% and 3.9%, respectively. Consistent with findings from other studies around the world, the annual prevalence of MDD in Canadians was found to be higher in females (4.9%) than in males (2.8%) and was highest for both genders in the 15-24 age category (9.0% in females, 5.3% in males) while lowest amongst those 65 years and older (1.8% in females, 1.4% in males). The age of onset of MDD can vary greatly but the illness most frequently develops in young adulthood, specifically between the ages 15 and 30 (American Psychiatric Association, 2013; Kessler et al., 2005). Other correlates for an increased risk
of MDD include unemployment, disability, poverty, being divorced or having never married (Kessler et al., 2003), chronic stress (Tennant, 2002; Paykel, 2003), and exposure to childhood trauma (Kessler & Magee, 1993; Kessler et al., 1997).

Major depressive disorder rarely occurs alone; it frequently presents with other psychiatric illnesses and with physical health conditions. Studies investigating this comorbidity have reported that 75-79% of those with MDD have one or more additional psychiatric illness (Melartin et al., 2002; Kessler et al., 2003; Kessler & Walters, 1998). Major depressive disorder is most highly comorbid with anxiety disorders, with up to 60% of those with MDD also having an anxiety disorder (Hirschfeld, 2001; Melartin et al., 2002; Kessler et al., 2003). To a lesser extent, MDD is comorbid with substance abuse, dysthymia, psychotic disorders, impulse control disorder, and personality disorders (Spaner et al., 1994; Melartin et al., 2002; Kessler et al., 2003; Thaapisuttikul et al., 2014; Patten et al., 2015). Depression is also one of the most important risk factors for suicide. According to the 2012 Canadian Community Health Survey – Mental Health, 47.7% of respondents with a history of MDD had experienced suicidal thoughts and 16.6% had made a suicide attempt, compared with 10.4% and 2.5%, respectively, for respondents without MDD (Patten et al., 2015). In addition, MDD frequently occurs alongside physical health conditions such as diabetes, cancer, arthritis, stroke, and asthma (Anderson et al., 2001; Thombs et al., 2006; Egede, 2007; Moussavi et al., 2007; Ng et al., 2011; Hackett & Pickles, 2014).

The symptoms of MDD can be debilitating, leading to a high degree of association between MDD and functional impairments such as impaired ability to work, reduced productivity, difficulty completing routine daily tasks, and impaired social
functioning. Combined with the prevalence of MDD, these impairments have resulted in a high global disease burden. Several studies have described MDD as a large contributor to days missed of work and reduced productivity at work (Broadhead et al., 1990; Kessler & Frank, 1997; Grzywacz & Ettner, 2000; Bruffaerts, 2012). The economic burden resulting from MDD in the United States was investigated by Greenberg et al. (2015), who reported that the incremental economic burden of individuals with MDD, which included costs due to days missed of work, reduced productivity at work, and costs for medical services and prescriptions, rose from $173.2 billion in 2005 to $210.5 billion in 2010. Furthermore, the WHO’s Global Burden of Disease 2004 update ranked MDD third worldwide in terms of the overall burden of diseases, with 94.5 million disability-adjusted life years, which expresses the number of healthy years lost due to ill-health and disability, worldwide and predicts it will rise to first by 2030 (Mathers et al., 2008).

2.1.3 Pathophysiology

Numerous approaches have been taken to investigate the pathophysiology of MDD. While the complete process behind it is not yet clear, there is evidence of the association of several abnormalities with the illness. Various biological and psychological models have thus developed over time that attempt to integrate this evidence into an explanation of the etiology of MDD.

One of the most widely studied abnormalities is dysfunction of the monoamine system, which has led to the development of the monoamine hypothesis of MDD. This theory postulates that the symptoms of MDD are a result of a deficiency in the levels of serotonin, norepinephrine, and dopamine in the central nervous system. Indeed, there is considerable evidence of the existence of this deficiency and how it could lead to
depressive symptomology. In healthy individuals, serotonergic neurons in the raphe nuclei of the brainstem project to various parts of the brain to regulate mood, sleep, and appetite. Evidence for a deficiency in serotonergic neurotransmission in MDD includes findings of reduced cerebrospinal fluid (CSF) levels of 5-hydroxyindoleacetic acid, a product of serotonin breakdown (Bowers et al., 1969; Goodwin et al., 1973; Mendels et al., 1972) and significant decreases in the number of serotonin transporters and receptors, as well as reduced serotonin 1A receptor binding in several cortical regions (Stockmeier, 2003). Furthermore, inhibition of serotonergic neurotransmission through various methods results in symptoms of depression in healthy subjects and those in remission (Delgado et al., 1990; Young et al., 1985), while serotonin 1A receptor agonists and reuptake inhibitors that increase the activity of serotonin are effective in treating depressive symptomology (Naughton et al., 2000).

Norepinephrine originates from noradrenergic cells in the locus coeruleus, a brainstem nucleus that projects to the cortex and limbic system to modulate a number of functions that are modified in MDD including executive functioning, sleep, and appetite. Post-mortem studies of individuals with MDD have found an increase in the density of $\alpha_{2A}$-adrenoreceptors in the prefrontal cortex and locus coeruleus, a finding that is thought to be a compensatory mechanism resulting from a deficiency in norepinephrine signalling, as well as a decrease in norepinephrine transporter binding in the locus coeruleus (Ordwall et al., 2003; Escribá et al., 2004; Valdizán et al., 2010; Klimek et al., 1997). As well, depressed patients in remission will rapidly experience depressive symptoms again following depletion of norepinephrine levels (Berman et al., 1999; Ruhe
et al., 2007), while treatment with antidepressants that increase the activity of norepinephrine improves symptoms in those with MDD (Papakostas et al., 2007).

There is also extensive evidence of decreased dopaminergic neurotransmission. Studies have found decreased CSF levels of homovanillic acid, the major metabolite of dopamine, in patients with MDD that increase following treatment (Bowers et al., 1969; Goodwin et al., 1973; Mendels et al., 1972). Additionally, dopamine reuptake inhibitors make efficacious antidepressants (Nutt, 2006). The mesolimbic and mesocortical pathways are two dopaminergic pathways that are likely impacted by deficient dopamine signalling in MDD (Dailly et al., 2004; Nestler & Carlezon, 2006). Both pathways are composed of dopaminergic neurons in the ventral tegmental area that project to either the nucleus accumbens (mesolimbic pathway) or the prefrontal cortex (mesocortical pathway). The mesolimbic pathway is well known to be involved in pleasure, reward, and motivation, while the mesocortical pathway is involved in cognition.

While the monoamine hypothesis is a compelling explanation for the symptoms of MDD, there are several biological findings outside of this theory that should be considered. Another neurochemical that appears to be affected in MDD is brain derived neurotrophic factor (BDNF), a growth factor important for neurogenesis and promoting the survival of existing neurons. A meta-analysis by Sen et al. (2008) found that not only were BDNF levels lower in depressed subjects than in healthy controls but these levels increased significantly following antidepressant treatment. While the connection between BDNF and MDD is not yet clear, it is of interest to note that post mortem studies have reported reduced levels of BDNF in the hippocampus, an area where neurogenesis is known to occur and that has been implicated in MDD (Dwivedi et al., 2003).
Abnormalities in neuroendocrine functioning, specifically hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis, are consistently reported in MDD. Depressed subjects have demonstrated hypercortisolism and greater HPA axis reactivity in response to psychological stressors, which is thought to be due in part to altered feedback inhibition (Varghese & Brown, 2001; Lopez-Duran et al., 2009). As well, HPA axis hyperactivity predicts worse treatment outcome (Brouwer et al., 2006) and worse performance on cognitive tasks in patients with MDD (Keller et al., 2016). Although it isn’t known whether it is a cause or a consequence of MDD, several lines of evidence point to a primary role for HPA axis dysfunction in the onset of MDD. The HPA axis is an important component of the stress response system and both chronic and early life stress result in neurobiological adaptations that increase the risk for MDD (Mazure et al., 2000; Kendler et al., 2003; Heim et al., 2004). Those with Cushing’s disease, a condition in which the pituitary gland releases too much adrenocorticotropic hormone, have a high rate of depressive symptomology (Sonino et al., 1998). Lastly, HPA axis dysfunction has been observed in healthy subjects with a family history of affective disorders, suggesting a genetic component that contributes to an increased risk for MDD (Holsboer et al., 1995). Indeed, polymorphisms in glucocorticoid and mineralocorticoid receptor genes have been associated with worse clinical and cognitive symptoms, as well as worse treatment outcomes (Brouwer et al., 2006; Keller et al., 2016). Thus, dysregulation of the HPA axis represents a significant pathophysiological theory of MDD that incorporates many known causal factors: chronic stress, early life trauma, and genetic vulnerability.

Neuroimaging studies have identified a number of structural and functional abnormalities associated with MDD, particularly in limbic and cortical areas. A meta-
analysis of 12 magnetic resonance imaging (MRI) studies found a significant reduction in hippocampal volume, with the total number of depressive episodes correlating highly with volume reduction (Videbech & Ravnkilde, 2004). Reduced hippocampal volume has also been linked with various cognitive deficits (Frodl et al., 2006; MacQueen et al., 2003; O’Brien et al., 2004; Shah et al., 1998). Abnormalities in the amygdala have been implicated but findings are less consistent. A meta-analysis of 13 MRI studies concluded that unmedicated depressed subjects show a decrease in amygdala volume compared to controls, while medicated depressed subjects show a significant increase (Hamilton et al., 2008). In addition, depressed subjects show evidence of increased amygdala activity, suggesting it may have a role in the emotional symptoms of MDD (Drevets et al., 1992; Sheline et al., 2001). These volume reductions are thought to be a consequence of hypercortisolism; high levels of glucocorticoids are excitotoxic and the amygdala and hippocampus are both dense in glucocorticoid receptors (Sapolsky, 2000; Hamilton et al., 2008). Abnormalities in cortical regions include volumetric reductions in frontal lobe white matter (Steingard et al., 2002) and the orbitofrontal cortex (Bremner et al., 2002), as well as hyperactivity in the ventromedial prefrontal cortex and hypoactivity in the dorsolateral prefrontal cortex (Drevets et al., 1992; Koenigs & Grafman, 2009; Miller et al., 2015). Differences have also been observed in the anterior cingulate cortex (ACC), which is involved in the modulation of emotional behaviour. Studies have shown significantly smaller volumes in depressed subjects (Caetano et al., 2006), in addition to hyperactivity in the subgenual ACC (Drevets et al., 2008; Miller et al., 2015).

Taking a more psychological approach is the diathesis-stress model, a theory that hypothesizes that MDD results when a pre-existing vulnerability is activated by stressful
life events. This model is driven by evidence that there is a strong correlation between the experience of stress and the development of MDD, which tends to be even stronger in those with certain vulnerabilities (Monroe & Simons, 1991). Pre-existing vulnerabilities that appear to modulate this relationship include specific genetic polymorphisms and personality traits. A family study by Weissman et al. (1993) found that first-degree relatives of those with MDD had a significant increase in lifetime risk of developing MDD, while a meta-analysis of twin studies by Sullivan et al. (2000) suggested the heritability of MDD was 37%. Though no genetic polymorphisms have reached genome-wide significance, several have been associated with an increased risk of MDD. These polymorphisms include variants in the genes for the serotonin transporter (SLC6A4), serotonin receptor 2A (HTR2A), tryptophan hydroxylase (TPH2), and glucocorticoid and mineralocorticoid receptors, in addition to the val66met polymorphism in the BDNF gene (Lohoff, 2010; Ripke et al., 2013; Brouwer et al., 2006; Keller et al., 2016). A considerable amount of research has also supported an association between personality traits, particularly perfectionism, neuroticism, introversion, and lower emotional strength and resilience, and MDD. It is thought that these traits make one more susceptible to the negative effects of life stress, thus increasing their risk of developing MDD (Kendler et al., 1993; Flett et al., 1995; Chioqueta & Stiles, 2005; Hirshfeld et al., 1989).

Finally, a rapidly emerging field of psychiatric research is investigating the health implications of the gut-brain axis. There are several lines of evidence that suggest that gut microbiota can influence brain chemistry and consequently mood. Stress can influence the composition of the gut microbiome, while animal studies have revealed that manipulating the gut microbiome alters anxiety- and depressive-like behaviours (Foster
& Neufeld, 2013). As well, preliminary investigations into the effects of probiotics on mood in humans have revealed a significant decrease in psychological distress (Benton et al., 2007; Messaoudi et al., 2011). While more work is needed to further elucidate the impact of the gut microbiome on mental health, it is a promising area of research.

As indicated by the wide range of literature on the etiology and pathophysiology of MDD, there are a variety of underlying factors that have been identified. This suggests that MDD is not only a complex disorder, but also a heterogeneous one whose etiology and pathophysiology vary between individuals. That is, MDD may not be the result of a single etiology but rather may arise as a result of various combinations of contributing factors. This is reflected in the heterogeneity of the groupings of symptoms that one can experience to meet the criteria for a diagnosis of MDD as well as in the wide range of treatments that have varying levels of efficacy in individual people.

2.2 Sleep

Sleep is a distinct physiological state characterized by closure of the eyes, relaxation of postural muscles, and an altered level of consciousness such that responsiveness to the external environment is significantly decreased (Roth, 2004). While sleep may seem like a passive state, it is actually an active neurophysiological state that is essential to our basic functioning. Sleep deprivation results in impairments in cognition and physical performance, with chronic sleep deprivation being associated with health conditions such as diabetes and hypertension (Alvarez & Ayas, 2004). The characteristics of sleep can be measured by polysomnography, a multi-parametric method that obtains information about brain wave activity using electroencephalography (EEG), muscle tone using electromyography (EMG), and eye movements using electrooculography (EOG).
2.2.1 Normal Sleep Architecture

Sleep can be separated into two main components that cycle throughout the night, NREM sleep and REM sleep. Non-rapid eye movement sleep can be further divided into stages 1, 2, 3, and 4, with stages 3 and 4 together comprising SWS, the deepest stage of sleep (Markov & Goldman, 2006). Each component of sleep is associated with a distinct set of physiological characteristics and electroencephalogram patterns.

Sleep is first initiated in stage 1 of NREM sleep, which lasts only a few minutes as one transitions from wakefulness to sleep in the first sleep cycle. During this transition, EEG patterns consisting of low-voltage alpha waves (8-13 Hz) that are associated with a relaxed mental state are replaced by low-voltage mixed frequency theta waves having a frequency of 4–8 Hz (Markov & Goldman, 2006). In subsequent sleep cycles, stage 1 serves as the transition from REM sleep in one cycle to NREM sleep in the next cycle. Slow, asynchronous eye movements occur, muscle activity begins to decrease, and individuals can be easily aroused (Markov & Goldman, 2006).

As one falls deeper asleep, they enter stage 2 where theta waves continue and sleep spindles and K-complexes appear. Sleep spindles are 12-14 Hz synchronized EEG waveforms with a duration of 1.5 seconds generated by GABAergic neurons in the thalamic reticular nucleus (De Gennaro & Ferrara, 2003). Rechtshaffen and Kales (1968) describe K-complexes as sharp, negative waves having a duration of 0.5 seconds that are followed by a positive component. Their origin is unknown. While in stage 2, no eye movements occur, muscle activity continues to decline, and the arousal threshold increases such that it becomes harder to awaken the sleeper (Markov & Goldman, 2006).
The sleeper then progresses into stages 3 and 4, known as SWS. Stage 3 is characterized by EEG patterns consisting of 20-50% delta waves of 2 Hz or slower, also called slow waves, while stage 4 is designated when delta waves comprise more than 50% of the EEG pattern (Hirshkowitz, 2004). As SWS has a much higher arousal threshold than stages 1 and 2, it is often referred to as deep sleep. No eye movements occur and muscle tone continues to decline (Markov & Goldman, 2006). During this stage, memory consolidation takes place and human growth hormone, an important factor in tissue repair, is secreted (Holl, Hartman, Veldhuis, Taylor, & Thorner, 1991; Walker & Stickgold, 2004).

Following NREM sleep is REM sleep. The first period of REM sleep is brief and occurs approximately 90 minutes after sleep onset (Markov & Goldman, 2006). The EEG pattern during REM sleep resembles that of early drowsiness as it consists of low-voltage, desynchronized alpha waves (8-13 Hz) (Markov & Goldman, 2006). Because of this, REM sleep is also referred to as paradoxical sleep as the brain waves produced resemble those seen during a relaxed waking state but, unlike the waking state, the individual is behaviorally unresponsive. Aside from middle ear muscle activity and the rapid eye movements for which this stage of sleep is named, the body is in full paralysis, called REM atonia. In addition, increases in heart rate, blood pressure, and respiratory rate occur (Erwin, Somerville, & Radtke, 1984). Most dreams transpire during REM sleep, with these dreams tending to be more vivid and memorable (Hobson, 2009).

In normal sleep architecture, three to seven NREM-REM cycles occur during an episode of sleep, lasting approximately 90 to 120 minutes each (Markov & Goldman, 2006). In healthy adults, most time asleep is spent in NREM sleep, which accounts for
75-80% of total sleep time. Specifically, the least amount of time is spent in stage 1, which constitutes 2-5% of total sleep time, while stage 2 and SWS generally comprise 45-55% and 15-23% of total sleep time, respectively. Altogether, REM sleep then consists of 20-25% of total sleep time (Markov & Goldman, 2006). The first period of REM sleep is brief; however, throughout the night, episodes of REM sleep progressively become longer as time spent asleep shifts from SWS to REM sleep. Thus, during the first third of the night, each sleep cycle consists predominately of SWS, which lasts on average 40 minutes per cycle, while REM sleep dominates sleep cycles in the last third of the night (Markov & Goldman, 2006). In a healthy adult, sleep onset generally occurs within 15 minutes and there are few nighttime awakenings such that sleep efficiency is around 95% (Hirshkowitz, 2004).

Sleep patterns change as a function of aging. During the first year of life, infants sleep twice as much as adults and enter directly into REM sleep. Infants spend about 50% of their total sleep time in REM sleep, which declines down to 20-25% by age three and remains stable until old age (Markov & Goldman, 2006). Slow wave sleep is not present at birth but is developed by the time the infant is six months old. From young adulthood, the percentage of time spent in SWS declines as one ages, with some elderly individuals experiencing no SWS at all (Hirshkowitz, 2004). This decline in SWS is associated with a greater percentage of time spent in stage 1 of sleep (Markov & Goldman, 2006). The elderly also experience greater sleep fragmentation and a decrease in their overall total sleep time. This may be due to sleep-related pathophysiology, such as arousals from sleep apnea, or may be a direct consequence of the aging process (Hirshkowitz, 2004).
2.2.2 Physiology of Sleep

Sleep-wake cycles in mammals are maintained both by circadian rhythms and homeostatic regulation. The suprachiasmatic nucleus (SCN), located in the anterior hypothalamus, is responsible for controlling circadian rhythms. Circadian rhythms are entrained to the light-dark cycle by the retinohypothalamic tract, which releases glutamate to the SCN when light hits retinal ganglion cells. This allows the hypothalamus to synchronize various neuronal and hormonal activities, including sleep regulation, to the light-dark cycle (Reppert & Weaver, 2002). This doesn’t fully account for sleep regulation, however, as sleep pressure and sleepiness during the day increase following sleep deprivation. When normal sleep is preserved, the homeostatic drive builds up during the day and reaches its peak at sleep time. Its strength then declines during sleep with the lowest point on awakening. When one is sleep deprived and has an increased need for sleep, the homeostatic drive to sleep increases further (Markov & Goldman, 2006). As the need for sleep increases, somnogens, which are circulating factors such as adenosine, prostaglandins, and certain cytokines that act upon many brain regions to promote sleep, accumulate in the brain, creating the homeostatic drive to sleep (España & Scammell, 2011). Circadian rhythms and homeostatic factors thus work together to regulate the complex set of interacting neurotransmitter systems that control sleep.

There are a variety of neurochemical systems that promote wakefulness by projecting to cortical and subcortical regions. These projections include the transmission of norepinephrine from the locus coeruleus, serotonin from the dorsal raphe nucleus, histamine from the tubermammillary nucleus (TMN) in the posterior hypothalamus, and acetylcholine from the basal forebrain and the laterodorsal and pedunculopontine
Tegmental nuclei (LDT and PPT, respectively) in the brainstem (España & Scammell, 2011). Two preoptic areas located in the anterior hypothalamus, the ventrolateral preoptic nucleus (VLPO) and the median preoptic nucleus (MnPO), are thought to be responsible for sleep onset and maintenance by inhibiting these arousal-promoting regions. Neurons in the VLPO and MnPO release the inhibitory neurotransmitter γ-aminobutyric acid (GABA) and innervate these arousal regions, turning off their activity (Markov & Goldman, 2006). The MnPO is mostly active just before the onset of NREM sleep and is thought to respond to somnogens, suggesting a role for the MnPO in the initiation of sleep (Saper, 2013). Conversely, the VLPO fires most frequently during NREM sleep and is inactive during wakefulness, indicating a role in sleep maintenance (España & Scammell, 2011). During wakefulness, monoaminergic and cholinergic signalling from the arousal regions inhibit the VLPO, disinhibiting their own activity in order to produce wakefulness. The transitions between wakefulness and sleep therefore rely on mutual disinhibition of these two systems in what is called a “flip-flop switch” to produce a stable cycle of wakefulness and sleep (España & Scammell, 2011).

The classic model of the cycle between NREM and REM sleep proposes that REM sleep is initiated by a subpopulation of cholinergic neurons in the LDT and PPT that remains active during REM sleep. During wakefulness and NREM sleep, these cholinergic neurons are inhibited by noradrenergic neurons in the locus ceruleus and serotonergic neurons in the dorsal raphe nucleus (España & Scammell, 2011). However, more recent evidence indicates that this model doesn’t sufficiently explain the NREM/REM cycle and suggests the involvement of two additional brain regions, the sublaterodorsal nucleus (SLD), a small cluster of cells ventral to the locus coeruleus, and...
the ventrolateral periaqueductal grey matter and lateral pontine tegmentum (vlPAG-LPT). The SLD is active during REM sleep but is inhibited during wakefulness and NREM sleep by GABAergic neurotransmission from the REM-suppressing vlPAG-LPT. The SLD in turn sends inhibitory GABAergic signals to the vlPAG-LPT to suppress its activity during REM sleep so that REM can be produced and maintained, creating a second flip-flop switch that is hypothesized to regulate the cyclical transitions between REM and NREM sleep (Lu & Zee, 2010). It is thought that the cholinergic neurons in the LDT and PPT modulate this switch by inhibiting the vlPAG-LPT and exciting the SLD to promote REM sleep, while the monoaminergic system additionally excites the vlPAG-LPT and inhibits the SLD to turn off REM sleep (Lu & Zee, 2010). Neurons in the SLD, LDT, and PPT are known to project to the cortex via the thalamus to produce the cortical activation that is required for dreams and to the ventromedial medulla to produce REM atonia (España & Scammell, 2011).

2.2.3 Relationship between Sleep Disturbances and Depression

Sleep disturbances are one of the most common symptoms of MDD, a finding that is reflected in their inclusion as one of the diagnostic criteria for MDD in the DSM-V (American Psychiatric Association, 2013). Indeed, reduced sleep quality is reported to occur in up to 90% of patients with MDD (Tsuno, Besset, & Ritchie, 2005). One of the most frequently seen sleep disturbances is insomnia, with about 66% of patients experiencing a MDE reporting significant difficulties falling asleep, frequent nighttime awakenings, and/or early-morning awakening (Perlis et al., 1997). Rates of hypersomnia, defined as excessive sleeping, vary across age groups and MDD subtypes, with a review by Kaplan and Harvey (2009) finding rates varying from 8.9% in childhood to 75.8% in
young adulthood. Other sleep disturbances include obstructive sleep apneas and nonrestorative sleep despite a normal duration of sleep (Lam, 2006).

Not only are sleep disturbances a common symptom of depression but depression frequently occurs in those with sleep disorders. The National Institute of Mental Health Epidemiologic Catchment Area study on sleep and psychiatric disorders (Ford & Kamerow, 1989) reported that 40.4% of people with insomnia and 46.5% of people with hypersomnia had a psychiatric disorder, compared to 16.4% of people who had no sleeping complaints. A systematic review by Ejaz et al. (2011) found that the prevalence of MDD in patients with obstructive sleep apneas is much higher than that of the general population, with rates ranging from 5% to 63%. Furthermore, the risk of developing MDD is much higher in those who have insomnia. A meta-analysis by Baglioni et al. (2011) found that non-depressed people with insomnia were twice as likely to develop depression compared to people with no sleep difficulties, while a separate study demonstrated that insomnia can be a prodromal symptom in recurrent MDD (Perlis, Giles, Buysse, Tu, & Kupfer, 1997). The correlation between insomnia and depression therefore appears to be bi-directional, with sleep problems being both a consequence of and a risk factor for MDD.

Of clinical interest are the findings that sleep difficulties are associated with illness severity and treatment response. A study assessing adolescents with MDD found that a greater number of sleep disturbances was associated with increasing depression severity, more depressive symptoms, and comorbid anxiety disorders (Liu et al., 2007). Furthermore, a meta-analysis by Malik et al. (2014) reported that compared to those without sleep disturbances, patients with MDD and co-morbid sleep disturbances were
significantly more likely to report suicidal behaviours. It has been demonstrated that sleep problems can predict treatment response, as at least two studies have shown that poorer sleep quality before the initiation of treatment was associated with a poorer treatment response (Buysse et al., 1999; Dew et al., 1997). Improvements in sleep quality have also been associated with lower recurrence rates of depression (Buysse et al., 1996).

2.2.4 Sleep Architecture in Depression

Several polysomnographic studies have demonstrated that sleep architecture is altered in those with MDD, with the two most significantly affected stages being SWS and REM sleep. Depressed sleep has consistently been characterized by a decrease in time spent in SWS, an increase in time spent in REM sleep, a shortened REM latency, and changes to the temporal distributions of REM and SWS (Ilanković et al., 2014; Kupfer & Foster, 1972; Pillai, Kalmach, & Ciesla, 2011). In those with MDD, the majority of SWS is generally shifted from the first to the second NREM period, while the distribution of REM sleep gets shifted towards the first half of the night (Gillin & Borbely, 1985). In addition, sleep fragmentation is often reported, with depressed patients experiencing a greater number of nighttime awakenings, decreased total sleep time, and early morning awakening (Kupfer & Foster, 1972).

These findings have several important implications. A meta-analysis by Pillai et al. (2011) discovered that not only are these abnormalities present in subjects with MDD but they can also be seen in their never depressed high-risk probands, suggesting a genetic component that may be useful as a biological marker for MDD. Latency to REM sleep has been correlated with depression severity such that those with more severe depression have significantly shorter REM onset latencies (Ilanković et al., 2014; Kupfer
& Foster, 1972). Furthermore, those that respond well to pharmacotherapy have been shown to have a significant increase in REM latency and decrease in REM sleep time and REM activity early on in their treatment, indicating that changes to sleep architecture may predict treatment response (Kupfer et al., 1976).

### 2.2.5 Physiology of Sleep Disturbances in Depression

The symptoms of abnormal mood and sleep regulation in MDD are thought to be a result of a common neurobiological underpinning – dysfunctional neurotransmission of serotonin, norepinephrine, and acetylcholine. As previously discussed, cholinergic neurons in the LDT and PPT are involved both in producing wakefulness and in the initiation of REM sleep, while serotonergic and noradrenergic neurons projecting to the vlPAG-LPT and SLD are involved in suppressing REM sleep. Proper regulation of REM sleep therefore relies on a balance between these two systems (Markov & Goldman, 2006). Both monoamine deficiency and elevated levels of acetylcholine have been observed in MDD (Drevets, Price, & Furey, 2008), resulting in an imbalance in the key neurotransmitters that regulate sleep. Thus, overactivation of these cholinergic neurons combined with deficient monoamine activity in those with MDD is likely responsible for the disinhibition of REM sleep, causing an increase in the time spent in REM and a decrease in REM onset latency. As cholinergic neurons are also responsible for promoting wakefulness, their increased activity may be what underlies the sleep fragmentation seen in MDD (Riemann, Berger, & Voderholzer, 2001).

Additionally, differences in activity in specific brain regions during sleep have been observed in MDD. An EEG and PET study by Nofzinger et al. (2004) found that, compared to healthy controls, depressed subjects showed greater activation in anterior
paralimbic structures, bilateral dorsolateral prefrontal, left premotor, primary sensorimotor, and left parietal cortices, and the midbrain reticular formation during REM sleep. The authors concluded that these findings reflect the increased REM activity in depressed sleep and are likely associated with cognitive and affective dysregulation. As well, a PET study by Ho et al. (1996) demonstrated that whole-brain absolute metabolic rate during NREM sleep was significantly greater in patients with MDD compared to healthy controls, reflecting hyperarousal of the cerebral cortex during depressed sleep that may impair one’s ability to restore higher-order cognitive functions during sleep.

2.3 Pharmacological Treatments of Depression

There are several pharmacological options available for the treatment of MDD. While most are antidepressants of various classes, other medications such as atypical antipsychotics may be prescribed as well. In a set of guidelines, the Canadian Network for Mood and Anxiety Treatment includes SSRIs, SNRIs, and the atypical antidepressants bupropion, mirtazapine, and agomelatine in its list of recommended first-line treatment options. Second-line recommendations include tricyclic antidepressants, the serotonin antagonist and reuptake inhibitor trazodone, and the atypical antipsychotic quetiapine, while recommended third-line options include monoamine oxidase inhibitors and reboxetine, a norepinephrine reuptake inhibitor (Kennedy et al., 2016).

2.3.1 Antidepressants and their Effects on Sleep

Antidepressant medications can be divided into several classes by their mechanism of action. The most commonly prescribed are the SSRIs. These antidepressants exert their effects by inhibiting the reuptake of serotonin from the synapse by the serotonin transporter (SERT) to increase serotonergic neurotransmission,
while having little to no affinity for other receptors (Hyttel, 1994). Several have been evaluated to elucidate their effects on sleep in those with MDD. Fluoxetine is one such SSRI that has been demonstrated to be safe and efficacious for treating MDD (Rossi, Barraco, & Donda, 2004). It inhibits the reuptake of serotonin, with no activity at the norepinephrine or dopamine transporters (Owens et al., 1997). Research into its effects on sleep in those with MDD has found that fluoxetine increases time spent in stage 1, decreases time spent in stage 2, and supresses REM sleep by increasing its onset latency and reducing the time spent in REM sleep, with no changes to SWS (Trivedi et al., 1999).

Sertraline is another SSRI that has proved efficacious for treating MDD, with one meta-analysis finding it more effective than others in its class (Cipriani et al., 2008). In addition to inhibiting the SERT, sertraline also has a low affinity for the dopamine transporter (MacQueen, Born, & Steiner, 2001). While treatment of depressed subjects with sertraline resulted in decreased REM onset latency and a fewer number of REM periods, the activity of the first and second REM periods was significantly increased. As well, the relative distribution of SWS was shifted from the second to the first sleep cycle, with a significant increase in time spent in SWS in the first cycle (Jindal et al., 2003).

Primarily an inhibitor of the serotonin transporter, the SSRI paroxetine also has a low affinity for the norepinephrine and dopamine transporters (Owens et al., 1997). Though it is effective in treating the symptoms of MDD, it has not been found to be better than other antidepressants (Katzman et al., 2007). One study of the administration of paroxetine to healthy volunteers found that it reduced the time spent in REM sleep, increased REM onset latency, increased nighttime awakenings, and reduced total sleep time (Sharpley et al., 1996). In depressed participants, time spent in stage 1 and the
number of nighttime awakenings increased early in treatment, resolving by the end of the study. Time spent in REM sleep and REM onset latency significantly decreased and increased, respectively, with no changes occurring in SWS (Hicks et al., 2002).

Citalopram, the racemic mixture of its R- and S-enantiomers, and escitalopram, composed purely of S-citalopram, are two SSRIs that have little to no affinity for other neurotransmitter transporters or receptors (Owens et al., 1997). Escitalopram has demonstrated greater efficacy and faster onset of action compared to citalopram, which is thought to be due to the inhibition of the effects of the S-enantiomer by the R-enantiomer (Sánchez et al., 2004). Treatment of depressed patients with citalopram resulted in a significant decrease in time spent in REM sleep and a significant increase in REM onset latency and time spent in stage 2, with no change to sleep continuity (van Bemmel et al., 1993). Escitalopram, however, has been shown to significantly decrease total sleep time, sleep efficiency, and SWS in addition to suppressing REM sleep in both healthy volunteers and depressed participants (Doerr et al., 2010; Quera-Salva et al., 2011).

Fluvoxamine is an SSRI that exclusively inhibits the reuptake of serotonin, with no effect on dopamine or norepinephrine (Claassen et al., 1997). It has been described as being efficacious in the treatment of MDD but not more so than other antidepressants (Omari et al., 2010). Two studies have reported that administration of fluvoxamine to depressed patients resulted in suppressed REM sleep, increased sleep onset latency, and decreased sleep efficiency early on, all of which returned to baseline after continued treatment (Kupfer et al., 1991; Wilson et al., 2000).

Serotonin norepinephrine reuptake inhibitors significantly inhibit the norepinephrine transporter (NET) in addition to the SERT, preventing the reuptake of
both serotonin and norepinephrine to increase their neurotransmission. Like SSRIs, 
SNRIs are a commonly prescribed class of antidepressants due to their well-established 
efficacy and tolerability (Stahl et al., 2005). Unlike SSRIs, however, research into the 
effects of SNRIs on sleep is lacking. One study found that compared to placebo, 
administration of venlafaxine resulted in an increase in REM sleep onset latency and a 
decrease in the total time spent in REM sleep in participants with MDD (Luthringer et al., 
1996). Another demonstrated that treatment of depressed patients with milnacipran 
significantly increased REM sleep onset latency, although total time spent in REM sleep 
was unaffected. As well, there was an increase in total sleep duration, with more time 
being spent in stage 2 (Lemoine & Faivre, 2004). More recently, an open-label trial found 
that duloxetine increased REM sleep onset latency and time spent in stage 3 and 
decreased the total time spent in REM sleep in depressed patients (Kluge et al., 2007).

Tricyclic antidepressants are an older class of antidepressants that are named for 
their three ringed chemical structure. Most TCAs work by blocking the SERT and NET, 
inhibiting their reuptake of serotonin and norepinephrine, respectively, to enhance their 
neurotransmission. Many TCAs also antagonize various serotonin receptors (5-HT$_{2A}$, 5-
HT$_{2C}$, 5-HT$_6$, and 5-HT$_7$), the histamine H1 receptor, the $\alpha_1$-adrenergic receptor, and 
muscarinic acetylcholine receptors (Gillman, 2007). Although their overall efficacy is 
comparable, SSRIs and SNRIs have fewer sites of action and have therefore largely 
replaced TCAs due to their favourable side effect profiles (Arrol et al., 2005; Stephens et 
al., 1997). Treatment with the TCA amitriptyline has been found to increase REM onset 
latency and reduce nighttime awakenings and time spent in REM sleep in depressed 
subjects (Gillin et al., 1978; Mendlewicz et al., 1991), while studies examining
imipramine and clomipramine have reported that both drugs suppress REM sleep but also reduce sleep efficiency and total sleep time (Kupfer et al., 1979; Kupfer et al., 1989).

Monoamine oxidase inhibitors are antidepressant medications that work by inhibiting the activity of the monoamine oxidase enzyme family, which prevents the breakdown of monoamine neurotransmitters to increase their activity (Thase et al., 1995). While efficacious in treating MDD, they are generally reserved as a last line of pharmacotherapy when no improvement has been seen with other treatments due to their potential for serious side effects and interactions with several dietary supplements and over-the-counter medications (Thase et al., 1995). Research suggests that the MAOI phenelzine dramatically suppresses REM sleep and increases time spent in stage 2 with no effect on SWS in patients with MDD (Landolt et al., 2001). These same effects have also been observed in moclobemide but to a lesser extent (Monti et al., 1990).

Atypical antidepressants are those whose mechanisms of action don’t fit into the other classes. Bupropion is one such medication as it acts as a dual norepinephrine and dopamine reuptake inhibitor with no clinically significant serotoninergic action (Stahl et al., 2004). It has shown positive efficacy and tolerability in treating MDD and may be combined with other antidepressants for patients failing antidepressant monotherapy (Moreira, 2011). Reports of the changes in the sleep architecture of depressed patients following bupropion treatment are inconsistent. Ott et al. (2004) reported that bupropion significantly lengthened REM latency, increased REM activity and density during the first REM period, and increased total REM density, while Nofzinger et al. (1995) found that REM latency was reduced and percentage of time spent in REM sleep increased. A
more recent study by Nofzinger et al. (2001) found no changes in REM sleep, though this study had a significantly smaller sample size.

Mirtazapine is another atypical antidepressant whose clinical effects are a result of the increase in noradrenergic and 5-HT\textsubscript{1A}-mediated serotonergic neurotransmission that occurs through mirtazapine’s blockade of inhibitory presynaptic adrenergic \(\alpha_2\)-autoreceptors and serotonergic \(\alpha_2\)-heteroreceptors (De Boer, 1996). Mirtazapine has little to no affinity for other receptors and so is an effective and well-tolerated antidepressant (Fawcett & Barkin, 1998). There have been several studies investigating its effects on sleep in depressed subjects, though they have produced conflicting results. Winokur et al. (2000) and Schmid et al. (2006) both found that mirtazapine administration had no significant effects on REM sleep. In a study by Schittecatte et al. (2002), however, REM onset latency increased and Shen et al. (2006) stated that the medication increased REM onset latency and the duration of the first REM episode, while decreasing the number of REM episodes. All four studies reported that sleep onset latency decreased while sleep efficiency increased and all but Winokur et al. (2000) found an increase in total SWS.

Agomelatine is a melatonergic antidepressant that acts as a MT\textsubscript{1} and MT\textsubscript{2} receptor agonist and a 5-HT\textsubscript{2C} receptor antagonist (Srinivasan et al., 2012). Blockade of the inhibitory 5-HT\textsubscript{2C} receptors increases dopaminergic and noradrenergic transmission in the frontal cortex (Millan et al., 2003). Studies show that not only is it an efficacious antidepressant with a good tolerability profile but it can also lead to the normalization of disturbed circadian rhythms (Farnaro et al., 2010; Kennedy & Rizvi, 2010). In an open-label study administering agomelatine to depressed subjects, agomelatine improved sleep
efficiency, increased total time spent in SWS, and normalized the distribution of SWS but had no significant impact on REM sleep (Salva et al., 2007).

Trazodone is an atypical antidepressant that inhibits the SERT and antagonizes both the 5-HT$_{2A}$ and 5-HT$_{2C}$ receptors (Stahl, 2009). Trazodone also acts as an agonist at 5-HT$_{1A}$ receptors, meaning its administration results in increased serotonergic activity exclusively at 5-HT$_{1A}$ receptors (Odagaki, Toyoshima, & Yamauchi, 2005). Given that increased activity at the 5-HT$_{2A}$ and 5-HT$_{2C}$ receptors is thought to be responsible for the side effects associated with SSRIs and SNRIs, trazodone avoids some of their tolerability issues. It also has antagonistic activity at $\alpha_1$- and $\alpha_2$-adrenergic receptors and histamine H$_1$ receptors (Stahl, 2009). Trazodone has proved to be an efficacious treatment for MDD (Al-Yassiri, Ankier, & Bridges, 1983; Cunningham et al., 1994). Studies by Mouret et al. (1988), Scharf and Sachais (1990), and vanBemmel, Havermans, and van Diest (1991) have shown that treatment of depressed patients with trazodone resulted in an increase in REM latency, with Mouret et al. (1991) and Scharf and Sachais (1990) additionally reporting an increase in total sleep time and time spent in SWS as well as a decrease in sleep latency and nighttime awakenings.

While each antidepressant has different effects on sleep, antidepressants of all classes generally suppress REM sleep, increasing REM onset latency and reducing time spent in REM sleep. Changes to the other stages, number of nighttime awakenings, and sleep efficiency are less consistent, with some medications having positive impacts and others resulting in negative or no changes. Few antidepressants have been consistently shown to improve sleep architecture in depressed patients beyond REM sleep.
2.3.2 Desvenlafaxine

Desvenlafaxine is a relatively novel SNRI antidepressant and is the synthetic form of the major active metabolite of venlafaxine. It produces its antidepressant effects through selective binding to the SERT and NET, inhibiting the reuptake of serotonin and norepinephrine back into the pre-synaptic neuron. This action increases their extracellular levels and thus increases their activity in the synapse. Desvenlafaxine has demonstrated a higher affinity for the SERT, being approximately 10-times more potent at inhibiting serotonin reuptake than that of norepinephrine, and a very low affinity for the dopamine transporter (Deecher et al., 2006). It has no significant activity at any other sites in the central nervous system, including at histamine, serotonin, and adrenergic receptors, which means a favourable side effect profile is associated with the administration of desvenlafaxine (Deecher et al., 2006).

Several studies have demonstrated the safety and efficacy of desvenlafaxine in treating MDD (DeMartinis, Yeung, Entsuah, & Manley, 2007; Liebowitz, Yeung, & Entsuah, 2007; Septien-Velez et al., 2007). Two pooled analyses of double-blinded, placebo-controlled clinical trials (Carrasco et al., 2016; Soares et al., 2009) concluded that treatment with desvenlafaxine at both 50 and 100 mg/day was well tolerated and was associated with significant improvements in functioning, depression scores, and well-being among depressed patients. While it is most commonly prescribed for depression, treatment with desvenlafaxine has shown modest improvement in anxiety symptomology as well, supporting its less common off-label prescription for generalized anxiety disorder (Tourian et al., 2010; Maity et al., 2014). The advantages of using desvenlafaxine over other antidepressants include no significant effects on sexual functioning (Clayton et al.,
2013), no clinically significant weight gain (Tourian et al., 2010), and low rates of discontinuation symptoms for the 50 mg dose (Khan et al., 2014). As well, as venlafaxine is metabolized into desvenlafaxine primarily by the cytochrome P450 (CYP) enzyme 2D6 in the liver, desvenlafaxine is a safer and more efficacious antidepressant for those who are CYP2D6 poor metabolizers (Lobello et al., 2010).

While several studies have examined the impact of SSRIs on sleep in depressed subjects, research into the effects of SNRIs is lacking. Studies have demonstrated improvements in the sleep architecture of depressed patients following treatment with duloxetine, venlafaxine, and milnacipran but no such research to date has been conducted on desvenlafaxine. The only studies reporting on changes in sleep following administration of desvenlafaxine have been those conducted in menopausal women, which have largely found that desvenlafaxine reduces the number of nighttime awakenings due to hot flushes (Speroff, Gass, Constantine, & Olivier, 2008; Archer, Seidman, Constantine, Pickar, & Olivier, 2009).
Chapter 3: Methods

This is a prospective, placebo-controlled, double-blinded repeated measures polysomnographic study of patients with MDD receiving desvenlafaxine as a treatment. This study was approved by the Queen’s University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board and the Health Canada Therapeutic Products Directorate.

3.1 Participants

A total of 21 participants were recruited by online advertisements and advertisements placed in general practitioner offices and on community bulletin boards. Of these, seven participants failed baseline screening – six due to subclinical mood symptoms and one due to potentially dangerous elevated liver enzymes – and five participants withdrew their consent before randomization and were therefore not included in the analysis as only their baseline clinical scales were completed. The remaining nine participants were included in the analysis. One participant relocated and subsequently withdrew consent before day 28-31 due to an inability to travel to the study location but remained in the analysis. A flow chart of participant selection and randomization can be seen in Figure 1. Participants were recruited and enrolled between September 2011 and May 2016.

All participants met inclusion criteria dictating they be between the ages of 18 and 65, meet DSM-IV-TR criteria for MDD, confirmed by the Mini International Neuropsychiatric Inventory version 6.0.0 (MINI 6.0.0), and be experiencing a major depressive episode as indicated by a Hamilton Depression Rating Scale-17 (HDRS-17)
score ≥ 17 at time of enrollment. Exclusion criteria included a current manic, hypomanic, or mixed episode as indicated by a Young Mania Rating Scale (YMRS) score > 12, a current or past diagnosis of schizophrenia or dementia, a history of seizures, substance or alcohol dependence (excluding caffeine and nicotine) within three months prior to enrollment, a known intolerance or lack of response to desvenlafaxine, an imminent risk of suicide or danger to self or others, any serious, unstable, or inadequately treated medical illnesses, previous enrollment in this study or participation in another drug trial within four weeks prior to enrollment, and any involvement in the planning of this study. Additionally, participants could not be taking lithium, sleep aids, or any other antidepressant medications at the time of enrollment and must have had no changes to their medication regimes (excluding discontinuation of sleep aids) in the four weeks prior. Female participants of child bearing potential must have had a negative urine human chorionic gonadotropin test and had to be willing to use a reliable method of contraception. Pre-existing medical conditions of participants can be seen in Table I of appendix A.

3.2 Medication

Within 7 days after the baseline assessment, participants were randomly assigned using a randomization table to receive either desvenlafaxine or a placebo. Desvenlafaxine was administered at a dose of 50mg once daily for the duration of the study. Participants were not taking any anti-psychotics, mood stabilizers, benzodiazepines, or any other antidepressants. A list of adverse events that occurred through the duration of the study can be seen in Table II of appendix A.
3.3 Clinical Measures

Participants were assessed with clinical scales at three time points throughout the study: baseline (prior to randomization) as well as 3-5 days and 28-31 days after randomization and initiation of study medication. At each assessment, the HDRS-17 (Hamilton, 1960), Montgomery Asberg Depression Rating Scale (MADRS) (Montgomery & Asberg, 1979), Hamilton Anxiety Rating Scale (HARS) (Hamilton, 1959), and YMRS (Young, Biggs, Ziegler, & Meyer, 1978) were administered to assess symptoms of mood and anxiety. As well, the self-administered Epworth Sleepiness Scale (ESS) (Johns, 1991), Pittsburgh Sleep Quality Index (PSQI) (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989), and a visual analogue scale (VAS) for sleep quality were completed by participants to assess subjective sleep quality. At the baseline assessment, the MINI 6.0.0 (Lebubier et al., 1997) and Clinical Global Impression-Severity scale (CGI-S) (Guy, 1976) were also administered, in addition to a physical examination and pregnancy test, while at the day 28-31 assessment, both the CGI-S and the Clinical Global Impression-Improvement scale (CGI-I) (Guy, 1976) were administered. Blood work was performed at the baseline and day 28-31 assessments.

3.4 Polysomnographic Recordings

Sleep architecture and objective sleep quality were assessed by overnight, at home polysomnography using the Cadwell Easy Ambulatory PSG (Cadwell Industries Inc., Kennewick, WA) at three time points throughout the study: at baseline and at 3-5 days and 28-31 days after randomization and initiation of study medication. Each evening, the ambulatory PSG equipment was brought to the participants’ homes and once set up, participants were asked to retire and rise at their usual times. Recording began as soon as
the set up was completed, generally around 9:30pm, and continued until the participant woke the following morning and turned off the PSG. Participants were asked to refrain from alcohol consumption on these nights.

The polysomnogram included four electroencephalogram channels – left and right centrocephalic electrodes (C3-A2, C4-A1) and left and right occipital electrodes (O1-A2, O2-A1) – as well as two electrocardiogram channels (left and right), two electrooculogram channels (left and right), four anterior tibialis electromyogram channels (two left and two right), and two masseter electromyogram channels. A finger pulse oximeter, nasal cannula to measure airflow, body position sensor, vibration snore sensor, and chest and abdomen movement belts were also used. Patients were not monitored overnight and were asked to replace any equipment that fell off throughout the night to the best of their ability.

Each PSG was scored by a trained PSG analyst who was blinded to the condition of the participants in 30 second epochs according to standardized criteria of Rechtschaffen and Kales using the Cadwell Easy Ambulatory III Ambulatory software system. Sleep onset latency was calculated as the total number of minutes from lights off to the first epoch of sleep. Latencies to each sleep stage were calculated as the total number of minutes from the first epoch of sleep until the first epoch of each sleep stage. Total sleep time (TST) was calculated as the total number of minutes spent asleep throughout the recording. The percentage of time spent in each sleep stage was calculated as the time spent in each stage divided by the TST, multiplied by 100. Sleep efficiency was calculated as the TST divided by the total time spent in bed, multiplied by 100. Arousals were scored based on American Sleep Disorders Association (1992) criteria as
being abrupt shifts in EEG frequency to alpha or theta that are at least 3 seconds in
duration and are preceded by at least 10 seconds of sleep. Arousals scored during REM
sleep must have been accompanied by concurrent increases in electromyogram tone.
Obstructive apneas and hypopneas were scored using the criteria from the American
Academy of Sleep Medicine Task Force (1999). Events were scored either when a
decrease of at least 50% from baseline (defined as the mean amplitude of stable breathing
during the two minutes preceding the event) occurred in the amplitude of the airflow
signal, lasting at least 10 seconds, or when a clear reduction of less than 50% from
baseline occurred for at least 10 seconds along with either an arousal or a greater than 3%
reduction in oxygen saturation.

3.5 Statistical Analysis

Due to the small sample size used in the study, the distribution of each of the
dependent variables was assessed for normality. Both visual inspection of histograms of
the data and Shapiro-Wilk’s test indicated that the data was not normally distributed ($p <
0.05$). As such, statistical analysis was performed using non-parametric tests.

The study design included 2 treatment groups (between-subjects) assessed across
three time points (within-subjects). Between-subjects comparisons for all clinical scales
and PSG parameters were assessed at each time point using Mann-Whitney U tests.
Within-subjects comparisons for all measures were performed for both treatment groups
using the Friedman test. Post hoc analyses were completed using pairwise comparisons
with a Bonferroni correction for multiple comparisons. Baseline sociodemographic
comparisons between the two groups were analyzed using Fisher’s exact test. All tests
and calculations were performed using IBM SPSS Statistics version 24.0.
Figure 1. Participant Selection and Randomization into the Placebo and Treatment Groups.
Chapter 4: Results

4.1 Sociodemographic Characteristics

A total of nine participants, two males and seven females, participated in this study. Their mean (± SD) age was 26 ± 10 years, ranging from 19 to 48 years old. For the placebo and treatment groups, the mean (± SD) age was 29 ± 16 years and 24 ± 6 years, respectively. Participants in the two groups did not differ significantly on gender, age, ethnicity, education level, employment status, marital status, or number of children ($p = 0.500; p = 1.000; p = 0.643; p = 0.333; p = 1.000; p = 0.583; p = 1.000$). Demographic characteristics for each group can be seen in Table 1.

4.2 Clinical Measures

4.2.1 Illness Severity

Mann-Whitney U tests found no significant differences at baseline, day 3-5, and day 28-31 in the distribution of HDRS, MADRS, HARS, YMRS, CGI-S, and CGI-I scores between the desvenlafaxine-treated and placebo groups. Tables 2, 3, and 4 present the medians and results of the Mann-Whitney U tests for these measures at baseline, day 3-5, and day 28-31, respectively. Freidman test results, however, detected significant differences over time in HDRS ($\chi^2(2) = 9.579, p = 0.008$), MADRS ($\chi^2(2) = 8.400, p = 0.015$), HARS ($\chi^2(2) = 6.000, p = 0.050$), and CGI-S ($\chi^2(2) = 0.000, p = 0.041$) scores for the desvenlafaxine-treated group. Post hoc analyses revealed that these changes were significant for the comparison of baseline to day 28-31. Median scores (± 95% confidence interval) decreased significantly from 20.500 ± 3.525 at baseline to 6.500 ± 5.128 at day 28-31 for the HDRS ($\chi^2(2) = 1.900, p = 0.008$) and from 26.000 ± 8.973 at baseline to 11.000 ± 9.133 at day 28-31 for the MADRS ($\chi^2(2) = 1.800, p = 0.013$).
Table 1. Sociodemographic Characteristics
P-value reported for Fisher’s exact test of each characteristic.

<table>
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**Table 2. Clinical Measures at Baseline**
The medians (± 95% confidence intervals) and Mann-Whitney U test results for illness severity and subjective sleep quality measures. HDRS = Hamilton Depression Rating Scale, MADRS = Montgomery Asberg Depression Rating Scale, HARS = Hamilton Anxiety Rating Scale, YMRS = Young Mania Rating Scale, CGI-S = Clinical Global Impression-Severity Scale, ESS = Epworth Sleepiness Scale, PSQI = Pittsburg Sleep Quality Index, VAS = Visual Analogue Scale.

<table>
<thead>
<tr>
<th>Scales</th>
<th>Desvenlafaxine (n = 6)</th>
<th>Placebo (n = 3)</th>
<th>U-value</th>
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<th>p-value</th>
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<td>Median (± 95% CI)</td>
<td>Mean Rank</td>
<td>Median (± 95% CI)</td>
<td>Mean Rank</td>
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<td>HDRS</td>
<td>20.500 ± 3.525</td>
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<td>20.000 ± 2.719</td>
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<td>MADRS</td>
<td>26.000 ± 8.973</td>
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<td>28.000 ± 14.503</td>
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<td>HARS</td>
<td>16.500 ± 10.095</td>
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<td>9.000</td>
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<td>YMRS</td>
<td>4.000 ± 2.884</td>
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<td>4.000 ± 3.626</td>
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<td>CGI-S</td>
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<td>ESS</td>
<td>10.000 ± 4.487</td>
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<td>8.500</td>
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<tr>
<td>PSQI</td>
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<td>10.000 ± 3.626</td>
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<tr>
<td>VAS</td>
<td>37.000 ± 17.626</td>
<td>5.50</td>
<td>28.000 ± 27.800</td>
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<td>12.000</td>
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</table>

**Table 3. Clinical Measures at Day 3-5**
The medians (± 95% confidence intervals) and Mann-Whitney U test results for illness severity and subjective sleep quality measures. HDRS = Hamilton Depression Rating Scale, MADRS = Montgomery Asberg Depression Rating Scale, HARS = Hamilton Anxiety Rating Scale, YMRS = Young Mania Rating Scale, ESS = Epworth Sleepiness Scale, PSQI = Pittsburg Sleep Quality Index, VAS = Visual Analogue Scale.

<table>
<thead>
<tr>
<th>Scales</th>
<th>Desvenlafaxine (n = 6)</th>
<th>Placebo (n = 3)</th>
<th>U-value</th>
<th>z-score</th>
<th>p-value</th>
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<tbody>
<tr>
<td></td>
<td>Median (± 95% CI)</td>
<td>Mean Rank</td>
<td>Median (± 95% CI)</td>
<td>Mean Rank</td>
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<tr>
<td>HDRS</td>
<td>15.000 ± 2.106</td>
<td>4.90</td>
<td>14.000 ± 5.439</td>
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<td>MADRS</td>
<td>21.000 ± 5.266</td>
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<td>21.000 ± 6.345</td>
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<tr>
<td>HARS</td>
<td>15.000 ± 7.021</td>
<td>4.20</td>
<td>17.000 ± 2.719</td>
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<tr>
<td>YMRS</td>
<td>4.000 ± 2.808</td>
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<td>3.000 ± 1.813</td>
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<td>ESS</td>
<td>10.000 ± 3.365</td>
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<td>9.000 ± 9.064</td>
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<td>10.000</td>
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<tr>
<td>PSQI</td>
<td>10.000 ± 4.326</td>
<td>6.00</td>
<td>8.000 ± 1.813</td>
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<td>VAS</td>
<td>41.500 ± 23.074</td>
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Table 4. Clinical Measures at Day 28-31
The medians (± 95% confidence intervals) and Mann-Whitney U test results for illness severity and subjective sleep quality measures. HDRS = Hamilton Depression Rating Scale, MADRS = Montgomery Asberg Depression Rating Scale, HARS = Hamilton Anxiety Rating Scale, YMRS = Young Mania Rating Scale, CGI-S = Clinical Global Impression-Severity Scale, CGI-I = Clinical Global Impression-Improvement Scale, ESS = Epworth Sleepiness Scale, PSQI = Pittsburg Sleep Quality Index, VAS = Visual Analogue Scale. * indicates that 95% confidence intervals could not be calculated as the sample size was too small.

<table>
<thead>
<tr>
<th>Scales</th>
<th>Desvenlafaxine (n = 6)</th>
<th>Placebo (n = 3)</th>
<th>U-value</th>
<th>z-score</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median (± 95% CI)</td>
<td>Mean Rank</td>
<td>Median</td>
<td>Mean Rank</td>
<td></td>
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<tr>
<td>HDRS</td>
<td>6.500 ± 5.128</td>
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<td>MADRS</td>
<td>11.000 ± 9.133</td>
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<td>HARS</td>
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<td>9.500*</td>
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<td>6.000</td>
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<td>YMRS</td>
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<td>4.000*</td>
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<td>CGI-S</td>
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<td>CGI-I</td>
<td>2.000 ± 0.801</td>
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<td>4.000*</td>
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<td>ESS</td>
<td>8.500 ± 6.570</td>
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<td>10.500*</td>
<td>5.50</td>
<td>4.000</td>
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<tr>
<td>PSQI</td>
<td>8.000 ± 4.967</td>
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<td>7.500*</td>
<td>4.50</td>
<td>6.000</td>
</tr>
<tr>
<td>VAS</td>
<td>54.500 ± 17.946</td>
<td>5.17</td>
<td>37.000*</td>
<td>2.50</td>
<td>10.000</td>
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</table>
Median (± 95% confidence interval) CGI-S scores decreased significantly from 4.000 ± 0.801 at baseline to 2.000 ± 1.442 at day 28-31 ($\chi^2(2) = 1.900, p = 0.008$). Post hoc analysis with significance levels uncorrected for multiple comparisons found a significant decrease in HARS scores from 16.500 ± 10.095 at baseline to 7.500 ± 7.211 at day 28-31 ($\chi^2(2) = 1.500, p = 0.018$). There were no significant changes over time for the placebo group in HDRS ($\chi^2(2) = 4.000, p = 0.135$), MADRS ($\chi^2(2) = 3.000, p = 0.223$), HARS ($\chi^2(2) = 2.000, p = 0.368$), and CGI-S scores ($\chi^2(2) = 0.000, p = 0.317$). Additionally, there were no significant changes in YMRS scores for either the desvenlafaxine-treated group ($\chi^2(2) = 1.444, p = 0.486$) or the placebo group ($\chi^2(2) = 0.000, p = 1.000$).

4.2.2 Subjective Sleep Quality

Mann-Whitney U tests found no significant differences in the distribution of ESS, PSQI, and VAS scores between the two groups any time point. Mann-Whitney U test results can be seen in Tables 2, 3, and 4. Investigation with Freidman tests revealed a significant difference over time in PSQI scores for the desvenlafaxine-treated group ($\chi^2(2) = 8.667, p = 0.013$) but not for the placebo group ($\chi^2(2) = 0.286, p = 0.867$). Post hoc analysis found that median PSQI scores (± 95% confidence interval) decreased significantly from 12.500 ± 4.326 at baseline to 8.000 ± 4.967 at day 28-31 ($\chi^2(2) = 1.417, p = 0.042$), as illustrated in Figure 2A. There were no significant changes in ESS or VAS scores for either the desvenlafaxine group ($\chi^2(2) = 0.737, p = 0.692$; $\chi^2(2) = 4.333, p = 0.115$) or the placebo group ($\chi^2(2) = 2.000, p = 0.368$; $\chi^2(2) = 0.000, p = 1.000$). However, as seen in Figure 2B, a non-significant trend of increasing VAS scores was observed over time only in the desvenlafaxine group. Indeed, VAS scores had improved for all but one participant in this group at day 28-31.
Figure 2. Subjective Sleep Quality.
A) Pittsburgh Sleep Quality Index scores, B) Visual Analogue Scale for sleep quality scores. The median (± 95% confidence interval) is presented for the desvenlafaxine-treated and placebo groups at each time point. * indicates a significant (p < 0.05) difference over time in the desvenlafaxine group. 95% confidence intervals could not be calculated at day 28-31 for the placebo group the sample size was too small.
4.3 Polysomnographic Measures

Mann-Whitney U tests found no significant differences at baseline between the desvenlafaxine-treated group and the placebo group for distributions of the total time spent asleep ($U = 3.000, z = -1.549, p = 0.167$), sleep efficiency ($U = 3.500, z = -1.432, p = 0.167$), percentage of time spent in SWS ($U = 7.000, z = -0.516, p = 0.714$), percentage of time spent in REM sleep ($U = 13.000, z = 1.037, p = 0.381$), latency to REM sleep ($U = 5.000, z = -1.033, p = 0.381$), or number of nighttime awakenings ($U = 13.500, z = 1.167, p = 0.262$). At day 3-5, Mann-Whitney U tests found a significant difference ($U = 15.000, z = 2.236, p = 0.036$) in the distribution of latency to REM sleep between the desvenlafaxine-treated group (median = 204.500 minutes ± 108.477) and the placebo group (median = 59.880 minutes ± 22.208). There were no significant differences at day 3-5 between the two groups for the distribution of the total time spent asleep ($U = 5.000, z = -1.033, p = 0.381$), sleep efficiency ($U = 5.000, z = -1.050, p = 0.381$), percentage of time spent in SWS ($U = 9.000, z = 0.000, p = 1.000$), percentage of time spent in REM sleep ($U = 4.500, z = -1.167, p = 0.262$), or number of nighttime awakenings ($U = 14.000, z = 1.291, p = 0.262$). Figures 3, 4A, and 4B illustrate the median sleep efficiency, percentage of time spent in REM sleep, and latency to REM sleep, respectively, for the two groups at each of the three time points. At day 28-31, no significant differences were found between the two groups for the distributions of the total time spent asleep ($U = 6.000, z = 0.000, p = 1.000$), sleep efficiency ($U = 3.000, z = -1.000, p = 0.429$), percentage of time spent in SWS ($U = 2.500, z = -1.181, p = 0.286$), percentage of time spent in REM sleep ($U = 6.500, z = 0.178, p = 1.000$), latency to REM sleep ($U = 11.000, z = 1.667, p = 0.143$), or number of nighttime awakenings ($U =
11.000, z = 1.677, p = 0.143). Tables 5, 6, and 7 present the medians and the results of the Mann-Whitney U tests for each PSG parameter at each time point.

Friedman tests investigating changes over time for the placebo group found that there were no statistically significant differences from baseline to day 3-5 to day 28-31 for the median total time spent asleep ($\chi^2(2) = 1.000, p = 0.607$), sleep efficiency ($\chi^2(2) = 0.000, p = 1.000$), percentage of time spent in SWS ($\chi^2(2) = 3.000, p = 0.223$), percentage of time spent in REM sleep ($\chi^2(2) = 4.00, p = 0.135$), latency to REM sleep ($\chi^2(2) = 3.000, p = 0.223$), or number of nighttime awakenings ($\chi^2(2) = 2.000, p = 0.368$). In the desvenlafaxine-treated group, Friedman tests found that there were significant changes in latency to REM sleep over time ($\chi^2(2) = 6.400, p = 0.041$). Post hoc analysis revealed a significant increase in median (± 95% confidence interval) latency to REM sleep from 73.500 minutes ± 48.231 at baseline to 204.500 minutes ± 108.477 at day 3-5 ($\chi^2(2) = -1.600, p = 0.034$) but not from baseline to day 28-31 (median = 90.250 minutes ± 26.759) ($\chi^2(2) = -0.800, p = 0.618$) or from day 3-5 to day 28-31 ($\chi^2(2) = 0.800, p = 0.618$).

Though the difference between baseline and day 28-31 was non-significant, REM sleep latency had increased at day 28-31 compared to baseline for four out of the six participants in the desvenlafaxine-treated group. There were no statistically significant differences over time for the desvenlafaxine-treated group for median total time spent asleep ($\chi^2(2) = 1.333, p = 0.513$), sleep efficiency ($\chi^2(2) = 0.333, p = 0.846$), percentage of time spent in SWS ($\chi^2(2) = 4.957, p = 0.084$), percentage of time spent in REM sleep ($\chi^2(2) = 5.200, p = 0.074$), or number of nighttime awakenings ($\chi^2(2) = 0.783, p = 0.676$).

Figure 4 displays the changes over time in percentage of time spent in REM sleep and latency to REM sleep onset for both groups.
Figure 3. Sleep Efficiency.
Median (± 95% confidence interval) sleep efficiency for the desvenlafaxine-treated and placebo groups at each time point. 95% confidence intervals could not be calculated at day 28-31 for the placebo group the sample size was too small.
Figure 4. Rapid Eye Movement Sleep
A) Percentage of Time Spent in REM Sleep, B) Latency to REM Sleep. The median (± 95% confidence interval) is presented for the desvenlafaxine-treated and placebo groups at each time point. * indicates a significant (p < 0.05) difference between the two groups at this time point. 95% confidence intervals could not be calculated at day28-31 for the placebo group the sample size was too small.
Table 5. Polysomnographic Measures at Baseline.
The median (± 95% confidence intervals) of each sleep parameter and Mann-Whitney U test results for between-group differences. SWS = Slow Wave Sleep, REM= Rapid Eye Movement.

<table>
<thead>
<tr>
<th>PSG Parameters</th>
<th>Desvenlafaxine (n = 6)</th>
<th>Placebo (n = 2)</th>
<th>U-value</th>
<th>z-score</th>
<th>p-value</th>
</tr>
</thead>
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<tr>
<td></td>
<td>Median (± 95% CI)</td>
<td>Mean Rank</td>
<td>Median (± 95% CI)</td>
<td>Mean Rank</td>
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<tr>
<td>Time Spent in Bed (min)</td>
<td>472.500 ± 43.344</td>
<td>4.33</td>
<td>517.500 ± 266.494</td>
<td>6.33</td>
<td>5.000</td>
</tr>
<tr>
<td>Time Spent Asleep (min)</td>
<td>408.250 ± 35.573</td>
<td>4.00</td>
<td>467.500 ± 238.394</td>
<td>7.00</td>
<td>3.000</td>
</tr>
<tr>
<td>Sleep Efficiency (%)</td>
<td>87.000 ± 5.288</td>
<td>4.08</td>
<td>92.000 ± 3.353</td>
<td>6.83</td>
<td>3.500</td>
</tr>
<tr>
<td>Sleep Period Time (min)</td>
<td>425.500 ± 31.567</td>
<td>4.00</td>
<td>489.500 ± 262.224</td>
<td>7.00</td>
<td>3.000</td>
</tr>
<tr>
<td>% of Time Spent in Stage 1</td>
<td>4.500 ± 5.448</td>
<td>5.00</td>
<td>4.000 ± 2.810</td>
<td>5.00</td>
<td>9.000</td>
</tr>
<tr>
<td>Stage 1 Latency (min)</td>
<td>23.250 ± 26.760</td>
<td>5.83</td>
<td>7.500 ± 22.851</td>
<td>3.33</td>
<td>14.000</td>
</tr>
<tr>
<td>% of Time Spent in Stage 2</td>
<td>54.500 ± 11.377</td>
<td>5.00</td>
<td>53.000 ± 5.804</td>
<td>5.00</td>
<td>9.000</td>
</tr>
<tr>
<td>Stage 2 Latency (min)</td>
<td>30.500 ± 29.003</td>
<td>6.00</td>
<td>12.500 ± 20.132</td>
<td>3.00</td>
<td>15.000</td>
</tr>
<tr>
<td>% of Time Spent in SWS</td>
<td>16.500 ± 9.774</td>
<td>4.67</td>
<td>24.000 ± 12.418</td>
<td>5.67</td>
<td>7.000</td>
</tr>
<tr>
<td>% of Time Spent in REM</td>
<td>21.000 ± 4.807</td>
<td>5.67</td>
<td>15.000 ± 14.956</td>
<td>3.67</td>
<td>13.000</td>
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<tr>
<td>REM Latency (min)</td>
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<td>138.500 ± 70.702</td>
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<td>5.000</td>
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<tr>
<td>Number of Awakenings</td>
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<td>15.000 ± 6.345</td>
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<td>13.500</td>
</tr>
<tr>
<td>Obstructive Sleep Apneas</td>
<td>0.000 ± 0.000</td>
<td>4.00</td>
<td>1.000 ± 371.108</td>
<td>7.00</td>
<td>3.000</td>
</tr>
<tr>
<td>Mixed Apneas</td>
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<td>5.50</td>
<td>0.000 ± 0.000</td>
<td>4.00</td>
<td>12.000</td>
</tr>
<tr>
<td>Central Apneas</td>
<td>1.000 ± 2.106</td>
<td>4.50</td>
<td>1.000 ± 3.511</td>
<td>4.50</td>
<td>7.500</td>
</tr>
<tr>
<td>Hypopneas</td>
<td>6.000 ± 6.670</td>
<td>4.10</td>
<td>6.000 ± 141.827</td>
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Table 6. Polysomnographic Measures at Day 3-5.
The median (± 95% confidence intervals) of each sleep parameter and Mann-Whitney U test results for between-group differences. SWS = Slow Wave Sleep, REM= Rapid Eye Movement. * indicates that 95% confidence intervals could not be calculated as the sample size was too small.

<table>
<thead>
<tr>
<th>PSG Parameters</th>
<th>Desvenlafaxine (n = 6)</th>
<th>Placebo (n = 2)</th>
<th>U-value</th>
<th>z-score</th>
<th>p-value</th>
</tr>
</thead>
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<tr>
<td>Time Spent in Bed (min)</td>
<td>417.500 ± 56.884</td>
<td>373.000 ± 86.928</td>
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<td>0.516</td>
<td>0.714</td>
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<tr>
<td>Time Spent Asleep (min)</td>
<td>313.000 ± 108.480</td>
<td>345.500 ± 82.577</td>
<td>5.000</td>
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</tr>
<tr>
<td>Sleep Efficiency (%)</td>
<td>87.000 ± 21.151</td>
<td>93.000 ± 0.997</td>
<td>5.000</td>
<td>-1.050</td>
<td>0.381</td>
</tr>
<tr>
<td>Sleep Period Time (min)</td>
<td>363.000 ± 100.148</td>
<td>351.500 ± 90.281</td>
<td>8.000</td>
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<td>0.905</td>
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<tr>
<td>% of Time Spent in Stage 1</td>
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<td>3.000 ± 1.360</td>
<td>13.000</td>
<td>1.042</td>
<td>0.381</td>
</tr>
<tr>
<td>Stage 1 Latency (min)</td>
<td>13.500 ± 58.807</td>
<td>26.500 ± 38.868</td>
<td>6.00</td>
<td>6.00</td>
<td>-0.775</td>
</tr>
<tr>
<td>% of Time Spent in Stage 2</td>
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<td>60.700 ± 27.193</td>
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<td>1.000</td>
<td>0.521</td>
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<td>Stage 2 Latency (min)</td>
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<td>% of Time Spent in SWS</td>
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<td>22.600 ± 10.877</td>
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<td>9.00</td>
<td>0.000</td>
</tr>
<tr>
<td>% of Time Spent in REM</td>
<td>12.000 ± 8.776</td>
<td>17.000 ± 19.851</td>
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<td>4.50</td>
<td>-1.167</td>
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<td>REM Latency (min)</td>
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<tr>
<td>Obstructive Sleep Apneas</td>
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<td>4.50</td>
<td>-1.381</td>
</tr>
<tr>
<td>Mixed Apneas</td>
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<td>10.500</td>
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<tr>
<td>Central Apneas</td>
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<td>1.000 ± 0.641</td>
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<td>6.00</td>
<td>-0.813</td>
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<tr>
<td>Hypopneas</td>
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<td>3.000 ± 379.844</td>
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Table 7. Polysomnographic Measures at Day 28-31.
The median (± 95% confidence intervals) of each sleep parameter and Mann-Whitney U test results for between-group differences. SWS = Slow Wave Sleep, REM= Rapid Eye Movement. * indicates that 95% confidence intervals could not be calculated as the sample size was too small.

<table>
<thead>
<tr>
<th>PSG Parameters</th>
<th>Desvenlafaxine (n = 6)</th>
<th>Placebo (n = 2)</th>
<th>U-value</th>
<th>z-score</th>
<th>p-value</th>
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<tbody>
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<td>Median (± 95% CI)</td>
<td>Mean Rank</td>
<td>Median (± 95% CI)</td>
<td>Mean Rank</td>
<td></td>
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<tr>
<td>Time Spent in Bed (min)</td>
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<td>396.500*</td>
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<tr>
<td>Time Spent Asleep (min)</td>
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<td>4.50</td>
<td>364.950*</td>
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<td>6.000</td>
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<tr>
<td>Sleep Efficiency (%)</td>
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<td>4.00</td>
<td>92.200*</td>
<td>6.00</td>
<td>3.000</td>
</tr>
<tr>
<td>Sleep Period Time (min)</td>
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<td>388.000*</td>
<td>4.50</td>
<td>6.000</td>
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<tr>
<td>% of Time Spent in Stage 1</td>
<td>5.000 ± 1.923</td>
<td>5.17</td>
<td>2.600*</td>
<td>2.50</td>
<td>10.000</td>
</tr>
<tr>
<td>Stage 1 Latency (min)</td>
<td>30.000 ± 54.881</td>
<td>4.33</td>
<td>69.430*</td>
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<td>5.000</td>
</tr>
<tr>
<td>% of Time Spent in Stage 2</td>
<td>56.500 ± 7.691</td>
<td>5.08</td>
<td>45.850*</td>
<td>2.75</td>
<td>9.500</td>
</tr>
<tr>
<td>Stage 2 Latency (min)</td>
<td>45.500 ± 55.682</td>
<td>4.83</td>
<td>22.430*</td>
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<td>8.000</td>
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<tr>
<td>% of Time Spent in SWS</td>
<td>18.500 ± 6.570</td>
<td>3.92</td>
<td>29.550*</td>
<td>6.25</td>
<td>2.500</td>
</tr>
<tr>
<td>% of Time Spent in REM</td>
<td>24.000 ± 4.326</td>
<td>4.58</td>
<td>22.500*</td>
<td>4.25</td>
<td>6.500</td>
</tr>
<tr>
<td>REM Latency (min)</td>
<td>90.250 ± 26.759</td>
<td>5.33</td>
<td>49.430*</td>
<td>2.00</td>
<td>11.000</td>
</tr>
<tr>
<td>Number of Awakenings</td>
<td>18.000 ± 7.371</td>
<td>5.33</td>
<td>7.000*</td>
<td>2.00</td>
<td>11.000</td>
</tr>
<tr>
<td>Obstructive Sleep Apneas</td>
<td>0.000 ± 0.000</td>
<td>4.00</td>
<td>121.000*</td>
<td>6.00</td>
<td>3.000</td>
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<tr>
<td>Mixed Apneas</td>
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<td>4.08</td>
<td>1.000*</td>
<td>5.75</td>
<td>3.500</td>
</tr>
<tr>
<td>Central Apneas</td>
<td>1.500 ± 1.282</td>
<td>4.08</td>
<td>3.000*</td>
<td>5.75</td>
<td>3.500</td>
</tr>
<tr>
<td>Hypopneas</td>
<td>7.000 ± 13.780</td>
<td>3.83</td>
<td>112.500*</td>
<td>6.50</td>
<td>2.000</td>
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</table>
Chapter 5: Discussion

In the present study, treatment of MDD with desvenlafaxine resulted in several findings. First, the results suggest that desvenlafaxine has minimal effects on sleep architecture in depressed subjects as compared to treatment with placebo. There were no significant differences between the effects of treatment with desvenlafaxine and treatment with placebo on time spent in SWS, measures of sleep continuity (including latency to sleep onset, sleep efficiency, and the number of nighttime awakenings), or time spent in REM sleep at any time point. Additionally, no significant changes over time in these measures were observed for either group. However, the median latency to REM sleep onset increased significantly at day 3-5 for those treated with desvenlafaxine, both from baseline and as compared to placebo. Though the median REM sleep latency was still increased at day 28-31 compared to baseline, this difference was no longer significant. This is in contrast to the non-significant decrease in median REM sleep latency that occurred over time in the placebo group.

To the best of our knowledge, this is the only study that has investigated the impact of the administration of desvenlafaxine on sleep architecture. Previous studies assessing the effects of other SNRIs on sleep have consistently reported that SNRIs suppress REM sleep. Venlafaxine treatment in depressed patients has resulted in increased REM sleep onset latency and decreased total REM sleep duration (Luthringer et al., 1996), while a study of healthy volunteers reported that venlafaxine completely suppressed REM sleep in all subjects after four days of treatment (Salín-Pascual, Galicia-Polo, & Drucker-Colín, 1997). Treatment of both healthy and depressed subjects with
duloxetine decreased the duration of REM sleep and increased REM sleep onset latency (Chalon et al., 2004; Kluge et al., 2007). Finally, Lemoine and Faivre (2004) found that milnacipran significantly lengthened latency to REM sleep early on in treatment but had no effect on REM sleep duration. As discussed in Chapter 2, improvements in REM sleep have similarly been produced by several antidepressants of other classes, including SSRIs, TCAs, MAOIs, and atypical antidepressants. Though it is a relatively consistent finding, REM sleep suppression following antidepressant treatment is not universally observed; studies on both mirtazapine (Schittecatte et al., 2002; Schmid et al., 2006; Shen et al., 2006; Winokur et al., 2000) and buproprion (Nofzinger et al., 1995; Nofzinger et al., 2001; Ott et al., 2004) have produced conflicting results, while agomelatine does not appear to modify REM sleep at all (Salva et al., 2007).

While a decrease in the duration of REM sleep was not seen in the current study, latency to REM sleep onset did increase significantly early on for all participants treated with desvenlafaxine, with the median increasing from 73.500 minutes at baseline to 204.500 minutes at day 3-5. This is consistent with results from the aforementioned studies of other SNRIs. Though this parameter was still increased at day 28-31, in contrast to the findings of Luthringer et al. (1996) and Lemoine and Faivre (2004), a significant increase above baseline levels was not maintained. It should be noted, however, that despite the change from baseline being non-significant, the median REM sleep onset latency at day 28-31 was 90.250 minutes; the normal latency to REM sleep onset that is seen in healthy individuals is approximately 90 minutes, indicating a non-significant trend towards the normalization of REM sleep latency at the chronic measurement (Markov & Goldman, 2006). Therefore, the trend in median REM sleep
latency changes over the course of treatment with desvenlafaxine was in line with our hypothesis; latency worsened at the acute measurement, increasing significantly above what is seen in healthy sleep, and then decreased at the chronic measurement to a value that is seen in healthy individuals. It is of interest to note that the median latency to REM sleep for the placebo group did not follow this trend and instead decreased non-significantly over time.

These changes in REM sleep are likely a result of increased levels of serotonin and norepinephrine in the CNS. Serotonergic neurons in the dorsal raphe nucleus and noradrenergic neurons in the locus coeruleus are actively involved in REM sleep suppression through their excitation of the vlPAG-LPT and inhibition of the SLD, two regions that are thought to be responsible for regulation of the NREM/REM cycle (Lu & Zee, 2010). Acute increases in the levels of serotonin and norepinephrine in these pathways following the administration of desvenlafaxine would result in increased REM suppression and therefore an increase in REM sleep latency. Sustained elevations in the levels of these monoamines by antidepressants cause the CNS to adjust by downregulating their pre- and postsynaptic receptors, which may explain why desvenlafaxine’s suppression of REM sleep was dampened at the chronic measurement, though further studies are needed to confirm whether this downregulation specifically occurs in the areas that regulate REM sleep (Blier & de Montigny, 1994).

The effects of other SNRIs on the stages of NREM sleep have been less consistent. The current study found no significant changes to the time spent in any stage of NREM sleep, consistent with findings from Lemoine and Faivre (2004) who observed no significant changes in sleep stages 1, 3, and 4 following treatment with milnacipran.
and Kluge et al. (2007) who reported that sleep stages 1, 2, and 4 were unaffected by treatment with duloxetine. Reports on duloxetine’s effects on sleep stage 3 are conflicting; Kluge et al. (2007) described a significant increase in the time spent in stage 3, while Chalon et al. (2004) reported similar findings to our data, as stage 3 remained unchanged. Additional outcomes not seen in the present study are Chalon et al. (2004)’s reports of a dose-dependent decrease in time spent in stage 4 and Lemoine and Faivre (2004)’s observations of a significant increase in the time spent in stage 2. Lastly, contrary to our findings, Salín-Pascual et al. (1997) detected an increase in time spent in stage 1 and a reduction in time spent in sleep stages 2 and 3 following the acute treatment of healthy volunteers with venlafaxine. As discussed in Chapter 2, antidepressants of other classes are similarly non-uniform in their effects on sleep stages 1 and 2 and SWS, with only sertraline (Jindal et al., 2003), trazadone (Mouret et al., 1991; Scharf and Sachais, 1990), and mirtazapine (Schittecatte et al., 2002; Schmid et al., 2006; Shen et al., 2006) having been shown to induce improvements to SWS.

The current study found no significant improvements in measures of sleep continuity, which includes latency to sleep onset, total sleep time, sleep efficiency, and number of night time awakenings. Kluge et al. (2007) similarly reported that after 7-14 days, all four of these sleep parameters were unaffected by treatment with 60mg of duloxetine. Conversely, Chalon et al. (2005) found that treatment with 80mg of duloxetine improved sleep efficiency while treatment with 60mg twice-daily of duloxetine increased the number of nighttime awakenings and decreased sleep efficiency, with no significant effects on the other parameters. Both Luthringer et al. (1996) and Salín-Pascual et al. (1997) reported in their studies on depressed and healthy subjects,
respectively, that treatment with venlafaxine resulted in significant reductions in sleep continuity, with subjects experiencing a decrease in total sleep time and a decrease in sleep efficiency. Finally, the open-label trial by Lemoine and Faivre (2004) suggested that milnacipran administration to depressed subjects resulted in a reduction in sleep onset latency and increases in sleep efficiency and total sleep time, with no effect on nighttime awakenings. Therefore, due to the inconsistent nature of past reports on the impact of SNRIs on sleep continuity, the results of the present study are consistent with select findings and contrary to others. Other classes of antidepressants have also been shown to have varying effects on measures of sleep continuity, as discussed in Chapter 2.

The second main finding of this study is that despite there being no significant long-term improvements in sleep architecture, participants who were treated with desvenlafaxine reported that their sleep quality improved. While there were no differences in the distribution of ESS, PSQI, and VAS scores between the two groups at any time point, a significant decrease in total PSQI scores from baseline to day 28-31 was observed in the desvenlafaxine-treated group only. The PSQI asks participants to report on various aspects of the quality of their sleep including the duration of their sleep, daytime dysfunction, latency to sleep, and overall sleep quality. Additionally, a non-significant trend of increased VAS scores was observed over time in the desvenlafaxine group, indicating a non-significant improvement that was not seen in the placebo group. Therefore, though no long-term significant objective sleep improvements were detected, participants subjectively reported that various aspects of their sleep quality improved following treatment with desvenlafaxine. Of the previous studies on other SNRIs, only Lemoine and Faivre (2004) and Chalon et al. (2005) reported on subjective sleep quality.
In contrast to the findings of the present study, Lemoine and Faivre (2004) stated that despite significant improvements in sleep architecture, participants did not report significant improvements in their sleep quality following treatment with milnacipran on the Spiegel and Norris sleep scales. Participants treated with duloxetine by Chalon et al. (2005) demonstrated significant improvements over placebo only on the “getting to sleep” subscale of the Leeds sleep evaluation questionnaire.

The final finding of this study was that there is evidence that illness severity decreased for participants treated with desvenlafaxine but not with placebo. Though there were no significant differences at any time point in HDRS, MADRS, HARS, CGI-S, and CGI-I scores between the two groups, significant improvements were seen over time in scores for the HDRS, MADRS, HARS, and CGI-S in the desvenlafaxine group only. Participants who received desvenlafaxine therefore reported significant improvements in their symptoms of depression and anxiety following just four weeks of treatment. These findings are consistent with the results of two pooled analyses investigating the efficacy of desvenlafaxine that reported improvements in HDRS scores as early as one week into treatment (Carrasco et al., 2016; Soares et al., 2009) and a study by Maity et al. (2014) that reported that desvenlafaxine improved HARS scores after four weeks of treatment. Additionally, desvenlafaxine was well-tolerated by the participants, with no serious adverse events occurring during treatment. As discussed in Chapter 2, the antidepressant and anxiolytic effects of desvenlafaxine are known to be a result of the antidepressant’s inhibition of the SERT and NET, which increases the extracellular levels of serotonin and norepinephrine and thus increases their activity in the synapse. These two neurotransmitters are known to be involved in mood regulation. It is also thought that
increased serotonergic and noradrenergic activity induces neuroplastic changes in various brain regions over time that contributes to the antidepressant effects (Andrade & Rao, 2010; Blier & de Montigny, 1994).

Though the current study has presented findings that support desvenlafaxine’s ability to improve REM sleep latency and subjective ratings of sleep quality and illness severity, the other findings differed from the expected results and from the findings of previous studies. There are several conceivable explanations for these differences. It was hypothesized that subjects treated with desvenlafaxine would show an overall deterioration in objective sleep measures at the acute measurement due to the initial surge in norepinephrine in the areas that regulate sleep, followed by an improvement at the chronic measurement as the CNS adjusted. Though this exact result was not observed, an acute significant effect on REM sleep latency occurred that nearly disappeared at the chronic measurement. It is likely that this acute finding was the result of the initial increase in norepinephrine that then disappeared as the brain compensated over time. As the only dose investigated in this study was 50mg taken once daily, it may be that the sleep effects of desvenlafaxine are dose-dependent and further changes to sleep architecture may have occurred had a higher dose been administered. As well, the decidedly small sample size of the present study was most likely a significant contributor to the lack of expected findings, as this leads to a low statistical power to detect potentially significant effects of desvenlafaxine on sleep. For example, there was a trend towards REM latency normalization and improvement in VAS scores in the desvenlafaxine group at the chronic measurement and inclusion of a larger sample size may have yielded statistically significant results.
In comparing the results of the current study with those of studies of other SNRIs, differences in the length of treatment and the participants included should be noted. Luthringer et al. (1996) and Lemoine and Faivre (2004) followed similar timelines to ours, assessing their participants at baseline, within the first week of treatment, and after 4 weeks of treatment. The other three studies of SNRIs, however, had much shorter timelines; Salín-Pascual et al. (1997), Chalon et al. (2005), and Kluge et al. (2007) collected polysomnographic recordings at baseline and then following four, six, and seven to 14 days of treatment, respectively. Therefore, these three studies presented results concerning only the acute effects of duloxetine and venlafaxine on sleep and so their results can only be compared to the acute assessment of our study. It is unknown whether their results would have persisted longer-term; had these studies persisted for a full month, allowing a longer period for the CNS to adjust to the increased monoamine levels, it is possible that they would have had similar conclusions to ours. Additionally, there are significant differences in the participants assessed in each of these studies. Similar to our study, Luthringer et al. (1996), Kluge et al. (2007), and Lemoine and Faivre (2004) recruited participants who were positive for MDD, while Salín-Pascual et al. (1997) and Chalon et al. (2005) assessed only healthy participants. It is conceivable that differences in baseline monoamine levels and neurotransmission in the CNS may result in differences in treatment responses between healthy and depressed subjects, though studies addressing this possibility by simultaneously comparing the sleep effects of antidepressants in depressed and healthy subjects are lacking.

Finally, the sleep architecture of the subjects included in the current study was more comparable to normal sleep architecture than to that of depressed sleep as it has
been characterized in other studies. Depression appears to most significantly affect SWS, REM sleep, and sleep efficiency. In healthy individuals, SWS accounts for 15-23% of the total sleep time while 20-25% of the total time is spent in REM sleep. Normal REM latency is 90 minutes and sleep efficiency is generally around 95% (Markov & Goldman, 2006). Kluge et al. (2007) and Lemoine and Faivre (2004) reported that their depressed participants initially spent 10.37% and 8.20% of their total sleep time in SWS, had a REM sleep onset latency of 58.5 and 43 minutes, and a sleep efficiency of 87% and 74%, respectively. Additionally, a study of 90 subjects with unipolar depression reported that 11.4% of their total sleep time was spent in SWS and the mean REM sleep onset latency was 55.8 minutes (Kerkhofs et al., 1988). Sleep continuity was also significantly affected, with Kerkhofs et al. (1988) reporting a sleep efficiency of 72.4%. In the present study, participants in the desvenlafaxine-treated group spent a median 16.5% of their total sleep time in SWS at baseline, which is within the normal range of time spent in this stage and is a greater amount of time than was reported by Kluge et al. (2007), Lemoine and Faivre (2004), and Kerkhofs et al. (1988). We reported a median REM sleep latency of 73.5 minutes at baseline in the desvenlafaxine-treated group, which is lower than the reported range for healthy sleep but is not as low as what was reported in the previously mentioned studies. Lastly, those treated with desvenlafaxine had a sleep efficiency of 87.0% at baseline, which is again lower than the normal reported range but better than the values reported by Lemoine and Faivre (2004) and Kerkhofs et al. (1988). Therefore, the participants observed in the present study did not display the same level of sleep dysfunction as was seen in other studies of depressed sleep and so they may have had less potential for sleep improvements following treatment with desvenlafaxine. Given the
non-homogenous nature of the symptomology and presentation of MDD, it is possible that disturbances in sleep architecture are not consistent in MDD but rather are a function of depression subtype, illness severity, length of illness, and/or age. Indeed, sleep disturbances have been consistently associated with illness severity (Liu et al., 2007; Malik et al., 2014) and with a mean age of 24 ± 6 years in the treatment group, it is likely that these participants had not experienced MDD for as long as the participants in other studies and may not have been as severely ill.

There are a number of limitations to the present study. The small number of participants assessed considerably lowers the statistical power to detect significant changes and to draw firm conclusions. A larger sample size would have reduced the likelihood of making a type II error, which is most relevant to the lack of change seen in SWS and REM sleep duration. Furthermore, though participants were subjected to few comorbid exclusions, the small sample size makes it difficult to generalize these results to the much larger clinical population. The short-term duration of this study may have also limited our ability to detect changes as a greater differentiation between the desvenlafaxine and placebo groups may have been observed had the study assessed participants after 6-8 weeks of treatment. Finally, this study only evaluated the effects of a 50mg dose, eliminating the ability to determine whether the sleep effects of desvenlafaxine are dose-dependent.

Further studies are necessary to build upon the findings presented here to better elucidate the impact of desvenlafaxine on sleep architecture. It would be beneficial for studies to include a larger sample size to increase statistical power and to consider administering different doses to determine if the sleep effects of desvenlafaxine are dose-
dependent. Once these effects are better established, long term studies employing an increased length of administration would be beneficial in determining how the effects of desvenlafaxine are maintained with chronic treatment. Investigations into whether improvements in sleep disturbances correlate with a decrease in the severity of individual symptoms of MDD or with particular MDD subtypes during treatment may be useful in contributing to our knowledge of how sleep disturbances interact with depressive symptomology. Finally, additional research comparing the sleep effects of desvenlafaxine to that of other antidepressants may also be useful in assisting clinicians with formulating treatment plans that target sleep disturbances.

Sleep disturbances are one of the core symptoms of MDD. Given the negative health and cognitive effects of poor sleep quality, sleep dysregulation represents an important treatment focus for improving quality of life in the clinical management of MDD. Research suggests a bi-directional relationship between sleep disturbances and depressive symptomology, suggesting that improvements in sleep quality may also lead to improvements in illness severity. Though several antidepressants have the ability to normalize REM sleep, few have been consistently proven to improve both SWS and sleep continuity as well. Therefore, continuing research into the best pharmacological methods for managing the sleep disturbances associated with MDD is critical. The results of the present study suggest that desvenlafaxine has the ability to improve subjective sleep quality and to suppress REM sleep by increasing REM sleep latency. However, the administration of desvenlafaxine did not significantly improve the duration of either SWS or REM sleep nor did it improve any measure of sleep continuity. Desvenlafaxine was well-tolerated and participants who received it reported significant improvements in their
symptoms of depression and anxiety following just four weeks of treatment. The main limitation is the particularly small size of the samples assessed, which restricts the statistical power to detect significant changes and the generalizability of the results. Nevertheless, these results suggest that desvenlafaxine may be useful in improving sleep quality in depressed patients, though further research is needed to better support this claim.
References


80


Appendix A

Table I. Pre-existing conditions of the placebo and desvenlafaxine groups at baseline.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Placebo (n =3)</th>
<th>Desvenlafaxine (n=6)</th>
<th>Total (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>1</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Low iron</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>TOTAL</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

Table II. Adverse events for the placebo and desvenlafaxine groups.

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Placebo (n =3)</th>
<th>Desvenlafaxine (n=6)</th>
<th>Total (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Fever</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Flu</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Headaches</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Increased difficulty sleeping</td>
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<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>TOTAL</td>
<td>4</td>
<td>7</td>
<td>11</td>
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