An Investigation of Sleep Architecture and Consequent Cognitive Changes in Olanzapine Treated Patients with Depression

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Abstract

Objective: Primarily, to determine the effect of olanzapine augmentation therapy on sleep architecture, specifically slow wave sleep (SWS), in the treatment of depression. Secondarily, to determine the effect of olanzapine augmentation therapy on illness severity and cognitive function. Finally, to examine the correlation between sleep architecture, illness severity and cognition. Methods: Prospective, double-blind, randomized, placebo-controlled study. Patients with major depressive disorder or bipolar disorder currently experiencing a major depressive episode were included. Patients were on a stable medication regime for 4 weeks prior and throughout the study. Sleep architecture was measured by overnight, ambulatory, polysomnography. Illness severity was determined using the Hamilton Depression Rating Scale (HDRS), Montgomery Asberg Depression Rating Scale (MADRS) and Hamilton Anxiety Rating Scale (HARS). Cognitive function was examined using Cambridge Neuropsychological Test Automated Battery (CANTAB): Spatial Working Memory (SWM), Spatial Span (SSP), and Reaction Time (RTI) tasks. Polysomnographs, clinical measures and cognitive test were administered at baseline, after 2-4 days of treatment and after 28-31 days of treatment. Results: Twenty-five patients participated in the study. There was no significant difference between olanzapine and placebo treated groups on age, gender, diagnosis, education level, employment or marital status and number of children. Latency to SWS, duration of SWS, sleep efficiency, total sleep time, total wake time and sleep latency significantly improved in olanzapine treated participants over placebo treated participants. Latency to and duration of rapid eye movement sleep was not significantly different between olanzapine and placebo treated participants. HDRS scores were significantly improved in olanzapine treated versus placebo treated participants. No significant difference between treatment groups was seen in MADRS, HARS, and subjective sleep quality scores.
olanzapine and placebo treated participants in SWM, SSP or RTI tasks. Change in sleep architecture was not significantly correlated to clinical change or change in SWM, SSP or RTI. Clinical change was not significantly correlated to SWM or SSP. Clinical change, however, was significantly correlated to change in RTI, in the placebo treated group only. **Conclusion:** Olanzapine augmentation treatment improves SWS, sleep continuity and depressive symptoms.
Co-Authorship

Dr. R. Milev, Dr. A. Lowe, Dr. R. Jokic, and Dr. R. du Toit of the Department of Psychiatry, Queen’s University contributed to this study. All co-authors contributed to study design, participant recruitment, as well as completing the physician required portions of the study visits. Dr. R. Milev assisted with analysis and preparation of this document.
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Chapter 1: General Introduction

Sleep disturbances are prominent in many psychiatric disorders, most often in the form of insomnia. It has been reported that 40% of people with insomnia and 47% of people with hypersomnia had a psychiatric disorder compared to 16% of people who had no sleep complaints. Disturbance of sleep is included in the diagnostic criteria for a range of affective and anxiety disorders. Insomnia is both a risk factor and a consequence of, depression. Sleep disturbance is one of the main symptoms of major depression and 90-95% of major depressive episodes are accompanied by disordered sleep. Previous research suggests that a focus on patient care should include an assessment of sleep function, as well as appropriate measures to improve and optimize sleep architecture.

Sleep can be separated into two main components: Rapid Eye Movement (REM) and Non-REM (NREM) sleep. The first hours of sleep normally include a high percentage of time spent in NREM sleep; stages one to four. Stage 3 and 4 are also referred to as slow wave sleep (SWS). SWS plays an important role in memory, and pain-aversion, so that disruption of this phase of sleep may have a significant effect on the quality of life of these patients. As sleep progresses, more time is spent in the REM stage, allowing dream sleep to occur. The physiology of sleep is however, altered in depression. The most common sleep abnormalities of depression are sleep continuity disturbance (usually consisting of prolonged sleep latency, increased number of nocturnal awakenings and early morning awakening), diminished SWS, shortened REM latency, and an alteration in the temporal distribution of REM sleep. In depression, the majority of slow wave activity is shifted from the first to the second NREM period, whereas normal controls usually show a linear decrease in SWS throughout the night. These specific sleep architecture features seen in depression are lacking in patients with chronic primary insomnia. Sleep, as one of the key effectors of healing and recovery
represents one of the most important benchmarks of disease management. There is evidence to suggest that 5-HT is a key neurotransmitter in sleep-wakefulness regulation. It has been suggested that the reduction in REM latency and increased REM sleep time seen in depression may be due to an overactive cholinergic system and a deficient REM inhibitory monoaminergic system.

Antidepressants can produce changes in the sleep electroencephalogram (EEG) of depressed patients. Not all antidepressants produce the same effects; even within classes of antidepressants the effects on sleep patterns differ. The most prominent effect of antidepressants on sleep is suppression of REM sleep. Few antidepressants have been shown to improve SWS. Antidepressants are thought to suppress REM sleep by increasing NA and/or 5-HT function or increasing cholinergic blockade, producing a beneficial effect. 5-HT receptors have also been shown to play a critical role in the regulation of SWS. Several antidepressants, particularly tricyclic antidepressants and trazodone, are thought to normalize SWS because of their affinity for 5-HT$_{2A}$ and 5-HT$_{2C}$ receptors.

Several psychotropic medications used as augmentation strategies in the treatment of depression have also been shown to alter sleep architecture. It has been estimated that up to 30% of patients with depression fail to respond to traditional antidepressant treatments alone and augmentation strategies may be required. Risperidone has been found to decrease REM sleep and wakefulness in depressed patients although a change in the amount of SWS was not seen. These findings have been attributed to 5-HT$_2$ receptor antagonism and sedation. Quetiapine has also been shown to increase sleep efficiency and the percentage of stage 2, and to decrease latencies to stages 1 and 2 and the percentage of time awake. The antidopaminergic and antiadrenergic properties of quetiapine are suggested to have a role in the mediation of its effects on sleep.
Augmentation of antidepressant therapy, with olanzapine, an atypical antipsychotic, is often used in routine clinical practice for the treatment of depression. Olanzapine, has been shown to increase SWS, sleep continuity and subjective sleep measures in healthy male and female volunteers\(^8\)-\(^{10}\). Administration of olanzapine in patients with schizophrenia has been shown to produce an overall improvement in sleep continuity, sleep efficiency and total sleep time\(^{11,12}\). Olanzapine has been shown to have potent antagonistic properties at the 5-HT\(_{2A/2C}\) receptors, which exceed its binding affinity for dopamine D\(_2\) receptors\(^{13,14}\). Olanzapine also has high affinity for cholinergic receptors. It is thought to normalize sleep through its mechanism of action at the 5-HT and cholinergic receptors. To date there has only been one study (by Sharpley and colleagues\(^{15}\)) examining the effect of olanzapine on sleep architecture in patients with depression. It was found that augmentation with olanzapine improved sleep continuity and increased slow wave sleep and these effects were maintained throughout the 3 weeks of olanzapine addition. This study also reported a transient acute increase in REM latency.

Olanzapine has been shown to improve cognition in schizophrenic patients\(^ {16}\). However, its impact on cognition in depressive patients has not yet been fully described. While the effects of olanzapine on cognition have not yet been correlated to improvement in SWS, it represents a plausible mechanism of action beyond the usually cited impact on 5HT\(_2\). The impact of SWS upon cognition was highlighted by the recent publication of Marshall et al\(^ {17}\) which demonstrated that stimulating SWS in healthy subjects significantly improved recall ability; a positive indicator of cognitive status. Therefore olanzapine augmentation in the treatment of depression may affect several symptoms of depression: sleep disruption, depressed mood and cognitive function.
Chapter 2: Literature Review

2.1 Depression

2.1.1 Clinical Characteristics

Two major subtypes of depression are described: unipolar and bipolar. The most prominent form of unipolar depression is Major Depressive Disorder (MDD), which consists of one or more major depressive episode(s)\(^{18}\). Bipolar disorder consists of periods of major depressive episodes, and periods of hypomanic or manic episodes\(^ {19}\).

According to the diagnostic and statistical manual of mental disorders (DSM IV-TR), major depressive episodes consist of five or more of the following symptoms occurring nearly every day for at least a two week period. These symptoms must cause clinically significant distress or functional impairment. The symptoms are: 1) depressed mood most of the day, 2) markedly diminished interest or pleasure in all or almost all activity, 3) significant weight loss or decrease or increase in appetite, 4) insomnia or hypersomnia, 5) psychomotor agitation or retardation, 6) fatigue or loss of energy, 7) feelings of worthlessness, or excessive or inappropriate guilt, 8) diminished ability to think or concentrate or indecisiveness, and 9) recurrent thoughts of death, suicidal ideation, or suicide attempt, or specific plan for committing suicide\(^ {19}\).

(Hypo)manic episodes, according to DSM IV-TR\(^ {19}\), are defined as distinct periods of abnormally and persistently elevated, expansive or irritable mood lasting at least one week. During these periods, three or more (four or more, if irritable mood) of the following symptoms must persist and be present to a significant degree. The symptoms are: 1) inflated self-esteem or grandiosity, 2) decreased need for sleep, 3) more talkative than usual or pressured speech, 4) flight of ideas or racing thoughts, 5) distractibility, 6) increase in goal-directed activity or psychomotor agitation, and 7) excessive involvement in pleasurable activities or risks where consequences are
ignored. The degree of severity of these symptoms and the level of distress associated separates hypomanic from manic episodes. Bipolar I disorder (BD-I) consists of periods of manic episodes and often periods of major depressive episodes. Whereas, bipolar II disorder (BD-II) consists of hypomaniac episodes and periods of major depressive episodes.

Depression can be further described by a number of specifiers. The two most prominent subtypes are melancholic depression and atypical depression. Melancholic depression is clinically characterized by a cluster of symptoms; psychomotor disturbance, lack of reactivity to the environment, terminal insomnia, weight loss, distinct quality of depressed mood, diurnal variation of mood with worsening in the morning, anhedonia, guilt, and often occurs in psychotic depression. Melancholic features also predict good response to electroconvulsive therapy (ECT) and other antidepressant treatments as well as a consistently better response to antidepressants than placebo. Although much of the classification of melancholic depression comes from clinical characteristics, it has been shown that these patients have greater biological abnormalities. These biological abnormalities include failure to suppress cortisol, increased hypothalamic-pituitary-adrenocortical (HPA) axis activity, reduction of right hemispheric processing and decreased latency to REM sleep. Melancholia does not appear to be associated with a more episodic or less chronic course and the melancholic characteristics are not stable across repeated episodes.

Atypical depression, according to the DSM-IV is characterized by mood reactivity and two or more of the following symptoms: 1) significant weight gain or increased appetite, 2) Hypersomnia, 3) leaden paralysis, or 4) long-standing pattern of interpersonal rejection sensitivity. MDD with atypical features has been found to have significantly higher rates of comorbidity with other psychiatric disorders, especially cluster B and C disorders. A differentially higher response to Monoamine Oxidase
Inhibitors (MAOI) is reliably reported in this population. Atypical depression may have a component of heritability, although no studies specifically examining heritability were identified, a portion of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, showed that maternal depression with atypical features was associated with notably higher risk of early-onset depressive (3.3-fold) and anxiety disorders (2.6 fold). This is probably due to a combination of heritability and the psychosocial effect of being raised by a mother with depression. The data examining the neurobiological effects of atypical depression are somewhat inconsistent and inconclusive. Recent research indicates that atypical depression may be associated with low HPA axis activity, cortisol suppression, REM sleep and sleep continuity, and preservation of right hemispheric processing. Atypical depression is also associated with significantly earlier onset and greater chronicity of illness.

2.1.2 Epidemiology

Recently, a large epidemiological study was undertaken by Kessler and colleagues, in the USA, this national survey was designed to update information on the prevalence, correlates and clinical significance of DSM disorders and their treatments. The lifetime prevalence of MDD was reported to be 16.2% and the 12-month prevalence was 6.6%. The lifetime prevalence estimates for Bipolar Spectrum Disorders were reported as 1.0% for Bipolar I Disorder, 1.1% for Bipolar II Disorder and 2.4% for subthreshold Bipolar Disorder. The 12 month prevalence for Bipolar I Disorder was 0.6%, for Bipolar II Disorder was 0.8% and for subthreshold Bipolar Disorder was 1.4%.

The risk for onset of MDD begins to increase in the early teens and thereafter increases in an approximately linear fashion. The median age of onset for mood disorders was reported to be 30 years of age. The mean age of onset for Bipolar I
Disorder was 18.2yrs, for Bipolar II Disorder was 20.3 years and for subthreshold Bipolar Disorder was 22.2yrs. Lifetime prevalence of MDD was increased for women, respondents in the “other” category of employment (including unemployed and disabled), those who were previously married, and those living near poverty. The 12-month prevalence was increased for homemakers, those with an employment status of “other”, the never married, those with less than 12 months of education, and those living near poverty. The prevalence of lifetime MDD was lower among people who were retired and non-Hispanic blacks. Bipolar Disorder is inversely related to age and education level. Risk of the development of bipolar disorder is elevated in the previously married, in the unemployed and disabled. Sex, race and income level are not related to the risk of development of bipolar disorder.

Both MDD and Bipolar Disorder are highly comorbid with other psychiatric conditions. 72.1% of respondents with lifetime MDD also met criteria for at least 1 other DSM-IV disorder, where comorbid anxiety disorders were the most common (59.2%), followed by substance use disorders (24.0%). 64.0% of respondents with 12 month MDD met criteria for at least 1 other DSM-IV disorder, with anxiety disorders as the most common (57.5%). MDD was reported to be temporally primary to all other comorbid psychiatric disorders in only 12.3% with lifetime MDD and 12.6% with 12 month MDD. 95.8% to 97.7% of respondents with Bipolar Disorder reported comorbidity with a least 1 other DSM-IV disorder, and a dramatically higher number with 3 or more comorbid DSM-IV disorders.

Mood disorders are not only highly prevalent but they can also result in significant role impairment for the afflicted individual. 96.2% of respondents with 12-month MDD reported at least 1 area of impairment (on the Sheenan Disability Scale (SDS)) with impairment reported to be greatest in social role domain and least in the work role domain. The level of impairment reported is striking, with 87.4% reporting at
least moderate impairment, 59.3% reporting severe impairment and 19.1% reporting very severe impairment. Of the respondents with 12 month MDD, a mean of 35.2 days in the last year were reported where the impairment was severe enough that the individual was totally unable to carry out work or normal activities. In Bipolar Disorder, severe role impairment due to 12 month (hypo) mania was reported by 73.1% with Bipolar I Disorder, 64.6% with Bipolar II Disorder, 45.9% with subthreshold Bipolar Disorder. Role impairment due to 12 month MDE was higher, with 89.3% of those with Bipolar I Disorder reporting severe impairment, 91.4% with Bipolar II Disorder reporting severe impairment and 78.8% with subthreshold Bipolar Disorder reporting severe impairment. Impairment was common in all domains of the SDS.

Taken together the high prevalence of mood disorders and the significant role impairments they cause result in a high burden of disease. In 2004 unipolar depressive disorders was the third leading cause of disability worldwide, resulting in 65.5x10^6 disability-adjusted life years (DALYs) or 4.3% of total DALYs. In the Americas, unipolar depressive disorders are the first leading cause of disability, accounting for 7.5% of total DALYs.

2.1.3 Pathophysiology of Depression

There are two major working models for the pathophysiology of depression. The first and also the oldest is the monoamine or chemical hypothesis of depression. The second hypothesis, which has only come to light in the last two decades, is the neurotrophic or network hypothesis of depression. The monoamine hypothesis postulates that mood disorders are the result of deficiencies in monoamines, especially serotonin and noradrenaline, at important receptor sites in the brain. This theory was developed in response to observations that various pharmacological agents that acted at monoamine receptors produced improvements in mood, these included the serotonin
receptor antagonist: lysergic acid diethylamide (LSD), an agent which diminished vesicular storage of serotonin and norepinephrine: reserpine, and an antimicrobial agent which acts as a monoamine oxidase inhibitor: iproniazid. These findings lead to the development of reuptake inhibitors of specific monoamine systems, e.g. fluoxetine. The efficacy of these selective reuptake inhibitors further strengthened the monoamine hypothesis of depression. The major criticism of this hypothesis is the observation that selective monoamine reuptake inhibitors act on the receptors within hours but it takes approximately 4-6 weeks to see a clinical effect 36.

The network hypothesis of depression postulates that mood disorders arise from problems with information processing in specific neural networks of the brain and that antidepressants function by improving processing in these networks 35,37. This hypothesis came about from observations that people with depression have reduced grey matter volume and glial density in the prefrontal cortex and hippocampus contributing to feelings of worthlessness and guilt; reduced activity in the amygdala and subgenual cingulated cortex (Cg25) contributing to dysphoric mood; and decreased production of neurotrophic factors including Brain-Derived Neurotrophic Factor (BDNF) which can lead to increased neuronal death 38. Another important contributing factor to the network hypothesis of depression is the relationship between stress and neurogenesis, it has been shown that chronic stress can cause decreases in adult neurogenesis 39. The monoamine/chemical hypothesis and the network hypothesis are not mutually exclusive, they can be taken together to further the understanding of the pathophysiology of depression. Increases in synaptic monoamines are now thought to mediate molecular and cellular plasticity through downstream transcriptional and translation effects on neurotrophic factor genes expression 38.

Serotonin (5-HT) is a key neurotransmitter in depression. The most important serotonin receptors subtypes in the pathophysiology of depression are 5-HT_{1A}, 5-HT_{2}, 5-
HT₄, 5-HT₆, and 5-HT₇. 5-HT has a significant role in the core symptoms of mood disorder, including: mood, sleep, appetite, sexual activity, circadian and seasonal patterns, motor activity and cognitive functions. Serotonin also plays a role in neurotrophic factor expression. 5-HT₂A receptor antagonism has been shown to diminish the effects of stress on BDNF expression in the hippocampus.

Norepinephrine (NE) is another neurotransmitter thought to be important in the pathophysiology of depression. The relationship between NE and depression is more complicated than a mere deficiency, NE’s role in depression is likely through modulation of the prefrontal cortex. The NE system also plays an important role in the acquisition of emotionally arousing memories. NE plays a role in memory consolidation and fear conditioning by conveying emotional significance to memories of prior experience through activity in the amygdala. This relationship is highlighted by the observation that propranolol (a β-adrenergic antagonist) blocks the formation of emotional significance tied to memories.

Dopamine (DA) also plays an important role in mood disorders. The DA system projects to the nucleus accumbens (NA), which has a role in reinforcing pleasurable activity and drug abuse. DA is released in the PFC and the core of the NA in response to stress and increases in the shell of the NA after the aversive stimuli. DA’s role in mood disorders may be related the anhedonic symptoms of depression in relation to stress. This hypothesis is strengthened by observations that DA agonists (ex. L-dopa, amphetamine) are associated with the development of manic symptoms and DA antagonists are effective treatments for mania. As well, DA reuptake inhibitors (ex. bupropion) are efficacious antidepressants. The lack of reward and pleasure from social interactions often experienced by people with depression has been suggested to be due to a dysfunction in the DA system.
The cholinergic system also plays a role in depression; it is thought to be overactive and/or hyper-responsive. Administration of an acetylcholine-esterase inhibitor to people experiencing a manic episode induced switching to a depressive episode and worsened depressive symptoms for those already experiencing a depressive episode. Cholinergic system dysfunction is also thought to be related to the memory and attentional deficits in depression. Cholinergic and muscarinic receptor agonists exasperated polysomnographic and neuroendocrine responses in people in a depressive state. Muscarinc2 receptor polymorphisms are associated with depression. Muscarinc2 receptor antagonists increase activity in the cingulate cortex and elicit a variety of feelings including sadness, fear and anxiety.

There are a number of CNS abnormalities associated with depression, varying with age of onset, capacity for developing mania or psychosis, and family history of mental illness. In MDD and Bipolar Disorder, it has been reported that there is a reduction in gray matter in the left anterior cingulate cortex (ACC) ventral to the corpus callosum and in the orbital and ventral prefrontal cortex. White matter reductions have been reported in the genu and splenium of the corpus callosum. It still remains unclear if there are volumetric changes in the amygdala and stratum of people experiencing a MDE. In MDD, there are gray matter reductions in the frontal dorsal anterolateral PFC and reductions in hippocampal volume. Reductions are reported in glial cell density in the pregenual ACC, the dorsolateral PFC and the amygdala. The mean size of neurons was diminished in the dorsal anterolateral PFC. Reductions are reported in Bipolar Disorder in the posterior cingulated cortex and the superior temporal gyrus grey matter and the anterior ventral CA1 region. Non-pyramidal neurons were diminished in the ACC, dorsal anterolateral PFC and hippocampus. Synapses and synaptic proteins in the hippocampal ventral CA1 region were reduced. From rodent models, reductions in grey matter in MDD and BD have been associated with repeated and chronic stress which
result in dendritic atrophy and reduced glial cell counts and proliferation \(^{49}\). Although stress reduces adult neurogenesis, antidepressants have been shown to improve neurogenesis and prevent or diminish the effect of stress on neurogenesis \(^{39}\).

Although much remains to be elucidated about the pathophysiology of depression, it is clear that it is a much more complicated picture than simply a reduction in synaptic monoamines. The pathophysiology of depression is more likely to be due to a dysregulation of a number of neurotransmitter systems affecting neurogenesis.

### 2.2 Sleep

Sleep, in humans, is defined both by the individual's behavior and changes in the brain's electrical activity between wakefulness and sleep. Sleep is an important physiological drive, requiring for survival. The behavioral characteristics of sleep include reclined position, closed eyes, decreased movement, and decreased responsiveness to the environment \(^{50}\). The brain's electrical activity is measured during sleep using the methodology of polysomnography. Brain activity is recorded by electroencephalogram (EEG), eye movements are recorded using an electro-oculogram (EOG) and muscle tone is recorded using electromyogram (EMG). Depending on the purpose of the polysomnograph (PSG), measurements can also include: nose and mouth airflow, respiratory effort measured by strain gauges, oxygen saturation, electrocardiogram (ECG), leg movement using EMG of the anterior tibialis muscles, as well as body position \(^{51}\).

#### 2.2.1 Sleep Architecture

As reviewed by Markov and Goldman \(^{52}\), there are two different states of sleep architecture, rapid-eye movement (REM) sleep and non-rapid eye movement (NREM) sleep. NREM is divided into 4 stages: stages 1, 2, 3, and 4. Stage 3 and 4 together
constitute slow wave sleep (SWS) or delta sleep. REM sleep is divided into two stages: tonic and phasic.

During the transitions between wakefulness and sleep, EEG patterns consist of low-voltage rhythmic alpha activity (8-13Hz) \(^{53}\). As the individual falls into stage 1 sleep, these alpha waves are replaced by low voltage mixed frequency (4-8Hz) theta waves. In stage 1 muscle activity is diminished from that of wakefulness, asynchronous eye movements are present for the first few minutes, and the individual may be easily aroused as this is the most “shallow” of all aspects of sleep \(^{54}\).

In stage 2 sleep, sleep spindles are seen; these are 12 to 14 Hz synchronized wave forms with durations of 1.5s. They arise from groups of thalamic neurons, which are synchronized by the GABAergic thalamic spindle pacemaker \(^{55}\). The arousal threshold is increased in stage 2 sleep, muscle tone declines and no eye movements are seen.

The SWS (stages 3 and 4) EEG pattern consists of synchronized high amplitude (>75μV) and slow (0.5-2 Hz) delta waves. EEG activity during stage 4 is characterized by a greater amount (>50%) of delta waves compared to stage 3 (20-50%). SWS is considered the deepest stage of sleep as it has a much higher arousal threshold, eye movements are not observed and muscle tone continues to decline \(^{56}\).

EEG patterns during REM sleep consist of low voltage, higher frequency (alpha or 8-13Hz) waves. This pattern may be activated or desynchronized; where activated is a pattern similar to that of wakefulness and can be accompanied by dream sleep, and desynchronized is a pattern of random appearing waveforms. Along with the activated periods of REM sleep, rapid eye movements and muscle atonia are seen \(^{51}\). Tonic REM sleep is continuous throughout this stage and is characterized by muscle atonia and desynchronized EEG. Intermittent phasic events of rapid eye movements and irregular respiration and heart rate are present during REM sleep \(^{56}\).
REM and NREM stages occur in cycles throughout sleep, cycles last approximately 90-120 minutes, typically there are 3-6 cycles per night in normal nocturnal sleep. Sleep cycles typically begin with NREM, starting with stage 1 and progressing towards deeper sleep into SWS. A period of REM sleep ends the sleep cycle. In the first sleep cycle the period of REM sleep is brief and the period of SWS is its longest. Stage 1 sleep either acts as a brief transition from wakefulness to NREM sleep or from REM to NREM sleep. Stage 1 is the least occupied stage; only 2%-5% of total sleep time is spent in stage 1. Stage 2 generally lasts only 10-20 minutes of each cycle; which constitutes 45%-55% of the total sleep time. SWS dominates the sleep cycles in the first third of the night, lasting on average 40 minutes per cycle and approximately 15%-20% of total sleep time. As SWS shortens in each cycle, the amount of REM sleep per cycle increases with REM sleep dominating each sleep cycle in the final third of the night. REM sleep constitutes 20%-25% of total sleep time.

In an adult who has no sleep abnormalities, sleep efficiency (ratio of time asleep/time in bed) is generally 95%, sleep onset occurs in less than 15 minutes and awakenings are brief and limited in number. There is little difference between sleep in adult men and women; however aging greatly affects sleep patterns. Aging is associated with greater sleep fragmentation (i.e. more time awake). The amount of REM sleep is stable through adulthood and declines in the elderly. In contrast, SWS begins to decline after adolescence and may not be present at all in some elderly.

There are many different types of sleep disorders and abnormalities. Of particular interest to the present study is sleep apnea. There are two major categories of sleep apnea: obstructive and central. Obstructive sleep apnea (OSA) is the most common and arises from an obstruction in the upper airway, often due to collapsing of the airway. This is due to reduced muscle tone during sleep and negative upper airway pressure. Central apnea is very rare and is an absence of ventilation; this is often due to a lack of
ventilation effort. Central apnea generally arises after a neurologic event, such as a seizure. The presence of OSA may diminish the effects of pharmacological treatments in depression.

2.2.2 Physiology of sleep

There are a number of important neurotransmitters in the regulation of sleep, the most clearly understood are γ-aminobutyric acid (GABA), acetylcholine, histamine, norepinephrine, and serotonin.

The GABAergic cells in the basal forebrain and the anterior hypothalamus are more active during NREM periods than REM periods or wakefulness. These neurons increase activity at sleep onset and remain active and release high levels of GABA as sleep continues. These GABAergic cells inhibit cells that are involved in arousal functions, specifically cholinergic neurons in the basal forebrain. This inhibition of cholinergic neurons results in deactivation of the cortex.

Cholinergic neurons promote both sleep and wakefulness; there are two subsets of cholinergic neurons important in sleep regulation. The first subset is responsible for cortical activation seen in REM sleep and restful wakefulness (fast frequency, low voltage EEG waveforms). The second subset is responsible for generation of REM sleep. These two types of cholinergic neurons originate in the laterodorsal and pedunculopontine tegmental nuclei and ascend through the thalamus and hypothalamus to reach the cortex. However, the cholinergic neurons that originate in the basal forebrain and project to the cortex and limbic areas are part of the waking system and thus must be inhibited for sleep to occur.

The posterior hypothalamus contains histaminergic cells that are important in sleep and wakefulness and have been strongly tied to the promotion of wakefulness when active and are inactive during REM sleep. These histaminergic cells are inhibited
by GABAergic neurons resulting in sleepiness\textsuperscript{59}. This is supported by the observation that lesions in the posterior hypothalamus produce continual sleepiness\textsuperscript{59} and lesions of the basal forebrain and the anterior hypothalamus produce consistent insomnia\textsuperscript{60}.

The locus ceruleus of the pons contains many norepinephrine neurons; these cells are inactive during REM sleep. The cessation of activity of norepinephrine cells during sleep is thought to be associated with the loss of muscle tone during sleep\textsuperscript{61}. Norepinephrine neurons suppress REM sleep by inhibiting REM promoting cholinergic neurons. Norepinephrine neurons promote cortical activation by rapid firing, the reduction in this firing rate occurs at the beginning of the first sleep cycle and results in disinhibition of the REM cholinergic neurons leading to the first REM sleep period\textsuperscript{52}.

Serotonergic neurons originate in the dorsal raphe nucleus, they are inactive during sleep and are thought to have a role in maintaining arousal and regulating some of the phasic events of REM sleep\textsuperscript{61,62}. Serotonergic neurons are active during waking and suppress phasic events by inhibiting cholinergic neurons that promote REM sleep, when inactive phasic events may occur. Serotonergic neurons follow a similar pattern as norepinephrine neurons\textsuperscript{52}.

Recently, functional neuroimaging, both positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), have given new insights into sleep physiology. Differences have been found in areas of activation between wakefulness and sleep and between REM and NREM sleep. Briefly, as reviewed by Dang-Vu and colleagues\textsuperscript{63}, NREM sleep is characterized by a decrease in blood flow in the dorsal pons, mesencephalon, thalami, basal ganglia, basal forebrain, anterior hypothalamus, prefrontal cortex, anterior cingulate cortex, and precuneus. When compared with wakefulness, NREM sleep showed deactivation in the dorsolateral prefrontal and orbital prefrontal cortex, as well as the parietal lobe. During NREM sleep an inverse relationship was seen with cerebral blood flow and delta activity in the ventromedial prefrontal...
regions. The activation pattern seen during REM sleep is very different pattern of activation. REM sleep is characterized by high, sustained neuronal activity and thus high cerebral blood flow requirements. Regional activations during REM sleep were seen in the pontine tegmentum, thalamus, amygdala, hippocampus, anterior cingulate cortex, temporo-occipital areas, basal forebrain, cerebellum, and caudate nucleus. Deactivations were seen in the dorsolateral prefrontal cortex, posterior cingulate gyrus, the precuneus and the inferior parietal cortex.

2.2.3 Relationship between sleep and depression

Disturbance in sleep quality is a symptom of depression, both in MDD and BD. The NIMH epidemiologic catchment area (ECA) study of sleep and psychiatric disorders reported that presence of a sleep disturbance is a highly significant risk factor for the development of depression (odds ratio: 39.8). In the study, 40% of respondents with insomnia, 46.5% with hypersomnia and 16.4% with no sleep complaints had a psychiatric disorder, demonstrating the high comorbidity of sleep disturbances and psychiatric disorders. Individuals with hypersomnia also have increased prevalence of mood disorders, 9.9%. Major depression was found to have the strongest association with sleep disturbances. In a large perspective study done at John’s Hopkins, 1300 male medical students were followed for 40 years to examine the relationship between sleep disturbance in young adulthood and the development of depression. Those who reported insomnia in young adulthood were twice as likely to develop clinical depression, even after controlling for class year, parental history of depression and temperament. Ninety percent of depressed patients complain of impairments in sleep quality, these include difficulty falling asleep, frequent awakenings and early morning awakenings. Sleep during a depressive episode is reported as “less deep” and not restful. Sleep disturbances are not just a symptom of depression; the severity of
disturbance is related to response to treatment and chronicity of the disorder. In a study of older adults with depression, it was reported that greater sleep continuity disturbances and higher amounts of REM sleep along with other psychosocial variables predicted a slower more variable pattern of response to treatment \(^{68}\). Another study of depression in the elderly showed that participants who did not report good subjective sleep quality after treatment relapsed sooner than those who did \(^{69}\). Therefore, the treatment of sleep disturbances in depression is an important aspect of disease management.

### 2.2.4 Sleep architecture in depression

Sleep architecture is altered in patients experiencing a major depressive episode. The extent of this has been widely characterized as reviewed by Riemann and colleagues \(^{3}\). Sleep continuity disturbances and decreased total sleep time are the most prominent features of sleep disturbance in depression \(^{70}\). Sleep in depression is also characterized by reduction in SWS, increased latency to SWS, increase in duration of REM sleep, especially in the first REM period, and shortened latency to REM sleep. The shortened latency to REM is thought to be one of the most significant alterations in sleep of patients with depression \(^{71-73}\). SWS reductions and REM disinhibition are seen in approximately 50% of patients with affective disorders \(^{70}\). Most recently, increasing attention has been paid to the reduction in SWS seen in depression. The reduction of SWS activity is strongly associated with severity of depression \(^{74,75}\) and is thought to have a significant role in the sleep impairment seen in depression \(^{76}\). It has been suggested that REM and SWS abnormalities may be biological markers for depression as the severity of the disturbance worsens during the acute phase of the illness and often does not recover completely during remission \(^{67}\).

Although, much of the objective research on sleep in depression has been carried out in populations of people with MDD, studies comparing patients with unipolar
and bipolar depression have not found any significant differences in nocturnal sleep patterns.  

### 2.2.5 Physiology of sleep abnormalities in depression

Monoaminergic neurotransmitters are thought to play a role in the relationship between sleep and depression. As discussed previously, the serotonergic, cholinergic, and noradrenergic systems all contribute to the pathophysiology of depression and underlying mechanisms of sleep. Overactivation of the cholinergic system may result in promoting increased wakefulness as well as increased REM sleep. Decreased noradrenergic and serotonergic activity seen in depression may be associated with REM disinhibition seen in patients with depression.  

Recently there have been functional imaging studies examining the role of sleep in depression. Relative to controls, depressed patients were found to have hypometabolism in the medial orbital prefrontal cortex, anterior cingulate gyrus and basal ganglia, areas which are thought to be important in NREM sleep. Depressed patients have also been shown to have relatively greater activity in the bilateral prefrontal, left premotor, primary sensorimotor, midbrain reticular formation and left parietal cortices. Accentuation in these areas during REM sleep may be associated with the increased REM activity seen in depression. REM density in sleep of patients with depression correlates to hypermetabolism in the striate cortex, posterior parietal cortices and the medial and ventrolateral prefrontal cortices.  

### 2.3 Pharmacological Treatments for Depression

There are many different pharmacological treatments available for the treatment of MDD and BD. There are three major classes of medications used in the treatment of a major depressive episode: 1) antidepressants; 2) mood stabilizers; and 3)
antipsychotics. The Canadian Network for Mood and Anxiety Treatment has published guidelines, using evidenced based medicine, for the treatment of MDD and BD. The guidelines for MDD indicate that the first-line treatment options for pharmacotherapy include Selective Serotonin Reuptake Inhibitors (SSRIs) and venlafaxine, the second line options are amitriptyline and clomipramine and third line options include Tricyclic antidepressants (TCAs) and MAOIs. For the treatment of BD, the first-line treatment options for an acute depressive episode are lithium, lamotrigine, divalproex + SSRI, olanzapine + SSRI, lithium + divalproex, divalproex + bupropion, or quetiapine monotherapy. The second line treatment options are quetiapine + SSRI, lithium or divalproex + lamotrigine. After second-line treatments have failed treatment options include other antidepressants in combination with atypical antipsychotics and mood stabilizers as well as non-pharmacological treatments.

2.3.1 Antidepressants

There are several classes of antidepressants, which include Selective Serotonin Reuptake Inhibitors (SSRIs), Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs), Norepinephrine Dopamine Reuptake Inhibitors (NDRIs), Tricyclic antidepressants (TCAs), Monoamine Oxidase Inhibitors (MAOIs) and a few various others that do not fit into these classifications.

Commonly used SSRIs include fluoxetine, paroxetine, sertraline, fluvoxamine, and citalopram. Two common SNRIs are venlafaxine and duloxetine. Bupropion is one of a few NDRIs. The TCAs include clomipramine, imipramine, desipramine, and amitriptyline and the most common MAOIs are phenelzine and moclobemide. Two commonly used antidepressants, which do not fit into any of these categories, are mirtazapine and trazodone. With the exception of the SSRI’s noted above, only the other antidepressants of significance to this study will be elaborated on.
Fluoxetine primarily acts as a serotonin reuptake inhibitor, however it also has a low affinity as a norepinephrine reuptake inhibitor \(^{85,86}\). Fluoxetine has been shown to be an efficacious treatment for depression \(^{87}\). The use of fluoxetine in healthy volunteers resulted in REM suppression as indicated by a decrease in REM sleep and an increase in latency to REM. Increases in the percentage of time spent in stage 2 and 3 were seen, however no change was seen in the time spent in slow wave sleep. There was also no difference in the number of awakenings with fluoxetine administration \(^{88}\). Similar results were seen when fluoxetine was administrated to patients with depression; a decrease in REM sleep and an increase in latency to REM was seen. However, an increase in the time spent in stage 1 and a decrease in time spent in stage 3 and 4 was observed. Sleep efficiency was significantly decreased and sleep latency was slightly improved with fluoxetine treatment in depression \(^{89}\).

Paroxetine acts primarily as a serotonin reuptake inhibitor as well. It also has moderate affinity as a norepinephrine reuptake inhibitor and slight affinity as a dopamine reuptake inhibitor \(^{85,90}\). Paroxetine is an efficacious treatment for depression \(^{91}\). Paroxetine administration in healthy volunteers resulted in REM suppression, reduced total sleep time, increased awakenings, and delayed sleep onset. However, increases in SWS were also seen with paroxetine administration in healthy volunteers \(^{92}\). When paroxetine was given to patients with depression, REM suppression was observed and increased awakening which resolved after 8 weeks of treatment, although no change was seen in SWS \(^{93}\).

Sertraline, also primarily acts as a serotonin reuptake inhibitor. It has moderate affinity as a norepinephrine reuptake inhibitor and slight affinity as a dopamine reuptake inhibitor as well \(^{85,94}\). Sertraline is an efficacious treatment for depression and it use has been shown to be beneficial over many of the other antidepressants in its class \(^{95}\). A study of the effects of sertraline on sleep in healthy volunteers could not be identified.
Sertraline administration to patients with depression resulted in an increase in REM activity in sleep cycle 1 and 2, increased average REM, a decreased number of REM periods and increased REM latency. However, sertraline administration also resulted in increased SWS in sleep cycle 1 and decreased SWS in sleep cycle 2. Sleep latency was improved with sertraline treatment\(^96\).

Fluvoxamine acts solely as a serotonin reuptake inhibitor and has no other significant mechanism of action\(^ {85,97} \). Fluvoxamine has been shown to be an efficacious treatment for depression, with similar efficacy as the TCA, imipramine\(^98\). Fluvoxamine treatment in depression has resulted in delayed sleep onset, increase stage 1 time, decreased time and percentage of time in SWS and may have resulted in worsened sleep continuity. REM suppression is seen with a decrease in the time spent in REM sleep and an increase in the time to onset of REM\(^ {99,100} \).

Citalopram and escitalopram (S-enantiomer of racemic citalopram) are highly selective inhibitors for the serotonin transporter. They have little affinity for other receptors, including norepinephrine\(^ {85,101} \). Escitalopram has been shown to be the more effective of the two antidepressants\(^ {102} \). A polysomnographic study of escitalopram on sleep of patients with depression could not be identified. However, the effects of citalopram on sleep have been studied. It was reported that citalopram administration did not change sleep latency or sleep continuity, however, there was a significant increase in REM latency, a decrease in REM time and an increase in time spent in stage 2 in patients with depression\(^ {103} \).

Venlafaxine is a potent serotonin reuptake inhibitor, at higher doses it is a potent norepinephrine reuptake inhibitor\(^ {85,104} \). Venlafaxine is an efficacious treatment for depression as well as for depression with comorbid anxiety\(^ {105} \). Administration of venlafaxine to healthy volunteers resulted in an increased amount of time awake and in stage 1, decreased stage 2, 3 and 4. REM suppression was seen with decreases in the
time spent in REM and REM frequency. At higher doses of venlafaxine no REM sleep was seen in the healthy volunteers. Venlafaxine treatment in patients with depression showed worsened sleep continuity, decrease in time spent in REM and increased latency to REM sleep.

Duloxetine is a dual reuptake inhibitor for serotonin and norepinephrine. Duloxetine is a more potent inhibitor for both neurotransmitter systems than venlafaxine. Duloxetine is an efficacious treatment for depression and may help to resolve somatic symptoms more than other antidepressants. In healthy volunteers, compared to placebo, duloxetine administration resulted in improved sleep efficiency, increased time spent in stage 2 sleep and REM suppression. Duloxetine treatment in patients with depression resulted in decreased time in REM sleep and increased time to REM onset. Duloxetine treatment may also decrease the latency to SWS and increase the time spent in SWS, although a study with a larger sample size is needed to confirm this.

Bupropion is a dual reuptake inhibitor of both norepinephrine and dopamine and does not have any serotonergic effects. The commonly studied formulation is bupropion SR, which requires twice daily dosing. Bupropion SR is an effective treatment for depression. The effects of bupropion on sleep architecture are unclear. Nofzinger and colleagues found only a significant change in time to sleep onset and no change in REM latency or duration in depressed patients treated with bupropion SR. A similar study was undertaken by Ott and colleagues, they reported that treatment with bupropion SR significantly increased the number of awakenings, increased REM latency, increased activity and density of the first REM period and increased overall REM density. The reason for these conflicting finding are unclear.

Trazodone is a heterocyclic antidepressant. It is a relatively weak serotonin reuptake inhibitor, compared to SSRIs. It has affinity for histamine H₁, 5-HT₁A and 5-HT₂.
receptors\textsuperscript{85,116}. Trazodone has been shown to be an efficacious treatment for depression among other disorders\textsuperscript{117}. In healthy volunteers trazodone has been shown to increase the percent of time spent in SWS and had no effect on REM sleep\textsuperscript{118}. In patients with depression, trazodone treatment resulted in an increase in total sleep time, decrease in sleep latency, and an increase in stage 2 and SWS. However, REM suppression was not seen\textsuperscript{119}. In contrast, another study of the effects of trazodone on sleep in patients with depression reported the presence of REM suppression and no change to sleep continuity or SWS\textsuperscript{120}. The differences seen in the two studies may be due to higher dosing and greater severity of baseline sleep disturbances in the former study.

Amitriptyline is a reuptake inhibitor of both norepinephrine and serotonin, it also has affinity for muscarinic, histaminergic (\textit{H}_1) and adrenergic (\textit{\alpha}_1) receptors\textsuperscript{85,121}. Amitriptyline in an efficacious treatment for depression and may be slightly more effective than other TCA’s and newer antidepressants\textsuperscript{121}. Amitriptyline treatment in patients with depression resulted in REM suppression, reduced number of awakenings and increased stage 2 sleep, although no changes to SWS were seen\textsuperscript{122,123}.

Phenelzine is an inhibitor of both monoamine oxidase type A and B enzymes. Phenelzine is an efficacious treatment for depression, although not used as frequently due to side effects and dietary restrictions\textsuperscript{26}. Phenelzine treatment in patients with depression resulted in a decrease in time and percentage of time spent in REM and stage 2 sleep and an increase in the percentage of time spent in SWS. REM suppression with phenelzine is dramatic, with only 4.9 min on average of REM sleep after 5 weeks of treatment with over half of the participants having no REM sleep after 5 weeks of treatment\textsuperscript{124}. Changes in SWS have not been seen consistently with phenelzine treatment\textsuperscript{125}.  

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For the most part, antidepressants of all classes suppress REM sleep in patients with depression. The effects of antidepressants on NREM sleep, especially SWS, and sleep continuity varies with each antidepressant even within classes. It is suggested that treatment with an SSRI resulted in either no change or a worsening of sleep continuity and SWS. Duloxetine, trazodone and phenelzine may result in improvements in SWS, however, there is contradictory data. Thus, to date few antidepressant treatments result in an improvement in sleep architecture above the suppression of REM sleep.

2.3.2 Augmentation Agents

Not all patients respond to antidepressant treatment alone. In a review of over 36 clinical trials involving over 3600 patients it was reported that 36% of patients were partial or nonresponders to antidepressant treatment. In unipolar depression, augmentation agents can include either mood stabilizers, antipsychotic medications or a combination of the two added to an antidepressant. In bipolar depression, augmentation is often the addition of an antidepressant or antipsychotic medication to an existing mood stabilizing regime, although any combination of the three can be used as first line treatment. This section will discuss the effects of mood stabilizers and antipsychotic medications on sleep and depression. The most frequently used mood stabilizers include lithium, lamotrigine and divalproex. There are two classifications of antipsychotics; typical and atypical. The most frequently used antipsychotic medications in depression are the new atypical antipsychotics (AAs), which include quetiapine, ziprasidone, risperidone and olanzapine.

Lithium is the most frequently studied mood stabilizer in respect of sleep and the treatment of depression. Lithium is thought to be a neuroprotectant which acts by inhibiting the action of glycogen synthase kinase -3 (GSK-3). Lithium is also thought to improve serotonergic neurotransmission and may inhibit 5-HT2 receptor function.
In a review of over 10 double blind randomized placebo controlled trials, patients with unipolar depression who received lithium augmentation, 50% reported improvement in mood. Lithium has long been an acute and maintenance treatment in bipolar disorder. Lithium treatment in healthy volunteers has been shown to increase the amount of time spent in SWS, decrease percent of actual sleep time, increase the amount of nocturnal wake time and decrease the amount of time spent in REM sleep. Lithium treatment in patients with depression showed increases in SWS and decreases in REM sleep. Although these results are not entirely clear, as the study by Kupfer and colleagues include patients in the manic phase of their illness. Information on the effects of lamotrigine and divalproex on sleep in patients with depression appears to be unknown at this time.

Risperidone is a novel antipsychotic medication. It has high affinity for serotonin 5-HT2, dopamine D2, and α1 adrenoreceptors, it has low affinity for α2 adrenoreceptors and histamine H1 receptors and no affinity for dopamine D1 and muscarinic receptors. Risperidone has been shown to be beneficial as augmentation in the treatment of mood disorders. In healthy volunteers, risperidone treatment resulted in a significant decrease in REM sleep when administered in the evenings. When risperidone was administered in the morning to healthy volunteers a decrease in the percentage of REM sleep and stage 2 sleep was seen. Risperidone treatment in treatment resistant depressed patients resulted in significantly decreased nocturnal wake time, decreased time in REM sleep and significantly increased time in stage 2 sleep.

Quetiapine is another novel antipsychotic medication; it has moderate affinity for serotonin 5-HT2A, α1 adrenoreceptors, muscarinic and histaminergic receptors. Quetiapine has minor affinity for dopamine D2 and 5-HT1A receptors and very low affinity for serotonin 5-HT2C, α2 adrenoreceptors and dopamine D1 receptors. Quetiapine has been shown to be an effective treatment in bipolar depression and in unipolar...
depression. There has been one study examining the effect of quetiapine on sleep in healthy volunteers. It was reported that quetiapine increased total sleep time, improved sleep efficiency, decreased latency to stage 1 and 2, increase percent of time in stage 2, decreased nocturnal awake time and decreased percent of time in REM. Latency to REM and SWS, however, were unaffected. Only one study to date has examined the effect of quetiapine on unipolar and bipolar depression. Quetiapine augmentation resulted in a decrease in REM sleep and an increase in NREM sleep, specifically stage 2, with acute treatment, which dissipated over a period of 4 weeks. No changes were seen with sleep continuity or SWS (Milev et al, 2009 unpublished data).

Ziprasidone in the newest of the atypical antipsychotics. Ziprasidone has a high affinity for 5-HT\textsubscript{2A/C}, 5-HT\textsubscript{1A} and 5-HT\textsubscript{1D} receptors, where is it an antagonist of 5-HT\textsubscript{2A/C} and an agonist of 5-HT\textsubscript{1A}. Ziprasidone has moderate affinity for \(\alpha_1\) and H\textsubscript{1}; and low affinity for \(\alpha_2\). Ziprasidone only has minimal affinity for muscarinic receptor M\textsubscript{1}. There are no randomized trials of the treatment of depression with ziprasidone, however one open label trial suggests ziprasidone may be an effective treatment of bipolar II depression. As well, studies in schizophrenia and schizoaffective disorder suggest ziprasidone may have some beneficial antidepressant effects. Ziprasidone administration in healthy volunteers resulted in improved total sleep time, sleep efficiency, percentage of time in stage 2 and percentage of time in SWS. Ziprasidone has also been shown to decrease the percentage of time awake, percentage of time in stage 1 and suppressed REM sleep (decreased density and time as well as increased latency to REM). To date there are no published studies examining the effects of ziprasidone treatment on sleep in depression.

There are a variety of augmentation agents available, most of which suppress REM sleep similar to that of antidepressants. However, more of the augmentation agents improve SWS and sleep continuity than the antidepressants.
2.3.3 Olanzapine

Olanzapine is an atypical antipsychotic with a broad pharmacologic profile. Olanzapine is a thiobenzodiazepine and was originally developed for use in schizophrenia. Olanzapine has affinity for dopamine D₁, D₃, and D₄; serotonin 5-HT₂A/C, 5-HT₃ and 5-HT₆; muscarinic M₁-M₅; adrenergic α₁ and histamine H₁ receptors. Olanzapine is an antagonist at these sites with highest affinity for the dopamine receptors and the serotonin receptors ¹³,¹⁴.

In the treatment of schizophrenia, olanzapine has been shown to reduce both positive and negative symptoms and is associated with fewer extrapyramidal symptoms ¹⁴⁵. Olanzapine administration to patients with schizophrenia has resulted in increased total sleep time and time in stage 2, decreased total wake time and time in stage 1. Olanzapine administration resulted in improved delta sleep and increased REM density. This pattern of change was seen in both acute and chronic administration ¹¹,¹². In patients with schizophrenia, delta sleep less than 10% of total sleep time at baseline predicted a good clinical response to olanzapine treatment ¹¹.

Olanzapine augmentation therapy has been shown to be beneficial in both bipolar depression and unipolar depression ¹⁴⁶,¹⁴⁷. The most frequently studied use of olanzapine augmentation is the olanzapine-fluoxetine combination. In treatment-resistant depression, the olanzapine-fluoxetine combination resulted in significantly decreased time to response, although decrease in illness severity was the same as either medication alone at the study endpoint ¹⁴⁸. In another larger study of treatment resistant depression, olanzapine-fluoxetine combination proved to significantly improve illness severity over either medication alone ¹⁴⁹. In bipolar depression, the olanzapine-fluoxetine combination resulted in significant improvement in illness severity over either medication alone as well as significantly greater percentage of early responders ¹⁵⁰.
Olanzapine monotherapy has been shown to be efficacious in the treatment of MDD. In the same study 5-HT$_{2A}$ receptor binding of olanzapine was examined using PET, this showed receptor binding in the anterior cingulate, dorsolateral prefrontal cortex, hippocampus, lateral temporal, occipital, gyrus rectus, lateral parietal and subgenual prefrontal cortex regions $^{151}$. Olanzapine monotherapy in the treatment of bipolar depression has been shown to be more efficacious than placebo, however, the olanzapine-fluoxetine combination was reported to improve depression greater than olanzapine monotherapy $^{152}$.

Few studies have examined the effects of olanzapine on sleep; those performed in patients with schizophrenia have already been discussed. In healthy volunteers, olanzapine increased total sleep time, increased sleep efficiency, decreased total wake time and percentage of time awake, and increased SWS both total time and percentage better than placebo, haloperidol and risperidone $^{138}$. Another study $^{8}$ of healthy volunteers supports these results. Olanzapine administration decreased sleep latency, increased total sleep time, increased time and percentage of stage 2 sleep and increased time and percentage of SWS $^{9}$. Another study of healthy volunteers also noted REM suppression along with the changes stated by Gimenez and Lindberg $^{9,138}$.

To date, only one study has been identified that examined the effect of olanzapine in patients experiencing a major depressive episode: Sharpley and colleagues $^{15}$. This was a small study of 12 participants who were administered olanzapine open-label and did not have a placebo or comparator control. The study only included participants with unipolar MDD who had failed adequate treatment with a serotonin-potentiating antidepressant. The study examined the effects of olanzapine augmentation on polysomnographic measures after 1 day and 3 weeks of treatment, and the effect on clinical measures after 1, 2, and 3 weeks of treatment. After 1 day of treatment, it was reported that participants had significantly increased percentage of
actual sleep time, sleep efficiency and total NREM percentage of sleep time; decreased total wake time was also seen. After 3 weeks of olanzapine treatment participants had significantly increased percentage of actual sleep time, sleep efficiency, total NREM percentage of sleep time and percentage of sleep time in SWS; decreased total wake time and sleep latency were also seen. An increase in REM latency was observed after 1 day of treatment, however, this effect dissipated by the end of 3 weeks. Total HDRS and item #1 of the HDRS significantly decreased after 1 week of treatment and continued to decline to the end of 3 weeks. Therefore, olanzapine has the potential to be an effective augmentation agent in the treatment of depression and this may occur through the improvement of sleep architecture. A larger controlled study is needed to examine the true effect.

2.4 Cognition in Depression

Research addressing the issue of cognitive deficits in depression has been growing in the last two decades. Although a general understanding of the deficits present in mood disorders is known, much remains to be elucidated regarding specific impairments and their underlying etiology. Deficits in unipolar and bipolar depression include executive function including working memory, attention and psychomotor speed\textsuperscript{153}. Cognitive dysfunctions appear to be more robust in elderly patients with depression\textsuperscript{154-156}.

Executive functions are the cognitive processes of planning, judgment, decision-making, reasoning, control of attention and task management. These depend on the functioning of the prefrontal cortex\textsuperscript{157,158}. Patients with both unipolar and bipolar depression have shown impairments in these areas of executive function\textsuperscript{159}. Patients with depression have shown significant deficits on the Wisconsin Card Sorting Task and oculomotor tasks, thus displaying evidence of prefrontal cortex dysfunction\textsuperscript{160,161}. The
extent of executive dysfunction in depression is unclear as some studies have shown no
difference in executive function skills in patients with depression compared to healthy
controls \(^{162-164}\) and others have shown patients with depression display dysfunction in a
number of domains of executive function including verbal fluency, concept formation,
attention and working memory \(^{165-167}\). Purcell and colleagues \(^{168}\) reported that with the
exception of attention, executive function of patients with depression was within the
normal range.

An important domain of executive function that may be impaired in depression is
working memory. Working memory is thought to support human thought process as it is
a system which temporarily maintains and stores information. It is the interface between
memory, perception and action \(^{169}\). Although the findings on the relationship between
working memory and depression are contradictory with some studies reporting no
impairment \(^{167,168,170,171}\) and other reporting a significant impairment \(^{165,172,173}\). Sweeny
and colleagues \(^{153}\) reported that bipolar patients in the mixed or manic phase had
significant impairment in working memory compared to healthy controls. But neither
unipolar, nor bipolar, depressed patients showed such deficits.

Another important aspect of executive function is attention. There are three
subtypes of attention. 1) Selective attention is the processing of incoming information
and ignoring competing information. 2) Sustained attention is the capacity to maintain
focus on an activity over a period of time and 3) divided attention is the ability to respond
to more than one task at a time. Most tests of attention measure global deficits and not
the subtypes individually \(^{157}\). Patients with both unipolar and bipolar depression are
thought to have impairments in attention and this is thought to be one of the key
neuropsychological impairments in mood disorders \(^{174}\). While there is much evidence in
support of attentional impairments, similar to that in other areas of executive functioning
the literature is conflicted. Some studies have reported no significant impairments in
attention of patients with depression\textsuperscript{171,175}. While the majority have reported significant attentional impairments\textsuperscript{166,168,174,176-180}. Nelson and colleagues\textsuperscript{181} demonstrated that patients with psychotic depression had attentional impairments versus those with non-psychotic depression, where those without psychosis did not differentiate from healthy controls.

Psychomotor retardation is a symptom, listed in the DMS-IV-TR,\textsuperscript{19} of a major depressive episode. Psychomotor retardation can consist of reduced speed, slowed speaking rate, delayed motor initiation, reduced facial expression, body immobility and postural abnormalities\textsuperscript{182} and approximately 40\% of unipolar and bipolar depressed patients exhibit severe psychomotor retardation and the remaining 60\% exhibiting some aspects of psychomotor slowing\textsuperscript{183}. Psychomotor slowing is reported to be more common in bipolar, than in unipolar, depression and correlated with the severity of depression\textsuperscript{179}. It has also been reported that attentional impairments are correlated with psychomotor slowing, with attentional impairment being markedly more severe is patients who also have psychomotor retardation\textsuperscript{176,179}. A study by Purcell and colleagues\textsuperscript{168} showed that patients with depression did not have impaired cognitive speed only impaired motor speed, indicating the impairment may not be related in the decision to make the movement but in the motor-neuronal pathway. Although not all literature supports the presence of psychomotor slowing in depression\textsuperscript{166,171}, slowing of reaction time has been reliably found in patients with depression\textsuperscript{184}.

The degree of impairment of cognition in depression may be correlated with illness severity but the literature is conflicting. Elliott and colleagues\textsuperscript{185} found significant correlation between learning and memory and illness severity. In contrast, studies by Grant and colleagues\textsuperscript{171} and Purcell and colleagues\textsuperscript{168} did not observe this correlation between depression severity and cognitive function. Even with successful treatment, often patients with both unipolar and bipolar depression are still observed to have
deficits in executive function, including working memory and attention, and psychomotor performance\textsuperscript{186,187}.

Executive functions have been thought to originate from the frontal lobes, especially frontal subcortical loops. Dysfunction in this area is thought to be related to the neuropsychological impairments in depression. Decreases in blood flow to the frontal, temporal, parietal areas and the cingulated cortex are associated with cognitive impairment in depression, with more robust neurological changes seen in older patients\textsuperscript{188}. Deficits to the frontostriatal area may also play a role in executive dysfunction of depression\textsuperscript{189}. The dorsolateral prefrontal cortex and the anterior cingulate have been shown to be active during the stroop test, a test of attention and executive function, in healthy volunteers\textsuperscript{190}. Thus dysfunction in these cortical areas may underlie the neuropsychological dysfunction seen in depression\textsuperscript{191}.

It has long been shown that sleep plays an important role in long term memory consolidation\textsuperscript{192,193}. Sleep deprivation has been shown to affect attention as well as short lasting reaction time tests. However, the role of sleep in executive and psychomotor function is not as clearly defined. In a study by Nilsson and colleagues\textsuperscript{194} sleep deprivation was associated with impairments in executive function in healthy volunteers, although working memory and psychomotor vigilance were unaffected. Although other studies have seen declines in working memory and psychomotor function with sleep deprivation. It has been suggested that the decline observed in working memory is attributable to impairment in attentional functioning with sleep deprivation\textsuperscript{195}. Impairments, however, are seen in executive function of young healthy volunteers after 36 hours of sleep deprivation\textsuperscript{196}. Neuroimaging studies have shown that one night’s sleep deprivation significantly reduces blood flow to prefrontal areas and is associated with impairments on neuropsychological tasks which require prefrontal activation (executive functions). There are, however, contradictory studies which indicate that one
night’s sleep deprivation is not associated with executive dysfunction, mostly in young adults. Chronic, not only a single night, sleep deprivation may affect cognition. Chronic sleep restriction below an individual's optimal level has been shown to be related to diminished attention, impaired working memory, and reduced cognitive throughput.

In healthy volunteers, slow wave sleep deprivation was associated with impaired cognitive performance upon awakening, where accuracy was more impaired than speed. Behavioral slowing, including a delayed reaction time was also observed. The role of slow wave sleep in working memory was further demonstrated in a study by Marshall and colleagues. They showed that increasing slow oscillation using transcranial stimulation during the onset of SWS resulted in improved declarative memory in healthy individuals. Studies examining the role of sleep in executive functioning of patients with depression were unable to be identified.

2.5 Research Hypothesis

Sleep dysregulation, either in the form of hypersomnia or insomnia is an important symptom and potential underlying biological mechanism in unipolar and bipolar depression. Therefore, treatments of depression that target both depressed mood and difficulties with sleep are essential in the management of both major depressive disorder and bipolar disorder.

Cognitive deficits, especially those of executive function like working memory and attention, and psychomotor function are thought to be impaired in depression and are a symptom of depression. These impairments can also result from acute or chronic sleep deprivation and sleep fragmentation. Therefore, treatments of depression that target improvements in sleep may also result in improvements in cognitive deficits.
The antipsychotic agent, olanzapine, has affinity for 5-HT\textsubscript{2A/C}, D\textsubscript{2}, and cholinergic receptors all of which are thought to play a role in sleep regulation and architecture. An overactive cholinergic system and deficient serotonergic system are thought to play a role in both sleep dysregulation and depressed mood in MDEs. Sleep deprivation, often a symptom of depression, results in reduced blood flow to prefrontal areas which have been shown to be important in sleep regulation, depression and executive function. Olanzapines antagonism at serotonergic and cholinergic receptors may result in improvement to sleep architecture which may in turn result in improvements in executive function and depressive symptoms.

Olanzapine has been shown to improve SWS and sleep continuity in healthy volunteers. A small study by Sharpley and colleagues\textsuperscript{15} observed that olanzapine augmentation to SSRI’s improved SWS, sleep continuity and depressed mood in patients with depression.

The primary aim of this study was to examine the effects of olanzapine augmentation treatment, in patients with either unipolar or bipolar depression, on sleep architecture, specifically slow wave sleep. The other aspects of sleep architecture including REM sleep and sleep continuity are also examined. Secondarily, the effects of olanzapine augmentation on illness severity and cognitive function, specifically working memory, attention, and psychomotor function are studied.

It is hypothesized that olanzapine augmentation as a treatment for depression will result in increased duration of SWS and decreased latency to SWS, compared to placebo. Olanzapine augmentation, compared to placebo, will result in increased sleep efficiency, decreased sleep latency, decreased duration of REM sleep and increased latency to REM sleep. It is also hypothesized that olanzapine augmentation will decrease HDRS and HARS scores. Augmentation with olanzapine will result in decreased reaction and movement time, increase span length, decrease strategy and
between error scores in spatial working memory task. It is hypothesized that these improvements in illness severity and executive function will positively correlate with improvements in SWS.
Chapter 3: Methods

This is a prospective, double-blind, placebo-controlled, repeated measures, polysomnographic study of patients receiving olanzapine as augmentation 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

31 participants were recruited and signed written informed consent prior to participation. Four participants failed baseline screening (three due to subclinical mood symptoms and one due to potentially dangerous liver function abnormalities), two participants withdrew between randomization and day 2-4 and were not included in the analysis, as they only had one PSG. The remaining 25 participants were included in the analysis. Three participants terminated from the study before day 28-31, all due to worsening of original mood symptoms, these participants remained in the analysis. Participants were recruited from a tertiary care mood disorders unit, from general practitioners offices, and from advertisements in the community. Participants were enrolled between November 2007 and May 2009. Participants were 18 years of age or older, met DSM-IV-TR criteria for MDD, Bipolar I Disorder, Bipolar II Disorder or Bipolar Disorder NOS, confirmed by the Mini International Neuropsychiatric Inventory (MINI). Participants were experiencing a MDE at enrolment in the study, defined as a Hamilton Depression Rating Scale-17 item (HDRS-17) score of >15, and not a mixed episode, defined as a Young Mania Rating Scale Score (YMRS) of ≤ 12. Female participants of child bearing potential must have had a negative human chorionic gonadotropin (HCG) test at enrolment, not be nursing and be willing to use...
contraception. Participants were excluded if they had a current or past diagnosis of schizophrenia or dementia, were experiencing a manic or mixed episode at enrolment (YMRS >12), had substance abuse within 3 months previous to enrolment (excluding caffeine or nicotine), were at an imminent risk of suicide or danger to themselves or others, had known intolerance to olanzapine, had a serious or inadequately treated medical illness, had a history of seizures, were previously enrolled in the study or enrolled in another treatment study within 4 weeks prior. Participants could not be taking any other antipsychotic medication at the time of enrolment. Participants must have been on a stable dose of all medications for 4 weeks prior to enrolment (excluding withdrawal of sleep aids and antipsychotic medications). Benzodiazepines and other sleep aids must be discontinued if not a stable dose for 4 weeks prior to enrolment. Participants who had administration of a depot antipsychotic medication within two dosing intervals of enrolment were excluded. Pre-existing medical conditions of participants can be seen in Table I of appendix A.

3.2 Clinical Measures

Participants were assessed at three time points, baseline (before randomization and administration of study medication), after 2-4 days and 28-31 days of study medication. Each clinical assessment consisted of Hamilton Depression Rating Scale-17 item (HDRS-17)\textsuperscript{203}, Montgomery Asberg Depression Rating Scale (MADRS)\textsuperscript{204}, Hamilton Anxiety Rating Scale (HARS)\textsuperscript{205,206}, Young Mania Rating Scale (YMRS)\textsuperscript{202} and participant-reported Pittsburgh Sleep Quality Index (PSQI)\textsuperscript{207}, Visual Analogue Scale (VAS) for sleep quality\textsuperscript{206}, and the Epworth Sleepiness Scale (ESS)\textsuperscript{209}. At each time point participants also completed cognitive testing using the 3 Cambridge Neuropsychological Test Automated Battery (CANTAB) tasks: Spatial Span (SSP), Spatial Working Memory (SWM) and Reaction Time (RTI)\textsuperscript{210,211} (Cambridge Cognition,
Cambridge, UK; www.camcog.com). At baseline the MINI and the Clinical Global Impression-Severity (CGI-S)\textsuperscript{212} were administered. At day 28-31 the Clinical Global Impression-Improvement (CGI-I) was administered. Baseline blood work, physical exams, and pregnancy tests (in women of childbearing potential) were performed. One participant did not complete the CANTAB testing.

### 3.3 Medication

Participants were randomly allocated to receive either placebo or olanzapine. The orally disintegrating (zydis) formulation of olanzapine was dispensed. Medication dosing was started at 2.5mg on day 1 and increased to 5mg at day 2; at the second visit (day 2-4) dosing may be titrated up or down, in increments of 2.5mg, as clinically needed to a maximum of 20mg. The median dose of olanzapine at the end of the study was 5mg and the mean was 6.67mg, actual dosages ranged from 5mg to 10mg. Concomitant medications can be seen in Table II of appendix A. Briefly, eight participants in the placebo treated group and twelve participants in the olanzapine treated group were taking at least an antidepressant; 1 participants in the placebo treated group and none in the olanzapine treated group was taking only a benzodiazepine; no participants in the placebo treated group and 1 participants in the olanzapine treated group was taking only a mood stabilizer; 1 participant in the placebo treated group and 2 participants in the olanzapine treated group were not taking any other psychotropic medications at enrolment. Adverse events are displayed in Table III of appendix A.

### 3.4 Polysomnographic Recordings

On each of the 3 study nights, baseline, day 2-4 and day 28-31, an overnight sleep polysomnograph (PSG) was performed at the participants’ home, using the
MediPalm Personal Recording Device (Breabon Medical Corporation, Carp, Canada.). Participants were asked to retire and rise at their usual time. Participants were asked to refrain from alcohol on study nights; however normal caffeine and nicotine intake was maintained. The routine overnight sleep PSG included 4 electroencephalogram channels (C4-A1, C3-A2, O2-A1, O1-A2), electro-oculogram (two channels), submental electromyogram (EMG), finger pulse oximetry, oronasal airflow (oronasalthermistor), chest and abdominal movement belts (respiratory inductance plethysmography), vibration snore sensor and anterior tibialis EMG. A position sensor was used to monitor position continuously (Ultima Body Position Sensor; Braebon Medical Corporation, Carp, Canada). Participants were not monitored and it was requested that they replace equipment, which fell off, to the best of their ability. The overnight sleep routine was applied starting around 1900hrs each study night, a timer was set to begin recording at the participants usual sleep time and record for 8 hours continuously or until the participant rose in the morning. One of two experienced and certified technicians scored all the sleep records in 30-second epochs according to standardized criteria of Rechtschaffen and Kales \textsuperscript{213}, using Pursuit Advanced Sleep System software (Braebon Medical Corporation, Carp, Canada). Technicians scoring were blinded to treatment status. Sleep onset was defined as the beginning of the first 2 minutes that were not scored as wake or movement. Latencies to each sleep stage were calculated to the first 2 continuous minutes of the stage. Obstructive apneas and hypopneas were scored using the criteria from the American Academy of Sleep Medicine Task Force, 1999 \textsuperscript{214}. Events were scored when a > 50% decrease (apnea) in airflow, or clear reduction (hypopnea) in amplitude of the airflow signal (compared to stable breathing during the 2 minutes preceding the event), occurred associated with an arousal, a greater than 3% reduction in oxygen saturation (SaO2), or both, and the event lasted for at least 10 seconds. Arousals were scored based on American Sleep Disorders Association criteria,
Arousals had to be preceded by at least 10 seconds of sleep, have an electroencephalogram frequency shift to alpha or theta for at least 3 seconds and up to 15 seconds, and be associated with concurrent increased electromyogram tone in REM sleep. An apnea-hypopnea index (AHI) and the respiratory disturbance index (RDI), which included apneas, hypopneas, and snore arousals for the number of events per hour of sleep, were calculated.

Sharpley and colleagues \(^4,216,217\) have demonstrated that the use of home sleep recordings provides a reliable and valid means of detecting the effects of drugs on sleep architecture.

### 3.5 Statistical Analysis

PSG recording and clinical measures (except the CGI) were analyzed using two-way repeated measures ANOVA. The design included 2 treatment groups (between subjects) across 3 time points (within subjects); this was divided into its linear and quadratic components with 1 degree of freedom. The linear component, change from baseline to day 28-31, was examined. Missing data for clinical scales and polysomnographic measures were replaced using multiple linear regression analysis. For the CANTAB testing, missing data was replaced using the last observation carried forward method. The CGI was analyzed using between groups t-tests. For all clinical measures one-tailed distributions were used, for polysomnographic and neurocognitive measures two-tailed distributions were used. Baseline sociodemographic comparisons between groups were analyzed using two-tailed independent samples t-tests. All calculations were performed in SPSS version 15.0 or 16.0.

In order to examine the relationship between the clinical, polysomnographic and neurocognitive measures the following was performed. For each measure the change from baseline to the end of study was calculated. For scores in which a decrease is
deemed an improvement, the change was reflected. Therefore, a positive change is an improvement with all measures. Scores were standardized to baseline values. In order to condense the number of variables, measures which report similar information were summed. For the clinical measures: the HDRS and MADRS standardized scores were summed to be a single “depression” score, the PSQI and VAS standardized scores were summed to be a subjective “sleep quality” score, and the HARS standardized score was used on its own as the “anxiety” measure. For the polysomnographic variables (only the main sleep architecture variables were included): the total sleep time, total wake time and sleep latency standardized scores were summed to be a measure of “sleep continuity”, and the standardized scores for latency and duration of each stage (Stage 1, 2, SWS and REM) were summed to represent a single score of each stage. For the neurocognitive measures: the standardized between errors and strategy scores of the SWM task were summed to represent a single “SWM” score, the standardized reaction time and movement time scores of the RTI task were summed to represent a single “RTI” score, and the standardized span length score of the SSP task was used on its own. For each set of condensed measures; clinical, polysomnographic and neurocognitive, principal components analysis were applied to determine the factorial structure of each set and ensure a substantial general factor which all the items of the set loaded on. This produced the logical bases for assembling general overall scores. Principal components analysis (table of loading values can be seen in table IV of appendix A) revealed, for the clinical measures, that the depression, sleep quality and anxiety scores factor together. Therefore, these three scores were summed to be a single measure of clinical change, referred to as “clinical”. For the polysomnographic measures, sleep continuity, stage 1, stage 2 and SWS scores factor together, however the REM score was found to be a single factor item and did not fit with the other polysomnographic measures. Therefore, the sleep continuity, stage 1, stage 2 and SWS
were summed together to be a measure of sleep architecture change and the REM score was left as a single item. For the neurocognitive measures, SWM, RTI and SSP scores did not factor together and represent three separate items. Therefore, these three measures were examined separately.

Two-tailed Pearson correlations were employed to examine the relationship between clinical change, sleep architecture, REM sleep, SWM, RTI and SSP. The differences between the olanzapine treated and placebo treated group for these measures of change were examined using independent samples t-tests, with a one-tailed (directional) test for clinical measures and two-tailed for the remaining variables.
Chapter 4: Results

4.1 Sociodemographic characteristics

Twenty-five participants were included in the study. Their mean (± SD) age was 46 ± 14 years ranging from 19 to 79 years of age. The mean (± SD) age of the olanzapine-treated group and placebo-treated group was 46 ± 17 years and 46 ± 9 years, respectively. Sociodemographic characteristic of both the olanzapine and placebo groups are presented in Table 1. There are no significant differences between the two groups on gender, diagnosis, education level, employment status, marital status and number of children ($t_{23} = 0.052$, $p=0.959$; $t_{23} = 0.476$, $p=0.639$; $t_{23} = -0.157$, $p=0.877$; $t_{23} = -0.965$, $p=0.345$; $t_{23} = 0.293$, $p=0.772$; $t_{23} = -0.110$, $p=0.913$, respectively). The participants had a mean (± SD) baseline weight of 82.6 ± 19.0 kgs ranging from 48.2 to 130.0 kgs. The mean (± SD) baseline weight of the olanzapine-treated group and placebo-treated group was 80.7 ± 16.4 and 85.7 ± 23.5 kgs, respectively. After 28-31 days of treatment the mean (± SD) weight of the olanzapine-treated group and placebo-treated group was 82.7 ± 16.9 and 85.9 ± 24.0 kgs, respectively. There was no significant difference between the two groups in baseline weight ($p=0.545$). However, the olanzapine group grained a mean (± SD) of 2.0± 1.7kgs and the placebo group gained significantly less at a mean (± SD) of 0.12 ± 2.3kgs ($p=0.031$). Weight was not available for 1 participant in the placebo group. The mean (± SD) height of the olanzapine-treated group and placebo-treated group was 168.1 ± 9.7cm and 166.8 ± 8.7 cm, respectively, there is no significant difference between the two groups ($p=0.774$). Height was not available for 3 participants from the placebo group and 1 participant from the olanzapine group.
Table 1. Sociodemographic characteristics. MDD = Major Depressive Disorder, BD = Bipolar Disorder. P-value reported for between group t-test of each characteristic.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo Group (N=10)</th>
<th>Olanzapine Group (N=15)</th>
<th>Between Groups</th>
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4.2 Polysomnographic Measures

Figure 1 shows the latency to SWS and duration of SWS in both olanzapine and placebo treated groups. Two-way repeated measures ANOVA showed a significant decrease in latency to SWS for the olanzapine group, from 104.11 ± 116.68min at baseline to 64.93 ± 69.05min at day 2-4 and 81.94 ± 60.19min at day 28-31 as compared to the placebo group which had a mean latency of 110.27 ± 74.73min, 105.60 ± 63.43min, and 184.81 ± 120.71min at baseline, day 2-4, and day 28-31, respectively. Duration of SWS significantly increased in the olanzapine group compared to placebo over time (F(1,23)=5.596; p=0.027). At baseline, day 2-4 and day 28-31, the olanzapine treated group had a mean SWS duration of 26.72 ± 24.06min, 43.63 ± 47.97min and 51.95 ± 37.33min, respectively, whereas the placebo group had a mean SWS duration of 48.55 ± 33.85min, 43.12 ± 30.98min and 42.90 ± 26.18min, respectively.

Figure 2 shows the latency to REM sleep and duration of REM sleep in both olanzapine and placebo treated groups. Two-way repeated measures ANOVA showed no significant changes in latency to REM from baseline to day 2-4 or day 28-31 with treatment with olanzapine, 163.62 ± 116.04min, 177.60 ± 97.01min and 161.20 ± 68.72min respectively, compared to treatment with placebo, 202.22 ± 94.25min, 205.45 ± 78.26min and 245.39 ± 94.45min respectively. Duration of REM sleep was not significantly different (F(1,23)=0.571; p=0.458) in the olanzapine treated group, 78.86 ± 49.31min, 82.59 ± 37.38min, and 81.22 ± 32.19min, compared to the placebo treated group, 58.74 ± 20.09min, 70.76 ± 25.61min, 47.59 ± 28.20min, at baseline, day 2-4 or day 28-31 respectively.

The sleep continuity measures, sleep efficiency and sleep latency, are shown in Figure 3 for both olanzapine and placebo treated groups. Two-way repeated measures ANOVA showed a significant increase in sleep efficiency from
Figure 1. Latency to Slow Wave Sleep and Duration of Slow Wave Sleep.
Mean ± Standard Error of the Mean for latency to and duration of Slow Wave Sleep in minutes, for both olanzapine and placebo treated groups. * indicates a significant (p<0.05) time x group interaction.
Figure 2. Latency to Rapid Eye Movement Sleep and Duration of Rapid Eye Movement Sleep.
Mean ± Standard Error of the Mean for latency to and duration of Rapid Eye Movement Sleep, in minutes, for both olanzapine and placebo treated groups. No significant time x group interactions were observed.
Figure 3. Sleep Continuity.
A) Sleep Efficiency B) Sleep Latency. Mean ± Standard Error of the Mean for both olanzapine and placebo treated groups. Sleep Efficiency: % = total sleep time/time in bed x 100, Sleep Latency is from time in bed to sleep onset. * indicates a significant (p<0.05) time x group interaction.
baseline to day 2-4 and day 28-31 for olanzapine treated participants, 70.65 ± 23.28%,
83.59 ± 14.90% and 85.42 ± 8.49% respectively, compared to placebo treated
participants, 68.94 ± 14.78%, 68.23 ± 13.31% and 61.15 ± 15.46% respectively. Sleep
latency significantly (F(1,23)=7.234; p=0.013) decreased from baseline to day 2-4 and
day 28-31 for olanzapine treated participants, 59.70 ± 80.44min, 43.98 ± 61.92min and
36.88 ± 37.10min respectively, compared to placebo treated participants, 67.40 ±
63.56min, 80.34 ± 62.82min, 99.56 ± 75.90min respectively.

Figure 4 displays the mean total sleep time and total wake time for both
olanzapine and placebo treated groups. Two-way repeated measures ANOVA showed
that the mean total sleep time from baseline to day 2-4 and day 28-31 of the olanzapine
group, 336.89 ± 110.05min, 381.23 ± 69.59min and 371.01 ± 74.76min respectively,
compared to the placebo group, 315.53 ± 61.99min, 303.34 ± 54.53min, and 286.20 ±
74.09min respectively, approached significance (F(1,23)=4.067; p=0.056). The mean
total wake time from baseline to day 2-4 and day 28-31 was significantly (F(1,23)=6.419;
p=0.019) decreased for the olanzapine treated group, 123.92 ± 107.35min, 75.93 ±
70.45min, and 67.68 ± 39.71min respectively, compared to the placebo treated group,
152.42 ± 66.54min, 144.79 ± 60.50min and 180.29 ± 66.44min respectively.

Table 2 shows the remaining polysomnographic measures for both the
olanzapine and placebo treated groups as well as p-values according to two way
repeated measures ANOVA. Significant effects were seen for latency to stage 1, latency
to stage 2 and duration of stage 2. The olanzapine treated group had significantly
decreased latency to stage 1 and stage 2 and significantly increased duration in stage 2,
F(1,23)=8.649, p=0.007; F(1,23)=5.343, p=0.030; and F(1,23)=4.321, p=0.049,
respectively.
Figure 4. Total Sleep Time and Total Wake Time.
Mean ± Standard Error of the Mean of total wake and sleep time, in minutes, for both olanzapine and placebo treated groups.
* indicates a significant (p<0.05) time x group interaction.
Table 2. Polysomnographic Measures.
The mean ± standard deviation (SD) of selected sleep parameters for both olanzapine and placebo treated group. TST = Total Sleep Time, SWS = Slow Wave Sleep, REM= Rapid Eye Movement.

<table>
<thead>
<tr>
<th>Selected Sleep Parameter</th>
<th>Placebo (N=10)</th>
<th>Olanzapine (N=15)</th>
<th>ANOVA Time x Group Interaction</th>
</tr>
</thead>
<tbody>
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<td></td>
<td>Baseline Mean ± SD</td>
<td>Day 2-4 Mean ± SD</td>
<td>Day 28-31 Mean ± SD</td>
</tr>
<tr>
<td>No. of awakenings</td>
<td>28 ± 19</td>
<td>21 ± 6</td>
<td>29 ± 16</td>
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<tr>
<td>No. of Stage Changes</td>
<td>143 ± 76</td>
<td>121 ± 43</td>
<td>117 ± 42</td>
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<tr>
<td>Respiratory Disturbance Index</td>
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<td>13.22 ± 11.46</td>
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<tr>
<td>Latency to Stage 1 (min)</td>
<td>34.47 ± 28.23</td>
<td>30.74 ± 14.69</td>
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<td>Duration of Stage 1 (min)</td>
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<td>9.99 ± 4.40</td>
<td>11.05 ± 5.65</td>
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<td>Duration of Stage 1 (% of TST)</td>
<td>73.62 ± 71.25</td>
<td>82.56 ± 62.97</td>
<td>103.65 ± 78.95</td>
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<tr>
<td>Latency to Stage 2 (min)</td>
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<td>161.41 ± 59.95</td>
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<tr>
<td>Duration of Stage 2 (min)</td>
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<td>52.42 ± 12.01</td>
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<td>Duration of Stage 2 (% of TST)</td>
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<td>Duration of SWS (% of TST)</td>
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<td>Duration of REM (% of TST)</td>
<td>63.10 ± 52.89</td>
<td>70.30 ± 51.86</td>
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</table>
4.3 Clinical Measures

Figure 5 shows the mean HDRS total score and HDRS item 1 score for both olanzapine and placebo treated participants. Two-way repeated measures ANOVA showed significant (F(1,23)=3.643; p=0.035) changes in total HDRS score from baseline to day 2-4 and day 28-31 with treatment with olanzapine 22.60 ± 4.84, 18.53 ± 6.36 and 14.73 ± 8.38 respectively, compared to treatment with placebo, 21.50 ± 5.50, 19.20 ± 5.92, and 18.00 ± 7.39 respectively. Also, overall there was a significant improvement in total HDRS across time (F(1,23)=24.687; p=0.000). The mean HDRS item 1 score from baseline to day 2-4 and day 28-31 of the olanzapine group, 2.20 ± 0.86, 2.13 ± 0.92 and 1.47 ± 1.25 respectively, compared to the placebo group, 2.10 ± 0.88, 2.00 ± 0.94, and 2.00 ± 1.06 respectively, was significantly different (F(1,23)=4.001; p=0.029).

Approximately 46% of olanzapine treated and 20% of placebo treated participants were responders at the final assessment. Approximately 26% of olanzapine treated and 10% of placebo treated participants reached remission by the final assessment. There was no significant difference between olanzapine and placebo treated groups on the number of responders in each group (t21.91=-1.414, p=0.171).

The mean response on the visual analogue scale for sleep quality of both the olanzapine and placebo treated groups is shown in Figure 6. Two-way repeated measures ANOVA showed no significant (F(1,23)=0.888; p=0.178) changes in VAS score from baseline to day 2-4 or day 28-31 with treatment with olanzapine 36.53 ± 27.14, 43.60 ± 27.87 and 58.87 ± 29.74 respectively, compared to treatment with placebo, 30.70 ± 14.55, 31.45 ± 19.26, and 43.15 ± 26.76 respectively. However, overall there was a significant improvement in VAS score across time (F(1,23)=10.995; p=0.003).

Table 3 shows the remaining clinician administered and self report rating scale scores for both the olanzapine and placebo treated groups as well as p-values across
Figure 5. Hamilton Depression Rating Scale.
A) Total Score B) Item 1 Score-Depressed Mood. Mean ± Standard Error of the Mean for both olanzapine and placebo treated groups. * indicates a significant (p<0.05) time x group interaction.
Figure 6. Subjective Sleep Quality.
Visual analogue scale for sleep quality, mean ± standard error of the mean, measured in millimeters, for both olanzapine and placebo treated groups. * indicates a significant (p<0.05) time x group interaction.
Table 3. Selected Clinical Measures.
The mean ± standard deviation (SD) of selected clinical measures for both olanzapine and placebo treated group.
MADRS = Montgomery Asberg Depression Rating Scale, HARS = Hamilton Anxiety Rating Scale, YMRS = Young Mania Rating Scale, CGI = Clinical Global Severity, PSQI = Pittsburg Sleep Quality Index, ESS = Epworth Sleepiness Scale.

<table>
<thead>
<tr>
<th>Selected Clinical Measures</th>
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<th>ANOVA</th>
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<td>PSQI Total</td>
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time and time x group according to two way repeated measures ANOVA. Clinician administered measures are the MADRS, HARS, and YMRS, the patient-reported measures are the PSQI and ESS. Significant improvement in the olanzapine group over the placebo group was seen in the MADRS (F(1,23)=3.741, p=0.033). There was no significant differences between groups on the HARS, YMRS, CGI, PSQI or ESS, over time (F(1,23)=1.362, p=0.127; F(1,23)=1.622, p=0.108; F(1,23)=0.411, p=0.264; F(1,23)=0.045, p=0.417, respectively). Overall, the MADRS, HARS, PSQI, and ESS significantly decreased over time (F(1,23)=9.218, p=0.003; F(1,23)=19.272, p=0.001 F(1,23)=4.748, p=0.020; F(1,23)=4.515, p=0.023, respectively). The clinician administered CGI (severity and improvement) were not significantly different between the placebo and olanzapine groups. The CGI-Severity at baseline of the olanzapine group was 5 ± 1 and the placebo group was 5 ± 1 (t_{23}=1.700, p=0.103). The CGI-Improvement at Day 28-31 of the olanzapine group was 3 ± 1 and the placebo group was 3 ± 2 (t_{23}=0.718, p=0.240).

4.4 Cognitive Measures

Figure 7 shows both the between errors and strategy score of the CANTAB SWM task of the olanzapine and placebo treated groups. Two-way repeated measures ANOVA showed no significant (F(1,22)=0.020; p=0.889) changes in between errors on the SWM task from baseline to day 2-4 or day 28-31 with treatment with olanzapine 31.64 ± 22.45 errors, 30.07 ± 18.35 errors and 31.64 ± 20.94 errors respectively, compared to treatment with placebo, 22.64 ± 26.33 errors, 22.50 ± 23.37 errors, and 21.70 ± 15.26 errors respectively. There were no significant (F(1,22)=0.209; p=0.652) changes in strategy score from baseline to day 2-4 or day 28-31 with treatment with olanzapine 30.86 ± 7.38, 31.00 ± 7.66 and 31.00 ± 7.10 respectively, compared to
Figure 7. Spatial Working Memory.
Between errors and strategy score on CANTAB spatial working memory task. Mean ± Standard Error of the Mean for both olanzapine (N=14) and placebo (N=10) treated groups. No significant time x group interactions were observed.
Overall no significant changes were seen in either the between errors or strategy score over time (F(1,22)=0.020, p=0.889; F(1,22)=0.110, p=0.743, respectively). There was no significant difference between olanzapine and placebo treated groups with varying difficulty level (4, 6 or 8 boxes to search) of the SWM task (F(1,22)=0.324, p=0.324; F(1,22)=0.349, p=0.561, respectively).

Figure 8 displays the mean spatial span length recalled on the CANTAB SSP task for both the olanzapine and placebo treated group. Two-way repeated measures ANOVA showed no significant (F(1,22)=1.144; p=0.296) changes in span length from baseline to day 2-4 or day 28-31 with treatment with olanzapine 5.43 ± 1.45, 5.43 ± 1.22 and 5.71 ± 1.43 respectively, compared to treatment with placebo, 5.80 ± 1.40, 5.70 ± 1.64, and 5.60 ± 1.58 respectively. Overall, there was no significant (F(1,22)=0.036; p=0.852) change in span length recalled over time.

The mean reaction time and movement time from the CANTAB RTI task for both the olanzapine and placebo treated groups are shown in Figure 9. Two-way repeated measures ANOVA showed no significant (F(1,22)=0.975; p=0.334) changes in reaction time from baseline to day 2-4 or day 28-31 with treatment with olanzapine 408.56 ± 114.60ms, 384.56 ± 91.71ms and 386.10 ± 112.04ms respectively, compared to treatment with placebo, 410.35 ± 80.57ms, 395.33 ± 43.29ms, and 405.67 ± 52.17ms respectively. There were no significant (F(1,22)=2.323; p=0.142) changes in movement time from baseline to day 2-4 or day 28-31 with treatment with olanzapine 519.01 ± 123.43ms, 559.15 ± 134.76ms and 524.29 ± 106.91ms respectively, compared to treatment with placebo, 579.01 ± 123.43ms, 559.15 ± 134.76ms, and 524.29 ± 106.91ms respectively. Overall, there was no significant changes in either reaction time or movement time over time (F(1,22)=2.273, p=0.146; F(1,22)=1.353, p=0.257).
Figure 8. Spatial Span.
Span length recalled on CANTAB spatial span task. Mean ± Standard Error of the Mean for both olanzapine (N=14) and placebo (N=10) treated groups. No significant time x group interactions were observed.
Figure 9. Reaction Time.
Reaction time and movement time on CANTAB reaction time task. Mean ± Standard Error of the Mean for both olanzapine (N=10) and placebo (N=14) treated groups. No significant time x group interactions were observed.
4.5 Correlations

There was a significant difference between the olanzapine treated and placebo treated
groups on the clinical measure ($t_{23}=-1.697$, $p=0.052$) and the sleep architecture measure
($t_{22}=-3.544$, $p=0.002$). There was no significant differences between the two treatment
groups on REM sleep ($t_{21}=0.969$, $p=0.344$), SWM ($t_{22}=0.278$, $p=0.784$), SSP ($t_{22}=-1.070$,
$p=0.296$) or RTI ($t_{17}=0.667$, $p=0.514$).

There was no significant correlation between the clinical and sleep architecture
measures ($r=0.085$, $p=0.693$) or between clinical and REM scores ($r=-0.003$, $p=0.988$). There was no significant correlation between clinical and SWM ($r=-0.082$, $p=0.705$) or
between clinical and SSP ($r=0.215$, $p=0.314$). A significant negative correlation was
present between clinical and RTI scores ($r=-0.467$, $p=0.044$). There was no significant
correlations between sleep architecture and SWM, SSP or RTI ($r=0.026$, $p=0.906$;
$r=0.199$, $0.363$; $r=0.078$, $p=0.750$ respectively). There were also no significant
correlations between REM sleep and SWM, SSP or RTI ($r=0.004$, $p=0.986$; $r=-0.041$,
$p=0.856$; $r=0.289$, $p=0.260$ respectively).

When the correlations were split by treatment group, RTI was only significantly
negatively correlated to the clinical score in the placebo treated group ($r=-0.742$, 
$p=0.014$) and not significantly correlated in the olanzapine treated group ($r=0.145$,
$p=0.710$). In further examination, the standardized movement time portion of the RTI
score was significantly negatively correlated to the clinical score ($r=-0.490$, $p=0.033$) and
the reaction time portion of the RTI score was not significantly correlated to the clinical
score ($r=-0.177$, $p=0.409$).
Chapter 5: Discussion

In the present study, addition of olanzapine to the current medication regimes of patients experiencing either unipolar or bipolar major depressive episodes resulted in six main findings. Firstly, significant improvements in slow wave sleep, both for latency and duration, were seen with olanzapine augmentation compared to placebo. Secondly, no changes were seen in REM sleep, either latency or duration, with olanzapine compared to placebo. Thirdly, sleep continuity measures, including sleep efficiency, total sleep time, total wake time and sleep latency, significantly improved with olanzapine augmentation in comparison with placebo. Fourthly, significant improvements in illness severity, both depressive and anxiety symptoms, were observed. There was no significant difference between participants who were treated with olanzapine or placebo in overall illness severity or anxiety symptoms. Significant improvements over placebo were seen only in the HDRS. Clinical global improvements were seen with both olanzapine and placebo treatments with no significant difference between groups. Fifthly, overall subjective sleep quality including daytime sleepiness significantly improved, however olanzapine treated participants did not improve significantly over placebo treated participants. Finally, no significant changes were seen overall or between groups in measures of executive and psychomotor function as measured by spatial working memory, span length and reaction time tasks.

To our knowledge, this is the first double blind randomized controlled study evaluating the effect of olanzapine augmentation treatment in depression. There is only one other similar study identified to date. This was performed by Sharpley and colleagues, 2005. They investigated the addition of olanzapine to SSRI treatment on overnight polysomnograph in patients with treatment resistant major depression. In general, our data supports what was found by Sharpley and colleagues. Sharpley reported significant improvements in sleep efficiency, actual sleep time, percentage of
time awake, total NREM percentage, REM latency, REM percentage, and subjective sleep quality after 1 dose of olanzapine. We reported similar improvements, with the exception of REM latency, percentage of REM sleep, and subjective sleep quality. After 3 weeks of olanzapine treatment, Sharpley reported significant improvement in actual sleep time, sleep efficiency, percentage of wake time, sleep onset latency, subjective sleep quality, percentage of SWS, total NREM percentage. After 3 weeks of treatment with olanzapine, the changes in REM sleep observed after 1 dose of olanzapine had returned to baseline values. We reported, after 4 weeks of treatment, similar improvements with the exception of changes in subjective sleep quality. Sharpley also reports significant improvements in HDRS scores, both the total score and the mean of item 1 after 1, 2 and 3 weeks of treatment. We observed similar improvements in depressive symptoms in both the total and item 1 score of the HDRS. Differences between these two studies may be due to the population studied and methodology. The study by Sharpley included only patients with treatment resistant (to SSRI treatment) major depression and olanzapine was administered open-label with no control or comparison group. We’ve included both patients with major depressive disorder and bipolar depression. We did not purposely select for patients with treatment resistant depression. However, most patients recommended to receive augmentation to their antidepressant treatment are treatment resistant to SSRI’s. In this study, olanzapine was administered in a randomized, double-blind manner with a placebo control. The presence of a placebo control group may account for the differences seen in subjective sleep quality as we reported significant improvements in both the placebo and olanzapine group; however, the olanzapine group did not improve reliably more than the placebo group. Improvements seen in the study by Sharpley cannot be determined to be solely due to olanzapine treatment and not to participation in a clinical trial.
Few medications have been reliably shown to improve slow wave sleep in the treatment of either unipolar or bipolar depression. Trazodone and duloxetine are the only antidepressant drugs identified which have been shown to improve SWS in the treatment of depression. Only one randomized controlled trial (RCT) examining the effects of trazodone on sleep using polysomnography was identified. This study by Saletu-Zyhlarz et al.\textsuperscript{218} studied insomnia patients with dysthymia. Saletu-Zyhlarz reported that trazodone administration significantly improved latency to stage 3, time and percentage in stage 3 and 4, sleep efficiency, and number of awakenings. A significant increase in the amount and percentage of REM sleep was also seen. As they reported on patients with dysthymia, the effects of trazodone on SWS in major depressive episodes remains unclear. Van Bemmel et al.\textsuperscript{120} conducted a single blind study of trazodone treatment on sleep architecture in patients with MDD, they reported no improvements to SWS and significant REM suppression. In contrast, Mouret et al.\textsuperscript{119} examined the effects of open-label trazodone on sleep in patients with MDD, they reported significant improvements in SWS and no affect on REM sleep. One study has been identified examining the effects of duloxetine open-label on sleep in major depression by Kluge et al.\textsuperscript{111}. Kluge reported significant improvement in latency to SWS and time in stage 3 sleep; however time in stage 4 sleep was not significantly improved with duloxetine treatment. Significant REM suppression was reported. No RCTs on the effects of duloxetine were identified. Antidepressants reliably suppress REM sleep however their effects on SWS are inconsistent in the treatment of major depressive episodes.

A few psychotropic augmentation strategies have also been reported to improve SWS: lithium and ziprasidone. Lithium has been shown to improve SWS in patients with affective disorders by Kupfer et al., 1974\textsuperscript{134}. However, this study did not have any controls, the medication was given open label and the study population consisted of
manic, bipolar depressed and unipolar depressed patients. Although lithium has shown to be an effective treatment for both unipolar and bipolar depression, it does have a number of associated adverse effects. The target therapeutic serum concentration range of lithium is narrow; two to three times the therapeutic serum level is toxic, lithium also has adverse metabolic effects. Studies examining the effects of ziprasidone augmentation on sleep architecture in depression could not be identified. A double-blind, placebo-controlled, randomized study of the effect of ziprasidone on sleep architecture in healthy male volunteers was performed by Cohrs and colleagues, 2005. Cohrs reported that ziprasidone treatment significantly improved percentage of SWS and displayed significant REM suppression. Although ziprasidone is a promising candidate for the improvement of SWS in depression, pharmacological effects in healthy individuals do not always carry over to affective illnesses. Therefore, olanzapine augmentation in depression may be one of a select few methods for improving SWS in the treatment of depression.

Almost all antidepressants have been shown to improve REM sleep by increasing the latency to REM and decreasing the total duration of REM sleep. REM suppression was not seen in this study. Although expected, the lack of REM suppression may be due to the concomitant medications of the participants. Only three participants were not taking any other medications, 80% of participants were taking at least one antidepressant, 1 participant was taking a benzodiazepine only and 1 participant was taking lithium only. Over 50% of participants were taking more than 1 medication at enrolment into the study. The antidepressants and lithium may have suppressed REM sleep at the onset of treatment with these medications and thus further suppression of REM sleep with the addition of olanzapine may not have been attainable. Although, previous studies of augmentation to SSRIs have shown REM suppression, the degree of polypharmacy was less in these studies, as each participant was only taking one
antidepressant. As shown with principal components analysis, change in REM sleep did not share a common factor with change in other measures of sleep architecture. This may reflect the changes often seen with psychotropic treatment to sleep architecture. As few medications have been reliably shown to suppress REM sleep and also improve SWS and sleep continuity. Many medications, especially antidepressants, suppress REM sleep and either have no effect or detrimental effects on SWS or sleep continuity. Also, several augmentation strategies, including olanzapine, have been shown to improve sleep continuity and SWS and have no effect on REM sleep. Therefore, it is plausible that REM suppression and other improvements in sleep architecture are due to separate underlying mechanisms and may need to be treated separately.

Improvements in sleep continuity are seen with other augmentation agents, especially risperidone and lithium. Antidepressants rarely improve sleep continuity, mostly it is seen with TCA’s. Some of the more stimulating antidepressant may have detrimental effects on sleep continuity, e.g. venlafaxine, bupropion and fluvoxamine. Increased total sleep time and sleep efficiency, as well as decreased sleep latency and total wake time were observed here, this is similar with what is seen with other augmentation agents, like risperidone. It is in contrast to the effects of quetiapine which did not alter sleep continuity in depression (Milev et al, 2009 unpublished data). The increases seen in total sleep time in our study, presented itself as both increases in duration of SWS and stage 2 sleep and did not result in an increase to stage 1, the lightest stage of sleep.

Improvement in depressive symptoms observed in this study are similar to that is seen with other atypical antipsychotic agents in the treatment of depression. Although both the olanzapine treated and placebo treated groups showed improvements in depressive symptoms, the olanzapine group had significantly greater improvement than placebo in the total score and mood item of the HDRS. The power of the study, however,
was not such as to determine efficacy. Clinical response was seen in 46% of olanzapine treated patients while only 20% of placebo treated patients did so. Twenty-six percent of olanzapine treated participants reached remission and less than half of that (10%) in the placebo group did so. Response rates in a randomized double blind study of olanzapine/fluoxetine combination for the treatment of depression, Thase et al \textsuperscript{22}, are similar to what is observed here. Where olanzapine/fluoxetine combination treatment resulted in a response rate of 40% and fluoxetine treatment alone resulted in a response rate of 30%. Thase et al observed similar improvements, as reported here, in anxiety symptoms with olanzapine/fluoxetine combination, a decrease in HARS score of 6.9, versus fluoxetine treatment alone, a decrease in HARS score of 5.7, with no significant difference between the two groups. Significant improvement in depressive symptoms with olanzapine/fluoxetine combination versus placebo in the treatment of bipolar disorder has been reported as well \textsuperscript{150}. Slightly higher rates of improvement have been reported for quetiapine use in bipolar disorder. Calabrese and colleagues \textsuperscript{140} reported that 57% of quetiapine treated patients responded to treatment with 52% reaching remission, versus 36% of placebo treated patients responding and 24% reaching remission. However, the length of treatment in the study by Calabrese was double that (8-weeks) of this study and thus higher response and remission rates would be expected. Similar remission and response rates are seen with aripiprazole as well. In a randomized double blind study by Bermann and colleagues \textsuperscript{220}, it was reported that after 4 weeks of treatment, the aripiprazole treated participants had a remission rate of 22.7% and the placebo treated was 11%, the response rate of the aripiprazole treated participants was 30% and the placebo treated was 16%. Risperidone augmentation in depression was studied by Reeves and colleagues \textsuperscript{221}. Risperidone augmentation significantly improved depressive symptoms after 8 weeks of treatment, and the improvement was not significantly different from that seen with placebo.
An overall improvement in self-reported sleep quality was seen, however, the improvement in the olanzapine group was not greater than that of the placebo group. This is similar to the subjective sleep quality reported by Sharpley and colleagues \(^6\), in their study of the effects of risperidone on sleep, where no change was seen. An open-label study of quetiapine on sleep architecture in depression by Milev and colleagues (2009, unpublished data) reported no significant change in subjective sleep quality. Although, not significantly different than placebo, the olanzapine group showed an improvement in subjective sleep quality on the VAS of 112%, and the placebo group showed an improvement of 90%; clinically this may be an important difference. Self-reported sleep quality may begin to show greater improvements and differentiation between groups with a longer duration of treatment, and as depressive symptoms are alleviated further. The presence of residual depressive symptoms may be masking any changes in sleep quality shown in self report questionnaires. The discrepancy between the magnitude of change seen with the VAS and the PSQI index may be due to the lengthy and complicated nature of the PSQI as participants often expressed difficulty completing the questionnaire. Both olanzapine and placebo treated groups reported a significant improvement in daytime sleepiness, had the trial been longer the placebo effect may have began to dissipate, allowing a more clear understanding of the effects of olanzapine on energy and daytime sleepiness.

The literature on cognitive function in depression is quite diverse and conflicting, there seems to be no clear pattern of dysfunction in major depressive episodes. The lack of changes seen here in working memory or psychomotor function was not completely unexpected. There are a large number of tests available to examine executive function and psychomotor function, both computerized and clinician administered. The system used here, CANTAB, is a computer based system and thus may not be directly comparable with results obtained using traditional clinician administered tests. A study
by Tavares and colleagues \(^{222}\) examined the neurocognitive function of both unipolar and bipolar depressed patients with matched healthy controls, using the CANTAB system. Tavares reported that participants with MDD made significantly more errors and had a worse strategy score than controls on the spatial working memory task, and BD patients were not significantly different than controls or MDD patients on this task. With the exception of the 8-box stage in which they made more errors than the controls. On the spatial span task, participants with MDD and BD did not differ significantly from controls or each other. Tavares did not report on the reaction time task. Similar results were observed by Sweeney and colleagues \(^{153}\), in which they examined the neurocognitive function of bipolar and unipolar patients using the CANTAB system. Sweeney reported that the unipolar and bipolar depressed patients did not differentiate from controls on the spatial working memory task or the spatial span task. Sweeney did not employ the reaction time task. Sweeney reported deficits in depressed patients in the delayed matched to sample task, indicating a disturbance of episodic memory which may not have been detected by the spatial working memory and spatial span tasks. Weiland-Fiedler et al \(^{186}\) have reported impairments in remitted patients with MDD on the CANTAB spatial working memory strategy score but not between errors, they also reported psychomotor speed deficits tested using the Rapid Visual Information Processing task. Although the presence of psychomotor slowing is a generally robust finding, it was not observed using the CANTAB reaction time task here. There is a significant negative correlation between clinical improvement and reaction time. The placebo-treated group showed a correlation between worsening movement time and clinical improvement, thus response to placebo is correlated with motor retardation. In addition, impairments seen in neurocognitive tests in depression may be due to a lack of motivation to complete the task accurately and thus psychotropic treatment or sleep normalization would not have an effect on this beyond improvement of depressive
symptoms. As only 26% of participants reached remission, many participants had residual depressive symptoms and may not have had an improvement in motivation. The lack of a normal control group precludes us from reporting if the level of baseline functioning is within the normal range or is impaired and did not improve with treatment.

There is a lack of connection between the change in illness severity and changes in sleep architecture. This is most evident in the placebo treated group where a decline was observed in some areas of sleep architecture, e.g. total sleep time and sleep latency, and an improvement in depressive and anxiety symptoms of the placebo group was observed. The decompensation seen in some sleep measures in the placebo group may be due to the type of patients recruited. Many participants were referred for participation in the study as their current medication regimes were no longer satisfactory and they were in need of a change. Thus many of the participants may have started to decompensate before entry into the study. Participants were monitored closely throughout the study and had frequent contact with study staff; this may have resulted in the improvement in clinical but not biological measures. Although, within the olanzapine treated group alone, the degree of clinical improvement did not correlate with improvement in sleep architecture.

The beneficial effects of olanzapine treatment on sleep architecture may be due to its diverse pharmacological profile. Primarily, olanzapine is an antagonist for 5-HT$_{2A/C}$, 5-HT$_3$ and 5-HT$_6$ receptors, with its highest affinity being for these receptors. Serotonin plays a number of roles in sleep physiology, serotonin suppresses REM sleep by inhibition of REM promoting cholinergic neurons and a reduction in serotonin firing rates which allows for the first sleep cycle to occur$^{52}$. As well, 5-HT$_2$ receptor blockade has been shown to increase SWS$^{223}$. Olanzapine may also promote normalization of sleep through antagonism of overactive cholinergic neurons, as olanzapine has affinity for muscarinic M$_1$-M$_5$ receptors. Cholinergic neurons are responsible for the initial activation
and ongoing generation of REM sleep. Olanzapine also has moderate affinity for the α-adrenergic receptor. The adrenergic system plays a role in the suppression of REM and the promotion of sleep cycles. Finally, olanzapine also has affinity for the histamine receptor. Histamine is thought to promote wakefulness and reductions in histamine will allow for sleep to occur. Therefore, the extensive pharmacological profile of olanzapine may affect a variety of neurotransmitter systems important for normal sleep architecture and thus the improvement in sleep architecture reported here is likely to be a direct result of the action of olanzapine as opposed to general improvement in depressive symptoms. This is also supported by the improvement in PSG measures seen after 2-4 days before improvements in mood symptoms were reported. Chronic restriction of sleep has been shown to result in decreased reactivity of the neuroendocrine and serotonergic system, especially the sensitivity of 5-HT₁A receptor, in rat models. Thus, pharmacological treatment in depression targeted at improving receptor sensitivity and neurotransmission may benefit both depressed mood and sleep dysfunction. Therefore, the action of olanzapine at 5-HT₂A/C, 5-HT₁A and muscarinic receptors potentially contributes to the improvement in sleep architecture and depressive symptoms. As well as potentially reversing damage to 5-HT₁A receptors and the decreased prefrontal cortex activity associated with sleep deprivation, which may be associated with executive dysfunction.

There are a number of potential confounding factors associated with this study. The foremost of those is concomitant medications. Participants were on a variety of medications including antidepressants, mood stabilizers and hypnotics. Antidepressants may affect both serotonin and norepinephrine systems. All medications were required to be at stable dosing for 4 weeks prior and throughout the study. In studies of the effect of antidepressant on sleep architecture changes occur within the first 4 weeks. Therefore this should not have been a confounding factor in this study however the potential is
present. As well there was a similar distribution of concomitant medications between both the placebo and olanzapine treated groups. Age is another potential confound, sleep architecture is altered in the elderly where greater sleep fragmentation and less SWS is seen. Elderly participants were included in the study, but controlling for age did not significantly change the sleep architecture effect. As well, there was no significant difference between the placebo and olanzapine treated groups on mean age. The exclusion of elderly participants from future studies may be useful. Comorbid diagnosis is also a potential confound. Patients with comorbid anxiety disorders were included in the study to ensure the generalizability of the information to clinical practice, as 57% of patients with current MDD have comorbid anxiety. Patients with primary anxiety disorders have been shown to have sleep continuity disturbances; long sleep latency, sleep fragmentation and increased time awake. These disturbances are also present in depression. However, patients with primary anxiety do not show sleep stage abnormalities as is seen in depression. As all participants in the study were experiencing a major depressive episode, the presence of comorbid anxiety is not thought to affect polysomnographic outcomes, although it may have affected self-reported symptoms as well as cognitive measures. The inclusion of both unipolar and bipolar depression is not thought to be a confounding factor as sleep disturbances, depressive symptoms and cognitive dysfunctions are thought to be similar in the two groups. There was no significant difference between patients with BD and MDD on baseline measures, with the exception of total sleep time where BD patients had significantly longer sleep time. The proportion of MDD and BD participants in the olanzapine and placebo treated groups was not significantly different.

There are a number of limitations in this study. The study was powered sufficiently to detect changes in the primary outcome variable, duration of SWS. However, there were a large number of secondary outcome measures and a larger
sample size would have reduced the likelihood of making a type II error. This is most relevant to the lack of change seen in REM sleep and on the neurocognitive measures. A larger sample size may also lend itself to a more precise differentiation between placebo and olanzapine treated participants on improvements in subjective sleep quality. The duration of this study only permitted evaluation of the short-term treatment of depression; it is well understood that to observe full improvement with many different psychotropic medications 6-8 weeks or even longer is needed. Thus a slightly longer duration may have shown greater differentiation between the olanzapine and placebo treated groups. Another minor limitation of this study is the lack of differentiation between stage 3 and stage 4 sleep. As stage 4 sleep, by definition, has a higher proportion of slow waves, this would have allowed for a more precise evaluation of the relationship between the increase in slow wave sleep and improvement of depressive symptoms.

Treating sleep disturbances in the treatment of depression is an important aspect of clinical management. Sleep disturbance has been reported to greatly affect the quality of life in 59% of patients with depression. Therefore treatment of sleep abnormalities within the treatment for depression can improve both quality of life and overall depressive symptoms \(^{227}\). With few antidepressants or augmentation agents available which have been proven to improve both sleep continuity and slow wave sleep, this study suggests olanzapine may be an effective tool in restoring sleep patterns in patients with depression, especially for those patients in which antidepressants have not proved to be beneficial. Importantly, acute improvements seen in SWS and sleep continuity continued to improve or remained consistent over the remaining 4 weeks and did not rebound. The results of this study are generalizable to a number of patients in the clinic population, as there were few comorbid exclusions and a variety of concomitant medications. The results of this study do not allow us to understand what effect
The effects of olanzapine on sleep presented in this study demonstrate the influence of the drug on sleep of patients with depression during short-term treatment. Further studies should evaluate the influence of different dosages and long term studies are needed to see if improvements continue from the acute phase into maintenance treatment. Further studies are also needed to corroborate the findings presented here. Comparison with a healthy control group would strengthen the understanding of sleep architecture and cognition in depression and the effects of treatment. A healthy control group would demonstrate if olanzapine treatment resulted in an improvement of sleep architecture to reflect that of a normal population. A study employing power spectral analysis would greatly enhance the understanding of the relationship between slow wave sleep, rapid eye movement sleep and clinical response. A risk-benefits analysis study may also be useful to gain a greater understanding of when olanzapine should be used for treating sleep dysfunction in depression. Finally, a large randomized, double-blind, controlled study comparing a variety of augmentation strategies on sleep architecture in the treatment of depression would be beneficial in determining efficacious treatment options for patients with severe sleep dysfunction as well as those with treatment resistant depression.
Chapter 6 : Conclusions

We have shown that olanzapine augmentation in the treatment of both unipolar and bipolar depression resulted in significant improvements in latency to and duration of SWS. Olanzapine augmentation also resulted in significant improvements in latency to sleep onset, total sleep time and sleep fragmentation. Olanzapine augmentation resulted in significant improvement in depressed mood. However, changes in cognition, both working memory and psychomotor function, were not observed. Olanzapine may be one of few medications which improves both SWS and sleep continuity, thus directly targeting symptoms of depression. Olanzapine may produce this effect through its high affinity for not only serotonin receptors but also muscarinic, adrenergic and histaminergic receptors. The heterogeneity of this study population allows for generalizability to clinical populations, and as such olanzapine may be a new tool in the treatment of depression.
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## Appendix A

### Table I. Pre-existing conditions of both olanzapine and placebo treated groups at baseline.

<table>
<thead>
<tr>
<th>Pre-Existing Condition</th>
<th>Placebo (N=10)</th>
<th>Olanzapine (N=15)</th>
<th>Total (N=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>1 (10%)</td>
<td>0 (0.0%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Abnormal ECG</td>
<td>0 (0.0%)</td>
<td>1 (6.7%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>1 (10%)</td>
<td>0 (0.0%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Arthritis</td>
<td>1 (10%)</td>
<td>4 (26.7%)</td>
<td>5 (20%)</td>
</tr>
<tr>
<td>Asthma</td>
<td>2 (20%)</td>
<td>2 (13.3%)</td>
<td>4 (16%)</td>
</tr>
<tr>
<td>Athlete's Foot</td>
<td>1 (10%)</td>
<td>0 (0.0%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>B12 Deficiency</td>
<td>0 (0.0%)</td>
<td>1 (6.7%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Blind in Left eye</td>
<td>0 (0.0%)</td>
<td>1 (6.7%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Carpal tunnel syndrome</td>
<td>1 (10%)</td>
<td>2 (13.3%)</td>
<td>3 (12%)</td>
</tr>
<tr>
<td>Cilliac</td>
<td>1 (10%)</td>
<td>0 (0.0%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>COPD</td>
<td>0 (0.0%)</td>
<td>1 (6.7%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Cough or Flu like symptoms</td>
<td>1 (10%)</td>
<td>1 (6.7%)</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>Degenerative Disk Disease</td>
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<td>0 (0.0%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Diabetes</td>
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<td>2 (13.3%)</td>
<td>2 (8%)</td>
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<tr>
<td>Dry Mouth</td>
<td>2 (20%)</td>
<td>1 (6.7%)</td>
<td>3 (12%)</td>
</tr>
<tr>
<td>Fibromyalgia</td>
<td>1 (10%)</td>
<td>1 (6.7%)</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>Gall-bladder problem</td>
<td>1 (10%)</td>
<td>0 (0.0%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Headaches</td>
<td>1 (10%)</td>
<td>0 (0.0%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Hemerroids</td>
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<td>1 (6.7%)</td>
<td>1 (4%)</td>
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<tr>
<td>Hepatitis C</td>
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<td>1 (4%)</td>
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<tr>
<td>Hernea</td>
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<td>1 (4%)</td>
</tr>
<tr>
<td>High Blood Pressure</td>
<td>2 (20%)</td>
<td>3 (20.0%)</td>
<td>5 (20%)</td>
</tr>
<tr>
<td>High Cholesterol</td>
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<td>1 (6.7%)</td>
<td>1 (4%)</td>
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<tr>
<td>Hypoglycemia</td>
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<td>1 (6.7%)</td>
<td>1 (4%)</td>
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<td>Irritable Bowl Syndrome</td>
<td>3 (30%)</td>
<td>2 (13.3%)</td>
<td>5 (20%)</td>
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<tr>
<td>Learning disability</td>
<td>0 (0.0%)</td>
<td>1 (6.7%)</td>
<td>1 (4%)</td>
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<tr>
<td>Limited right hand mobility</td>
<td>1 (10%)</td>
<td>0 (0.0%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>No Right peripheral vision</td>
<td>0 (0.0%)</td>
<td>1 (6.7%)</td>
<td>1 (4%)</td>
</tr>
<tr>
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<td>1 (10%)</td>
<td>0 (0.0%)</td>
<td>1 (4%)</td>
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<tr>
<td>Pain or Inflammation</td>
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<td>10 (66.7%)</td>
<td>12 (48%)</td>
</tr>
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<td>0 (0.0%)</td>
<td>1 (4%)</td>
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<td>Restless Legs</td>
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<td>2 (13.3%)</td>
<td>2 (8%)</td>
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<td>Seizure Disorder</td>
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<td>1 (6.7%)</td>
<td>1 (4%)</td>
</tr>
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<td>Skin irritation/leisons</td>
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<td>3 (12%)</td>
</tr>
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<td>1 (4%)</td>
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<tr>
<td>T-cell lymphoma</td>
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<td>1 (4%)</td>
</tr>
<tr>
<td>Testicular inflammation</td>
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<td>1 (4%)</td>
</tr>
<tr>
<td>Thyroid Dysfunction</td>
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<td>1 (4%)</td>
</tr>
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<td>Urinary infection</td>
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<td>1 (4%)</td>
</tr>
<tr>
<td>Weakend right side</td>
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<td>1 (4%)</td>
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**TOTAL** 28 280 46 306.7 74 296
Table II. Concomitant medications of olanzapine and placebo treated groups.

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<tr>
<th>Medication</th>
<th>Placebo (N=10)</th>
<th>Olanzapine (N=10)</th>
<th>Total (N=25)</th>
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<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
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<tr>
<td>None</td>
<td>1</td>
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<td>Antidepressants</td>
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<td>Bupropion hcl</td>
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<td>2</td>
</tr>
<tr>
<td>Cipralex</td>
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<td>10.00</td>
<td>2</td>
</tr>
<tr>
<td>Citalopram</td>
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<td>10.00</td>
<td>4</td>
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<tr>
<td>Doxepine</td>
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</tr>
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<td>Trazodone</td>
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<td>17</td>
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<tr>
<td>Oxazepam</td>
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</tr>
<tr>
<td>TOTAL</td>
<td>4</td>
<td>40</td>
<td>7</td>
</tr>
<tr>
<td>Mood Stabilizer</td>
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<td>Valproic acid</td>
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</tr>
<tr>
<td>TOTAL</td>
<td>1</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
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<td>Topamax</td>
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<tr>
<td>TOTAL</td>
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<td>20</td>
<td>3</td>
</tr>
<tr>
<td>Adverse Events</td>
<td>Placebo (N=10)</td>
<td>Olanzapine (N=15)</td>
<td>Total (N=25)</td>
</tr>
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<td>---------------</td>
<td>------------------</td>
<td>--------------</td>
</tr>
<tr>
<td>None</td>
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<td>Constipation</td>
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<td>1 (4)</td>
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<tr>
<td>Dizziness</td>
<td>0.0 (0.0)</td>
<td>1 (6.7)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>1 (10.0)</td>
<td>3 (20.0)</td>
<td>4 (16)</td>
</tr>
<tr>
<td>Fibromyalgia</td>
<td>0.0 (0.0)</td>
<td>1 (6.7)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Frequent Urination</td>
<td>1 (10.0)</td>
<td>0.0 (0.0)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Hallucinations</td>
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<td>1 (6.7)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Hand Shaking</td>
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<td>1 (6.7)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Headaches</td>
<td>2 (20.0)</td>
<td>4 (26.7)</td>
<td>6 (24)</td>
</tr>
<tr>
<td>hypersonsomolence</td>
<td>2 (20.0)</td>
<td>3 (20.0)</td>
<td>5 (20)</td>
</tr>
<tr>
<td>Increased snoring</td>
<td>0.0 (0.0)</td>
<td>1 (6.7)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Increased suicidal ideation</td>
<td>0.0 (0.0)</td>
<td>1 (6.7)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>irritability</td>
<td>0.0 (0.0)</td>
<td>3 (20.0)</td>
<td>3 (12)</td>
</tr>
<tr>
<td>Irritation from PSG hook-up</td>
<td>0.0 (0.0)</td>
<td>1 (6.7)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Nausea</td>
<td>0.0 (0.0)</td>
<td>3 (20.0)</td>
<td>3 (12)</td>
</tr>
<tr>
<td>racing heart</td>
<td>0.0 (0.0)</td>
<td>1 (6.7)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Shaking hands</td>
<td>0.0 (0.0)</td>
<td>1 (6.7)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Sleep Walking</td>
<td>0.0 (0.0)</td>
<td>1 (6.7)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Vomitting</td>
<td>0.0 (0.0)</td>
<td>1 (6.7)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Worsening asthma symptoms</td>
<td>0.0 (0.0)</td>
<td>1 (6.7)</td>
<td>1 (4)</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>10 (100.0)</strong></td>
<td><strong>28 (186.7)</strong></td>
<td><strong>38 (152)</strong></td>
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</table>
Table IV: Component Matrix. Loading values for each variable within each set are displayed. Principal components analysis was performed on A: clinical measures B: sleep architectural measures and C: cognitive measures. Each variable is a standardized change from baseline. SWS: slow wave sleep, REM: rapid eye movement, SWM: spatial working memory, SSP: spatial span, RTI: reaction time. Boxed loading values indicated variables which share a common factor.

<table>
<thead>
<tr>
<th>Component</th>
<th>Factor 1</th>
<th>Factor 2</th>
<th>Factor 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A) Clinical</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>0.913</td>
<td>-0.346</td>
<td>0.216</td>
</tr>
<tr>
<td>Anxiety</td>
<td>0.932</td>
<td>-0.043</td>
<td>-0.359</td>
</tr>
<tr>
<td>Sleep Quality</td>
<td>0.907</td>
<td>0.392</td>
<td>0.151</td>
</tr>
<tr>
<td><strong>B) Sleep Architecture</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep Continuity</td>
<td>0.926</td>
<td>-0.235</td>
<td>0.219</td>
</tr>
<tr>
<td>Stage 1</td>
<td>0.703</td>
<td>0.410</td>
<td>-0.529</td>
</tr>
<tr>
<td>Stage 2</td>
<td>0.912</td>
<td>-0.023</td>
<td>0.304</td>
</tr>
<tr>
<td>SWS</td>
<td>0.778</td>
<td>0.304</td>
<td>-0.008</td>
</tr>
<tr>
<td>REM</td>
<td>-0.324</td>
<td><strong>0.885</strong></td>
<td>0.314</td>
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<tr>
<td><strong>C) Cognitive</strong></td>
<td></td>
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<tr>
<td>SWM</td>
<td>-0.039</td>
<td><strong>0.978</strong></td>
<td>-0.203</td>
</tr>
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<td>SSP</td>
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<td>-0.204</td>
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<td>RTI</td>
<td><strong>0.996</strong></td>
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<td>0.0749</td>
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