

Investigating Chronotherapeutic Interventions for the Treatment of Depression

by

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Abstract

Major depressive disorder is one of the most frequently diagnosed psychiatric disorders, and has widespread negative impacts on both the individual and on society. Current standard treatment options for depression have significant limitations, including side effects, contraindications, and barriers to accessing care. Chronotherapies, which make use of sleep and circadian rhythms, provide a promising alternative treatment route for depression. Cognitive behavioural therapy for insomnia (CBT-I), bright light therapy (BLT), and combined chronotherapies used to treat depression were systematically reviewed. Both CBT-I and BLT have evidence to support their efficacy in treating depression; combined therapy including sleep deprivation, BLT and/or sleep phase advance may also be effective. We propose a novel combined chronotherapeutic treatment, consisting of telehealth CBT-I and BLT, which we believe would be efficacious, accessible, and which would help to relieve the considerable burden of depression in Canada.

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For contributions, please see Appendix 3.

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List of Abbreviations

ADM	Antidepressant medication
AE	Adverse events
BBB	Blood Brain Barrier
BDI	Beck Depression Inventory
BDI-II	Beck Depression Inventory II
BLT	Bright light therapy
CBT-I	Cognitive Behavioural Therapy for Insomnia
CES-D	Centre for Epidemiological Studies-Depression
CSSRS	Columbia Suicide Severity Scale
DLPFC	Dorsolateral prefrontal cortex
DSM	Diagnostic and Statistical Manual of Mental Disorders
ECT	Electroconvulsive therapy
EEG	Electroencephalography
EPDS	Edinburgh Postnatal Depression Scale
FU	Follow-up
GDS	Geriatric depression scale
GRID-HAMD	Hamilton Rating Scale for Depression-GRID
GWAS	Genome wide association study
HADS	Hospital Anxiety and Depression Scale
HAMD-12	Hamilton Rating Scale for Depression-12
HAMD-17	Hamilton Rating Scale for Depression-17
HPA	Hypothalamic pituitary adrenal (axis)
HRSD ₁₇	Hamilton Rating Scale for Depression-17
ICD	International Classification of Diseases
LTP	Long term potentiation
MADRS	Montgomery-Åsberg Depression Rating Scale
MADRS-S	Montgomery-Åsberg Depression Rating Scale Self-Rating
MAOI	Monoamine oxidase inhibitors
MDD	Major depressive disorder
MPFC	Medial prefrontal cortex
NNT	Number needed to treat
PHQ-9	Patient Health Questionnaire 9
QIDS-SR	Quick Inventory of Depressive Symptoms Self-Report
RCT	Randomized controlled trial
RDC	Research diagnostic criteria
REM	Rapid eye movement
RHT	Retinohypothalamic tract
RT	Retention
SAD	Seasonal affective disorder
SCID	Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders
SCN	Suprachiasmatic nucleus
SH	Sleep Hygiene
SIGH-SAD	Structured interview guide for the HAM-D – Seasonal affective disorders
SNRI	Serotonin and Norepinephrine Reuptake Inhibitors

SPA	Sleep phase advance
SSRI	Selective Serotonin Reuptake Inhibitors
SWA	Slow wave activity
SWS	Slow wave sleep
TMS	Transcranial magnetic stimulation
TSD	Total sleep deprivation
VLPCF	Ventrolateral prefrontal cortex

Chapter 1: General Introduction

1.1 Preamble

Major depressive disorder is one of the most commonly diagnosed mental illnesses, and is the third leading contributor to the global burden of disease worldwide (World Health Organization, 2008). In addition to the disruptive primary symptoms of depression, such as depressed mood, lack of energy, and diminished ability to concentrate (American Psychiatric Association, 2013), depression is associated with suicidality, increased risk of cardiac death, and increased risk of all-cause mortality (Lepine and Briley, 2011). Current treatments for depression, such as antidepressant medications and psychotherapy, have two significant limitations; first, that they are not effective for many patients, or may not be an ideal treatment (e.g. due to conflicting prescriptions, or pregnancy), and second, that there are many barriers to accessing these treatments, such as cost and treatment provider availability.

Over three quarters of individuals with depression also endorse sleep and circadian complaints, which is perhaps unsurprising given that it is one of the main diagnostic criteria for the disorder (American Psychiatric Association, 2013). Shifted circadian rhythms and deficient homeostatic sleep drive may also play a role in the development and maintenance of depression (Germain and Kupfer, 2008), and specifically targeting these problems as a part of overall depression treatment leads to lower rates of relapse and greater mood improvement (Buysse et al., 1999, Fava et al., 2006, Perlis et al., 1997).

Treatments employing techniques which alter or re-establish circadian rhythms and homeostatic sleep drive are here referred to as chronotherapies. Non-pharmacological chronotherapies are a promising avenue for the treatment of depression, both because they avoid the limitations of conventional antidepressant treatments, and because they address the sleep and circadian disturbances which are nearly ubiquitous in depression. Common chronotherapies include cognitive behavioural therapy for insomnia, bright light therapy, sleep phase advance procedures, and sleep deprivation therapy.

1.2 Thesis Organization

This thesis is organized into a delineated paper format, rather than a traditional continual thesis. This layout allows for the sequential presentation of evidence supporting the use of chronotherapies in depression, culminating in an overall discussion of the findings of these systematic investigations and recommendations for future research. The review of evidence

begins in Chapter 2, where a general overview of the state of the literature regarding depression, sleep, and circadian rhythms is discussed, along with supporting neurobiological evidence. Chapter 3 systematically investigates the use of cognitive behavioural therapy for insomnia (CBT-I) in the treatment of unipolar depression, and critically reviews the results of peer-reviewed evidence on the topic. Similarly, Chapter 4 is a systematic investigation of bright light therapy, as well as the combined use of various chronotherapeutics, as a treatment for unipolar depression. Following these papers, Chapter 5 proposes future directions for research, including a proposed research study investigating the combined use of telehealth CBT-I and bright light therapy to treat depression. Finally, Chapter 6 provides a general discussion of these reviews in the context of the overall relevant body of literature, as well as limitations and future directions for research.

Chapter 2: Depression, Circadian Rhythms, and Sleep

2.1 Introduction

This chapter reviews literature on four main topics, followed by a section outlining the main aims and hypotheses of this thesis. The first section of the literature review discusses depression, its impact on society, current standard treatment options for the disorder, and relevant models of the development and maintenance of depression. This is followed by the second section, which discusses chronobiology and circadian rhythms, including the interplay between circadian rhythms and sleep. The third section outlines the relationship between sleep, circadian rhythms, and depression, while the fourth summarizes non-pharmacological chronobiology-based therapies (chronotherapeutics) which can be used to treat depression.

2.2 Depression

2.2.1 Impact of Depression on Society

Major depressive disorder (MDD) is one of the most commonly diagnosed mental illnesses, with a 12% lifetime prevalence of major depressive episodes in Canada (Patten et al., 2006). Depression often has widespread negative impacts for individuals who have the disorder, often including low mood, loss of pleasure in enjoyable activities, change in appetite, sleep disturbances, feelings of worthlessness, and diminished concentration. These symptoms understandably cause distress and often interfere with personal, work, and social life, as well as general functioning (American Psychiatric Association, 2013).

In addition to the impact of the symptoms themselves, depression also has an associated increased mortality risk. Individuals with depression are much more likely to commit suicide. The risk of suicidal behaviour in this population is 20-27 times higher than that of the general population. The lifetime prevalence of suicide in individuals with affective disorders (including depression) is 2.2%, with lifetime prevalence of suicide attempts in patients with MDD as high as 31% (Dong et al., 2018). In addition to risk of suicidal behaviour, the risk of cardiac death and stroke are both higher when depression is present, especially in individuals already at high risk of developing coronary artery disease. All-cause mortality risk is also higher in depressed individuals (Lepine and Briley, 2011).

Given the high burden that depression places on afflicted individuals, it is not surprising that there is a high societal cost to the illness. Symptoms of depression often interfere with workplace functioning, potentially leading to decreased workplace productivity, as well as absenteeism and ‘presenteeism’ (present but working at diminished capacity). As a result,

depression is also associated with lower annual salaries, and the severity of depression is associated with rates of unemployment in this population (Lepine and Briley, 2011). In fact, it is estimated that less than 17% of depressed individuals work full time and function at their optimal level (Conference Board of Canada, 2018).

Of all of the individuals with depression who ever seek treatment in Canada, approximately 53% receive minimally adequate treatment (at least 4 sessions of counselling/therapy, or prescription of at least 84 days of antidepressant medications). If this rate increased to 75%, it would significantly increase the number of individuals who are able to function optimally at full-time employment, and could increase Canadian GDP by \$2.6 billion, or 0.16%. Additionally, this change in minimally adequate treatment could reduce the number of hospitalizations as a result of the illness, potentially saving the Canadian economy another \$5.7 million dollars in these direct health care costs (Conference Board of Canada, 2018). There are several potential ways by which access to minimally adequate treatment could be accomplished; namely, more accessible treatments, e.g. in terms of cost and/or availability (Fortney et al., 1999, Starkes et al., 2005), decreased stigma regarding treatment for depression (Clement et al., 2015), and more highly desirable treatments (e.g. fewer side effects, or less unpleasant overall) (Cascade et al., 2009).

2.2.2 Standard Treatment Options for Depression

Currently, the most common treatments for depression include antidepressant medications and psychotherapy, often in combination. For severe depression, electroconvulsive therapy (ECT) and/or transcranial magnetic stimulation (TMS) may also be used. There are several types of antidepressant medications; the most common being selective serotonin reuptake inhibitors (SSRIs), serotonin and noradrenalin reuptake inhibitors (SNRIs), tricyclic antidepressants, and monoamine oxidase inhibitors (MAOIs). Psychotherapy components may include cognitive therapy, behavioural therapy and/or activation, dialectical behaviour training, psychodynamic therapy, interpersonal therapy, and others. Psychotherapy may take place in individual, group, family, or telehealth format. When ECT is used, the procedure is completed under general anaesthesia, and electric currents are passed through the brain in an attempt to influence brain function and induce therapeutic benefit. TMS involves the non-invasive use of magnetic fields in order to stimulate neuron firing. This is typically done with a TMS “wand” held near to the surface of the scalp, in a specified cranial location, delivering repeated ‘pulses’ of magnetic waves at a pre-determined Hz. Generally, ECT and TMS are only used if both

antidepressant medications and psychotherapy fail to improve an individual's depression symptoms.

While these treatments do work for many people, there is still room for improvement in treating depression. While generally antidepressant medications work better than placebo, different antidepressant medications have varying profiles of both efficacy and tolerability/acceptability, with some commonly used antidepressants ranking low on both of these factors (e.g. clomipramine, reboxetine; Cipriani et al., 2018). Side effect profiles can also range considerably, and may result in changing antidepressant medications or adding additional prescriptions for side effect management (Dording et al., 2002). Additionally, while antidepressant medications are very effective for individuals with severe depression, they may have little benefit over a placebo prescription for individuals with mild or moderate symptoms of the disorder (Fournier et al., 2010). Antidepressant medications also typically take weeks to months to correct symptoms of depression (Quitkin et al., 1984). They may also be undesirable, for example due to medication contraindication, pregnancy, or other such factors.

There are also limitations inherent in the use of psychotherapy in the treatment of depression. There is a wide variety of psychotherapeutic treatments targeted at depression, and certain types of therapy may be less effective than others (e.g. cognitive versus behavioural for severely depressed patients; Dimidjian et al., 2006). Additionally, psychotherapy is typically not funded by provincial health care plans in Canada unless provided by a psychiatrist, with the result that there are long wait times for individuals who do not have private insurance and are unable to pay out-of-pocket for private therapy. Thus, there is an unmet need for depression treatment for low-income individuals, as well as individuals in rural areas, who may not have access to a health care provider at all (Starkes et al., 2005) or for whom travel times to a health care practitioner may lead to a reduction in appropriate depression treatment (Fortney et al., 1999).

Similarly, TMS also requires repeated visits to a trained professional such as a physician. Additionally, it may not be covered by provincial health care, requiring patients to pay out of pocket. Thus, while TMS may be very effective for some patients, including those with refractory depression (Li et al., 2014), it is still not a widely accessible treatment option. Additionally, TMS can lead to side effects including local muscle spasms or twitching, warming or irritation of the scalp, headaches, or in some cases seizures (Wassermann, 2000).

Electroconvulsive therapy, designed to induce convulsions/seizures, has been shown to be one of the most effective treatments for depression, in comparison to both placebo and sham

ECT as well as antidepressant medications (Pagnin et al., 2004). However, it often induces a host of (mostly transient) side effects, potentially including delirium, disorientation, retrograde and anterograde memory impairment, psychomotor speed reductions, changes in attention, and muscle pain with side effects usually worse for individuals with neurological illnesses or for who are older (Ingram et al., 2008, Payne and Prudic, 2009). Thus, it is generally only indicated for patients with severe, treatment-resistant depression. Even in these cases, patients may not want to undergo the procedure given the side effects and associated stigma (Payne and Prudic, 2009) and not all patients who have had ECT find it helpful or would elect to have it again (Rose et al., 2003). Additionally, given the need for general anaesthesia and medical professionals to carry out the treatment, and the fact that ECT is usually done as an inpatient procedure (Payne and Prudic, 2009), ECT is subject to many of the same barriers to accessing care as is psychotherapy.

Overall, while these treatment strategies are effective for some patients, it is clear that more research must be done into treatments for depression which avoid the drawbacks of the therapies discussed above. Namely, there is a need for treatments which are fast-acting, have fewer (if any) side effects, and which work for patients of varying depression severities. Additionally, there is a need for depression treatments which are more widely available and with fewer barriers to accessing care, including stigmatization. This could be accomplished in one of two ways; first, if existing treatments were made to be more widely accessible and less stigmatized, for example through public funding of psychology services or public education campaigns, or second, if new treatments were developed which were inherently more accessible and/or less stigmatized, such as sleep-based treatments delivered through a telehealth modality, for example.

2.2.3 Models of Depression

2.2.3.1 *Diathesis-stress and inflammation models of depression*

The diathesis-stress model, introduced to modern depression research in the 1980s (Bebbington, 1987), posits that an intrinsic individual vulnerability, or diathesis (e.g. biological or cognitive), when combined with stress, leads to the manifestation of depression (Figure 1). This idea of diathesis interacting with stress has been present in medical literature for some time. For example, Dr. H.P. Stearns described it as the following in *Insanity: its causes and prevention* (1883):

“a nervous system so sensitively constituted, and illy adjusted with its surroundings, that when brought in contact with unusually exciting influences, there may occur deranged instead of natural mental action, and it becomes more or less continuous instead of evanescent” (Stearns, 1883).

Less clear, however, is the precise nature of the relationship between diatheses and stressors. For example, a common model posits that in the presence of diathesis, a stressor (such as the loss of a job) would interact in a summative manner with the pre-existing vulnerability. If the combination met some predetermined threshold for the illness, depression would occur. However, this model neglects questions of interaction; namely, does the type of diathesis impact the perceived stress? And does the stress impact the underlying diathesis? For example, if a cognitive diathesis exists, it may affect the perception of events to bias them towards being perceived as stressful (Monroe and Simons, 1991), or may lead individuals to select more stressful life situations (Kendler et al., 1999). Thus, it is likely that rather than simply additive, diathesis and stress may also be multiplicative, or synergistic. Further, it is likely that some types of stressors may be more likely to lead to depression, such as those higher on the Social Readjustment Rating Scale (Holmes and Rahe, 1967), especially when in combination with facilitative diatheses. A theoretical model of this possibility is given by Monroe & Simons (1991) as: $Depression = b_0 + b_1(stress) + b_2(diathesis) + b_3(stress + diathesis)$, where depression is a result of not only the summation of stress and diathesis, but also the unique interaction between the particular stress and underlying vulnerability.

One study of morning cortisol in vulnerable (but not depressed) women provides some evidence for this model. In this study, major depressive disorder onset was separately associated with higher levels of average baseline morning cortisol; the presence of a severe adverse life event; and the combined presence of low self-esteem, negative interpersonal interactions and subclinical depression/anxiety. However, the cortisol levels alone were not associated with recent life events or psychosocial vulnerability (Harris et al., 2000). While psychosocial vulnerability is clearly a diathesis, and a severe life event a stressor, it is unclear where high baseline cortisol fits into the model. Perhaps it is a biological diathesis, independent of vulnerability, though it could conceivably also represent a state of heightened stress, as individuals with chronic stress (women especially) have been shown to have higher levels of morning cortisol (Schulz et al., 1998). Most likely, it represents an interaction between diathesis and stress, subsequently associated with the development of depression.

Research in the field of genetics also somewhat supports the diathesis-stress model. It is highly unlikely that there is “a gene for” depression, but rather that genes of interest in depression interact with environment to produce the illness (Kendler, 2005, Kendler et al., 1995). For example, this has been demonstrated with a functional polymorphism of the serotonin transporter gene (5-HTTLPR). While not directly related to depression onset, the short allele of this gene has been shown to increase vulnerability to adverse life events in the subsequent development of major depression. The gene was not shown to increase the odds of experiencing a stressful life event, however (Wilhelm et al., 2006, Caspi et al., 2003). The presence of this allele also has predictive value. For individuals with no prior history of depression, the presence of the s allele in combination with a stressful life event between the ages of 21 and 26 can predict depression and suicidality at age 26. Similarly, the prediction from childhood maltreatment to adult depression is also moderated by the presence of the s allele of the gene (Caspi et al., 2003). However, given that it is likely that biological risk for depression is polygenic, evidence from genome wide association studies (GWAS) and related polygenic risk scores must also be considered. Here, the evidence is more mixed; some studies (Colodro-Conde et al., 2017, Peyrot et al., 2014) show that stress (or trauma) interacts with diathesis to increase risk of depression, while others (Musliner et al., 2015, Mullins et al., 2016) show diathesis and stress playing more additive roles. As GWAS analysis increases, more light may be shed on the precise nature of the diathesis-stress model.

More recently, an inflammation model of depression has also been proposed which builds on the idea of diathesis and stress interaction as a causative factor in depression. In this model, psychosocial stress interacting with inflammatory pathways contributes to the development of depression. Thus, the presence and activation of these inflammatory pathways (which may be at least partly genetically determined) constitute the biological diathesis.

Proponents of the inflammation model of depression argue that inflammation and depressive behaviour, demonstrated in response to pathogens, predators, and aggressive conspecifics has been evolutionarily selected for, given that immunological and sedentary responses would both contribute to higher rates of healing and subsequent fitness. Over time, this reliable pairing between increased vigilance and stress (e.g. in response to a predator) and subsequent immune activation and depressive symptomology has led to a genomic bias toward these responses, such that vigilance and stress in the absence of a tangible threat lead to the development of these responses. This pairing has persisted into modern day society, where psychosocial stress is unfortunately common (Miller and Raison, 2016). According to this

model of depression, psychosocial stress “hijacks” these evolutionary pathways, triggering both inflammatory response and depressive symptomology (Miller and Raison, 2016), and indeed, both of these results have been experimentally demonstrated (Pace et al., 2006). Trauma can also contribute to inflammation, and thus subsequently depression (Baumeister et al., 2016). Additionally, given the relative sterility of developed societies, depression may be more prevalent in these societies due to a lack of regular interactions with normal (non-lethal) organisms, for example present in soil, which may have served a function in providing immunological checks and balances (Miller and Raison, 2016).

The route by which stress translates into inflammation and subsequent depression likely includes several possible mechanisms, including changes in HPA axis, sympathetic nervous system, and inflammasome regulation in response to stress. In the latter case, damage-associated molecular patterns caused by stress trigger inflammasome activation, which then activates the production of cytokine cells. Interestingly, inflammasome activation may also mediate the relationship between mood and the gut microbiome, and molecules from the gut can activate inflammasomes (Miller and Raison, 2016). From here, the inflammatory signals are transmitted to the brain, with subsequent inflammation in the brain contributing to depression. Cytokines are likely able to influence across the blood-brain barrier (BBB) through two main pathways; the first ‘humoral’ pathway through leaky areas in the BBB, and the second ‘neural’ pathway through binding to nerves in the periphery, causing downstream neural effects across the BBB and ultimately leading to increased cytokine signals in the central nervous system. Additionally, there is a third ‘cellular’ pathway, where active immune cells are attracted to the brain due to central production of attractive molecules. As a result of the inflammatory response in the brain, neurotransmitter systems are then affected due to a reduction in available monoamines (for example, inflammatory cytokines can lead to a reduction in available serotonin) and an increase in available glutamate, leading to the behavioural symptomology seen in depression (and anxiety) as well as potentially to treatment-resistance (Miller and Raison, 2016).

These models of depression and the impact of diathesis, stress, and inflammation must also be taken into account when considering treatments for depression. For example, for individuals with depression, both selective serotonin reuptake inhibitor (SSRI) plus supportive care and supportive care alone treatments are less likely to lead to remission when adverse life events and difficulties are also present (Brown et al., 2010). Additionally, considering the diathesis-stress model in epidemiological models of the disease may help to more simply account for patterns of current epidemiologic data (Patten, 2013). Finally, patients may be

resistant to traditional antidepressant treatments due to increased inflammation; decreasing inflammation mechanisms (for example through administration of anti-cytokine pharmaceuticals) may lead to increased antidepressant treatment response (Shariq et al., 2018), and thus may prove to be an effective antidepressant agent, at least for depressed patients with high levels of peripheral inflammation (Miller and Raison, 2016, Shariq et al., 2018).

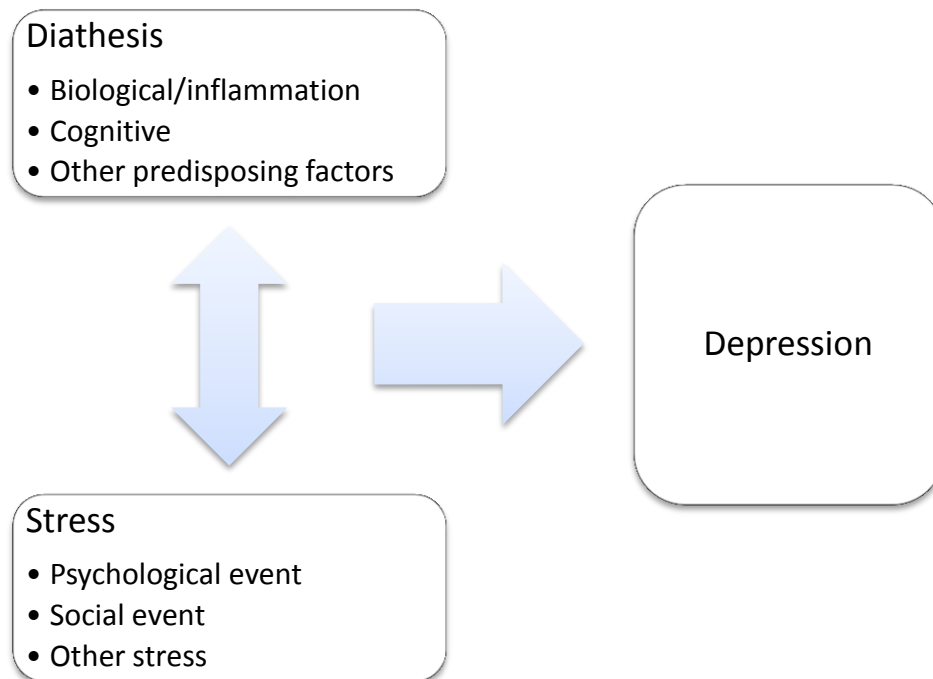


Figure 1 The diathesis-stress model of depression, illustrated. Predisposition to depression (e.g. biological or cognitive) interacts with stress (e.g. a psychological or social event) to meet the threshold for depressive symptomology.

2.2.3.2 Cognitive Model of Depression

The cognitive model of depression, introduced in the 1960s (Beck, 1967), builds on the diathesis-stress model and may help to explain the relationship between underlying genetic and cognitive vulnerabilities to the disorder, as well as changes in serotonin and cortisol levels in depressed individuals. In this model, at the beginning of the proposed pathway to depression, genetic diathesis modifies and enhances the functioning of the amygdala (Beck, 2008). For example, there is an association between the short variant of the 5-HTTLPR allele and heightened amygdala activation to emotional stimuli, which may mediate the relationship between the gene and risk of depression (Munafo et al., 2008). From these genetic and limbic

changes, and in reaction to adverse life events, arise maladaptive cognitive schemas, including dysfunctional attitudes and cognitive vulnerability, which then activate the “depressive mode,” or network (Figure 2; Beck, 2008, Disner et al., 2011).

The depressive mode is comprised of several schemas, and when activated (in response to stress) results in the symptoms associated with depression. These include cognitive, behavioural, affective, motivational and physiological schemas. The depressive mode is developed when an individual experiences stress and interprets an event negatively as a result of dysfunctional attitudes (e.g. regarding self-worth), cognitive reactivity and altered attentional focus, resulting in the activation of some or all of the depressive mode schemas (Disner et al., 2011, Beck, 2008). Over time, repeated activation strengthens the relationships of the depressive mode, and a major depressive episode “locks” it into place. At this point, the mode can then function autonomously, without the need for a precipitating event, leading to the presence of depression (Beck, 2008).

As the depressive mode is developed following the negative interpretation of life events, certain cognitive biases must be present in order for this development to occur. The cognitive model posits that adverse life events lead to the maladaptive cognitive schemas and biases necessary for the depressive mode (such as a schema of personal worthlessness). When these schemas are activated by stressful life events, it then leads to selective attentional biases to negative events (potentially as a result of impaired attentional inhibition), as well as cognitive reactivity (Beck, 2008, Disner et al., 2011). Cognitive reactivity (the daily fluctuations of patient self-esteem and negative perception in response to various life events, also termed ‘self-esteem lability’) is a predictor of depression onset and recurrence. Additionally, for individuals with higher cognitive reactivity, less stress is required in order to ‘kick-start’ depression (Butler et al., 1994). Cognitive reactivity is also associated with higher sensitivity to acute tryptophan depletion and reduced serotonin concentration, predicting depressive onset under these conditions (Booij and Van der Does, 2007).

As a result of these cognitive schemas and enhanced amygdala activity, there is further exaggeration and rumination in reaction to stressful or emotional events (Siegler et al., 2002). Additionally, in response to stressful events, the hypothalamic pituitary adrenal (HPA) axis is activated, leading to excessive cortisol response (Parker et al., 2003). This is especially true in individuals who are homozygous for the short allele of the 5-HTTLPR gene, for whom cortisol response to stress may be both sharper and more sustained (Gotlib et al., 2008). This

hypercortisolemia has been hypothesized to lead to loss of neurons in the hippocampus, which may contribute to the development of depression (Sapolsky, 2000).

Another key aspect of the cognitive model of depression is the imbalance between top-down and bottom-up processing, especially in reaction to stressful events and the reappraisal of negative cognitions (Beck, 2008). This imbalance favours bottom-up processing, linked to the altered functioning of the limbic system and enhanced amygdala reactivity, as previously discussed (Fales et al., 2008). This bottom-up processing facilitates the automatic activation of negative cognitive schemas in the depressive mode (and consequently, the rest of the mode; Beck, 2008). Additionally, there is attenuated functioning of top-down processes of cognitive control, potentially due to deficits in the dorsolateral prefrontal cortex (DLFPC; Fales et al., 2008, Disner et al., 2011), medial prefrontal cortex (MPFC) and/or ventrolateral prefrontal cortex (VLPFC; Disner et al., 2011). However, the conscious use of cognitive control to challenge dysfunctional cognitive schemas and beliefs can attenuate the salience of the depressive mode. These skills can be taught through psychotherapy, and is likely one of the main mechanisms by which this treatment improves symptoms of depression (Beck, 2008).

Overall, the cognitive model of depression posits that it is through the network of processes, starting with genetic diathesis, formulating and cementing the depressive mode, and leading to dysregulation of top-down versus bottom-up cognitive and limbic process, that depression develops and reoccurs (Figure 3).

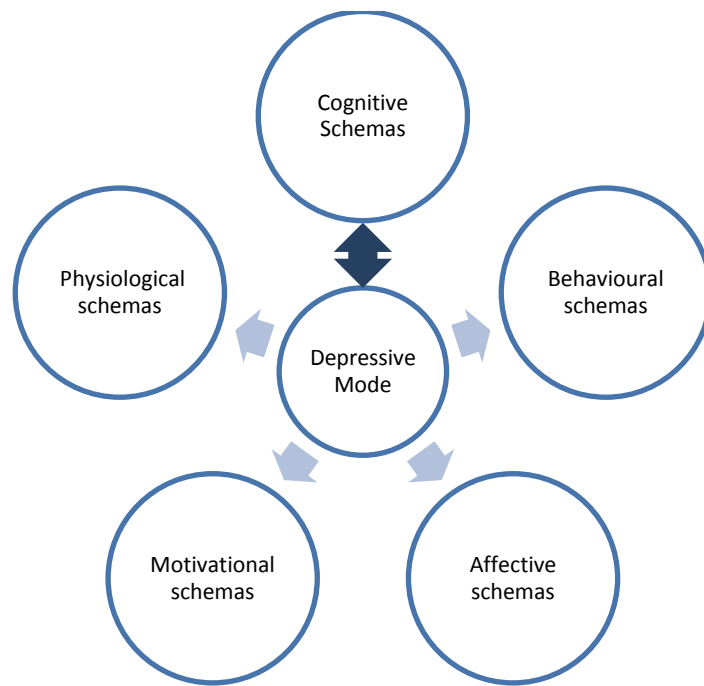


Figure 2 The depressive mode, or network, is comprised of several schemas, which then produce the symptoms displayed in depression. These include behavioural, affective, motivational, and physiological schemas, as well as cognitive schemas. Cognitive schemas both influence the depressive mode, and are activated by it. Modified from Beck, 2008.

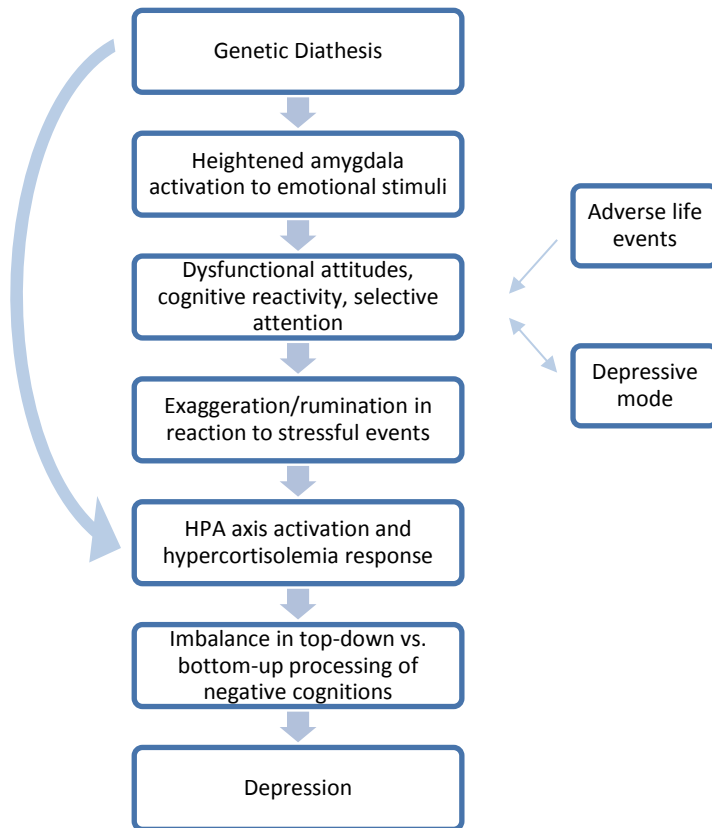


Figure 3 Illustration of the pathways of the cognitive model of depression. Adapted from Beck, 2008.

2.2.3.3 Monoamine Hypotheses of Depression

There are two main monoamine hypotheses of depression, both primarily based on evidence that modifying neurotransmitter systems in the brain can improve symptoms of the disease: the catecholamine hypothesis, and the serotonin hypothesis of depression.

The catecholamine hypothesis of depression was originally proposed in 1965. This hypothesis posits that affective disorders, including depression, are caused by a reduction in available catecholamines (especially norepinephrine) at adrenergic receptor sites in the brain (Schildkraut, 1965). However, since the time that this model was introduced, research evidence has been mixed. Some primary research findings support the hypothesis, including the measurement of reduced global brain norepinephrine and dopamine levels in depressed individuals (though with questionable impact on clinical symptomology; Lambert et al., 2000). The most supporting evidence comes from the clinical efficacy of drugs which act on catecholamine systems, such as MAOIs and SNRIs (Cipriani et al., 2018). However, other research does not support this hypothesis. For example, the drug reserpine, which was widely accepted to deplete brain catecholamines and cause depressive symptoms, may not actually be depressogenic, calling into question some of the key evidence for the catecholamine hypothesis (Baumeister et al., 2003).

More widely accepted is the serotonin hypothesis, especially given the efficacy of the wide variety of selective serotonin reuptake inhibitors (SSRIs) in treating depression (Cipriani et al., 2018). The serotonin hypothesis was also proposed in the mid-1960s, and postulated that depression was caused by serotonin deficits in the brain which could be corrected by antidepressant medications (Albert et al., 2012). There is some evidence for this model, including a reduction in cortical serotonin binding potential in depressed individuals even after depressive remission (Bhagwagar et al., 2004), and links between depression and the 5-HTTLPR polymorphism (Benedetti et al., 1999, Gotlib et al., 2008, Albert and Benkelfat, 2013). However, like the catecholamine hypothesis, this hypothesis is overly simplistic and there is considerable inconsistency in the relevant literature (e.g. while SSRIs are fairly effective, for many depressed individuals they will not lead to remission). Thus, while it is clear that serotonin plays a role in the development and maintenance of depression, for example through alterations in serotonin receptors, transporters, and/or transcription factors (Albert et al., 2012), it is unlikely that deficiencies in brain serotonin levels alone are responsible for the disorder. More likely, changes in monoamine systems contribute to risk of depression as a form of diathesis,

while also interacting with other factors such as stress, circadian rhythms, and sleep loss, to eventually lead to development of the disorder.

2.2.3.4 Sleep, Circadian, and Synaptic Plasticity Models of Depression

Circadian and sleep models of depression posit that abnormalities in these systems contribute to the development of depressive symptoms, either through circadian asynchrony, and/or deficient ‘process S.’ The latter may also be reflected in the synaptic plasticity model of depression, which provides neurological correlates for the proposed mechanism of depressive development. Circadian and sleep models of depression may work together or independently to facilitate the development and duration of the illness.

Firstly, the phase-shift hypothesis of depression posits that depression is a result of asynchrony between the body’s circadian rhythms, and specifically those of the central pacemaker and related rhythms, versus those of sleep-wake rhythms (Germain and Kupfer, 2008; Figure 4). Evidence for this model comes from the findings that specifically timed bright light and melatonin can improve depressive symptomology through the shifting of circadian rhythms (Lewy et al., 2006, Lam et al., 2016, Khalsa et al., 2003). This model related to the ‘process C’ aspect of the two-process model of sleep regulation (discussed further below).

Secondly, it has been proposed that a deficiency in ‘process S,’ or homeostatic sleep drive, is responsible for the development and duration of depression (Wu and Bunney, 1990, Borbely, 1982). This may also be reflected in a deficiency of slow wave sleep (SWS) stages, and overall slow wave activity (SWA; Germain and Kupfer, 2008). Evidence for this model comes from the fact that sleep deprivation has such a reliable antidepressant effect in approximately 60% of depressed individuals; in this case, it is hypothesized that sleep deprivation resets the deficient homeostatic sleep drive, but “reverts” to the depressive baseline following recovery sleep (Wu and Bunney, 1990).

On a neurological level, this ‘process S’ may be represented by changes in synaptic plasticity. The synaptic plasticity model of depression posits that it is a deficiency in synaptic plasticity, rather than neurotransmitter system impairment, that results in depression. It is thought that there is an increase in long-term depression, and a decrease in long-term potentiation (LTP) of glutamatergic synaptic transmission in depressed individuals, resulting in the weakening of synaptic connections. The authors of the synaptic plasticity model of sleep deprivation hypothesize that this decreased synaptic plasticity in depression is reflected in decreased SWS/SWA, and that sleep restriction remedies plasticity deficits by shifting the

depressed individual into the ideal LTP window, which they would otherwise be unable to achieve. This model accounts for the relapse seen after recovery sleep as well, as individuals shift out of the ideal LTP window (Wolf et al., 2016).

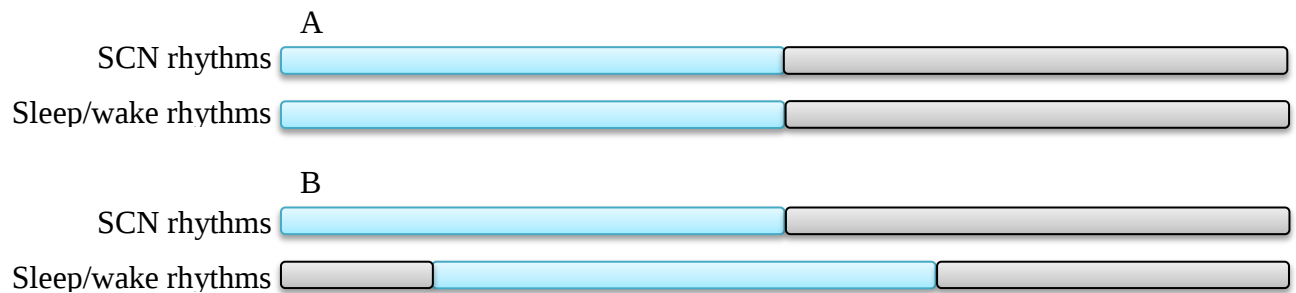


Figure 4 Illustration of the phase-shift hypothesis of depression. A. SCN rhythms align with sleep/wake rhythms, as might be seen in a non-depressed individual B. Sleep/wake rhythms are delayed compared to SCN rhythms, as might typically be seen in depressed patients.

2.3 Chronobiology and Circadian Rhythms

Chronobiology is the study of time-based rhythms in biological systems (also referred to as biological rhythms). The lengths of these rhythms can vary; for example, the yearly patterns of bear hibernation and bird migration, and the daily patterns of bats becoming active at night, are all examples of biological rhythms. This last example is of a daily, or roughly 24-hour rhythm, which is also called the circadian rhythm – from *circa*, meaning about, and *diem*, meaning day. Circadian rhythms have been scientifically investigated since 1729, when Jean-Jacques d’Ortous de Mairan first investigated the daily rhythms of the leaves of the *Mimosa pudica* plant when not exposed to light. Since that time, almost all organisms have been shown to have circadian rhythms that are endogenously produced (Zordan et al., 2000).

Circadian rhythms can be free-running on a near-24-hour schedule, or can be entrained to environmental cues (called *zeitgebers*). Zeitgebers influence the phase of the circadian rhythm to match that of the 24-hour day-night cycle. The primary zeitgeber is light; for example, in humans (who are diurnal), the presence of light is activating, and the absence of light acts as a sleepiness cue. If the light timing shifts (e.g. with travel across time zones), the body will slowly re-entrain to the new light-dark cycle, causing phase shifting (either advanced or delayed) and eventual adaptation. Similarly, with the purposeful strategic timing of bright light, individuals’ circadian rhythms can be temporarily shifted to be earlier or later in the day, depending on the timing of the light (Duffy et al., 1996). This is similar to sleep disorders where

the circadian clock is shifted. In these disorders, the body's circadian rhythm does not match the light-dark cycle in the same way as that of most of society; as such, individuals with these conditions are termed to be "phase advanced," waking up and going to bed earlier than most other people, or "phase delayed," waking up and going to bed much later than most other people. Additionally, it is possible for internal circadian rhythms such as those of sleep, digestion, and cognitive performance, to become desynchronized from one another. In these cases, for example when experiencing jet lag or doing shift work, individuals may experience symptoms such as sleepiness, worsened mood, and lack of appetite.

2.3.1 Neurological Basis of Circadian Rhythms

In order for there to be endogenous circadian rhythms, there must be a physiological mechanism by which these rhythms are created. Indeed, research has shown that in mammals there is one central 'pacemaker,' responsible for setting the circadian rhythm. The pacemaker is located in a cluster of neurons just above the optic chiasm, termed the suprachiasmatic nucleus (SCN; Ralph et al., 1990). The neurons in the SCN produce this rhythm through roughly 24 hour oscillating molecular mechanisms (expression of genes and proteins, protein phosphorylation, and electrical activity) shown both in vivo and in vitro, within the cells themselves. Not all SCN cells are endogenously rhythmic, however; rhythmic cells tend to cluster in the rostral, dorsomedial, and ventromedial areas of the SCN (the "shell"), while non-rhythmic cells occupy more central "core" areas of the nucleus (Lee et al., 2003).

Light reaches this pacemaker (in mammals) primarily by way of photopigments in the retina called melanopsins, which are found in retinal ganglion and amacrine cells (but not in typical photoreceptor cells; Provencio et al., 2000). From here, signals travel via the retinohypothalamic tract (RHT), where the ganglion cells of the retina synapse with the dendrites of SCN neurons (Moore and Lenn, 1972), releasing glutamate (Ding et al., 1994). Light also reaches the SCN indirectly from the retina via the intergeniculate leaflet, in the lateral geniculate complex, by way of the geniculohypothalamic tract. The receiving SCN neurons are primarily located in the ventral, ventrolateral, and central areas of the SCN. Light effects cellular change in light-responsive cells by way of light-responsive genes, both clock (e.g. *Per1*) and non-clock (e.g. *Fos*; Lee et al., 2003). Thus, the SCN is able to entrain to the light/dark cycles of the external environment, and the application of glutamate to the SCN can also induce circadian phase shifts (Hannibal, 2002, Mintz et al., 1999). Additionally, non-photoc phase information is brought to the SCN by way of serotonergic synapses from the midbrain raphe

nucleus (Moore and Speh, 2004), and serotonin application to the SCN can also induce phase shifts in circadian rhythms (Prosser, 2003).

In order for the SCN to act as a pacemaker at a systemic level in an organism, it must have projections or outputs to a wide range of other physiological systems. It must also be able to influence behaviour. Studies in mammals have shown that the SCN projects to a variety of areas in the brain, both from the shell and the core of the SCN. The shell projects more widely than the core, with dense output to the hypothalamus (medial preoptic area, dorsomedial hypothalamic nucleus, medial subparaventricular zone) and midline thalamus (paraventricular thalamic nucleus), as well as sparse output to the basal forebrain (bed nucleus of the stria terminalis) and ventral thalamus (zona incerta). The core projects densely to the hypothalamus (the peri-suprachiasmatic region, lateral subparaventricular zone), and in varying densities to the basal forebrain (e.g. sparse in lateral septum, dense in ventral tuberal area). Both the shell and core projects sparsely to the paratenial thalamic nucleus of the midline thalamus; additionally, the core of the SCN projects to the shell region, but not vice versa. Given the larger number of efferent pathways from the shell than the core, it seems as if the core's function is to entrain to visual stimuli via the RHT, and send this information to both core-specific efferent projections as well as the shell of the SCN, while the shell of the SCN integrates the information received from both the core region as well as other incoming pathways (e.g. hypothalamus, thalamus, brainstem) and sends this information to the SCN effectors (Leak and Moore, 2001).

More generally, it is also clear that the SCN is responsible for the generation of behavioural circadian rhythms in mammals as well. The first line of evidence supporting this comes from SCN ablation studies; when the SCN is surgically lesioned, behavioural circadian rhythms such as those of feeding and drinking disappear (Ven den Pol and Powley, 1979). Secondly, transplantation of an intact SCN into an animal whose SCN was ablated is able to restore behavioural circadian rhythms (Sawaki et al., 1984). Finally, when transplanting a SCN into a lesioned animal, after transplantation the animal displays the circadian phenotype expected of the donor animal, rather than their own pre-surgery phenotype (Ralph et al., 1990).

2.3.2 Circadian Rhythms and Sleep

The SCN, controlling circadian rhythms ('process C'), also interacts with homeostatic sleep drive ('process S') in order to drive sleep-wake rhythms; this is known as the two-process model of sleep regulation (as was briefly touched upon in the sleep and circadian model of depression). In this model, sleep drive accumulates during wakefulness and dissipates during

sleep, to an extent determined by circadian phase. When sleep drive hits a critical high point, relative to the circadian rhythm, sleep occurs; when it hits a critical low, wakefulness occurs. This process S is mainly reflected in SWS during sleep, and theta EEG activity during wake, whereas process C is reflected in changes in melatonin levels and core body temperature (Borbely et al., 2016).

In the original two-process model of sleep regulation, processes S and C were independent, and it was the phase relation between the two which determined the onset of sleep or wake. However, there is now evidence to suggest that the relationship between process S and process C is more complicated than a simple independent, or even additive, model (Borbely et al., 2016). For example, sleep restriction, which increases both homeostatic sleep drive and extracellular levels of adenosine, can reduce the phase-shifting effect of bright light, but caffeine (an adenosine antagonist) can potentially reverse this effect (van Diepen et al., 2014). Thus, there is at least some ability for process S and process C to interact and influence each other, though the exact mechanisms by which this occurs is unclear (Borbely et al., 2016).

2.4 Sleep, Circadian Rhythms, and Depression

There is a large degree of overlap between disturbances in sleep and circadian rhythms and depression. Individuals with insomnia are more than twice as likely as individuals without insomnia to subsequently develop depression (Li et al., 2016). As many as 90% of individuals with depression have disturbed sleep, and altered sleep architecture (e.g. decreased REM sleep latency) is often considered to be a typical feature of depression (Tsuno et al., 2005). Examples of circadian disturbances in depressed patients include changes in core body temperature as well as variable cortisol and melatonin secretion, in addition to diurnal depressive symptom fluctuation (Germain and Kupfer, 2008). Disturbed sleep (insomnia or hypersomnia) is also one of the DSM-5 diagnostic criteria for major depressive disorder (American Psychiatric Association, 2013) and is one of the most common features of the disorder (Hamilton, 1989).

Unfortunately, the presence of sleep and circadian disturbances in depression predict worse clinical outcomes following treatment (Germain and Kupfer, 2008). For example, in one study, individuals with worse subjective sleep and altered sleep architecture were less likely to go into remission following psychotherapy than individuals without these characteristics (Buysse et al., 1999). Additionally, the presence of hypersomnia or insomnia is associated with increased suicidality in individuals with depression (Agargun et al., 1997). Thus, it is perhaps

not surprising that sleep and circadian disturbances are associated with depressive relapse following successful treatment (Perlis et al., 1997), and that treatments also targeting sleep symptoms often result in larger mood improvements than those which do not target these symptoms (e.g. Fava et al., 2006). However, many common antidepressant treatments do not target these symptoms, and in fact may alter sleep architecture and/or exacerbate insomnia or other sleep disorder symptoms (Cascade et al., 2009, Wichniak et al., 2017).

2.5 Chronotherapeutic Treatments for Depression

Chronotherapies are a branch of treatment that seek to make use of the body's chronobiology and circadian rhythms in order to effect therapeutic benefit. For example, one type of chronotherapy is termed 'chronotherapeutic drug delivery,' in which medication schedules are arranged around the circadian rhythm of a particular illness in a way predicted to maximize the benefit of the drug, while also potentially minimizing possible side effects (Sajan et al., 2009). Chronotherapies are used in different forms of depression, including seasonal, non-seasonal, unipolar and bipolar. These chronotherapies (discussed further below) include cognitive behavioural therapy for insomnia (CBT-I), bright light therapy (BLT), sleep deprivation/restriction, and sleep phase advance.

2.5.1 Cognitive Behavioural Therapy for Insomnia

Cognitive behavioural therapy for insomnia (CBT-I) is comprised of a variety of cognitive and behavioural strategies designed to combat the main underlying causes of primary insomnia: disruption of the endogenous homeostat, disruption of circadian rhythms, autonomic arousal (and other sleep inhibitory factors), and dysfunctional cognitions and beliefs (Edinger and Means, 2005). These strategies include sleep hygiene instruction, psychoeducation, stimulus control, sleep restriction, relaxation therapy, and other cognitive strategies (Edinger and Means, 2005, Morin, 2006; Table 1).

Table 1 Typical cognitive and behavioural components of cognitive behavioural therapy for insomnia; adapted from Morin, 2006, Edinger and Means, 2005.

Cognitive/ Behavioural Strategy	Mechanistic Target	Strategy Description
Sleep hygiene instruction	Autonomic arousal/sleep inhibitory factors	Sleep hygiene instructions are designed to facilitate a healthy sleep environment, and conditions surrounding sleep. Typical sleep hygiene instructions include limiting caffeine and alcohol intake, especially before bedtime; implementing a wind-down period approximately an hour before bedtime; limiting exposure to screens and bright light in the hours preceding bedtime; exercising regularly; and sleeping in a cool, dark, and quiet bedroom.
Psychoeducation	Dysfunctional cognitions and beliefs	Psychoeducation strategies are designed to combat maladaptive beliefs and cognitions which contribute to the development and persistence of insomnia. Examples of psychoeducation topics may include dispelling myths about sleep, and outlining the circadian and homeostatic sleep systems.
Stimulus Control	Autonomic arousal/sleep inhibitory factors; circadian disruption; homeostatic disruption.	Stimulus control is designed to reduce the pairing between autonomic arousal and the bedroom/bedtime environment, and to re-associate bedtime and successful sleep. This is accomplished by instructing the patient to only go to bed when sleepy; to get out of bed after an unsuccessful sleep attempt; to get out of bed if worrying in bed; to only use the bed for sleep and sexual activity; and to refrain from napping during the day.
Sleep restriction	Homeostatic disruption	This therapy is designed to restrict the amount of time spent in bed (bed restriction) to the actual sleep time, reducing the time spent “lingering” in bed. This produces mild sleep deprivation in the patient. The time spent in bed can be increased gradually over the course of therapy, usually by 15 minutes per week, until optimal sleep efficiency is achieved.
Relaxation therapy	Autonomic arousal/sleep inhibitory factors; dysfunctional cognitions and beliefs	Relaxation therapy is designed to combat high autonomic arousal, including muscle tension and sleep-interfering thoughts. Relaxation therapy may include progressive muscle relaxation, meditation, positive imagery training, biofeedback, etc.
Cognitive strategies	Dysfunctional cognitions and beliefs	Cognitive strategies are designed to challenge dysfunctional beliefs about sleep, insomnia, and daytime consequences, as well as reduce anxiety and worry around sleep. This may include components of psychoeducation and/or sleep hygiene, as outlined above, paradoxical intention, interalia.

In order for insomnia to occur, a variety of circumstances must be present including predisposing, precipitating, and perpetuating factors. Predisposing factors are those that increase risk for insomnia in an individual; for example, history of insomnia, female sex, and anxiety. Factors which lead to acute onset of sleep disturbance are considered precipitating factors. These may include stress (for example, in the workplace or at home), illness, or travel. However, while many individuals may experience sleep disturbances, most do not continue on to develop chronic insomnia; perpetuating factors (the targets of CBT-I) must be present for this to occur. The development of insomnia is typically cyclical, where dysfunctional cognitions and beliefs (e.g. worry about sleep) lead to maladaptive behaviours (e.g. extending time in bed) as well as increased arousal, which then leads to worsened sleep, causing the cycle to repeat itself. CBT-I targets this cycle, while simultaneously addressing disrupted homeostatic and circadian processes, in order to reduce (and hopefully eliminate) symptoms of insomnia (Morin, 2006).

CBT-I is a very effective treatment for primary insomnia, and is usually considered to be the preferred choice of treatment for the disorder (especially given the limitations of hypnotic medications; Qaseem et al., 2016, van Straten et al., 2018). Effect sizes for treatment outcomes generally range from $g = 0.29$ (for number of awakenings after sleep onset) to $g = 0.98$ (for change in insomnia severity index). Total sleep time is the least affected by CBT-I (effect size $g = 0.16$), and overall effect sizes for CBT-I are roughly similar to effect sizes for psychological treatments for other mental illnesses (van Straten et al., 2018). CBT-I is effective in both primary and comorbid insomnia (van Straten et al., 2018), and is an effective treatment for sleep disturbances that often occur in depression. CBT-I as a stand-alone treatment, without concurrent depression-specific treatments, may also improve symptoms of depression in addition to reducing insomnia (Cunningham and Shapiro, 2018).

The factor most likely to account for the improvement in depressive symptomology following CBT-I is the sleep restriction associated with most CBT-I protocols. Sleep restriction has been shown to produce an antidepressant effect (see “Sleep Restriction” section below), though usually the effect is transient, and disappears following recovery sleep (Wu and Bunney, 1990). Another possible mechanism by which CBT-I exerts its antidepressant effect is by realigning or re-synchronizing circadian rhythms, through the enforcement of a strict sleep schedule with a constant wake time. Other aspects of CBT-I including relaxation therapy, sleep hygiene, and cognitive therapy may also lead to lowered depressive symptomology, for example by reducing worry and stress or improving lifestyle habits (Jorm et al., 2008, Sochos and Kotonou, 2017, Strohle, 2009, Lai et al., 2014, Morin, 2006).

2.5.2 Bright Light Therapy

Bright light therapy involves the timed daily dosage of light set to a specific brightness level and spectrum, typically for a period of at least several weeks. Modern clinical light boxes (for example, see Figure 5) usually emit bright white light between 2,500 and 10,000 lux, with light typically administered daily for between 30 minutes and 2 hours. In order for bright light boxes to be most effective, patients are instructed to sit a specific distance away from the box; patients do not have to stare at the apparatus, but should sit facing it, and may carry out activities such as eating a meal or reading the newspaper. Early morning light seems to be the most helpful for improving symptoms of affective disorders, though this may be modified based on individual circadian timing (Westrin and Lam, 2007, Cunningham et al., unpublished).

Bright light therapy was originally used as a treatment for seasonal affective disorder (SAD) in both unipolar and bipolar patients, starting in the mid-1980s (Rosenthal et al., 1984). Since then, bright light therapy has been shown to be effective by many randomized controlled trials and several reviews and meta-analyses (e.g. Golden et al., 2005, Terman and Terman, 2005) for treating SAD. More recently, bright light has been investigated as a treatment for non-seasonal depression, with some evidence in both bipolar and unipolar patients of its efficacy (e.g. Lam et al., 2016, Al-Karawi and Jubair, 2016, Cunningham et al., unpublished).

The specific mechanism of action of how bright light impacts affective disorder symptomology is unclear. It is likely that it acts by correcting and re-synchronizing circadian rhythms, both in seasonal (Levitan, 2007) and non-seasonal (Germain and Kupfer, 2008) depression, given the known phase shifting that occurs in humans in response to bright light (Khalsa et al., 2003), and the circadian disturbances associated with these disorders. However, the phase shifting response to bright light may not be strongly associated with mood improvement (Burgess et al., 2004), and thus it is unclear to what degree the effects on mood can be attributed to phase correction. It is also possible that bright light acts on similar neural systems as antidepressants; namely, on serotonergic and catecholaminergic pathways (Neumeister et al., 1998). Notably, individuals homozygous for the long allele of the 5-HTTLPR gene (discussed in the “diathesis-stress” section) seem to preferentially respond to light therapy following sleep deprivation, whereas individuals homozygous for the short allele may benefit much less, if at all from this combined treatment (Benedetti et al., 2003). In this case, bright light may act to regulate dysfunction in serotonergic pathways, and the allele type

may influence the individual's receptiveness to changes in serotonergic neurotransmission. Most probably, the mechanism of action of bright light is some combination of these two possibilities.



Figure 5 An example of a bright light box used to treat seasonal affective disorder.

2.5.3 Sleep Restriction Therapy

Sleep restriction therapy is when an individual is deprived of some or all of their normal sleep, with the goal of exerting a beneficial therapeutic effect. There are several different types of sleep restriction therapy: acute, where individuals are deprived for one period (e.g. one night); chronic, where individuals are deprived of sleep more than once, often consecutively; partial, where individuals are still allowed to sleep for part of the night; total, where individuals are made to stay awake for a whole night; rapid eye movement (REM) sleep restriction, where individuals are selectively deprived of sleep when they go into the REM sleep stage (Wu and Bunney, 1990), and slow wave sleep (SWS) restriction, where individuals are deprived of sleep when they go into slow wave stages of sleep (Landsness et al., 2011). There are both benefits and drawbacks to these types of sleep restriction. While some may be less difficult for individuals (e.g. partial rather than total), the impact of these types of sleep restriction may also differ, for example in mood, cognitive, and physical effects.

One night of total sleep deprivation (TSD) has been the most reliably demonstrated to lead to decreases in depressive symptoms. Since the 1970s, it has been demonstrated that approximately 50-60% of depressed individuals (both unipolar and bipolar) who undergo TSD will have an improvement in mood the day following sleep deprivation. Partial sleep restriction, especially when occurring in the later half of the night, has also been shown to be effective in improving mood in depressed individuals (Wu and Bunney, 1990). Sleep restriction is effective for patients regardless of depressive severity. Predictors of response to sleep deprivation therapy

include high arousal, variations in mood, certain types of depression (e.g. “endogenous,” “melancholic”), and bipolar illness (Voderholzer, 2003).

The greatest limitation to the use of sleep deprivation in the clinical setting is the very high rate of relapse, which usually occurs immediately after the first sleep period particularly following sleep restriction (also termed ‘recovery sleep’). Typically, less than 15% of patients sustain the therapeutic mood response of sleep restriction after this period of recovery sleep (Wu and Bunney, 1990), though it may be possible to extend the mood response with the prescription of antidepressant medications (Benedetti et al., 2007) and/or the strategic timing of recovery sleep (Wiegand et al., 1993). However, another barrier to the clinical use of sleep restriction is the demanding nature of the treatment; patients may be unwilling to repeat the protocol due to the increased fatigue and sleepiness they experience the following day, or may be unwilling to ‘give up’ their sleep in the first place, even for the prospect of an improvement in mood.

Given these limitations, alternative (and less demanding) forms of sleep restriction may be highly advantageous if proved effective. Indeed, selective REM sleep deprivation (completed using polysomnography) has shown some promise in alleviating depressive symptoms the day following the treatment (Wu and Bunney, 1990, Landsness et al., 2011). Similarly, selectively depriving individuals of slow wave sleep (and suppressing slow wave amplitude) may also lead to subsequent mood improvement, though a combination of slow wave and REM sleep reduction may be most effective (Landsness et al., 2011).

It is likely that at least part of the mechanism of action of sleep restriction’s antidepressant effect is through pathways similar to those of antidepressant medications. Notably, sleep deprivation has been shown to alter several aspects of the serotonin pathway, affecting the transmission of the neurotransmitter via adaptation at autoreceptors. These changes mimic those seen after antidepressant medications (Adrien, 2002, Benedetti et al., 2007). Additionally, individuals homozygous for the long variant of the functional polymorphism of the serotonin transporter gene (5-HTTLPR, discussed above in the “diathesis-stress” section) may preferentially respond to sleep deprivation therapy (and serotonergic medications; Benedetti et al., 1999). Sleep deprivation is also postulated to work through norepinephrine and dopamine pathways, though the evidence for these mechanisms is less clear (Benedetti et al., 2007). One possibility is that there is differential D₂ receptor affinity in the basal ganglia, or a difference in dopaminergic release between responders and non-responders to sleep restriction (Ebert et al., 1994). More research is required to determine the exact role of dopamine and

norepinephrine in the mechanism of action of the antidepressant response to chronotherapeutic treatments.

It is also theorized that sleep deprivation's mechanism of action is through circadian and homeostatic ('process C' and 'process S') changes (Wu and Bunney, 1990, Dallaspezia and Benedetti, 2015). Similarly to bright light treatment, it is possible that sleep deprivation corrects and re-synchronizes circadian rhythms in the SCN (Dallaspezia and Benedetti, 2015). It has also been proposed that sleep deprivation resets a deficient 'process S' by increasing sleepiness and restoring normal homeostatic sleep drive. In this case, relapse following recovery sleep can be attributed to a return to baseline 'process S' performance (Dallaspezia and Benedetti, 2015, Wu and Bunney, 1990). 'Process S' may also reflect changes in cortical excitability and synaptic strength. According to the synaptic plasticity model of sleep deprivation in depression, which combines theories of synaptic plasticity deficits in depression with those of sleep based synaptic homeostasis, individuals with depression have dysfunctional synaptic homeostasis mechanisms (reflected in changes in sleep architecture). Non-depressed individuals have a gradual build-up in net synaptic strength over the day, resulting in net synaptic strength falling into the optimal window for synaptic long-term potentiation (LTP) during the waking day (after a small lag period in the morning immediately following sleep). Sleep leads to down-scaling of the net synaptic strength, whereas sleep deprivation leads to further build-up of net synaptic strength. However, in depressed individuals, the net synaptic strength during the day never increases to the point of falling within the optimal window for LTP. Thus, over the course of sleep deprivation, net synaptic strength is allowed the opportunity to increase, until ultimately it falls within this LTP window, and we subsequently see an improvement in depressive symptoms (Wolf et al., 2016). Theoretically, responders to sleep deprivation therapy would be able to reach this optimal level of net synaptic strength, where non-responders to the treatment would fall short (Wolf et al., 2016); and indeed, this pattern is seen in cortical response to transcranial magnetic stimulation in depressed individuals, with the post-sleep deprivation cortical excitability of non-responders not even reaching the baseline levels of those of treatment responders (Canali et al., 2014).

2.5.4 Sleep Phase Advance

Sleep phase advance (SPA), as it sounds, is a circadian therapy whereby an individual's sleep-wake rhythm is advanced (i.e. having them wake up and go to bed earlier than usual within the 24-hour period), usually for at least several consecutive days. Sleep phase advance

may also be an indirect result of bright light therapy and/or cognitive behavioural therapy for insomnia. Additionally, SPA is often paired with sleep deprivation therapy, as it can help to sustain the antidepressant effect of sleep deprivation past the usual relapse following recovery sleep. Sleep phase delay has not shown the same beneficial effects (Riemann et al., 1999).

Despite the early evidence of sleep phase advance's therapeutic effect (Wehr et al., 1979), there is a relative scarcity of evidence evaluating the efficacy of sleep phase advance as a stand-alone treatment. This may be due to the fact that it is more effective when used in combination with sleep deprivation (Riemann et al., 1999, Souetre et al., 1987), or bright light and sleep deprivation (e.g. Echizenya et al., 2013). Alternatively, it may be due to the fact that advanced sleep schedules may be undesirable to patients and difficult to maintain, given that the prescribed sleep schedule may not be optimal for the patient's work, social, or other regular schedules. In this case, combining sleep phase advance with sleep deprivation and/or bright light may serve to facilitate the shift in sleep schedule, and in the case of bright light, maintain the prescribed sleep schedule.

It is likely that the mechanism of action of sleep phase advancement is by re-aligning circadian rhythms, such that the circadian rhythms of the SCN, sleep-wake cycles, temperature, and other related rhythms once again align with those of other parts of the body (digestion, etc.; Germain and Kupfer, 2008).

2.6 Research Aims and Hypotheses

The primary goal of this thesis is to systematically review the use of chronotherapeutic treatments for unipolar depression, and to evaluate their efficacy in reducing symptoms of the disorder. Given the theoretical framework on which these treatments are based, we predict that chronotherapeutic treatments, especially in combination, will be effective as a treatment for depression, though we also predict that there may not be standardized treatment methodology. This is especially true given that much of the literature regarding chronotherapies in depression uses bipolar patients or mixed patient samples, for whom some chronotherapies may have differential treatment effects (e.g. Deltito et al., 1991).

Based on our findings from the primary systematic review, our secondary goal is also to propose the use of a novel combination of chronotherapeutic treatments for unipolar depression, involving the use of bright light therapy and cognitive behavioural therapy for insomnia (in a telehealth format). This combination treatment has the potential to significantly improve symptoms of depression, while also avoiding some of the negative aspects of other treatments (e.g. side effects, barriers to accessing care).

Overall, this research will help clarify the state of chronotherapeutic treatments in the relevant literature, and highlight critical gaps in our current knowledge and treatment strategies. The proposed novel combination treatment would help to fill these gaps, and provide a valuable alternative for individuals for whom traditional antidepressant options (e.g. psychotherapy, antidepressant medications) are not ideal or are ineffective.

Chapter 3: Cognitive Behavioural Therapy for Insomnia (CBT-I) to treat depression: A systematic review

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3.1 Abstract

Major depressive disorder is one of the most commonly diagnosed psychiatric illnesses, and it has a profound negative impact on an individual's ability to function. Up to 90% of individuals suffering from depression also report sleep and circadian disruptions. If these disruptions are not effectively resolved over the course of treatment, the likelihood of relapse into depression is greatly increased. Cognitive Behavioural Therapy for Insomnia (CBT-I) has shown promise in treating these sleep and circadian disturbances associated with depression, and may be effective as a stand-alone treatment for depression. This may be particularly relevant in cases where antidepressant medications are not ideal (e.g. due to contraindications, cost, or treatment resistance).

A systematic literature review was conducted of trials investigating the use of CBT-I to treat depression in adults. Therapy included in-person CBT-I, as well as telehealth and group CBT-I.

CBT-I presents a promising treatment for depression comorbid with insomnia. In-person therapy has the most supporting evidence for its efficacy, though treatment effects may not be additive with those of antidepressant medications. Insomnia improvement due to CBT-I may mediate the improvement in depressive symptoms. There is less evidence for the use of telehealth, though a stepped-care approach is indicated based on baseline depressive severity. More research on group therapy and telehealth modalities of delivering CBT-I are required before making recommendations.

3.2 Introduction

Major depressive disorder (MDD) has widespread negative effects on an individual's life, involving the presence of pervasive depressed mood or loss of pleasure and enjoyment, as well as distress or impairment in important areas of life including social and occupational functioning (American Psychiatric Association, 2013). It is also one of the most frequently diagnosed psychiatric disorders (Caverzasi et al., 2012), with a lifetime prevalence of approximately 16% (Kessler et al., 2003). First-line treatment of depression often consists of the prescription of an antidepressant medication (ADM). However, drug-resistant depression is of increasing concern (Echizenya et al., 2013). Additionally, many antidepressant medications have questionable clinical efficacy compared to a placebo (e.g. Ashworth et al., 2015, Lam et al., 2016). For example, a study by Fournier et al. found that antidepressant medications had limited therapeutic effect for patients displaying only mild or moderate symptoms of depression (Fournier et al., 2010). Additionally, ADMs usually take several weeks to exert therapeutic effect on mood, which can lead to further disruption in personal, social, and occupational life, as well as increase the risk of suicide (Bernier et al., 2009, Machado-Vieira et al., 2008, Wu and Bunney, 1990). There is currently a dearth of clinically accepted non-pharmacological treatments for depression, especially those which have a rapid mechanism of action and which work for patients of varying symptom severity. If such treatments were developed, it would have a positive impact on public health (Lam et al., 2016, Machado-Vieira et al., 2008).

One possible avenue for future such treatments is by targeting sleep and circadian systems. Sleep and circadian disturbances frequently are reported in individuals suffering from depression (Germain and Kupfer, 2008, Smith et al., 2005, Tsuno et al., 2005), with up to 84-90% of individuals suffering from depression endorsing sleep complaints (Franzen and Buysse, 2008, Tsuno et al., 2005). These sleep complaints predict worse clinical and treatment outcomes, and are associated with increased suicidal ideation and risk (Agargun et al., 1997, Franzen and Buysse, 2008, Germain and Kupfer, 2008, Smith et al., 2005, Tsuno et al., 2005). Sleep-wake disruptions often need be addressed in treatment in order to avoid relapse of depression after successfully treating the disorder (Tsuno et al., 2005). If sleep or fatigue complaints are the only symptoms remaining after successful treatment, the risk of relapse in depression is greatly increased (Alpert, 2006, Franzen and Buysse, 2008, Kennedy et al., 1998). Thus, it makes sense that treatments targeting both sleep complaints and depressive symptoms often lead to larger and more sustained mood improvements than those treatments which target the depression alone (Asnis et al., 1999, Fava et al., 2006, Franzen and Buysse, 2008, Smith et

al., 2005). However, not only do most treatments for depression not target sleep-related symptoms (Franzen and Buysse, 2008), many commonly prescribed antidepressant medications such as selective serotonin reuptake inhibitors (SSRIs) are known to cause or worsen insomnia symptoms. This is a common side-effect, and in addition there is an alteration of normal sleep architecture. This exacerbates the problem of sleep disruption (Franzen and Buysse, 2008, Germain and Kupfer, 2008), though some have suggested that it is the change in sleep architecture that facilitates the effectiveness of the antidepressant response (Vogel et al., 1990).

Overall, it is clear that there is a need for non-pharmacological, sleep-based treatments for depression as an alternative or complement to ADMs in clinical practice. Several such treatments (“chronotherapeutics”) exist and have varying levels of empirical support for their efficacy. One such treatment is Cognitive Behavioural Therapy for Insomnia (CBT-I). CBT-I is a multi-component approach to treating sleep disturbances, and is an applicable treatment for the sleep disturbances associated with depression. It is comprised of several different elements. These include: stimulus control (to overcome conditioning between wake and the bedroom environment); sleep restriction; cognitive therapies (e.g. regarding dysfunctional attitudes and beliefs towards sleep); sleep hygiene; and relaxation training (Taylor and Pruiksma, 2014). It has been shown to be extremely effective in reducing symptoms in sufferers of primary insomnia (Franzen and Buysse, 2008, Smith et al., 2005).

CBT-I is especially relevant for individuals with depression considering the nature of many of the insomnia and sleep-related complaints associated with depression, as well as the behaviours which often exacerbate these problems. While the sleep complaints may begin as an acute problem, preceding, co-occurring, or even contributing to depression, unfortunately many individuals will adopt maladaptive coping strategies (such as trying to “catch sleep”) which leads to the insomnia persisting beyond the depressive disorder (Smith et al., 2005). CBT-I is designed to address these maladaptive coping strategies and behaviours, with therapeutic targets such as conditioned arousal and disrupted homeostatic sleep drive (Smith et al., 2005).

The focus of the current review is to highlight and critically review previous research on Cognitive Behavioural Therapy for Insomnia, delivered both remotely and by a trained therapist in individual and group settings, as a treatment for unipolar, non-seasonal depression.

3.3 Literature Search Methods

A systematic review was conducted using PubMed and PsycINFO. A meta-analytic approach was considered, but was rejected due to lack of power after completion of a prospective power analysis (Appendix 1). All English-language literature published prior to November 8, 2017 was considered for inclusion. Initial search terms included *cognitive behavioural therapy*, *cognitive behavioral therapy*, *CBT-I*, *insomnia*, *depress** and *depression*, cross-referenced as appropriate. Relevant references were also checked and included at this point, as applicable. 1327 results were returned. After duplicates were eliminated, there remained a list of 405 references. Following a title and abstract screen, 374 were eliminated, leaving 31 for a full-text screen. After reading these articles, a total of 18 studies met inclusion criteria, and were included in this review. Articles were considered for inclusion if they met the following criteria: 1) primary research article 2) main participant sample was depressed (major depressive disorder [MDD] diagnosis not required) 3) depression outcomes were explored 4) Cognitive Behavioural Therapy for Insomnia was employed and 5) five or more human adult subjects were included. Additionally, if multiple articles met these criteria but reported outcomes on the same patient population (e.g. Shimodera et al., 2014, Watanabe et al., 2011), the most relevant citation was selected, and the other was not included.

Many of the included studies investigated sleep-related outcomes (both subjective and objective), depression-related outcomes, and other outcomes (e.g. quality of life). For the purposes of this review, only depression-related outcomes are presented. Outcome variables include Beck Depression Inventory (BDI), BDI-II, the Centre for Epidemiological Studies-Depression (CES-D), the Edinburgh Postnatal Depression Scale (EPDS), the Hospital Anxiety and Depression Scale (HADS), the Hamilton Rating Scale for Depression-17 (HAM-D-17; HRSD₁₇) and -12 (HDRS₁₂), as well as the modified GRID version (GRID-HAM-D), the Montgomery-Åsberg Depression Rating Scale Self-Rating (MADRS-S), the Patient Health Questionnaire 9 (PHQ-9), the Quick Inventory of Depressive Symptoms Self-Report (QIDS-SR), and the Depression Portion of the Structured Clinical Interview for the DSM (SCID).

3.4 Critical Review of the Literature

3.4.1 Individual, In-person CBT-I

Nine of our identified studies (440 total participants, 6 randomized controlled trials [RCTs], 3 within-subjects designs) investigated the impact of individual, in-person CBT-I as a

treatment for depression (Table 2). These studies were published between 2007 and 2017, and include patients with comorbid insomnia and depression of varying degrees, as well as some patients with other comorbidities (e.g, obstructive sleep apnea). Mean CBT-I dosage was 4.9 sessions, or 233.9 total therapy minutes (calculated from known therapy minutes from 7 studies). Average therapy duration in weeks was 8.

Three of the included 9 studies included both antidepressant medication (ADM) treatment as well as CBT-I. In the first study, by Manber et al. in 2008, all patients were prescribed open-label escitalopram (5-10-20mg) over 12 weeks. Simultaneously, patients received either CBT-I or a credible control treatment. While the rate of remission was higher in the CBT-I group (62% compared to 33%), this effect was non-significant (Manber et al., 2008). However, it is possible that improvement hit a “ceiling” due to the presence of the antidepressant medication. This is supported by the results of the study by Carney et al. (2017), which compared CBT-I to ADMs (10 mg escitalopram) directly. This study showed no significant between-group differences on the HAM-D-17 (HRDS₁₇) measure, and only a very small effect size between CBT-I + ADM and CBT-I + placebo groups ($d = 0.02$). Similarly, the between-group effect sizes for CBT-I + ADM versus ADM + sleep hygiene, and CBT-I + placebo and ADM + SH were also small ($d = 0.32$). Within-group effect sizes from baseline to post-treatment were similar for the groups, ranging from $d = 1.36$ (CBT-I + placebo) to $d = 2.13$ (ADM + sleep hygiene; Carney et al., 2017).

Similar to the Manber et al. 2008 study, a study by Manber et al. in 2016 found no significant differences in HDRS12 scores or time to remission between their CBT-I + ADM (escitalopram, sertraline and desvenlafaxine in a prescribed sequence) and ADM + control groups. However, approximately one-sixth more patients in the CBT-I group achieved remission than in the control group (43.8% versus 36.0%; Manber et al., 2016). Overall, it seems that when comparing antidepressants to CBT-I for the treatment of depression, while CBT-I may be effective, the combination of CBT-I and antidepressants is likely not additive.

Interestingly, in the CBT-I group in this study, the improvement in insomnia in the first 6 weeks of treatment was a mediator for eventual remission in depression (Manber et al., 2016). This mediation by insomnia was also found by Ashworth et al. in their 2015 randomized-controlled trial. In this study, which compared self-help CBT-I to in-person CBT-I, there was a significant main effect of treatment group in favour of the in-person treatment ($p < 0.001$), with an effect size of $d = 1.65$ at 3-month follow-up. At the follow-up, 94% of the in-person group improved by at least 7 points on the BDI-II, compared to 39% of the self-help group, and this

difference was shown to be mediated by change in insomnia severity. At follow-up, 61% of the in-person therapy group were in remission for both their depression and insomnia, compared to only 6% of the self-help group (NNT = 1.8; Ashworth et al., 2015). Further supporting this mediation are the results of a 2015 trial in which patients with refractory depression who had undergone CBT-I were then split into two groups for data analysis, comparing those whose sleep had improved (64% of relevant subsample) to those whose sleep had continued to decline (36% of relevant subsample). Of those in the former group, 44% had clinically relevant improvement in their depression, and 50% were no longer depressed, compared to none in the latter group (for clinically relevant reduction, odds ratio = 1.381, $p = 0.025$; Rusch et al., 2015).

Of the remaining 4 studies included in this section, results are mixed, with three showing improvement due to CBT-I and one showing no significant difference between CBT-I and sleep hygiene treatments. This last study was a randomized-controlled trial, which included patients from Veterans Affairs who had diagnoses of MDD and insomnia. This study used an abbreviated CBT-I protocol (two short in-person sessions, and two short phone calls, in addition to a workbook), and found that while both groups had a significant decline in scores ($p < 0.001$), there was no significant time by group interaction at either post-treatment or follow-up, with or without sleep items, indicating that the sleep hygiene treatment was as effective as the CBT-I (Pigeon et al., 2017). Possibly, this combination included the “worst of both” in-person and telehealth modalities, though this is speculative, and further research should investigate this question.

In contrast, two-within subjects studies and one randomized controlled trial (RCT) show that CBT-I treatment ranging from 4 to 6 weekly sessions can significantly improve depressive symptoms, in patients both allowed and not allowed concurrent psychotropic medications. These effects were found in patients with mild depression, where a within-subjects decrease in BDI scores was significant at 3-month follow-up ($p = 0.027$, $d = 1.18$), and 87.5% of patients had depression levels which were in the “normal” range at post-treatment and follow-up. However, it should be noted that this study included only 8 patients (Taylor et al., 2007). Improvement in depression was also seen in women with post-partum depression, who had significant improvement in EPDS ($p \leq 0.01$, $d = 1.13$) and QIDS-SR ($p \leq 0.001$, $d = 1.61$) scores without sleep items following treatment, with 67% having EPDS scores in the “normal” range (Swanson et al., 2013); and in patients with partially remitted mild to moderate refractory depression, where treatment as usual plus CBT-I was significantly better than treatment as usual at both post-treatment ($p = 0.005$) and four-week follow-up ($p = 0.008$; Watanabe et al., 2011).

3.4.2 Telehealth CBT-I

One limitation of traditional CBT-I is the need for a trained professional to administer the therapy. This may present barriers for patients in terms of time, as patients often need to travel long distances to the closest urban centre, and in terms of money, as therapy and travel can be costly, and there is a striking paucity of people trained to administer CBT-I. One treatment option that can avoid these issues is telehealth, where the therapy is delivered remotely without the need for one-on-one contact with a therapist. There has been some evidence that CBT-I can be effective in a telehealth setting. In this review, we found 9 studies (including two discussed in the previous section) which incorporate components of telehealth CBT-I and investigate its use in treating depression (Table 3). These studies are recent (2003 to 2017), including two follow-up studies, and include a total of 1,923 patients with both insomnia and varying degrees of depression. The outcomes of these telehealth programs are mixed; in four of the studies, and one follow-up study, CBT-I significantly improved depression, in one and its follow-up, CBT-I was as effective as an alternative treatment for depression, and in two, depression was not significantly improved.

The largest RCT of the group, completed by Christensen et al. (2016) compared an online self-help CBT-I program to a placebo health-based online program. It comprised eight sequential modules over six weeks, and depression was significantly reduced in the CBT-I group compared to control at both 6-weeks and 6-months follow-ups ($p < 0.0001$, $d = 0.69$ and 0.48 between groups respectively). The within-groups effect sizes were also much larger for the CBT-I group both at 6-weeks ($d = 1.34$ versus 0.41) and at 6-months ($d = 1.17$ versus 0.59 ; Christensen et al., 2016). A follow-up study of outcomes at 12 and 18 months found similar results, with CBT-I more effective than control at both 12 ($p = 0.001$, $d = 0.43$) and 18 ($p < 0.001$, $d = 0.63$) months (Batterham et al., 2017). Similarly, another large trial recruited individuals with varying degrees of depressive severity, and categorized into groups for analysis based on this depression score (falling into “low,” “mild,” or “high” depressive categories). After completing a 6-week written CBT-I intervention (based on established treatment manuals, and including aspects such as stimulus control, sleep hygiene, sleep restriction, and cognitive restructuring (Lancee et al., 2012)), all three groups improved from baseline to the follow-up at 4-weeks (low: $p < 0.01$, $d = 0.33$; mild: $p < 0.001$, $d = 0.88$; and high: $p < 0.001$, $d = 1.03$) and follow-up at 18-weeks (low: $p < 0.01$, $d = 0.38$; mild: $p < 0.001$, $d = 1.36$; and high: $p < 0.001$, $d = 1.24$; Lancee et al., 2013). Two smaller within-subjects studies also found improvements. In

the first, mean depressive scores were reduced ($p < 0.001$) after 6 online CBT-I sessions and phone calls with an eTherapy coordinator, and 68% of participants who initially scored in the depressed or anxious range had scores in the recovery range by the end of treatment (Luik et al., 2017). The second study found similar results; in those depressed patients whose sleep improved, 57% were not depressed at follow-up, and 13% had improved by at least a third (of their depression score) at follow-up. Of those patients whose sleep did not improve, none had improved their depressive outcomes by a third or more ($p < 0.0001$; Morawetz, 2003).

As previously mentioned, one study (and its follow-up study) found that CBT-I was as effective in treating depression as an alternative depression treatment. This RCT compared guided internet-based CBT-I to CBT for depression, in individuals with comorbid insomnia and MDD. While there was no significant interaction between time and group for depressive symptoms, both groups showed similar and significant improvement from pre- to post-treatment ($p \leq 0.002$, CBT-I: $d = 0.74$, CBT-D: $d = 0.66$), to 6-month follow-up ($p \leq 0.002$, CBT-I: $d = 1.30$, CBT-D: $d = 1.14$), and to twelve-month follow-up ($p \leq 0.002$, CBT-I: $d = 1.12$, CBT-D: $d = 0.94$). Thus, this online CBT-I was as effective as a similar online CBT for depression program (Blom et al., 2015). These results were upheld at a three-year follow-up, where there was no difference in the rate of MDD or in depression scores between groups ($p = 0.45$, $d = 0.33$; Blom et al., 2017).

Two studies in this group did not support the positive effects of CBT-I in treating depression. It is worth noting that these studies, and the RCT by Blom and colleagues (2015, 2017) all included patients with major depressive disorder, while the studies discussed previously included individuals with varying depressive severity. These two studies were also discussed in the section on “in-person” CBT-I; the first by Ashworth et al. (2015), who found that in-person CBT-I was significantly more effective than self-help CBT-I ($p < 0.001$), with 39% of the self-help group improving by at least 7 BDI-II points and 17% reaching remission (Ashworth et al., 2015), and the second by Pigeon et al. (2017), who found that a combination of brief in-person CBT-I and brief telephone-based CBT-I was not significantly more effective than sleep hygiene (Pigeon et al., 2017).

3.4.3 Group CBT-I

Another treatment option which may reduce the cost barrier is group therapy, which has also shown some promise. Our review includes two studies of group therapy which show

conflicting results (Table 4). The first, which includes 301 participants, stratified individuals into two groups (“high depression” and “low depression”), based on their baseline depressive severity. Following the therapy, there was a significant reduction in depressive symptoms for the whole group ($p < 0.0001$) and for the “high depression” subgroup ($p < 0.0001$, $d = 1.45$). There was also a reduction in suicidal ideation ($p < 0.0001$, $d = 1.83$; Manber et al., 2011). However, the other study of group therapy ($n = 64$) comparing CBT-I to relaxation therapy found that both groups improved over time ($p < 0.001$), with no significant interaction between group and time ($p = 0.597$). These results were similar even after parsing out depression severity; there was no significant difference between groups for MDD ($p = 0.597$), or for subthreshold depression ($p = 0.066$; Norell-Clarke et al., 2015).

3.5 Possible Mechanisms of Action

Cognitive behavioural therapy for insomnia is comprised of several complimentary psychological and behavioural therapies: sleep restriction, stimulus-control therapy, relaxation training, sleep hygiene instruction, and cognitive therapy (Morin, 2006). It is highly likely that the sleep restriction, and restriction associated with stimulus-control therapy, are responsible for a large part of the antidepressant effect of CBT-I, given the previous evidence of its antidepressant effect (Wu and Bunney, 1990).

The two-process model of depression is involved with an individual’s endogenous homeostat, or the build-up of sleepiness through wakefulness throughout the day (known as ‘process S,’) and circadian rhythms (known as ‘process C’). Since the 1980s, various REM sleep abnormalities have been noted in individuals with depression, including lower REM latency, more frequent REM sleep, and an atypical pattern of REM sleep throughout the sleep cycle (Vogel et al., 1980). This may lead to reduced SWS and slow wave amplitude (Germain and Kupfer, 2008). It has been hypothesized that this abnormal sleep pattern is attributable to a deficient process S. Thus, the antidepressant mechanism of sleep restriction, and thus of CBT-I, may come from enhancing this process and increasing sleepiness drive (Germain and Kupfer, 2008, Wu and Bunney, 1990).

Another proposed mechanism of action of CBT-I comes from the ‘phase-shift’ (or ‘phase-advance’) model of depression. This theory posits that depression is at least partially a result of shifted circadian rhythms (‘process C’), such that the circadian rhythm of the central pacemaker (the suprachiasmatic nucleus) and related REM sleep, melatonin, cortisol and

temperature rhythms are shifted relative to an individual's sleep-wake rhythm and other bodily circadian rhythms. In this case, CBT-I would work to re-entrain the body's circadian rhythms and to phase advance or stabilize the depressed patient. Alternatively, phase advancing the individual could reduce awakenings from a 'sensitive period' in the circadian cycle, at which time an individual becomes depressed if they are not awake. However, evidence for this hypothesis is limited (Germain and Kupfer, 2008, Wu and Bunney, 1990).

It is also possible that the other aspects of CBT-I, namely relaxation therapy, sleep hygiene, and cognitive therapy are also contributing to the antidepressant effects of the treatment. Relaxation therapy has been used in the past as a stand-alone treatment for depression, and has been shown to decrease depression ratings (Jorm et al., 2008). While the cognitive therapy component and sleep hygiene are not used independently to target depression, both could have an impact on depressive symptoms, through targeting worry and anxiety (Morin, 2006, Sochos and Kotonou, 2017), increasing physical activity (Strohle, 2009, Morin, 2006), and improving diet (Morin, 2006, Lai et al., 2014).

3.6 Discussion and Conclusions

Overall, CBT-I presents a promising treatment for unipolar depression comorbid with insomnia, and especially in-person versions of the therapy. The literature reviewed here has indicated that the effect of in-person CBT-I can have treatment effects of roughly the same magnitude as antidepressant medications (Carney et al., 2017), with fewer side effects and contraindications. However, the combination of CBT-I and antidepressants together may or may not be additive, as there may be a "ceiling" effect in these treatment outcomes (Manber et al., 2016, Manber et al., 2008). Given the limited number of trials (three) investigating the use of antidepressants and CBT-I concurrently, further research is required before drawing firm conclusions.

In-person CBT-I as a stand-alone treatment for depression comorbid with insomnia has also shown promising results, with many of the studies reviewed in this section demonstrating its clinical efficacy (RCT: (Ashworth et al., 2015, Carney et al., 2017, Watanabe et al., 2011), within-subjects: (Rusch et al., 2015, Swanson et al., 2013, Taylor et al., 2007)). RCTs not indicating its effectiveness include Manber et al., 2008 and Manber et al., 2016. Additionally, the improvement in depression seems to be mediated by an improvement in insomnia symptoms, in patients who receive in-person CBT-I (Ashworth et al., 2015, Manber et al., 2016,

Rusch et al., 2015). Future studies should be designed to clarify the nature of this relationship, which may also improve our understanding of the mechanism of action of CBT-I treatment effects on depressive symptomology.

The evidence regarding the use of telehealth (online, phone and mail-based treatment) is less clear. The studies reviewed using telehealth treatment options were divided. Many of the studies, which included a variety of baseline depressive severity, showed improvement in depressive symptoms (RCT: (Batterham et al., 2017, Christensen et al., 2016), within subjects or sub-groups: (Lancee et al., 2013, Luik et al., 2017, Morawetz, 2003)), or no difference between online CBT-I and CBT for depression (RCT: (Blom et al., 2015, Blom et al., 2017)). However, Ashworth et al. (2015, RCT) showed that in-person therapy was significantly more effective than self-help CBT-I, and Pigeon et al. (2017, RCT) demonstrated that a combination of brief in-person and telephone sessions was not more effective than sleep hygiene. It is possible that the in-person CBT-I may appear more effective due to differing patient “investment;” patients who are the most motivated to improve may be more likely to participate in treatments with an in-person treatment component. Alternatively, these two studies (Ashworth et al., 2015, Pigeon et al., 2017) included exclusively patients with MDD. Thus, it is possible that a stepped-care approach may be appropriate, i.e. patients with lower depressive severity may benefit from telehealth CBT-I, reducing barriers to access care, with a progression to in-person therapy as appropriate. Additionally, in-person therapy may be more appropriate for individuals who require motivation to “stick to” the CBT-I recommendations (e.g. implementing a sleep restriction routine), or who require modifications to the CBT-I program, for example due to comorbid health conditions.

Finally, only two studies included group CBT-I, and the results were mixed. The first, which was a within-subjects design, stratifying the sample based on baseline depression severity, found a significant therapeutic effect of the group CBT-I for the whole sample, and for those patients with a high initial depressive score (Manber et al., 2011). Contrastingly, Norell-Clarke et al. (2015) found no difference between randomized group CBT-I versus relaxation training, as both groups improved over time. Relaxation training is often a component of CBT-I, so this may not have been an inactive control (Norell-Clarke et al., 2015). Additionally, relaxation training has been shown to lower self-reported depression ratings in previous research (Jorm et al., 2008). However, as in-person CBT-I is often shown to have greater effect than active control groups (e.g. quasi-desensitization control, (Manber et al., 2008)), and relaxation treatment is often less effective than cognitive behavioural interventions for depression (Jorm et

al., 2008), it is likely that these results are indicative of only a moderate treatment effect of group CBT-I in this context. Given the lack of other research on group CBT-I (i.e., more than one RCT), future studies are required to determine its efficacy in treating depression.

Overall, the literature is unclear on the ideal number or frequency of CBT-I sessions required in order to optimize treatment outcomes. It is also unclear whether telehealth or group CBT-I is as effective as in-person CBT-I for treating depression, though there is suggestion that a stepped-care approach may be worthwhile. Finally, there is minimal literature investigating a combination of CBT-I and other chronotherapies, such as sleep deprivation or bright light therapy, as an aggregate treatment for depression. Given the interplay between sleep and circadian systems in depression, these avenues are worth exploring in future study.

Table 2 Characteristics of 9 studies which investigate the use of in-person Cognitive Behavioural Therapy for Insomnia (CBT-I) to treat depression

First Author, Year	Subjects	n	Study Design	Treatment Groups/ Reference	Depression Outcome Measure	Medication Use	CBT-I Dosage	Outcomes	Effect size	Retention (RT) and Adverse Events (AE)
Ashworth, 2015	Comorbid MDD and insomnia, treatment resistant	41	RCT	Self-help CBT-I, in-person CBT-I groups	BDI-II	6 weeks, stable ADMs; No sleep medication	4 X 50 min sessions over 8 weeks	CBT-I more effective than self-help CBT-I, p < 0.001	d = 1.24 (post-tx) d = 1.65 (FU)	RT at post-tx: In-person CBT-I = 21/21 Self-help = 20/21 RT at follow-up: CBT-I = 18/21 Self-help: 18/20
								94% of in-person group improved at least 7 points (39% of self-help group) at 3 month FU; p < 0.001		
								78% of in-person group were in clinical remission (17% of self-help group) at FU; p < 0.001		
								61% of in-person group was in remission (6% of self-help group) for insomnia and depression at FU; p < 0.001	NNT = 1.8	
								Difference in depression between groups at FU mediated by change in insomnia severity		
Carney, 2017	MDD, insomnia	107	RCT	ADM ^a +CBT-I, CBT-I + placebo, ADM+SH groups	HAM-D-17	No hypnotics, ADMs part of trial	4 X 60 min sessions, biweekly	All groups improved over time, p < 0.05		RT at post-tx: ADM+CBT-I = 26/36 CBT-I + placebo = 21/36 ADM+SH = 20/35 RT at FU: ADM+CBT-I = 9/11 CBT-I + placebo = 9/10
								No differences between groups on HAMD-17 after treatment, p = 1.0		
								Very small between group effect size between CBT-I + ADM and CBT-I + placebo	d = 0.02	
								Small between group effect size between CBT-I + ADM and ADM + SH (HAM-D-17)	d = 0.32	

								Small between group effect size between CBT-I + placebo and ADM + SH (HAMD-17)	d = 0.32	ADM+SH = 6/8 AE: reason for withdrawal from ADM+SH group
Manber, 2008	MDD, insomnia	30	RCT	ADM ^b + CBT-I or ADM + Quasi-Desensitization Control	HRSD ₁₇ , Depression portion of SCID	No hypnotics, ADMs part of trial	7 sessions, 5 weekly then 2 biweekly	Rate of remission numerically higher in CBT-I group (62%) than control (33%), p = 0.13		RT at post-tx: CBT-I = 10/15 Control = 12/15
								Change in score over time for CBT-I group (12) larger than control (9.7)	d = 0.27	
								Change in score (no sleep item) over time for CBT-I group (9.7) larger than control (7.9)	d = 0.24	
Manber, 2016	MDD, insomnia	150	RCT	ADM ^c + CBT-I or ADM + Quasi-Desensitization Control	HDRS12, Depression portion of SCID	ADMs part of trial	7 X 45 min sessions over 16 weeks (4 weekly, 2 biweekly, final after 4 weeks)	43.8% in CBT-I group attained remission (36.0% in control)	NNT = 15	RT at post-tx: CBT-I = 58/75 Control = 51/75
								No significant difference in time to remission by group (p = 0.33)		
								No significant difference in HDRS scores between groups after treatment (p = 0.48)		
								Insomnia improvement in first 6 weeks mediated depression remission in CBT-I group (p = 0.0004)		
Pigeon, 2017	Veterans Affairs primary care patients with MDD and insomnia	27	RCT	Brief CBT-I or SH	PHQ-9	No hypnotic medications	4 weekly sessions (40 min in-person, 20 min call, 30 min in-person, 20 min call) + workbook	No difference between groups post-treatment (p = 0.863)	g = -0.04	RT at post-tx: SH = 13/14 CBT-I = 11/13
								No difference between groups at FU (p = 0.725)	g = .27	
								Both groups had a significant decline in PHQ-9 scores (p < 0.001)		

Rusch, 2015	Subset of study, depressed + insomnia military personnel, some with OSA	28	Within Subjects	Within subjects, sleep improved versus sleep declined	QIDS-SR	50% of sample used relevant medications (hypnotics, ADMs)	4-8 biweekly sessions of CBT-I, or CBT-I + APAP, or "sleep education + APAP	64% had improved sleep quality	OR = 1.381	Subset of depressed patients = 28/44 in total sample
								36% had sleep quality decline		
								Of those with improved sleep, 44% had clinically relevant improvement (5pts) in depression following treatment (p = 0.02)		
								Of those with improved sleep, 50% were no longer depressed (QIDS-SR < 11) following treatment		
								In those with sleep decline, 0% had clinically significant improvement in depressive symptoms		
Clinically relevant difference in symptom reduction between groups (p = 0.025)										
Swanson, 2013	Women with post-partum depression, insomnia	12	Within Subjects	Within Subjects	EPDS, QIDS-SR	Stable medication use allowed	5 X 45-60 min weekly sessions	Significant improvement in EPDS (without sleep item) pre- to post-treatment (p ≤ 0.01)	d = 1.13	RT: 11 out of 12 completed all CBT-I sessions 11/12 completed 4/5 CBT-I sessions
								Significant improvement in QIDS-SR (without sleep item) pre- to post-treatment (p ≤ 0.001)	d = 1.61	
								Significant improvement in EPDS (with sleep item) pre- to post-treatment (p = 0.001)	d = 1.38	
								Significant improvement in QIDS-SR (with sleep item) pre- to post-treatment (p = 0.001)	d = 1.91	
								67% of treatment completers had sub-threshold EPDS scores following treatment		

Taylor, 2007	Insomnia, “mild” depression with MDE in past 6 months	8	Within Subjects	Within Subjects	BDI	No sleep active or psychotropic medications	6 X 30-60 min weekly sessions	87.5% of participants were no longer depressed following treatment; maintained at 3-month follow-up	8/8 participants completed all aspects of the study
								Decrease in BDI scores after treatment was at trend level (p = 0.053)	d = 1.08
								Decrease in BDI scores continued and was significant at the 3-month FU (p = 0.027)	d = 1.18
Watanabe, 2011	Partially remitted, refractory, mild or moderate depression; insomnia	37	RCT	TAU or TAU + brief behavioural treatment for insomnia	GRID- HAMD	At baseline, all patients were taking antidepressant medications	4 X 60 min weekly sessions	Combined (including CBT-I) therapy was significantly better than TAU at 4 weeks (p = 0.004) and at 8 weeks (p = 0.013)	RT: CBT-I = 18/20 completed TAU = 16/17 completed All participants completed study measures
								Combined (including CBT-I) therapy was significantly better than TAU at 4 weeks (p = 0.005) and at 8 weeks (p = 0.008) when the sleep item is omitted	
								55% of participants in the combined treatment had remission in depression after 4 weeks (5.9% in TAU group)	Risk ratio = 9.35, NNT = 2
								50% of participants in the combined treatment had remission in depression after 8 weeks (5.9% in TAU group)	Risk ratio = 8.5, NNT = 2

Table 3 Characteristics of 9 studies which investigate the use of telehealth Cognitive Behavioural Therapy for Insomnia (CBT-I) to treat depression

First Author, Year	Subjects	n	Study Design	Treatment Groups/ Reference	Depression Outcome Measure	Medication Use	CBT-I Dosage	Outcomes	Effect size	Retention (RT) and Adverse Events (AE)
Ashworth, 2015	Comorbid MDD and insomnia, treatment resistant	41	RCT	Self-help CBT-I, in-person CBT-I groups	BDI-II	6 weeks, stable ADMs; No sleep medication	4 X 15 min sessions over 8 weeks to complete measures (no discussion of material), self-directed written materials relevant to session	CBT-I more effective than self-help CBT-I, $p < 0.001$ 94% of in-person group improved at least 7 points (39% of self-help group) at 3 month FU; $p < 0.001$ 78% of in-person group were in clinical remission (17% of self-help group) at FU; $p < 0.001$ 61% of in-person group was in remission (6% of self-help group) for insomnia and depression at FU; $p < 0.001$ Difference in depression between groups at FU mediated by change in insomnia severity	$d = 1.24$ (post-tx) $d = 1.65$ (3-month FU) NNT = 1.8	RT at post-tx: In-person CBT-I = 21/21 Self-help = 20/21 RT at follow-up: CBT-I = 18/21 Self-help: 18/20
Batterham, 2017 (follow-up of Christensen, 2016)	Insomnia and depressive symptoms, but not MDD	1149	RCT	Online self-help CBT-I (SHUTi) versus placebo online program	PHQ-9	Stable medications permitted, 1% of each group taking mood- or sleep-related medications	8 sequential modules over 6 weeks	SHUTi was more effective at treating depression than control at 12 month ($p = 0.001$) and 18 month ($p < 0.001$) FU 3% of SHUTi group vs 13% of control had PHQ-9 score ≥ 10 at 12 month FU	12 month FU: $d = 0.43$ 18 month FU: $d = 0.63$	RT: SHUTi: 28% 12 month, 17% 18 month FU Control: 40% 12 month, 21% 18 month FU

								2% of SHUTi group vs 19% of control had PHQ-9 score ≥ 10 at 18 month FU		
Blom, 2015	MDD, insomnia	43	RCT	Guided internet based CBT-I versus CBT-D	MADRS-S	Stable ADMs permitted, sleep medications not restricted	8 modules over 9 weeks, guided internet-delivered CBT-I; online therapist email access for questions (within scope of manual)	No difference between groups for depression severity (p = 0.93)		RT: CBT-I: 82% module completion CBT-D: 93% module completion CBT-I: out of 22, 17-21 at post-tx, 15-20 at 6 month, 14-18 at 12 month FU CBT-D: out of 21, 16-21 at post-tx, 15-17 at 6 month, 15-18 at 12 month FU AE: 4 per group at post-tx
								Both groups improved from pre-to post-treatment (p ≤ 0.001)	CBT-I: d = 0.74 CBT-D: d = 0.66	
								Both groups improved from pre-treatment to 6-month FU	CBT-I: d = 1.30 CBT-D: d = 1.14	
								Both groups improved from pretreatment to twelve-month FU	CBT-I: d = 1.12 CBT-D: d = 0.94	
								No difference between groups in depression remission at post-treatment (37% CBT-I, 21% CBT-D)		
Blom, 2017 (follow-up of Blom, 2015)	MDD, insomnia	43	RCT	Guided internet based CBT-I versus CBT-D	MADRS-S	Stable ADMs permitted, sleep medications not restricted	8 modules over 9 weeks, guided internet-delivered CBT-I; online therapist email access for questions (within scope of manual)	No difference in rate of MDD at 3 year FU between groups		RT: 86% response rate at 3 year FU CBT-D: out of 21, 14-17 at 3 year FU CBT-I: out of 22, 16-20 at 3 year FU
								Both groups improved, no significant difference between groups at 3 year FU in MADRS-S scores (p = 0.45)	d = 0.33 (3 year)	
Christensen, 2016	Insomnia and depressive	1149	RCT	Online self-help CBT-I (SHUTi)	PHQ-9	Stable medications permitted, 1%	8 sequential modules over 6 weeks	Depression was significantly reduced in the CBT-I group compared to control at 6-weeks		RT: SHUTi: 43% 6 week, 39% 6

	symptoms, but not MDD			versus placebo online program		of each group taking mood- or sleep-related medications		and 6-months ($p < 0.0001$)	d = 0.48 (6-months)	month Control: 58% 6 week, 49% 6 month No AE reported
								At 6 weeks and 6 months, SHUTi mean score not in depressed range, control mean score in mild depressive range		
Lancee, 2013	Insomnia, depression of varying severity (including low)	479	Within Sub-groups	Stratified by baseline depression severity, within-group comparison	CES-D	Not exclusionary	6 weeks, 9000 words	The low depression group improved significantly from baseline to 4-week ($p < 0.01$) and to 18-week ($p < 0.01$) FU	4-week: d = 0.33 18-week: d = 0.38	RT: Low depress.: 4 week: 72.7% questionnaires (q), 55.6% sleep diary (sd) 18 week: 57.1% q, 47% sd Mild depress.: 4 week: 74.7% q, 54.4% sd 18 week: 54.4% q, 41.8% sd High depress.: 4 week: 71.7% q, 47.5% sd 18 week: 43.4% q, 36.4% sd AE: 3 worsened
								The mild depression group improved significantly from baseline to 4-week ($p < 0.001$) and to 18-week ($p < 0.001$) FU	4-week: d = 0.88 18-week: d = 1.36	
								The high depression group improved significantly from baseline to 4-week ($p < 0.001$) and to 18-week ($p < 0.001$) FU	4-week: d = 1.03 18-week: d = 1.24	
Luik, 2017	Poor sleep, self-reported depression or anxiety	98	Within Subjects	Within subjects	PHQ-9	Not exclusionary	6 X 20 min digital interactive sessions, administered by "virtual therapist"+ 6 X 20-30 min calls with eTherapy coordinator	Depression improved from pre-to post-treatment ($p < 0.001$)		RT: 73% finished treatment 15% completed 4-6 sessions 11% withdrew before session 4
								68% of participants who originally scored above depression threshold were in recovery by the end of treatment		

Morawetz, 2003	Insomnia, 2/3 of participants depressed	86	Within subjects	Within subjects	BDI	22% taking table ADMs, 60% taking hypnotics	Self-help book and audio cassettes, over 6 weeks	57% of sleep improved patients who were initially depressed were not at FU		Sample taken from private practice
								13% of sleep improved patients who were initially depressed were at least 40% less depressed at FU		
								Of patients whose sleep didn't improve, none had improved their depression scores by a third (p < 0.0001)		
Pigeon, 2017	Veterans Affairs primary care patients; MDD and insomnia	27	RCT	Brief CBT-I or SH	PHQ-9	No hypnotic medications	4 weekly sessions (40 min in-person, 20 min call, 30 min in-person, 20 min call) + workbook	No difference between groups post-treatment (p = 0.863)	g = -0.04	RT at post-tx: SH = 13/14 CBT-I = 11/13
								No difference between groups at FU (p = 0.725)	g = .27	
								Both groups had a significant decline in scores (p < 0.001)		

Table 4 Characteristics of 2 studies which investigate the use of group Cognitive Behavioural Therapy for Insomnia (CBT-I) to treat depression

First Author, Year	Subjects	n	Study Design	Treatment Groups/Reference	Depression Outcome Measure	Medication Use	CBT-I Dosage	Outcomes	Effect size	Retention (RT) and Adverse Events (AE)
Manber, 2011	Insomnia, depression (high or low, cut-off = 14 on BDI); insomnia	301	Within sub-groups	Stratified by baseline depression severity, within-group comparisons	BDI (no sleep item)	Not exclusionary	7 X 90 min group sessions, 5 weekly then 2 biweekly	Depression significantly reduced overall ($p < 0.0001$) Significant reduction in depression for high depression subgroup ($p < 0.0001$)	 $d = 1.45$	The sample was taken from clinical records; only included patients who completed treatment
Norell-Clarke, 2015	Insomnia and depression	64	RCT	Group CBT-I versus relaxation training (active control)	BDI-II	Stable medication use allowed	4 X 120 min group sessions, biweekly	Both groups improved over time ($p < 0.001$) No significant difference between groups ($p = .104$) These results were similar when parsing out MDD and subthreshold depression No significant difference between groups for MDD, $p = 0.597$ No significant difference between groups for subthreshold depression, $p = 0.066$	 $d = 0.31$ (post-tx), 0.34 (6 month FU) $d = 0.11, 0.14$ $d = 0.58, 0.86$	RT: CBT-I: 30/32 completed, 34/32 at 6 month FU Relaxation: 23/29 completed, 10/29 at FU

Chapter 4: Sleep and Major Depressive Disorder: A Review of Non-Pharmacological Chronotherapeutic Treatments for Unipolar Depression

This chapter is modified from:

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4.1 Abstract

Depression is a significant public health issue, made worse by the absence of response to antidepressant medications by many patients. Given the high degree of overlap between sleep and circadian complaints and depression, chronotherapies are a promising avenue for novel, effective, and fast-acting treatments for depression.

A critical literature review was conducted of bright light therapy as a treatment for unipolar depression. Additionally, a separate critical literature review was also conducted of several promising, non-pharmacological, *combination* chronotherapeutic treatments, including bright light therapy, sleep deprivation/wake therapy, and sleep phase advance.

Results of bright light therapy as a treatment for depression are encouraging, especially when used as an adjunct to antidepressant medications. It may also be desirable in special populations, such as geriatric and perinatal patients, given the potential contraindications to antidepressant medications. Overall, results from combination chronotherapies are encouraging, though none has strong empirical support. Combining chronotherapies is an avenue of treatment which should be further explored.

4.2 Introduction

With a 16% lifetime prevalence, depression is a significant public health issue involving widespread distress and impairment in daily functioning (Kessler et al., 2003). Antidepressant medications (ADMs) are often the first-line treatments that physicians and psychiatrists turn to in order to combat this disorder. Unfortunately, many ADMs may not help much more than a placebo (Khan and Brown, 2015), especially for patients with drug-resistant depression, and ADMs may take several weeks to develop full therapeutic benefits (Quitkin et al., 1984, Posternak and Zimmerman, 2005, Quitkin et al., 2005). Additionally, ADMs may be contraindicated or undesirable in many patients, such as geriatric patients who often have a variety of prescriptions, and perinatal women. There is a clear need for additional evidence-based non-pharmacological treatments for depression which are not only effective, but fast-acting. Given the high frequency with which sleep and circadian disturbances are reported in depressed individuals and that increased sleep complaints are predictive of more negative treatment outcomes (Tsuno et al., 2005, Franzen and Buysse, 2008, Germain and Kupfer, 2008), it follows that treatments targeting these systems could improve depression itself.

Bright light therapy (BLT) has been used for seasonal affective (depressive) disorder (SAD) for decades (Rosenthal et al., 1984), and has more recently been shown to be a promising treatment for non-seasonal major depressive disorder (Benedetti et al., 2007, Germain and Kupfer, 2008, Lam et al., 2016). BLT has been robustly demonstrated to be a safe, effective and well-tolerated treatment, both alone and in conjunction with ADMs for SAD (Westrin and Lam, 2007). Until recently, however, there has not been robust evidence for its efficacy in treating non-seasonal depression (Al-Karawi and Jubair, 2016, Tuunainen et al., 2004, Martensson et al., 2015, Terman and Terman, 2005, Golden et al., 2005, Even et al., 2008). This paper reviews the use of BLT to treat non-seasonal, unipolar major depressive disorder. Additionally, this paper will separately review research on *combination* non-pharmacological, sleep-focused treatments for unipolar, non-seasonal depression, including sleep deprivation therapy (also known as wake therapy), bright light therapy, and sleep phase advance. While Cognitive Behavioural Therapy for Insomnia (CBT-I) is designed to impact sleep and circadian factors, and can influence symptoms of depression, it will not be discussed here. For a recent review of the effects of CBT-I on depressive symptoms, see Cunningham and Shapiro, 2018.

4.3 Literature Search Methods

4.3.1 Bright Light Therapy Review

PubMed and PsycINFO were systematically searched, with English-language articles published prior to December 11, 2017 eligible for inclusion. Initial search terms included “*bright light*,” *depression*, and *depress**. Following identification of initial articles, relevant references from these initial articles were also included as appropriate. 1850 initial results were returned, which included citation duplications between databases. Additionally, references from reviews on the topic were also included if relevant (Pail et al., 2011, Tuunainen et al., 2004, Martensson et al., 2015, Khalifeh, 2017, Terman and Terman, 2005, Kripke, 1998, Golden et al., 2005, Even et al., 2008, Al-Karawi and Jubair, 2016). Following deletion of duplicate citations, 706 articles remained. 659 were eliminated by title and abstract information, leaving 47 for full-text screen. Of these 47 articles, 25 were selected for inclusion in this review. Articles were considered for inclusion if they met the following criteria: 1) primary research article in a peer-reviewed journal 2) main participant sample was depressed 3) main participant sample did not include individuals with a diagnosis of bipolar depression (given the potential differential response to light therapy, e.g. Deltito et al., 1991) or SAD, unless results were given separately by diagnosis 4) main participant sample was not comprised of individuals with a primary health concern (e.g. cancer, Parkinson’s, anorexia) 5) depression outcomes were reported 6) BLT was used 7) there were five or more adult (human) subjects.

Depression outcome variables of studies included in this review include the Beck Depression Inventory (BDI), the Geriatric Depression Scale (GDS), the Hamilton Depression Rating Scale (HAM-D) and modifications thereof, the Montgomery-Asberg Depression Rating Scale (MADRS), the Quick Inventory of Depressive Symptoms – Self Report 16 (QIDS-SR), the Structured Interview Guide for the Hamilton Depression Rating Scale – Seasonal Affective Disorders (SIGH-SAD), and the Zung Self-Rating Depression Scale. Lux-hours were calculated by multiplying the brightness of the supplied bright light (lux) by the number of hours the patients received the treatment (hours); for example, a 10,000 lux treatment for 30 min would constitute 5,000 lux-hours.

4.3.2 Combined Chronotherapeutics Review

PubMed and PsycINFO were systematically searched, with English-language articles published prior to January 1, 2018 eligible for inclusion. Initial search terms included “*bright*

light", *depression*, *depress**, *"wake therapy"*, *"phase advance"*, and *"sleep deprivation"*, in various permutations. Following identification of initial articles, relevant references from these initial articles were also included as appropriate. 7609 initial results were returned, which included citation duplications between databases. Additionally, references from reviews on the topic (Dallaspazia et al., 2015, Khalifeh, 2017) were also included if relevant. After duplicates were removed, 2689 citations remained. 2654 were discarded by title and abstract, leaving 35 for full-text screen. Of these 35 articles, nine were selected for inclusion in this review. Articles were considered for inclusion if they met the following criteria: 1) primary research article in a peer-reviewed journal 2) main participant sample was depressed 3) main participant sample did not include individuals with a diagnosis of bipolar depression or SAD, unless results were given separately by diagnosis 4) main participant sample was not comprised of individuals with a primary health concern (e.g. cancer, Parkinson's, anorexia) 5) depression outcomes were reported 6) a combination of any of the following was used: BLT, sleep phase advance, wake therapy/sleep deprivation 7) there were five or more adult (human) subjects.

Depression outcome variables of studies included in this review also include the BDI, the GDS, the HAM-D and modifications thereof, the MADRS, the SIGH-SAD, and the Zung Self-Rating Depression Scale, as well as the Columbia Suicide Severity Scale (CSSRS). Lux-hours were calculated in the same fashion as above.

4.4 Bright Light Therapy (BLT)

18 of the studies (600 total patients, 15 with randomized controlled trial (RCT) elements, four with within-subjects elements) included in this review studied the effects of BLT on unipolar non-seasonal depression in the general population. Studies range from 1985-2016. Average daily lux-hours was 7278 (calculated using lowest indicated lux hours per included study). Mean treatment duration was 18 consecutive days.

4.4.1 Bright Light Therapy as an Adjunct to Antidepressant Medications

Of these 17 studies, nine investigated the use of BLT to augment treatment response to ADMs (Table 5). The results of these studies were encouraging, though not entirely consistent. The original trial by Levitt and colleagues (1991) used a within-subjects design to test the use of 5,000-10,000 morning/afternoon lux-hours, continuing ADMs as per previous care. In this pilot test, seven of the 10 enrolled patients had an improvement of mood following BLT (Levitt et al.,

1991). Following this initial proof of concept, eight between-subjects studies of the treatment were completed, of which seven indicated effectiveness. First, Schuchardt et al. (1993) compared bright light (5,000 lux-hours, daytime) to dim light in 40 patients receiving fluoxetine, and saw a larger antidepressant response following bright light. Similarly, a second study of 29 patients found that three weeks of bright light (10,000 morning lux-hours) led to equivalent depressive symptomology decrease as imipramine treatment (by 9.1 and 6 HAM-D points, respectively), and that more patients in the BLT group responded (50% decrease in HAM-D score to a score <8) to treatment (66.7%) than did patients in either the imipramine group (33.3%) or the combination bright light and imipramine group (36.4%; Prasko et al., 2002). Sertraline was also found to be effective in combination with BLT, with a significantly larger treatment response (50% decrease in HAM-D score to score <8) found in patients receiving bright light (10,000 morning lux-hours) than of those receiving dim light, over the course of bright light treatment (Martiny, 2004, Martiny et al., 2006). Similarly, venlafaxine hydrochloride combined with BLT (7,000 morning lux-hours) led to improved depressive symptoms over the drug alone (Guzel Ozdemir et al., 2015). A small trial of 15 patients found that there was no additional treatment benefit with the addition of fluoxetine to bright light (5,000 morning lux-hours; Agargun et al., 2013). Finally, in the largest RCT to date, of 122 patients, both bright light alone (5,000 morning lux-hours) and bright light in combination with fluoxetine were shown to have a significantly larger effect than placebo treatments, while fluoxetine alone was not shown to be significantly different than placebo. Additionally, both response and remission rates were highest in the combination group (Lam et al., 2016).

In contrast, some studies have not supported the efficacy of adding bright light as an adjuvant to ADMs. First, as noted above, Prasko and colleagues found that bright light alone produced a greater benefit than bright light combined with imipramine, though this is the only study to have found such a result (Prasko et al., 2002). Similarly, Muller et al. (1997) found no group differences between trimipramine monotherapy, and trimipramine plus bright light (10,000 evening lux-hours). However, this is one of the few studies which used evening bright light, which may be less effective in this treatment application.

Overall, the evidence suggests that morning BLT is an effective adjunct treatment to ADMs. Typical lux-hours range from 5,000 to 10,000, with therapy commenced not long after typical wake time. BLT was shown to be effective in as little as one week, though three to five weeks was more typical, and the longest range in a single trial was eight weeks.

4.4.2 Bright Light Therapy as a Stand-alone Treatment Option

Nine studies, spanning 1985 to 2013, investigated the use of BLT as a stand-alone treatment for depression (Table 6). Additionally, three of the studies discussed previously investigated at least one stand-alone BLT group; one (Lam et al., 2016) which found the treatment to be beneficial, though not as beneficial as a combination of bright light and fluoxetine, another (Agargun et al., 2013) which found no additional benefit of an ADM in addition to BLT, and the third (Prasko et al., 2002) which found that stand-alone bright light was actually more effective than a combination of bright light and ADM (imipramine).

The literature regarding the use of BLT as a stand-alone treatment for depression is mixed. Two studies have shown that bright light treatment is more effective than a dim red light control. The first (1,500-5,000 morning/evening lux-hours) was a preliminary within-subjects study, which demonstrated significant improvement following bright but not dim light after five days (Kripke et al., 1985). The second, by Putilov and colleagues, was also within-subjects, and showed a significant improvement in depression scores after treatment with bright light after seven days (Putilov et al., 2005). Additionally, a third within-subjects study comparing pre- and post-treatment results on a self-report questionnaire also suggested that BLT was effective in ameliorating depressive symptoms (Naus et al., 2013). Finally, another study demonstrated that bright light (10,000 morning lux hours) was more effective than a low-density ion generator control after five weeks (Goel et al., 2005). However, this study also showed that bright light was as effective as a high-density ion generator, and the previous study by Putilov et al. demonstrated that an active exercise control was more effective at reducing symptoms of depression than the bright light treatment (Putilov et al., 2005).

Three studies investigating bright light, however, demonstrated it to be no more effective than dim light in reducing symptoms of depression. First, Deltito and colleagues used 5,000 morning lux-hours for seven consecutive days and found no difference between groups (Deltito et al., 1991). Volz et al. also used 5,000 morning lux-hours for seven consecutive days and found no main effect of light group (Volz et al., 1991). Finally, Lande et al. used 15,000 lux-hours for five consecutive days, and found what they reported as a trend ($p < 0.05$) for bright light scores (but not dim light) to be reduced half-way through the treatment protocol (Lande et al., 2011).

It is worth noting that almost all of these studies of bright light as a stand-alone treatment used a much shorter treatment duration than those of studies measuring bright light as an adjunct treatment to ADMs. Additionally, here, the treatment and study protocols vary, as do the comparison conditions (exercise, negative ions, dim light, within-subjects, etc.). Thus, before reaching conclusions regarding the efficacy of bright light alone as a treatment for depression, it is recommended that further research be conducted using a standard methodology and treatment protocol (e.g. 10,000 lux for 30-60mins within 15 mins of wake), and further that the treatment protocol be lengthened to several weeks to resemble those trials using BLT as an adjunct.

Finally, the remaining two studies of bright light as a stand-alone treatment option investigated the timing of the treatment itself as the question of interest. Here, too, results were mixed. The first study found a numerically larger reduction in symptoms of depression after seven days of morning light than evening light (Yamada et al., 1995), whereas the second found no difference in treatment outcomes after administering three days of morning bright light, evening bright light (both at 15,000 lux-hours), or only dim light (Gordijn et al., 1998). However, it is possible that the number of consecutive days was too short to definitively determine treatment effects. This, too, should be investigated further.

4.4.3 Bright Light Therapy in Geriatric Patients

Depression in geriatric patients is unfortunately common, with an estimated prevalence of 1.0% to 36.4% in community samples worldwide (Tsai et al., 2004), contributing to negative health outcomes and premature death (Sumaya et al., 2001). ADMs may be effective, however given the number of other medications that many geriatric patients are prescribed, as well as potential changes in pharmacokinetics over the life span, in many cases the prescription of ADMs is not ideal (Sumaya et al., 2001, Loving et al., 2005a). Thus, the use of bright light to treat depressive symptoms may be especially appealing in this population.

Three studies have investigated the use of BLT in geriatric patients (Table 7), two (comprising 10 and 89 patients respectively) comparing bright and dim light (Sumaya et al., 2001, Lieveise et al., 2011), and one (n = 60 patients) comparing bright light to a no treatment control (Tsai et al., 2004). The results of all three studies were consistent, with BLT lowering depression scores significantly more than the control condition after at least five days of treatment in the range of 4,167-7,500 lux-hours in the morning. Additionally, significantly more patients were treatment responders or went into remission following BLT in two of the three

studies (Sumaya et al., 2001, Lieverse et al., 2011). Overall, it seems that BLT may be an effective treatment for depression in the geriatric population.

4.4.4 Bright Light Therapy in Perinatal Women

Perinatal depression (onset during pregnancy or first 12 months postpartum) has an estimated prevalence of 10-20% in pregnant and postpartum women. For many perinatal women, the treatment of depression with ADMs is not ideal, due to contraindications, side effects, and the possibility of impacting the child through pregnancy and breastfeeding (Crowley and Youngstedt, 2012). Thus, treatment with BLT may present an appealing treatment option for these women. However, to date, very little research has been done on this population. Four studies were found studying the use of BLT in women in the perinatal period; one investigating postpartum and three investigating antepartum depression (Table 8). For women with postpartum depression, BLT was not shown to be more effective than dim red light (Corral et al., 2007). However, given that only one study, with fifteen patients, has investigated the use of BLT in postpartum depression, further research is required before making clinical recommendations.

Of the three studies investigating the use of bright light in antepartum depression, one (Oren et al., 2002) was within subjects, and two (Wirz-Justice et al., 2011, Epperson et al., 2004) compared the use of bright and dim light. While the within-subjects study showed a clinical benefit within three weeks following the use of bright light (Oren et al., 2002), the other two reports (Wirz-Justice et al., 2011, Epperson et al., 2004) were somewhat conflicting regarding required treatment duration (5 vs. 10 weeks to see treatment benefits). In all three of these studies, treatment timing was 7000 to 10,000 lux-hours timed within 10 minutes of wake time. BLT in antepartum depression is promising, but requires further validation as to ideal treatment length.

4.5 Sleep Deprivation Therapy

Sleep deprivation therapy (SDT) for unipolar depression entails depriving a depressed individual of some or all of their normal night's sleep for a specified number of nights. The amount and type of sleep that is restricted depends on the type of SDT that the patient is undergoing. It has been well-established that roughly 50% of depressed individuals who undergo total SDT (missing a full night's sleep for at least one night) respond with positive

mood improvements the following day (Wu and Bunney, 1990). In a foundational 1990 review, Wu & Bunney (Wu and Bunney, 1990) reviewed 61 studies of SDT involving over 1700 participants, and found that 59% of depressed individuals experienced profound decreases in depressive symptoms the day following SDT. SDT has also been shown to be effective for patients of varying depressive severity (Voderholzer, 2003), and predictors of positive response to SDT are similar to those that predict response to ADMs (Benedetti et al., 2007, Voderholzer, 2003). Studies have also shown efficacy when partially sleep restricting patients, but the evidence for how much or at what time a patient should sleep is inconclusive for both total and partial sleep restriction (Dallaspazia et al., 2015).

One limitation of SDT alone is the high rate of relapse following recovery sleep (the first night's sleep, or nap, following the SDT). Following recovery sleep, only 5-12% of patients show a sustained positive mood response (Benedetti et al., 2007, Wu and Bunney, 1990), though this can be improved by co-administration of ADMs (Benedetti et al., 2007), and may be dependent on nap timing (Wiegand et al., 1993). Some patients have also been shown to develop tolerance to treatment effects after multiple days of sleep restriction (Benedetti et al., 2007). Of patients who do not develop tolerance, many may be unwilling to continue the protocol repeatedly due to resulting increased fatigue and sleepiness the next day. Given that no single sleep deprivation treatment has shown sustainability as a stand-alone treatment strategy, sleep deprivation is likely a more useful strategy when used in combination with other chronotherapeutics, as discussed in following sections.

4.6 Sleep Phase Advance

Sleep phase advance is a circadian treatment for depression. With this treatment the circadian rhythm is shifted, such that patients wake up and go to bed earlier in a 24-hour period than they previously would. Advancing the sleep phase is often a by-product of BLT, but may be addressed in CBT-I, and has usually been used in combination with total SDT in order to prolong its antidepressant effects. Sleep phase advance as a stand-alone treatment has minimal evidence as to its efficacy for patients with unipolar depression. Most classic studies touting the treatment include at least some bipolar patients as study participants (Wehr et al., 1979, Souetre et al., 1987, Riemann et al., 1999).

4.7 Combination Chronotherapeutic Treatments

4.7.1 Combination Chronotherapeutic Treatments in the General Population

These chronotherapeutic treatments have also been used together in combination, and in combination with ADMs, in order to reduce treatment limitations and enhance therapeutic effects. Only a handful of studies on this topic has been completed, most within-subjects and with small sample sizes (the largest of which had 35 patients; Table 9).

The earliest of these studies, investigating one-hour night-time awakenings in dim vs. red light, found mixed results. While depression scores were significantly lower after bright as compared to dim light, there were no significant changes from baseline measurements (Kripke et al., 1983). Another of the studies found mixed, but encouraging results; while total sleep deprivation and bright light did lower depression ($p = 0.002$), and led to a 25% recovery rate, it did not lower depression as much as a combination of total sleep deprivation and exercise (75% recovery; $p < 0.05$; Putilov et al., 2005). The other five studies on the topic found positive results. The first, by Vollmann & Berger (1993), had a 53% response rate to total sleep deprivation, as measured in Hamilton Depression Rating Scale scores. None of these responders had a relapse in depressive symptoms following a week of subsequent sleep phase advance. Interestingly, the 47% of patients who did not respond to total sleep deprivation had improvement in their depressive symptoms following sleep phase advance therapy (Vollmann and Berger, 1993).

Loving et al. (2002) tried a similar technique, using BLT following partial sleep deprivation. This study found that the group treated with bright white light improved significantly more than the group treated with dim red light, with the exception of one outlier patient who responded to red light. All of these patients were treated with ADMs (Loving et al., 2002). In a study of patients not taking ADMs, a combination of chronotherapeutics including partial sleep deprivation, dawn simulation and BLT were found to improve symptoms of depression and maintain these improvements at 4-week follow-up (Moscovici and Kotler, 2009). Finally, sleep phase advance and BLT following total sleep deprivation were shown to significantly decrease depressive scores and result in a high rate of remission in patients currently medicated following their treatment-as-usual. In addition, these patients endorsed suicidal ideation at the beginning of the trial protocol, and there was a significant decrease in this suicidal ideation by the end of the treatment period (Sahlem et al., 2014). Total sleep deprivation followed by BLT was also shown to reduce symptoms of depression in unmedicated

patients, leading to a 55% rate of remission three months after the end of the treatment (Dallassezia and van Jaarsveld, 2016).

These results indicate that combining these chronotherapies may result in a more efficacious and prolonged antidepressant effect than using any one of these treatments uniquely. However, until randomized controlled research is conducted comparing the efficacy of these combined treatments to current standard-of-care treatments, the true benefit of these combined treatments is unclear.

4.7.2 Combination Chronotherapeutic Treatments in Geriatric Patients

Only two studies, by the same researchers, investigated the use of combined chronotherapeutic treatments in geriatric patients (Table 10). Neither provided support for the use of these treatments in this population. Both used late partial wake therapy followed by bright light (white (Loving et al., 2005a) or green (Loving et al., 2005b)) or a dim red light control. In both cases, there was no significant difference in depression scores following treatment, and there was no immediate improvement in depressive symptomology immediately following wake therapy (Loving et al., 2005a, Loving et al., 2005b). When compared to results of BLT as a stand-alone treatment in this population, these results would seem to imply that BLT alone is more effective than BLT in combination with other chronotherapeutics. However, given that these two studies compared wake therapy and BLT to wake therapy and dim red light, the unique effects of the chronotherapeutics compared to a non-chronotherapeutic control cannot be determined. The only conclusion that can be drawn is that BLT as an adjunct to wake therapy does not lead to significantly better therapeutic outcomes than wake therapy and a control light condition. Until more research is conducted, recommendations regarding combined chronotherapies in this population cannot be made at this time.

4.8 Conclusions

Given the relatively limited effect of ADMs (Khan and Brown, 2015), the long time to response (Quitkin et al., 1984, Quitkin et al., 2005, Posternak and Zimmerman, 2005), and concerns in some populations regarding ADM use, alternative treatments for depression must be sought. Chronotherapies have several advantages that target these areas, often including a large and rapid response and fewer contraindications.

However, chronotherapies also have limitations which should be considered. Sleep deprivation, either on its own or as a part of other therapies (e.g. CBT-I, combination therapies) should be undertaken with caution, as it can induce daytime sleepiness and attentional impairment. Additionally, it is of limited use as a stand-alone chronotherapy given the high rates of rapid relapse following recovery sleep. BLT can have side effects, though these are usually transient and mild, and usually thought to be less severe than many ADMs (Germain and Kupfer, 2008). Finally, it is important to consider whether a given chronotherapy or combination thereof is appropriate for a patient given their ability to carry out the therapy at home, given the time- and effort-consuming nature of many of the treatments discussed.

This paper has extensively reviewed BLT and combination chronotherapies, which show varying degrees of promise in treating unipolar depression. BLT is a promising adjunct treatment to ADMs, and may also be effective as a stand-alone treatment. Combination chronotherapies also show promise, but a clearer notion of which combination and dosage is ideal for which patient is needed. Additionally, further research elucidating the role of ADMs in addition to these combined chronotherapies is recommended. Further research (notably RCTs) on optimal combination treatment protocols is severely needed, especially before the suggestion of any clinical standard of care.

Table 5 Characteristics of studies investigating the use of bright light therapy as an adjunct treatment to antidepressant medication. Effect sizes included where possible.

First Author, Year	n	Diagnosis	Medications	Lux	Treatment Duration (wks: duration (h): start time)	Lux-hours	Control Condition (s)	Primary Depression Outcome	Outcomes	Effect Size
(Levitt et al., 1991)	10	Treatment resistant major depression (RDC)	Antidepressants as per treatment as usual	5,000	2: 1: 06:00 to 07:00 if no response, additional 1h in afternoon	5,000-10,000	Within subjects	Hamilton Depression Rating Scale	7/10 improved following treatment	
(Schuchardt et al., 1993)	40	Treatment resistant major depression (DSM-III-R)	Fluoxetine (20mg); other antidepressants for some patients	2,500	4: 2: 08:00 to 20:00	5,000	300 lux dim light	Unknown	Larger antidepressant response with bright light	
(Muller et al., 1997)	28	Major depressive disorder (DSM-III-R)	Trimipramine (200mg) from day 3	5,000	4: 2: 17:30 to 19:30	10,000	Five weeks of trimipramine vs. 5 weeks trimipramine + bright light for weeks 2-5	Hamilton Depression Rating Scale	No difference between groups in depression at week 2	
									Trimipramine monotherapy significantly more effective at week 5 ($p < 0.05$)	
(Prasko et al., 2002)	29	Recurrent major depressive disorder (DSM-III-R)	Imipramine (150mg)	5000	3: 2: 06:00 to 08:00	10,000	Bright light + imipramine (A); bright light + placebo drug (B); dim red light (500 lux) + imipramine (C)	Hamilton Depression Rating Scale, Beck Depression Inventory (BDI), Montgomery Asberg Depression Rating Scale	Greater improvement after B than after A ($p < 0.05-0.01$)	
									Only the BDI showed a significant benefit of B over C ($p < 0.05$)	
									Response rate after B 66.7%, C 33.3%, A 36.4%.	

(Martiny, 2004)	102	Major depressive disorder (DSM-IV)	Sertraline (50mg), increments/ reductions allowed, mianserin and oxazepam for some patients	10,000	5: 1: before 10:00	10,000	Dim red light (50 lux), 30 mins in morning	Hamilton Depression Rating Scale (SIGH-SAD [*])	Bright light more effective from week 1 (p < 0.05)	
									Bright light superiority maintained until week 5 (p < 0.01)	
									Response in 40.7% of dim light patients and 66.7% of bright light patients by week 5	
									Remission in 14.8% of patients in dim light and 41.7% in bright light by week 5	
(Martiny et al., 2006) Follow-up from (Martiny, 2004)	102	Major depressive disorder (DSM-IV)	Sertraline (50mg), increments/ reductions allowed, mianserin and oxazepam for some patients	10,000	5: 1: before 10:00 Medication continued after wk 5 for 4 wks	10,000	Dim red light (100 lux), 30mins in morning	Hamilton Depression Rating Scale (SIGH-SAD [*])	No significant difference between groups on response or remission at weeks 6 and 9	
(Agargun et al., 2013)	15	Major depressive episodes (DSM-IV)	Fluoxetine (20 mg)	10,000	1: 0.5: 07:00 to 08:00	5,000	Bright light or bright light + Fluoxetine	Hamilton Depression Rating Scale, Beck Depression Inventory	No significant difference between groups after treatment	
(Guzel Ozdemir et al., 2015)	50	Major depressive disorder (DSM-IV-TR)	75-150 mg venlafaxine hydrochloride	7,000	1: 1: 07:00	7,000	Bright light + antidepressant vs. antidepressant	Hamilton Depression Rating Scale	Depression was lower in the combination group after 2-4 wks (p < 0.05)	

									76% combination vs. 44% drug group had "mild" depression after 4 wks (p<0.05)	
(Lam et al., 2016)	122	Major depressive disorder (DSM-IV-TR)	Fluoxetine hydrochloride (20mg/day) or placebo	10,000	8: 0.5: 07:00 to 08:00	5,000	Bright light + placebo drug (A); fluoxetine + inactivated ion generator (B); bright light + fluoxetine (C); inactive ion generator + placebo (D)	Montgomery Asberg Depression Rating Scale	A and C more effective than D (p=0.006; p<0.001)	B vs D: d = 0.24 A vs D: d = 0.80 C vs D: d = 1.11
									No significant difference between B and D	
									C more effective than B (p=0.02)	
									Response at wk 8: 75.9% of C, 50.0% of A, 29% of B and 33.3% of D	
									Remission at wk 8: 58.6% of C, 43.8% of A, 19.4% of B and 30.0% of D	

Table 6 Characteristics of studies investigating the use of bright light therapy as a stand-alone treatment for depression.

First Author, Year	n	Diagnosis	Medications	Lux	Treatment Duration (wks: duration (h): start time)	Lux-hours	Control Condition (s)	Primary Depression Outcome	Outcomes	Effect Size
(Kripke et al., 1985)	8	Major depressive disorders	Unknown	1,500 - 2,500	5 days: 1-2: 05:00 to 06:00 and 21:00 to 22:00 for some	1,500-5,000	Dim red light, < 50 lux (counterbalanced, within subjects)	Hamilton Depression Ratings, Beck Depression Inventory (modified - no sleep items)	Significant improvement on Day 5 after bright light ($p=0.05, 0.02$) but not red light; direct comparison between groups not significant	
(Deltito et al., 1991)	11 out of 17	Major depressive disorder or disorders not otherwise specified; dysthymia (DSM-III-R)	Psychotropic and hypnotic medication free	2,500	1: 2: within 1 h of wake	5,000	400 lux dim light	Hamilton Depression Rating Scale (SIGH-SAD*)	No effect of light intensity on depressive outcome	
(Volz et al., 1991)	42	Major depressive disorder (RDC, ICD-9)	Psychotropic free, except 1,000mg chloralhydrate (max) for some patients	2,500	1: 2: 07:00 to 09:00	5,000	Dim red light (50 lux)	Hamilton Depression Rating Scale	No difference in depression improvement between groups	
(Yamada et al., 1995)	17/27	Major depressive disorder (DSM-	Psychotropic free	2,500	1: 2: 06:00 to 08:00	5,000	Morning or evening (18:00 to 20:00h), bright or	Hamilton Depression Rating Scale	Bright light led to greater improvement than dim light	

		III-R)					dim (500 lux, yellow) light		Numerically larger reduction after morning than evening light	
(Gordijn et al., 1998)	8	Major depressive disorder and dysthymia (DSM-III-R)	Psychotropic free	2,500	3 days per condition: 6: 3 h in morning and 3 h in evening	15,000	Dim light (<10 lux); bright (morning) then dim (evening) light; dim (morning) then bright (evening) light (randomized crossover for latter two conditions)	Hamilton Depression Rating Scale, Beck Depression Inventory	No difference in depression reduction between the three groups	
(Goel et al., 2005)	32	Single episode major depressive disorder (DSM-IV)	2 patients on antidepressants, otherwise psychotropic, recreational drug and alcohol free	10,000	5: 1: wake	10,000	High-density (A) or low-density (B) negative air ions	Hamilton Depression Rating Scale (SIGH-SAD*)	Largest change after bright light (53.7%) and A (51.1%) vs. B (16.4%); $p < 0.05$	h=1.58
									Remission: 50% (bright light), 50% (A), 0% (B)	
(Putilov et al., 2005)	18/138	Major or minor depressive disorder or dysthymia (DSM-IV)	Psychotropic free	2,500	1: 2: 14:00	5,000	1 h physical exercise	Hamilton Depression Rating Scale	Exercise was more effective than bright light ($p < 0.001$)	
									Bright light significantly improved depression ($p < 0.001$)	
									Recovery: 0% after bright light, 33.3% after exercise	
(Lande et al., 2011)	20	Mild-Severe Depression (score ≥ 50) on Zung Self-Rating Depression Scale	Treatment as usual (individual and group therapy, leisure skills, medication management)	10,000	5 days: 1.5: unknown	15,000	50 lux dim light	Zung Self-Rating Depression Scale	Scores reduced halfway through bright light treatment ($p < 0.05$)	
									Depression was reduced for both groups over time ($p < 0.02$)	

(Naus et al., 2013)	48	Major depressive disorder (DSM-IV-TR)	No medications (bright light treatment before care as usual)	5,000-10,000	Up to 3: 0.5: 08:00 to 10:00	2,500-5,000	Within subjects, within subgroups (melancholic vs. atypical)	Quick Inventory of Depressive Symptoms – Self Report 16	Bright light significantly improved depression at the end of treatment ($p<0.05$) and 4 week follow-up ($p<0.001$)	d = -0.53, -0.73
									Depression subtype didn't predict symptom improvement	

Table 7 Characteristics of studies investigating the use of bright light therapy as a treatment for depression in geriatric adults.

First Author, Year	n	Diagnosis	Medications	Lux	Treatment Duration (wks: duration (h): start time)	Lux-hours	Control Condition(s)	Primary Depression Outcome	Outcomes	Effect Size
(Sumaya et al., 2001)	10	Moderate to severe depression (Geriatric Depression Scale)	Antidepressant free	10,000	5 days: 0.5: 09:30 to 12:00	5,000	300 lux placebo and no treatment controls [within subjects, randomized, crossover]	Geriatric Depression Scale	Depression score significantly lower after bright light ($p < 0.01$), but not the other conditions 50% of patients were no longer in the depressed range of scores after bright light	
(Lieverse et al., 2011)	89	Major depressive disorder (DSM-IV)	33-38% used antidepressants	7,500	3: 1: early morning	7,500	Dim red light, approximately 50 lux	Hamilton Depression Rating Scale (SIGH-SAD*)	Bright light led to more improvement in depression than control after 3 weeks (43% versus 36%, $p = 0.03$)	$d=0.5$
									Bright light led to more improvement in depression than control at 3-week post treatment follow-up (54% versus 33%, $p = 0.001$)	$d=0.93$
									58% of bright light group responded at follow-up, vs. 34% of placebo ($p = 0.05$)	$NNT^{\Delta} = 5$
(Tsai et al., 2004)	60	Major depressive disorder or disorders (DSM-IV)	Psychotropic free	5,000	5 days: 0.83: 09:00 to 12:00	4,167	No treatment	Geriatric Depression Scale	Significantly lower depression after bright light but not control ($p=0.000$)	

Table 8 Characteristics of studies investigating the use of bright light therapy as a treatment for depression in pregnant and post-partum women.

First Author, Year	n	Diagnosis/State	Medications	Lux	Treatment Duration (wks: duration (h): start time)	Lux-hours	Control Condition (s)	Primary Depression Outcome	Outcomes	Effect Size
(Oren et al., 2002)	16	Major depressive disorder (DSM-IV); pregnant women	Psychotropic free	10,000	3: 1: within 10 min of wake	10,000	Within subjects (Control - TX - Control)	Hamilton Depression Rating Scale (SIGH-SAD [*])	Patients improved by 49% after 3 weeks (p<0.001); 8 of 16 improved by >50% Patients who completed 5 weeks of treatment improved by 59% (p<0.05); 4 of 7 participants increased by >50% and achieved complete remission	
(Epperson et al., 2004)	10	Major depressive disorder (DSM-IV); pregnant women	Psychotropic free	7,000	5: 1: within 10 min of wake; option of extending to 10: 1.25	7,000-8,750	500 lux light box	Hamilton Depression Rating Scale (SIGH-SAD [*])	No significant difference between groups at 5 weeks Over ten weeks of individual dosing (n=3), significant effect of bright light (p = 0.001)	0.43
(Corral et al., 2007)	15	Major depressive disorder, post-partum onset; post-partum women	Antidepressant free	10,000	6: 0.5: 07:00 to 09:00	5,000	600 lux red light	Hamilton Depression Rating Scale (SIGH-SAD [*])	No significant difference between groups in improvement	
(Wirz-Justice et al., 2011)	27	Major depressive disorder (DSM-IV); pregnant women	Stable, previous antidepressant use allowed	7,000	5: 1: within 10 min of wake	7,000	70 lux dim red light	Hamilton Depression Rating Scale (SIGH-ADS [#])	Significant effect of all factors on improvement in depression (p < 0.05)	

									Significantly greater treatment effect and % improvement in bright light group ($p<0.05$)	Pillai V= 0.403
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Table 9 Characteristics of studies investigating the use of combined chronotherapies to treat depression in the general population.

First Author, Year	n	Diagnosis	Medications	BL Treatment Duration	Lux-hours	Other Therapy 1	Other Therapy 2	Other Therapy 3	Control Condition(s)	Primary Depression Outcomes	Study Outcomes
(Kripke et al., 1983)	12	"Depressed"	Most were "drug free"	1 h per night	1,000 - 2,000	Three consecutive nights: Night 1: woke 1-2 h before normal wake, with BLT	Night 2: woke 1-2 h before normal wake with dim red light	Night 3: woke 2-3 h after bedtime with dim red light	Counterbalanced, within subjects	^Δ Hamilton Depression Rating Scale (HAM-D), Beck Depression Inventory	HAM-D significantly lower after bright than dim light ($p < 0.05$) None of the three had significantly lower ratings from baseline
(Vollmann and Berger, 1993)	17	Major depressive disorder melancholia subtype (DSM-III-R)	Most on antidepressants for >1 month and treatment resistant	n/a	n/a	One night total sleep deprivation (TSD [#])	Phase advance following TSD, starting at 5pm and shifting toward midnight by 1 hour each day, for 7 days	n/a	Within subjects	HAM-D	Nine patients were responders to TSD: none relapsed during phase advance Non-responders to TSD did respond to phase advance

(Loving et al., 2002)	13	Major depressive disorder (DSM-IV), resistant to treatment	Antidepressants	1 week, 0.5 h, 06:00 to 09:00 start	5,000	Late partial wake therapy, woken at 3:00am, at home; first day of bright light started immediately	n/a	n/a	Dim red light (100 lux)	Hamilton Depression Rating Scale (SIGH-SAD-SR*)	Significant difference between groups (outlier patient who improved following dim red light was removed); $p < 0.025$
(Putilov et al., 2005)	35/138	Major or minor depressive disorder or dysthymia (DSM-IV)	Psychotropic free	1: 2: 14:00	5,000	One night total sleep deprivation (TSD)	n/a	n/a	TSD + 1 h physical exercise or (A) 1 h physical exercise under bright light (B) or 1 h physical exercise (C)	HAM-D	TSD + bright light less effective than A ($p=0.013$) and B (trend; $p=0.077$)
											TSD + bright light equally effective as C
(Moscovici and Kotler, 2009)	12	At least 4 main criteria symptoms of major depressive episode (ICD-10)	Antidepressant free for 5 wks	4 days, 1 h per day upon wake	7,500	Partial sleep deprivation, woke at 2:30 am day 1, 3:00am days 2-4	Each day: dawn simulation to wake; green light (525nm) immediately following	Sleep phase advance (7:00pm bedtime), days 2-4	12x single case designs (within subjects)	HAM-D, ^o Montgomery Asberg Depression Rating Scale (MADRS), Zung Self-Rating Depression Scale	All patients improved: HAM-D ($p < 0.001$), MADRS ($p < 0.001$), Zung ($p < 0.001$)
											Improvement was not lost at follow-up

(Sahlem et al., 2014)	10	Unipolar depression; suicidal ideation	Antidepressants	4 days, 0.5 h, 06:00 to 08:00 start	5,000	One night total sleep deprivation (TSD)	Three days of sleep phase advance following TSD (sleep window 6pm-1am; 8pm-3am; 10pm-5am)	n/a	Within subjects	HAM-D	Significant decrease in HAM-D score from baseline
											60% of patients met HAM-D remission criteria at the end of the study
(Dallassepezi and van Jaarsveld, 2016)	27	Major depressive disorder (DSM-IV)	Antidepressant free	5 days after sleep deprivation : 0.5: morning (chronotype based)	5,000	One night total sleep deprivation (TSD)	n/a	n/a	Within subjects	Beck Depression Inventory	Remission: 37% 1 week after treatment, 55% 3 months after treatment
											Depression scores decreased during treatment (p<0.00001)

Table 10 Characteristics of studies investigating the use of combined chronotherapies to treat depression in geriatric patients (59-80 yrs old).

First Author, Year	n	Medications	Brightness (lux)	BLT Duration (wks: duration (h): start time)	Lux-hours	Color/Temperature	Other Therapy	Control Condition (s)	Primary Depression Outcome Measure	Outcomes
(Loving et al., 2005a)	81	Treatment as usual (37% took antidepressants)	8,500	4: 1: morning or mid-day or evening (chronotype based)	8,500	Bright white	Wake therapy (late partial, 4hrs sleep duration) prior to light therapy	Dim red light (<10 lux) + wake therapy	Hamilton Depression Rating Scale (SIGH-SAD-SR*), Geriatric Depression Scale	No significant differences between groups following treatment
										Few participants were able to complete wake therapy as directed
(Loving et al., 2005b)	33	Treatment as usual (39% took antidepressants)	1,200	4: 1: 1 h of wake	1,200	Bright green	Wake therapy (late partial, 4hrs sleep duration) prior to light therapy	10 lux dim red light + wake therapy	Hamilton Depression Rating Scale (SIGH-SAD-SR*), Geriatric Depression Scale	No significant difference between groups
										No significant improvement following wake therapy

Chapter 5: Future Directions – Proposing the Use of a Novel
Combined Chronotherapy to Treat Depression – CIHR Project Grant
Application

5.1 Identify Participants

5.1.1 Participant Information

1. Nominated principal applicant (Colin – Independent Researcher, senior investigator)
2. Nominated co-applicant (Jasmyn – trainee)

5.1.2 Most significant contributions

Jasmyn Cunningham is currently completing her Master's of Medical Science at the University of Toronto, investigating the use of sleep and circadian based treatments for depression (as an alternative to pharmacotherapy). She has published a systematic review on this topic (Cunningham and Shapiro, 2018), and has submitted another for peer review. Ms. Cunningham has also attended and presented data at several national and international conferences, notably the World Sleep Congress (2017), and the Canadian Sleep Society Conference (2017, 2015). Ms. Cunningham has been training at the Ryerson Sleep and Depression Laboratory with Dr. Colleen Carney since September of 2016, performing diagnostic interviews (SCID) and shadowing therapists delivering cognitive behavioural therapy for insomnia as a part of a CIHR-funded clinical trial.

Dr. Colin Shapiro is a professor of psychiatry at the University of Toronto. He has published over 300 peer-reviewed publications, largely in the sleep field, and approximately a dozen books (both academic and for the lay public). He has a long-standing interest in the interplay of sleep, circadian rhythms, and mood. This interest has led to two books; *Defeating Depression* (with Kennedy and Parikh) and *Detecting Depression in Children and Adolescents* with three colleagues. He is particularly keen to pursue this study as it potentially offers a path to a non-pharmacological and easily available treatment of depression, which would be especially useful for underserved areas.

5.1.3 Attachments

Consent to submit information to CIHR.

5.2 Enter Proposal Information

5.2.1 Overview

5.2.1.1 Project Title: Investigating Cognitive Behavioural Therapy for Insomnia (CBT-I) and Bright Light Therapy (BLT) as a novel combination treatment for depression.

5.2.1.2 Lay Title: Investigating the use of sleep-based treatments (bright light and insomnia therapy) for depression

5.2.1.3 Lay Abstract:

There is a 12% lifetime prevalence of major depressive episodes in Canada (Patten et al., 2006). Antidepressant medications are usually the first treatment prescribed to combat these symptoms. However, these don't work for everyone (Fournier et al., 2010), and they often have negative side effects (Cascade et al., 2009). If treatments for depression were developed which avoided these drawbacks, it would significantly improve public health.

Our proposed research study investigates the use of a combination of sleep-based treatments (bright light and insomnia therapy) to treat depression. Bright light treatment involves the use of a bright light box each morning, and helps to correct body rhythms including sleep. Insomnia therapy, referred to as cognitive behavioural therapy for insomnia, uses a variety of strategies to combat poor sleep and the factors which contribute to it. While this insomnia therapy is traditionally completed in a one-on-one format with a trained therapist, recent evidence has shown that the therapy delivered in an online format can also be effective.

Individually, both bright light treatment and insomnia therapy have been shown to help with symptoms of depression (Cunningham et al., 2018; Cunningham et al, unpublished), especially in people who also have sleep difficulties. Additionally, these treatments usually have fewer (if any) negative side effects, and may be less stigmatizing given their presentation as a treatment for sleep, rather than depression. Light boxes are relatively inexpensive, and our insomnia therapy is delivered in an online format. Thus, this combination treatment would also reduce barriers to accessing care, which is especially necessary for individuals in remote or rural areas of the country, and for individuals from low-income households. Overall, if our research shows that a combination of bright light treatment and online insomnia therapy is effective in combatting symptoms of depression, it would provide a much-needed alternative to antidepressant medications which is more accessible, has a lower side effect profile, and is less stigmatized.

5.2.1.4 Institution Paid: University of Toronto

5.2.2 Details

Does your application include a partner AND/OR a knowledge user? No

Certification Requirements: Both Colin Shapiro and Jasmyn Cunningham have completed TCPS 2: CORE certifications for research involving human subjects.

Containment Level: Containment level 1 (CL1)

Environmental Impacts: Minimal foreseeable impact.

Is this a clinical trial? Yes.

Does this application contain a randomized controlled trial? Yes.

In order to carry out the proposed research in this application, is an exemption from Health Canada under Section 56 of the Controlled Drugs and Substances Act required? No.

Does this application propose research involving Indigenous peoples? No.

Does your proposal address the TCPS 2 - Chapter 9 Research Involving the First Nations, Inuit and Métis Peoples of Canada and Indigenous partnering community/organizational ethical guidelines? No.

Are sex (biological) considerations taken into account in this study? No.

Are gender (socio-cultural) considerations taken into account in this proposal? No.

If no, explain why sex and/or gender are not applicable in your research design (limit of 2000 characters): The nature of this research design is a pilot trial, designed to give a preliminary idea of intervention effectiveness, as well as general intervention feasibility. As such, it includes a small group of subjects, and therefore has insufficient statistical power to investigate variables such as sex and gender. Sex will be controlled as a covariate in statistical analysis.

5.2.3 Descriptors

Descriptors: Bright light therapy, depression, combination treatment, telehealth, insomnia, sleep, circadian rhythm

Themes: Clinical Research

Suggested Institutes: Neurosciences, Mental Health and Addiction

Areas of Science: Mental Health and Behavioural Conditions → Mental Health and Addiction
Mental Health and Behavioural Conditions → Psychology and Psychiatry

Methods/Approaches: Experimental Study → Clinical Trial

Experimental Study → Randomized Trial

Intervention, Treatments & Prevention → Cognitive Behavioural Therapy

Study Populations/Experimental Systems: Humans → Humans

Life Stages → Adults

Patients and Caregivers → People with diseases or conditions

5.2.4 Attachments:

5.2.4.1 Research Protocol

5.2.4.1.1 The Need for a Trial

5.2.4.1.1.1 What is the problem to be addressed?

Major depressive disorder is one of the most frequently diagnosed psychiatric disorders, with a 12% lifetime prevalence of major depressive episodes in Canada (Patten et al., 2006). Depression has widespread negative consequences for afflicted individuals, potentially resulting in disruption of personal, work, and family life. There is also a higher risk of mortality associated with depression; depressed individuals are 20-27 times more likely than the general population to commit suicide, with a 2.2% lifetime prevalence of suicide in outpatients with affective disorders. Additionally, severity of depressive symptoms is associated with greater risk of cardiac death, especially following initial hospitalization for myocardial infarction, as well as greater risk of all-cause mortality and of stroke (Lepine and Briley, 2011).

Depression leads not only to burden on afflicted individuals, but also on society. For individuals in the work force, depression is associated with reduced workplace productivity, lower annual salaries and an increase in absenteeism. Depression severity is also associated with unemployment (Lepine and Briley, 2011), with less than 17% of individuals with depression working full time and functioning optimally in the workplace (Conference Board of Canada, 2018). If treatments were improved for depressed individuals in the workforce, the Canadian economy could potentially stand to gain \$32.3 billion dollars per year, not including direct health care savings. Specifically, for individuals who seek treatment, if the proportion who received minimally adequate treatment increased from 53% to 75%, it would potentially result in 700 fewer hospitalizations, and a resulting \$5.7 million dollars in saved health care spending.

Overall, this improvement in minimally adequate treatment would lead to an approximate increase in Canada's GDP of \$2.6 billion (Conference Board of Canada, 2018).

Prescription of antidepressant medications (ADMs) is often the first-line treatment for depression. However, the benefits of ADMs may be minimal for individuals with mild or moderate symptoms of depression (Fournier et al., 2010). In addition, antidepressant medications can take weeks or months to have substantial effects on mood (Machado-Vieira et al., 2008), may be contraindicated in some patients, and often have a negative side effect profile (Cascade et al., 2009). While therapy (e.g. cognitive behavioural) avoids the side effect and contraindication problems of ADMs, it is often difficult to access care, with the choice between long wait times or expensive private care, and requires high patient investment. There is a large unmet need for depression treatment in Canada, especially for low-income individuals, and individuals living in rural areas (Starkes et al., 2005), for whom longer travel times may lead to a reduction in accessing both therapy and medication based depression treatment (Fortney et al., 1999). Additionally, stigma associated with mental health treatments are associated with lowered help-seeking behaviour (Clement et al., 2015), potentially further increasing unmet treatment need and increasing barriers to accessing care.

Sleep and circadian disturbances, often including alterations in sleep architecture, are extremely common in depression (Germain and Kupfer, 2008, Tsuno et al., 2005), with up to 90% of individuals with depression also endorsing sleep complaints (Tsuno et al., 2005). These sleep and circadian disturbances are predictors of who will develop new and recurrent episodes of depression (Franzen and Buysse, 2008). They also predict worse clinical outcomes (Franzen and Buysse, 2008, Germain and Kupfer, 2008), and are associated with an increase in suicidal behaviour (Agargun et al., 1997). Regulation of these sleep disturbances is often necessary in order to minimize relapse in depression (Franzen and Buysse, 2008), and treatments for both insomnia and depression often lead to greater clinical improvement than treatments targeting depressive symptomology alone (Asnis et al., 1999, Fava et al., 2006, Franzen and Buysse, 2008). Not only do most treatments for depression not focus on resolving sleep problems, but many commonly prescribed antidepressant medications, including some selective serotonin reuptake inhibitors, have been reported to cause insomnia and restless legs as possible side effects, in addition to altering aspects of normal sleep architecture (Franzen and Buysse, 2008, Germain and Kupfer, 2008).

Previously, there have been a limited number of randomized controlled trials investigating treatments for depression which also target sleep and circadian symptoms (Smith et al., 2005, Cunningham and Shapiro, 2018, Cunningham et al., unpublished). Often, these trials investigate the co-prescription of hypnotic medications such as zolpidem (Asnis et al., 1999) or eszopiclone (Fava et al., 2006) with other antidepressant medications. However, in many cases, patients' sleep returns to baseline after discontinuing the hypnotic medications (Asnis et al., 1999, Edinger and Wohlgemuth, 1999), and may not help reduce the occurrence of early-morning awakenings, due to a short half-life (Smith et al., 2005). Additionally, the prescription of additional medications may not be advisable in all situations; for example, due to economic or contraindication factors, or due to potentially disruptive side effects (Edinger and Wohlgemuth, 1999). Thus, when considering the limitations inherent to both the use of antidepressant medications and the co-prescription of hypnotic medications, it is clear that there is a need for non-pharmacological treatments for depression which also effectively address the commonly comorbid sleep and circadian disruptions as well.

Bright light therapy (BLT) is a relatively novel treatment for major depressive disorder comorbid with insomnia (Cunningham et al., unpublished, Lam et al., 2016), though it has been used to successfully treat seasonal affective disorder for some time (Westrin and Lam, 2007). Bright light therapy is a safe and well-tolerated treatment, with side effects usually in the mild and transient range (Terman and Terman, 2005). Recent evidence has shown that it is a promising treatment for depression, both as a stand-alone treatment and especially in combination with antidepressant medications (Cunningham et al., unpublished). While a clear mechanism of action for these treatment results is unclear, one possibility is that bright light therapy may correct the circadian rhythm disruptions and altered sleep-wake cycles that are often present in both major depressive disorder and seasonal affective disorder (Levitan, 2007, McClung, 2011, Lewy et al., 2006, Germain and Kupfer, 2008). This may be mediated through interactions with melatonin and serotonin neurotransmitter systems (Levitan, 2007, McClung, 2011). Overall, bright light therapy is a promising non-pharmacological treatment for depression.

Cognitive behavioural therapy for insomnia (CBT-I) is a multi-component approach to treating sleep disturbances which is extremely effective in reducing insomnia symptoms in sufferers of primary insomnia (Morin, 2006, van Straten et al., 2018). It is an especially appropriate treatment strategy for the sleep disturbances associated with depression, given both

the frequency of the occurrence of such sleep disturbances, as well as the factors which precipitate and perpetuate insomnia symptoms. While sleep complaints and insomnia symptoms often start as an acute problem, preceding, co-occurring, or a result of depression, maladaptive thought patterns (e.g. worrying about falling asleep), coping strategies, and behaviours (e.g. trying to “catch” more sleep) often contribute to the persistence of insomnia even after the resolution of depressive symptoms. CBT-I is designed to address these maladaptive thoughts and behaviours, with therapeutic targets such as increased circadian variability, conditioned arousal, and disrupted homeostatic sleep drive (Morin, 2006). CBT-I in psychiatric conditions has approximately the same magnitude of effect (Cohen’s *d* between 0.35-2.2) as when used to treat primary insomnia (Smith et al., 2005), and recent evidence has found that CBT-I is a promising treatment for depression in individuals with comorbid insomnia (Cunningham and Shapiro, 2018, Carney et al., 2017).

One limitation of cognitive behavioural therapy for insomnia is the need for a therapist who has been trained to administer CBT-I. This may present both time and cost barriers for patients, potentially requiring long trips to the therapy location as well as money, as both travel and therapy itself can be quite costly. Additionally, there is a lack of skilled therapists trained in the delivery of CBT-I. One treatment option that can avoid these issues is telehealth, where remote delivery of CBT-I eliminates the need for a trained and local therapist. There has been some evidence that CBT-I can be effective in a telehealth setting; of nine studies found investigating this technique, seven found that telehealth CBT-I was effective in treating symptoms of depression (Cunningham and Shapiro, 2018). Overall, CBT-I in various forms is showing promise in the treatment of depression and comorbid insomnia.

While both CBT-I and bright light therapy have shown promise in the treatment of depression, there is minimal literature investigating a combination of chronotherapeutic treatments for the treatment of depression (Cunningham et al., unpublished). The goal of the proposed trial is to assess the efficacy of a combination of bright light therapy and online CBT-I in reducing depressive symptomology, compared to a current standard of care (antidepressant medication). Should this treatment prove successful, it will have several benefits over treatment with standard antidepressant medications; namely, fewer side effects, contraindications, and barriers to accessing care. This may make the study treatment preferable with patients for whom antidepressant medications may not be ideal, such as those from geriatric and perinatal populations, and with patients who may experience difficulty accessing standard treatment, such

as those from rural, northern, and/or low-income populations. Additionally, patients may prefer the combination treatment proposed in the trial over traditional antidepressant medication therapy as insomnia treatment is less stigmatized than treatment for depression.

5.2.4.1.1.2 What is/are the principal research question(s) to be addressed?

The primary study objective is to test a novel combination treatment for depression (online CBT-I + bright light therapy) against the standard treatment for depression (the prescription of antidepressant medications). We hypothesize that in patients with depression, a combination of treatment with a light box (10,000 lux for 30 minutes per day) and online CBT-I, as well as a placebo antidepressant medication, will be more effective at treating depression than treatment with standard antidepressant medication, a sham light box (deactivated negative ion generator) and online sleep hygiene information sessions. This improvement in depression will be reflected in improved Montgomery Asberg Depression Rating Scale (MADRS) scores, as well as secondarily in improved Centre for Epidemiologic Studies Depression (CES-D), Beck Depression Inventory (BDI), and Quick Inventory of Depressive Symptomology: Self Report (QIDS-SR) scores.

The secondary trial objective is to test the effects of this novel combination chronotherapeutic treatment on fatigue, insomnia, alertness, sleep architecture, and non-restorative sleep symptoms. We predict that the combined chronotherapeutic treatment will have a greater impact on these factors, as measured by the Fatigue Severity Scale (FSS), Insomnia Severity Index (ISI), Nonrestorative Sleep Scale (NRSS) and Toronto Hospital Alertness Test (THAT), and portable polysomnography, than will the antidepressant medication.

5.2.4.1.1.3 Why is a trial needed now?

E.g. provide evidence from the literature. Furthermore, give references to any relevant systematic review(s) and discuss the need for your trial in light of the(se) review(s). If you believe that no relevant previous trials have been done, give details of your search strategy for existing trials.

There is currently a need for effective, fast-acting, and accessible non-pharmacological treatments for depression. A combination treatment including both bright light therapy and online CBT-I is a unique proposal, as to our knowledge this combination of chronotherapeutic and sleep treatments has not yet been investigated. However, there is reason to believe that such

a combination treatment would effectively treat depression without the need for antidepressant medications. We have recently published a systematic review outlining the recent evidence for using CBT-I to treat depression in individuals with comorbid insomnia. This review identified that telehealth CBT-I is a promising treatment for individuals with both depression and insomnia, while mitigating the barriers to accessing care of traditional in-person therapy (Cunningham and Shapiro, 2018). Similarly, we have a systematic review of both bright light therapy and combined chronotherapies currently undergoing reviews at a peer-reviewed journal. This paper summarizes evidence which indicates that bright light therapy combined with other chronotherapeutics (sleep restriction, sleep phase advance) likely results in more pronounced antidepressant effects than using bright light therapy alone, though more research on such combination chronotherapeutic treatments is required (Cunningham et al., unpublished). Overall, the research indicates that investigations into effective combination chronotherapeutic treatments for depression is both timely and much-needed.

5.2.4.1.1.4 How will the results of this trial be used?

(E.g. contribute to knowledge translation, such as improving understanding, informing decision making and treatment guidelines, etc.)

The results of our study will be disseminated at both national and international conferences, as well as through peer-reviewed publication. Results of this trial will contribute to knowledge translation in several ways, including improving our understanding of depression and insomnia, and informing treatment guidelines for individuals with comorbid depression and insomnia. If the proposed intervention for depression is successful, it would provide an alternative treatment option for depression that avoids the drawbacks of antidepressant medication, while also increasing access to care. By incorporating accessible treatment alternatives such as ours into clinical treatment guidelines, the unmet need for psychiatric care in Canada could be reduced, especially in areas far from urban centres (for example, in rural and/or northern areas of the country) or where stigma against mental illness is particularly high. Following this trial, should the treatment be successful, further research can build off of the results and investigate the use of chronotherapeutic treatments in youth, and the application of chronotherapeutics to reduce suicide; both areas where there is minimal, yet promising, research (Gest et al., 2016, Sahlem et al., 2014).

5.2.4.1.1.5 Are there any risks to the safety of participants involved in the trial? Please describe.

There are several possible risks to the safety of participants involved in the trial. First, there are possible side effects from the use of bright light therapy (BLT). BLT is a fairly safe and well-tolerated treatment. Side effects are usually mild and transient. Possible side effects may include headaches, nausea, eyestrain, blurred vision, and agitation (Terman and Terman, 2005). Additionally, similarly to other antidepressant medications, BLT may induce hypomania (Terman and Terman, 2005) and may not be suitable for unmedicated individuals with bipolar disorder. There is no evidence to suggest that BLT causes damage to the eyes/retinas at the specified dose. There may be higher risk of eye injury to individuals who are photosensitive or who have retinal disease (Gallin et al., 1995); these individuals are not eligible to participate in the present study.

It is possible that participants using the online CBT-I may be uncomfortable, as topics may include worries about sleep. Participants will be told they can skip parts of the therapy if they are uncomfortable. Participation in CBT-I often involves disruption of normal routine, as behavioural changes are often necessary to invoke change in insomnia symptoms. Additionally, participants will be required to fill out daily sleep logs, though these take only a few minutes to complete. Additionally, there is often transient increased sleepiness during the first week or two of participation in CBT-I. Participants will be instructed to take caution in driving and during other activities where sleepiness might be dangerous; participants will also be instructed to take naps for safety purposes whenever necessary (e.g. when driving on a long road trip).

Fluoxetine is a widely prescribed drug which is commonly used to treat depression. Side effects are rare, and usually mild. Common side effects may include sexual dysfunction, nausea, sleep disruption, and headaches; these side effects are usually transient, disappearing within two weeks of the start of the medication regimen. It is also possible that agitation and increased suicidal ideation may present as side effects. Suicidal ideation will be regularly assessed throughout the trial protocol. Fluoxetine has similar side effects as other commonly prescribed selective serotonin reuptake inhibitors (Rossi et al., 2004). As with any medication, there is also the risk of medication interactions if participants do not disclose all current medications and herbal supplements that they are currently taking. While the study personnel will ask for this information, there is no guarantee that participants will be honest, which could lead to medication interactions. Additionally, participants will have to discontinue taking alternate

antidepressant medications in order to participate in this trial. For participants prescribed antidepressant medications at the time of their intake into the trial, their prescribing physician will be contacted, and will be required to agree to their participation in the trial for the participant to be eligible. Participants previously prescribed antidepressant medications will undergo a tapering process and washout period, as appropriate, before their new prescription for the trial (for participants in both trial intervention groups). There is a risk of worsening depressive symptoms, as well as increased side effects during the tapering and wash-out period. These symptoms would likely be transient, as the participant would then begin the trial antidepressant intervention immediately following this period.

When using the portable polysomnography device, it is possible that participants may experience mild skin irritation as a result of the adhesive used to affix electrodes to the skin. In cases where irritation or allergic reaction occurs, either a different adhesive will be used, or participants will not be required to complete polysomnography measures. Additionally, it is possible that participants may experience worsened insomnia symptoms during the night of polysomnography recording, as a ‘first-night effect’ is common when recording these measures (Tamaki et al., 2005). We have attempted to minimize this effect as much as possible by using portable polysomnography devices, which allow participants to record in the comfort of their own homes. Thus, while sleep may be slightly disrupted, it will likely be disrupted less than it would be when recording in the laboratory environment.

Participants will be asked about any adverse events when they come to the laboratory at each visit, as well as during weekly ‘check-in’ phone calls from the study coordinator and/or study psychiatrist. Should serious adverse events occur (e.g. negative side effects from study intervention, or increase in suicidality as measured by the Columbia Suicide Severity Scale), participants will be brought in to the lab for assessment by the study psychiatrist, and/or will be referred for alternate treatment, as appropriate. Participants experiencing adverse events will be withdrawn from the trial when it is in the best interest of their safety and/or comfort.

Finally, there is always the risk in research of accidental disclosure of study information or break in confidentiality, though all possible steps will be taken by study personnel to minimize this risk. At the beginning of their study participation, participants will be informed of the potential risks of participation. Written, informed consent must be obtained in order for a participant to enroll in the proposed trial.

5.2.4.1.2 The Proposed Trial

5.2.4.1.2.1 What is the proposed trial design?

E.g. Open-label, double or single blinded, etc.

The proposed trial will use a double blind, randomized, prospective cohort design.

5.2.4.1.2.2 What are the planned trial interventions? Both experimental and control.

Study Group One (active antidepressant medication treatment):

The intervention for this group will involve;

- 1) Standard antidepressant medication treatment (20mg fluoxetine), prescribed by the study physician, to be taken as prescribed over the 8-week trial treatment period. If necessary, a medication washout period will occur before the prescription of antidepressant medication.
- 2) Online sleep hygiene instructions, accessed on weeks 1, 2, 3, 5 and 7. This is an active control for the sleep treatments provided in the second study group.
- 3) A disabled ion generating box used daily in their homes, as an active control for the bright light treatments provided in the other study group. Participants will be instructed to start using this within 15 minutes of waking in the morning (at desired or usual wake time). Participants will be instructed to sit within arm's reach of the box for 30 minutes. Participants will be verbally instructed on the procedure before leaving the laboratory, and will also be given standard written instructions.
- 4) Weekly phone calls from the study investigator inquiring about side effects, adverse effects, change in depressive symptoms, and co-committant medication use.

Study Group Two (active combined chronotherapy treatment):

The intervention for this group will involve;

- 1) A combination of bright light therapy (BLT) and online cognitive behavioural therapy for insomnia (CBT-I) interventions over than 8-week treatment period.
 - a. BLT will be administered via daily 30-minute exposure to a broad-spectrum white fluorescent light, set at 10,000 lux. This will be self-administered by patients with a "light box," and will be started within 15 minutes of waking at a desired or usual wake time (kept relatively consistent throughout the treatment protocol). Participants will be instructed to sit 35 cm away from the light box, and told that looking directly at it is not necessary, as long as they are facing it. All

participants will be verbally instructed on light box procedure before leaving the lab with the light box, and will also be given standard written instructions.

b. CBT-I will be administered online on weeks 1, 2, 3, 5 and 7.

2) Placebo antidepressant medications (ADMs), to act as an active control for the ADM treatment received by study group one.

3) Weekly phone calls from the study investigator inquiring about side effects, adverse effects, change in depressive symptoms, and co-committant medication use.

Table 11 Two randomized study groups for proposed clinical trial.

Study Group One	Study Group Two
Fluoxetine (20mg)	Placebo antidepressant medication
Sleep hygiene	Online CBT-I
Deactivated negative ion generator	Bright light therapy box

5.2.4.1.2.3 What are the proposed practical arrangements for allocating participants to trial groups?

E.g. randomization method. If stratification or minimization are to be used, give reasons and factors to be included.

Patients will be randomized into treatment groups. Randomization will be stratified in blocks of 6 based on initial Quick Inventory of Depressive Symptoms Self Report (QIDS-SR) scores, with two stratification groups (≤ 15 , indicating mild or moderate depression, and ≥ 16 , indicating severe or very severe depression). Given the small sample size proposed for this study, stratification will help ensure roughly equal average depressive severity in both study groups, with roughly the same number of patients in each study group.

Randomization will occur at the first study visit, following the informed consent procedure and eligibility verification. Randomization will be completed using a computer-generated randomization schedule by blocks for the two stratification groups. Randomization schedules will be obtained from www.randomization.com, which generates a randomization schedule based on a seed number obtained from the clock of the requesting computer. This seed number is output with the randomization schedule, and is thus reproducible and verifiable.

5.2.4.1.2.4 What are the proposed methods for protecting against sources of bias?

E.g. blinding or masking. If blinding is not possible please explain why and give details of alternative methods proposed, or implications for interpretation of the trial's results.

The proposed study will use a double-blind research design. Patients will be blinded to their medication condition, receiving either an antidepressant medication or an appearance-matched placebo drug. Patients will receive either cognitive behavioural therapy for insomnia (CBT-I) online, or online sleep hygiene instructions, but will not be told which is the active treatment or which they are actually receiving. While these treatment conditions are not identical, sleep hygiene is a common control treatment for CBT-I and generally has high credibility in research studies, as it is often used in clinical practice. Finally, one group will be receiving bright light treatment, and the other group will receive sham treatment with a deactivated negative ion generator. Patients will not be told that the negative ion generator is deactivated, and thus will also be under the impression that they are receiving an active treatment for depression with the device.

The study coordinator will not be blinded to patients' randomization, given the logistical needs of the trial and the inherent lack of ability to blind to the CBT-I/sleep hygiene and bright light/deactivated negative ion generator conditions. However, the psychiatrists performing the regular depression assessments (using the Montgomery Asberg Depression Rating Scale) will be blinded to the patients' group assignment, and the patients will be instructed not to discuss their treatment during these assessments. Thus, depression symptom assessments will be unbiased by the treatments received by the patients.

5.2.4.1.2.5 What are the planned inclusion/exclusion criteria?

The current study aims to enroll participants who currently have major depressive disorder as well as insomnia. By only including patients who meet criteria for both diagnoses, this does limit the potential real-world applicability of our research outcomes, given that many depressed clinic patients may have symptoms of insomnia or circadian disruption without meeting threshold for the disorder. However, given that this specific combination of treatments (bright light and online cognitive behavioural therapy for insomnia) has not yet been tested, we feel that initial research should be conducted including participants for whom the combined therapy is most likely to work, focusing on determining efficacy before testing effectiveness.

In order to be eligible for the study, patients must be between 18-55 years old. While we recognize that improved treatments for depression in youth, and especially treatments which reduce barriers to accessing care, are highly needed (Mental Health Commission of Canada, 2015), there has been minimal research to date investigating the use of chronotherapies in youth, and what research there has been has not indicated that a combination of chronotherapies would necessarily be the most effective chronotherapeutic treatment strategy (Gest et al., 2016). Thus, it is unclear whether the combined chronotherapy proposed in this study would be an effective treatment for juvenile depression in youth with comorbid sleep and circadian disturbances. Similarly, it is possible that geriatric patients may benefit from the combined chronotherapies proposed in this trial. While some research has indicated that chronotherapies can be effective in this population for reducing depression, there have only been two studies to date (by the same research group) investigating this possibility, neither necessarily supporting the use of combined chronotherapeutics in geriatric patients (Cunningham et al., unpublished).

Further exclusion criteria for patients in the proposed trial include: 1) significant mental health disorders or DSM-V Axis 1 psychiatric disorders besides unipolar depression and anxiety, as self-reported or suspected during eligibility screening; 2) any history of psychosis; 3) any history of seizure disorders; 4) pregnant women, women of childbearing age not currently using adequate contraception methods, and breastfeeding women; 5) any disease of or involving the retina; 6) current or recent (within the last 24 months) use of Fluoxetine (Prozac); 7) current or recent (last 6 months) use of any medication that results in or may result in photosensitivity; 8) current use of any drug or medication contraindicated for use with Fluoxetine; 9) any severe or unstable physical illness or disease; 10) individuals currently seeking or planning to seek any other treatments for depression, including but not limited to therapy and antidepressant medications; 11) serious risk of suicidal behavior (as measured by the Columbia Suicide Severity Rating Scale); and 12) self-reported current substance abuse.

5.2.4.1.2.6 What is the proposed duration of the treatment period?

The treatment period will last for eight weeks. During this time, antidepressant medication (or placebo) will be taken daily, and bright light therapy (or sham) will be used every morning. Online CBT-I (or sham) will be delivered on treatment weeks 1, 2, 3, 5 and 7.

5.2.4.1.2.7 What is the proposed frequency and duration of follow-up?

During the treatment protocol, a research assistant will follow up with patients on a weekly basis to enquire about treatment side effects, adverse events and other relevant novel information. Patients will complete a post-treatment assessment and symptoms follow-up immediately following treatment completion, at week 9. At this point, patients will also engage in an informal feedback interview regarding how the patient felt that treatment went, and how they might change it in the future (regarding usability, side effects, things they liked/disliked about any aspect of their treatment, etc.). Patients will be unblinded as to their treatment group at this visit, and may choose to continue with their treatment, switch treatment groups, or be given a referral for alternate treatment. A second follow-up visit will occur at week 16, where patients undergo the same post-treatment assessments, regardless of the course of treatment they have undergone in the weeks since the first follow-up meeting.

5.2.4.1.2.8 What are the primary and secondary outcome measures?

Primary outcome measures will be the change in depressive symptomology from pre- to post- treatment, as measured by the Montgomery Asberg Depression Rating Scale (a clinician-administered semi-structured clinical interview). Secondary outcome measures will include change in depression, measured by the Centre for Epidemiologic Studies Depression, the Quick Inventory of Depressive Symptomology and the Beck Depression Inventory (a self-report questionnaire; change in insomnia, measured by the Insomnia Severity Index; change in fatigue, measured by the Fatigue Severity Scale; change in alertness, measured by the Toronto Hospital Alertness Test; change in non-restorative sleep, measured by the Non-Restorative Sleep Scale; and change in objective measures of sleep, as measured by a portable polysomnography device.

5.2.4.1.2.9 How will the outcome measures be measured at follow up?

Patients will come back to the lab for follow-up visits at weeks 9 and 16. A clinician (psychiatrist or psychologist) will administer the MADRS at this visit, and the patient will complete a questionnaire booklet with all self-report measures. The patient will take the portable polysomnography device home with them following this visit, and will use the device on that same night to measure objective markers with their sleep. They will then be instructed to return the device to the laboratory within one week of the follow up visit.

5.2.4.1.2.10 What is the proposed sample size and what is the justification for the assumptions underlying the power calculations?

Include both control and treatment groups, a brief description of the power calculations detailing the outcome measures on which these have been based, and give event rates, means and medians, etc. as appropriate. (N.B. It is important to give the justification for the size of the difference that the trial is powered to detect. Does the sample size calculation take into account the anticipated rates of non-compliance and loss to follow-up given below?)

In order to have study power of 80%, and a significance level of 0.05, we will need to enroll 56 participants per study group, for a total of 112 study participants. We used the change in MADRS score (the primary outcome) from baseline to post treatment in groups receiving bright light therapy versus fluoxetine in a similarly constructed trial (Lam et al., 2016) to estimate the group difference we could expect to see on our primary outcome measure, and set this value as 4.6. Similarly, we estimated our groups' standard deviation on this measure from this previous trial, and set that parameter to 8.7. Using the formula $n = \left(2(\sigma^2)(z_{1-\alpha/2} + z_{1-\beta})^2 \right) / \Delta^2$ (Zlowodzki et al., 2004) and our estimated parameters, we then determine that our required sample size is 112. Given that we expect a 72% completion rate at post treatment (see sections 2.13 & 2.14 below), we will need to recruit 78 participants per study group, for a total of 156 study participants who are eligible and agree to participate at baseline in order to meet the 80% statistical power threshold.

For elaborated calculations, see Appendix 2.

5.2.4.1.2.11 If applicable, are health service research issues to be addressed?

Justify inclusion/exclusion of health economics and quality of life measures. If these measures are to be included full details should be given including power calculations.

Health economics and quality of life measures will not be assessed in this trial. This is a preliminary trial assessing the efficacy of the combined novel intervention on depression (primary outcome) and sleep (secondary outcomes) symptoms. Given the wide range of measures already employed, and the tangential nature of quality of life and health economics measures to the research questions addressed in this study, we judge that these measures are better left to future study, should our intervention prove effective.

5.2.4.1.2.12 What is the planned recruitment rate?

How will the recruitment be organized? Over what time period will recruitment take place?

What evidence is there that the planned recruitment rate is achievable?

The planned recruitment rate is 13 patients per study site, at twelve study sites in the province of Ontario, over the span of one year. Several study sites will be in the city of Toronto. Toronto is a large city, with a population of over 6 million in the Greater Toronto Area, and potential recruitment rate that is unmatched by most other Canadian cities. Evidence from other trials which have recruited in the Toronto area (e.g. Lam et al., 2016, Carney et al., 2017), as well as the personal experience of the study investigators, indicate that this recruitment rate is more than achievable. Other study sites will be at primary care clinics with a demonstrated unmet need for depression treatment, where recruitment on this scale would also be achievable.

While this study will be run primarily out of the University of Toronto, this university also has relationships with 8 major teaching hospitals and two mental health hospitals in the downtown Toronto area. Additionally, the primary applicant holds clinical practice in Parry Sound, in northern Ontario. Study sites include the clinics of both psychiatrists and general medical practitioners who see patients with depression, who will recruit patients seeking treatment. Recruitment will primarily be from these sources, but will also occur through referrals from clinics and hospitals, and community advertising (e.g. in newspapers, community posters, and online community classifieds).

5.2.4.1.2.13 Are there likely to be any problems with compliance?

On what evidence are the compliance figures based?

Previous literature of clinical trials using chronotherapeutics (Lam et al., 2016) and CBT-I (Carney et al., 2017) with and without antidepressant medications indicates a range of 57-87% completion rate at post-treatment for depressed trial patients. Typical reasons for discontinuation during the trial period include time commitment, lack of efficacy, improved symptoms, adverse events, patient relocation, and poor treatment adherence (lack of compliance). It is likely that our trial will face these same issues; thus, we have calculated our sample size based on a rate of 72% of trial patients complying to trial protocols and continuing through to post treatment.

We will measure treatment compliance for each of the three ‘arms’ of treatment. For antidepressant medications, we will count pills remaining in prescription bottles at each lab

visit, and will ask patients to self-report how many doses they missed at each time they log in online. Similarly, we will have patients self-report how many doses of bright light or sham they missed at each time they log in online. For online CBT-I/sham, we will be able to monitor their progress through the use of the software delivering the material online. We will remove patients from the trial who demonstrate a lack of compliance to study procedures.

5.2.4.1.2.14 What is the likely rate of loss to follow up?

On what evidence is the loss to follow-up rate based?

As detailed above, the approximate rate of loss at post-treatment is expected to be 28%. At 16-week follow up, which is eight weeks after the end of the treatment period, we expect to retain 80% of treatment completers, or roughly 58% of the original study sample. This loss to follow-up rate is based on a range of attrition rates from similar studies investigating chronotherapeutic interventions for depression, and is on the lower end of the range (Carney et al., 2017, Martiny et al., 2006, Blom et al., 2015).

5.2.4.1.2.15 How many centers will be involved?

Eleven satellite centres and one primary study centre (at the primary applicant's private clinic in Toronto) will be involved in patient recruitment and collection of study measures. The satellite centres are comprised of psychiatric and general practice physicians who see patients with depression; they will recruit patients who are actively seeking treatment. While most study procedures (e.g. randomization) will still occur at the University of Toronto by the research coordinator, patients will be able to receive study devices (e.g. PSG, bright light boxes) and complete some measures (e.g. self-report questionnaires) at their usual clinic, thereby reducing the burden inherent to study participation. Ideally, depression symptom assessment (MADRS) will occur at the University of Toronto central site, but where this presents undue burden on study participants, telehealth assessment by the study psychiatrist may be used.

5.2.4.1.2.16 What is the proposed type of analyses?

The primary outcome variable is the change in MADRS score from baseline to post treatment. This will be compared using analysis of covariance (ANCOVA), while controlling for covariates including baseline MADRS score, study site, and sex. Secondary outcomes will be analyzed similarly. Follow up data will be incorporated into repeated measures ANCOVA.

5.2.4.1.2.17 What is the proposed frequency of analyses?

Full analyses of all primary and secondary outcome variables will be conducted once all participating study patients have completed post-treatment assessments, and again once all participating study patients have completed follow-up assessments. Interim analysis of primary outcome variables will occur yearly during the ongoing trial, should the timeline take longer than anticipated, to assess for large group differences in treatment outcomes.

5.2.4.1.2.18 Are there any planned subgroup analyses?

While sex, study site, and baseline MADRS scores will be included as covariates in the analysis, there are no specifically planned subgroup analyses.

5.2.4.1.2.19 Has any pilot study been carried out using this design?

There has been no pilot study carried out using this design.

5.2.4.1.3 Trial Management

5.2.4.1.3.1 What are the arrangements for day to day management of the trial?

E.g. Randomization, data handling, and who will be responsible for the coordination.

Randomization and data entry will occur on a password protected computer, located at the private clinic of the nominated principal applicant (Dr. Colin Shapiro). Randomization schedules will be kept in a password protected document, and a member of staff (with minimal involvement otherwise with the study) will randomly assign patients to groups based on the randomization schedule on their first lab visit, as per the study protocol. Study coordination (e.g. scheduling patient lab visits, distribution of study materials, etc.) will be completed by the study coordinator, Jasmyn Cunningham. She will also be responsible for data handling and input, online CBT-I response collection, etc.

5.2.4.1.3.2 What will be the role of each principal applicant and co-applicant proposed?

The nominated principal applicant, Dr. Colin Shapiro, will be the primary study psychiatrist/clinician. Dr. Shapiro will conduct all MADRS clinical interviews and scoring, including by telehealth, if necessary. Additionally, Dr. Shapiro will supervise (directly and/or

indirectly) other clinical measures, including the M.I.N.I, portable polysomnography, and questionnaires.

The nominated co-applicant and trainee, Jasmyn Cunningham, will be the primary study coordinator for the trial. She will be responsible for logistical requirements including participant recruitment and scheduling at the primary study site, and coordination with satellite study sites. Additionally, she will conduct all study measures at the primary study site including questionnaires, the M.I.N.I interview, training and providing patients with bright light boxes, deactivated negative ion generators, online CBT-I or sleep hygiene, and medication tablets (fluoxetine or placebo). Ms. Cunningham will be responsible for collecting, compiling, and managing study data from all study sites, as well as completing study analyses.

Table 12 Role of each applicant in proposed clinical trial.

Role	Responsible party	Hours/week
Clinical interviews	Colin Shapiro	4
Clinical supervision	Colin Shapiro	2
		Total: 4 hours per week
Patient coordination	Jasmyn Cunningham	3
Satellite site coordination	Jasmyn Cunningham	5
Data collection	Jasmyn Cunningham	6
Data management	Jasmyn Cunningham	4
		Total: 24 hours per week

5.2.4.1.3.3 Describe the trial steering committee and if relevant the data safety and monitoring committee.

The trial steering committee will be comprised of the co-applicant's thesis committee. This group will also serve as the data safety and monitoring committee; they will review all interim calculations and will have full access to interim study data (as well as randomization of current participants) in order to make their safety determinations.

5.3 Complete Summary

3500 characters maximum, including spaces

Major depressive disorder is one of the most frequently diagnosed psychiatric disorders, with a 12% lifetime prevalence of major depressive episodes in Canada. Depression has widespread negative consequences both for afflicted individuals and for society. Usual treatments include the prescription of antidepressant medications (ADMs), or therapy, both of which have notable limitations including lack of efficacy in individuals with mild or moderate depression, slow-acting treatment effects, and negative side-effect profiles (ADMs); and barriers to accessing care (therapy and ADMs). Overall, there is a large unmet need for depression treatment in Canada, especially for individuals in remote areas, for whom longer travel times may lead to a reduction in accessing both therapy and medication based treatment.

Up to 90% of individuals with depression also endorse sleep and circadian complaints. These sleep and circadian disturbances are predictors of who will develop new and recurrent episodes of depression, and they predict worse clinical outcomes. Most treatments for depression don't address sleep symptoms. It is clear that there is a need for novel treatments for depression which also effectively address the commonly comorbid sleep and circadian disruptions.

There is minimal literature investigating a combination of chronotherapeutic treatments for the treatment of depression. The goal of the proposed trial is to assess the efficacy of a combination of bright light therapy and online CBT-I in reducing depressive symptomology, both of which have evidence indicating their efficacy in depressed populations. This treatment will be compared to a current standard of care (ADMs). The primary outcome measure will be change in Montgomery Asberg Depression Rating Scale from baseline to post-treatment, after an eight-week treatment protocol. Both the ADM and chronotherapies will be sham controlled; individuals receiving ADMs will receive sleep hygiene treatment and will use a deactivated negative ion generator, common sham controls for their respective treatments. Individuals receiving chronotherapies will also receive a placebo ADM. The trial will take place in Toronto, Ontario, under the supervision of Dr. Colin Shapiro, an esteemed sleep researcher with dozens of publications in the field of sleep and depression. Study recruitment strategy primarily be through satellite study sites in the province of Ontario. Secondary recruitment strategies include 1) community advertisement and 2) referrals from clinics and hospitals in the downtown Toronto area.

Should this treatment prove successful, it will have several benefits over treatment with standard ADMs; namely, fewer side effects, contraindications, and barriers to accessing care. This may make the study treatment preferable with patients for whom antidepressant medications may not be ideal, such as those from geriatric and perinatal populations, and with patients who may experience difficulty accessing standard treatment, such as those from rural, northern, and/or low-income populations. Additionally, patients may prefer the combination treatment proposed in the trial over traditional antidepressant medication therapy as insomnia treatment is less stigmatized than treatment for depression. Our treatment, if successful, would provide a much-needed treatment alternative for individuals with depression.

5.4 Identify Application Partners (Optional)

There are no application partners identified with this project grant application.

5.5 Enter Budget Information

For 2 year project duration.

5.5.1 Research Staff:

Table 13 Budgeted amounts for research staff, for proposed clinical trial.

Item	Hours per year	Cost per hour	Cost per year	Number of years	Total
Polysomnography technician	100	\$30	\$3,000	2	\$6,000
Research coordinator	Full-time		\$45,000	2	\$90,000
Total (rounded to nearest \$1000)					\$96,000

5.5.2 Trainees

Table 14 Budgeted amounts for trainees, for proposed clinical trial.

Item	Cost per year	Number of years	Total
Graduate student stipend	\$28,000	2	\$56,000
Total (rounded to nearest \$1000)			\$56,000

5.5.3 Consumables

Table 15 Budgeted amount for consumables, for proposed clinical trial.

Item	Cost	Number of units or length of time	Total
Qualtrics Survey Software	\$1000 USD per year	2 years	\$2,000 USD = ~2,600 CAD
Disbursements	\$300 per year	2 years	\$600
Newspaper advertisements	\$500 per year	2 years	\$1,000
Polysomnography consumable equipment (e.g. electrodes)	\$50 per participant	156 participants x 3 nights recorded	\$23,400
Antidepressant medications	\$1 per tablet (real and placebo)	156 participants x 8 weeks x 7 days	\$8,736
Bright light box	\$300	10	\$3000
Disabled negative ion generators	\$300	10	\$3000
Portable polysomnography software license	\$1000 per year	2 years	\$2000
Total (rounded to nearest \$1000)			\$45,000

5.5.4 Non-Consumables

Table 16 Budgeted amounts for non-consumables, for proposed clinical trial.

Item	Cost	Number of units	Total
Portable polysomnography devices	\$10,000	2	\$30,000
Total (rounded to nearest \$1000)			\$30,000

5.5.5 Knowledge Translation

Table 17 Budgeted amounts for knowledge translation, for proposed clinical trial.

Item	Cost	Number of units	Total
Manuscript Submission fee	\$50 USD		\$50 USD = ~\$65 CAD
Conference registration	\$200 per conference	7 conferences x 2 individuals	\$2800
Conference travel	\$1000 per conference	7 conferences x 2 individuals	\$14,000
Total (rounded to nearest \$1000)			\$17,000

5.5.6 Other

Table 18 Budgeted amounts for other expenses, for proposed clinical trial.

Item	Cost	Number of units	Total
Total (rounded to nearest \$1000)			\$0

5.5.7 Total budget request:

(rounded to nearest \$5000)

\$245,000

5.6 Complete Peer Review Administration Information

5.6.1 Suggested Reviewers for this Application (optional)

1. Raymond Lam
2. Rachel Manber
3. Jack Edinger
4. Allison Harvey
5. David Kupfer

5.6.2 Reviewers to exclude for this Application (optional)

1. Colleen Carney – personal relationship with applicants
2. Benjamin Rusak – personal relationship with applicants

5.6.3 Suggested Committees

1. Behavioural Sciences – B (BSB) (Clinical Behavioural Sciences)
2. Randomized Controlled Trials (RC1)

5.7 Attach Other Application Material

List of attachments:

1. Questionnaires
2. Consent Forms
3. Portable PSG User Manual
4. Light box device details

5. Online CBT-I Content
6. Sleep Hygiene Content
7. 2 recent systematic reviews (CBT-I, chronotherapeutics → depression)

5.8 Apply to Priority Announcements/Funding Pools (Optional)

Relevant Priority Announcement: Neurosciences, Mental Health and Addiction

5.9 & 5.10: Preview, Consent, and Submit the Application

Chapter 6: Concluding Summary, General Discussion, and Future Directions

6.1 Concluding Summary

While antidepressant medications and psychotherapy are effective for many patients, there is still a significant unmet need for alternative treatments which are effective, fast-acting, and which reduce barriers to accessing care. Chronotherapies, designed to alter circadian and sleep-wake rhythms, provide a promising alternative avenue for targeting the symptoms of depression. The primary objective of this thesis was to systematically review the use of chronotherapies to treat unipolar depression, including cognitive behavioural therapy for insomnia (CBT-I), bright light therapy, sleep deprivation therapy and sleep phase advance. Secondly, this thesis aimed to incorporate the findings from these reviews in order to propose a novel combined chronotherapeutic treatment for depression, which would be evidence-based, accessible, and effective.

This systematic investigation into this use of chronotherapies was conducted in three parts; firstly, we reviewed the use of cognitive behavioural therapy for insomnia, secondly, we reviewed the use of bright light therapy, and thirdly, we reviewed the use of combined chronotherapies. The results of the first part of the investigation were generally positive, indicating that in-person CBT-I is effective in reducing symptoms of depression in individuals with both unipolar depression and insomnia. However, this benefit may not be additive with those of antidepressant medications, as there may be a ‘ceiling effect’ in terms of benefit. Telehealth CBT-I was less strongly supported, but may still be worthwhile as a part of a stepped-care approach, especially for individuals with less severe forms of depression. Group therapy, however, has insufficient evidence to determine its effectiveness in this population.

The results of the second part of the investigation, regarding the use of bright light therapy, were more mixed. While bright light therapy in conjunction with antidepressant medication use seems to be an effective strategy for the treatment of depression, the research in stand-alone use of bright light therapy was less conclusive. Standard methodologies for the use of bright light in treating depression should be developed and further tested; these will likely involve the use of 5,000-10,000 lux-hours starting shortly after wake time, with a treatment duration of at least three to five weeks. Similarly, the results of the third part of the investigation, reviewing the use of combined chronotherapies, also indicated that literature on these treatments is minimal, and treatment protocols are widely varied. Typically, sleep deprivation is combined with bright light and/or sleep phase advance, and it is possible that the

combination of these therapies may be more effective than the therapies on their own, however given small studies using within-subjects methods, definitive recommendations can't be given at this time.

In order to address the results of this multi-part investigation, we have developed the protocol for a study designed to test a novel combination of chronotherapeutic treatments, which uses a methodology indicated in the literature to most likely be effective. This combination of treatments includes online cognitive behavioural therapy for insomnia as well as daily bright light therapy, and involves an eight-week treatment protocol. The proposed study will be submitted in consideration for a Canadian Institutes of Health Research project grant in the next available competition pool (Fall 2018).

6.2 General Discussion

Given the multiple sequential paper layout of this thesis, individual discussions were included in each chapter. This general discussion will be a brief consideration of how our findings relate to our research aims and the relevant pre-existing literature, especially as discussed in the literature review chapter. Primarily, this will involve two questions: 1) how can chronotherapies contribute to lessening the burden of depression? and 2) which chronotherapies are most effective in achieving this goal?

Chronotherapies make use of various mechanisms in order to effect sleep and mood changes in patients. CBT-I, for example, employs a wide variety of pathways, including enhancing process S through sleep restriction, correcting misaligned circadian phase, and reducing stress and dysfunctional cognitions. Similarly, bright light therapy and sleep phase advance improve depression through circadian phase realignment (Germain and Kupfer, 2008), and sleep deprivation exerts therapeutic effect through improvement in deficient homeostatic sleep drive and related long-term potentiation and synaptic plasticity (Dallassezia et al., 2015, Wolf et al., 2016). Additionally, bright light therapy and sleep deprivation likely also affect monoamine pathways, similarly to the mechanism of antidepressant medications (Neumeister et al., 1998, Adrien, 2002, Benedetti et al., 2007).

It is through these varied mechanisms that chronotherapies are able to improve mood, both directly and indirectly. For example, CBT-I could directly improve depression by addressing dysfunctional beliefs and anxieties about daytime functioning and perceived

workplace performance, and increasing effortful use of cognitive control in order to reduce the salience of the depressive mode. However, it would likely also improve depression indirectly by having patients engage in mild sleep restriction, thereby increasing process S and improving deficiencies in monoamine neurotransmitter systems. Other chronotherapies would affect similar systems in order to improve mood.

Given their efficacy, chronotherapeutics provide a promising alternative treatment to antidepressant medications and other typical treatments for depression, such as psychotherapy. Chronotherapies also avoid many of the negative aspects of typical treatments. For example, unlike antidepressant medications, chronotherapies typically have minimal side effects, and what side effects are present are usually transient. Chronotherapies also work for individuals of varying depressive severities, while antidepressant medications often are less effective for individuals with mild or moderate depression (Fournier et al., 2010). In order to access antidepressant medications, psychotherapy, or electroconvulsive therapy, depressed individuals must usually meet repeatedly with a highly-trained health care provider, such as a psychologist or psychiatrist; chronotherapies eliminate this barrier to accessing care, especially when delivered through telehealth modalities. Overall, chronotherapies constitute effective, accessible, and desirable treatment options for depression.

If chronotherapies for depression were widely adopted, it could significantly reduce the societal burden of depression. By reducing the barriers to accessing treatment for depression, and by providing less stigmatized treatment options, more individuals would seek and be able to access care (Fortney et al., 1999, Clement et al., 2015). Additionally, if more individuals who access care are able to receive a minimally adequate treatment, as may be the case with an easily delivered chronotherapeutic treatment, many more individuals would be able to function with more productivity in the workplace, and the number of hospitalizations due to depression would decrease. These factors alone would lead to an increase in Canadian GDP in the billions, and millions of dollars of saved health care costs (Conference Board of Canada, 2018).

The second main topic to be addressed in this discussion is the question of which chronotherapies, or combinations thereof, are most effective. In our investigation, cognitive behavioural therapy for insomnia was shown to be effective in treating depression, though improvement following this therapy may not be additive with antidepressant medications. Conversely, bright light therapy in conjunction with antidepressant medications was shown to be effective, as was bright light therapy on its own (though with less supporting evidence).

Thus, for patients currently prescribed antidepressant medications, bright light therapy may be a more appropriate treatment option.

The most effective combination of chronotherapies (excluding CBT-I) tends to involve sleep restriction and bright light and/or sleep phase advance, indicating that the inclusion of both homeostatic and circadian based treatments is the most effective grouping. This makes sense, given that this combination of therapies would effectively address several of the likely sources of depression: misaligned circadian rhythms, deficient homeostatic sleep drive, and deficiencies in monoamine (and specifically serotonergic) pathways. We propose that a combination of CBT-I and bright light would also be an effective treatment for depression, for several reasons. First, this combination also includes both sleep and circadian components, as does the combination of sleep restriction and bright light. Indeed, improvement in depression following CBT-I is mediated by improvement in insomnia, indicating that CBT-I specifically targets and improves both sleep and mood symptoms. Secondly, CBT-I typically includes some sleep restriction, but on a sustainable scale, allowing the patients to experience the benefits of sleep restriction without the associated downfalls (e.g. extreme daytime sleepiness, relapse following recovery sleep). Finally, one of the typical elements of CBT-I is sleep time stabilization, thereby potentially incorporating some of the elements of sleep phase advance, especially in depressed individuals whose sleep windows are often delayed when allowed to follow their natural course.

6.3 Future Directions

Given the rationale provided above, a combination of CBT-I and bright light therapy was chosen as our immediate next step in researching chronotherapeutics. Additionally, we chose to use telehealth CBT-I given the evidence that it would likely be effective in a stepped-care model, and because of the ability to engage in this therapy without the need for contact with a trained therapist or physician. The combined therapy proposed in Chapter 5, if shown to be effective, could be implemented by clinicians with less extensive training, including nurse practitioners in areas where populations are medically underserved. For example, in Canada, there are many rural and northern areas where there is a dearth of practitioners available to provide healthcare. With this protocol, should it be proven effective, it would be possible for individuals in these remote areas to access a treatment for depression through a combination of internet (for the telehealth CBT-I) and mail (to receive bright light devices), with any additional required support provided by available local healthcare practitioners, if present, or over the

phone. Additionally, if this combined chronotherapy is effective, it may be particularly well suited for northern areas of Canada, where rates of depression and suicide are particularly high (Chachamovich et al., 2015), there is a lack of available healthcare, and where daylight hours differ drastically by season. It may also, as a result of being more accessible, be delivered sooner to patients, and could potentially therefore reduce symptom progression to more severe forms of depression. Future research would be required to evaluate this possibility. Other interesting avenues of future research include evaluating the impact of our proposed intervention on both cognitive and metabolic changes, as well as investigating which symptoms of depression, if any, are preferentially targeted by the proposed treatment.

Though we believe that this combination of chronotherapies would be ideal, given its potential efficacy as well as sustainability and ease of implementation, other combinations of chronotherapies would likely also be effective. Specifically, further research should be conducted to develop and test a standard protocol using sleep deprivation, subsequent bright light and potentially sleep phase advance. Ideally, this would include at least one night of total or late partial sleep deprivation, followed by a sleep phase advance and stabilization phase of approximately one week. Simultaneously, morning bright light (5,000-10,000 lux for 30 mins to 2 hours) would begin, and would continue for several weeks.

This thesis has specifically focussed on non-pharmacological chronotherapeutics. However, in future research, it would be interesting to investigate whether the hormone melatonin could also be used to exert antidepressant effect, given its phase-shifting effect (similar to bright light). If melatonin were to be used, it should be given in the evening, rather than the morning, approximately 2-4 hours before an individual's desired bed time. While (minimal) past evidence has not indicated that melatonin is effective as an antidepressant on its own (Hansen et al., 2014), it may be useful in combination with other chronotherapies; for example, to replace the bright light element for individuals who would prefer to reduce the amount of time spent in the morning on their treatment.

Finally, our analysis was limited by the fact that there was not enough available evidence to conduct meta-analysis (see Appendix 1), and thus we were limited to qualitatively reviewing the literature on chronotherapies and their effects on depression. Additionally, the studies of chronotherapies were highly heterogeneous; future research would benefit from using the current state of the literature to standardize treatment methodology in order to demonstrate (and subsequently replicate) both the efficacy and effectiveness of these treatments. Following this,

meta-analytic methods can more appropriately be used to determine the quantitative nature of chronotherapeutic treatment effects (e.g. effect size), in addition to analyzing any potential publication bias that may exist.

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Appendix

Appendix 1 Prospective power analysis and theoretical meta-analytic approach to “Cognitive Behavioural Therapy for Insomnia to treat depression: A systematic review.”

There are two main methods available for conducting meta-analysis, fixed and random effects (Field and Gillett, 2010). Given that effect sizes are likely not homogeneous between studies included in this systematic review, and the authors would like to generalize the results of a meta-analysis further than very similarly conducted studies, a random-effects meta-analysis would be the appropriate choice for this analysis (Field and Gillett, 2010). Thus, a prospective test of statistical power for a random effects model was conducted (Valentine et al., 2009).

In order to complete this test of statistical power, several input variables had to be estimated from the relevant literature. First, an estimation of between-studies variance was conducted. Given the variation in effect sizes reported in relevant literature, a large degree of heterogeneity was assumed, reflecting an I^2 value of 75% (Valentine et al., 2009). This translates to a population variance, or τ^2 value of 3, as there is a 3 to 1 ratio of variance explained by between-study versus within-study variance. Secondly, the overall effect size of interest had to be estimated. Many of the studies of interest use the Hamilton Depression Rating Score 17 (HDRS₁₇ or HAM-D₁₇) as their primary depression outcome measure. For this measure, clinically meaningful outcomes include remission in depression, defined as a score equal to or less than 7 at post-treatment, or response, defined as a post-treatment score at least 50% reduced from baseline score. Thus, examples of clinically meaningful mean differences in HDRS₁₇ scores following treatment could potentially be a reduction from 24 to 7, 24 to 12, 15 to 7.5, or 15 to 7. Assuming this treatment was compared to an active control, as we investigated in this review, a realistic control group score might drop from 24 to 15, or from 15 to 9. Assuming a pooled standard deviation of 6, the between-group effect sizes for change scores would be 1.33, 0.5, 0.5, and 0.33. The average of these theoretical effect sizes is 0.67, which is what we will assume for our mean effect size ($\overline{ES}$) for this power analysis. We must also include an average value for approximate mean sample size per group (treatment and control) for our included studies. These vary widely in the literature; a mean sample size of 25 per group (n_T or n in treatment group, and n_c or n in control group), for a total of 50, was assumed for the purposes of this power analysis. Finally, we need to approximate the number of studies which

will be included in the meta-analysis (k); as this is an emerging field with relatively few completed randomized controlled trials, we estimate there may be ten studies included.

The first step in conducting the power analysis is calculating an estimation of the typical sampling variance of the random effects estimate of effect size (Valentine et al., 2009). This is given by:

$$v^* = \left(\frac{n_T + n_c}{n_T n_c} + \frac{\overline{ES}}{2(n_T + n_c)} \right) + \tau^2$$

$$v^* = \left(\frac{25 + 25}{(25 * 25)} + \frac{0.67}{2(25 + 25)} \right) + 3$$

$$v^* = \left(\frac{50}{(625)} + \frac{0.67}{100} \right) + 3$$

$$v^* = (0.08 + 0.0067) + 3$$

$$v^* = (0.08 + 0.0067) + 3$$

$$v^* = 3.08$$

Following this, the variance weighted by the number of included studies is as follows:

$$v_o = \frac{v^*}{k}$$

$$v_o = \frac{3.08}{10}$$

$$v_o = 0.308$$

Next, we find the mean of the Z statistic normal distribution:

$$\lambda = \frac{\overline{ES} - 0}{\sqrt{v_o}}$$

$$\lambda = \frac{\overline{ES} - 0}{\sqrt{v_o}}$$

$$\lambda = \frac{0.67 - 0}{\sqrt{0.308}}$$

$$\lambda = \frac{0.67}{0.555}$$

$$\lambda = \frac{0.67}{0.555}$$

$$\lambda = 1.207$$

Finally, the two-sided random effects power analysis:

$$p = 1 - \Phi(c_\alpha - \lambda)$$

where $c_{\alpha} = 1.96$

$$p = 1 - \Phi(1.96 - 1.207)$$

$$p = 1 - \Phi(1.96 - 1.207)$$

$$p = 1 - \Phi(0.753)$$

and $\Phi(0.753)$ is the standard normal cumulative distribution function, which is calculated with =normsdist(0.753) in excel. This results in:

$$p = 1 - 0.774$$

$$p = 0.23$$

Thus, with these estimated meta-analysis parameters, there is low power to detect a true population effect of $d = 0.67$, and only a 23% chance of correctly rejecting a false null hypothesis (or a high probability of Type II error). With the parameters estimated as they are here, it would not be appropriate to conduct a meta-analysis of this topic until more randomized controlled trials of the topic are conducted.

Power analyses were also conducted for a variety of other estimated parameters (see below). For studies with a large degree of heterogeneity, an average effect size of 0.67, and 25 patients per group, a minimum of 55 randomized controlled trials would be required to reach 80% statistical power. Similarly, with a moderate degree of heterogeneity between studies, the same effect size and patient group, a minimum of 34 randomized controlled trials would be required to meet 80% statistical power. Finally, with a low degree of heterogeneity between studies, and the same effect size and patient group, a minimum of 19 randomized controlled trials would be required to meet 80% statistical power.

Power calculations using varied estimated study parameters

Population variance (τ^2)	Included studies (k)	Effect Size ($\overline{ES}$)	Group size (n_T / n_c)	Power (p)
3	10	0.1	25	0.04
3	10	0.3	25	0.08
3	10	0.67	25	0.23
3	10	0.8	25	0.30
1.86	10	0.1	25	0.04
1.86	10	0.3	25	0.10
1.86	10	0.67	25	0.33
1.86	10	0.8	25	0.44
1.00	10	0.1	25	0.05
1.00	10	0.3	25	0.15
1.00	10	0.67	25	0.53
1.00	10	0.8	25	0.68
3	50	0.1	25	0.06
3	50	0.3	25	0.23
3	50	0.67	25	0.77
3	50	0.8	25	0.90
1.86	50	0.1	25	0.07
1.86	50	0.3	25	0.33
1.86	50	0.67	25	0.92
1.86	50	0.8	25	0.98
1.00	50	0.1	25	0.10
1.00	50	0.3	25	0.53
1.00	50	0.67	25	0.99
1.00	50	0.8	25	0.99
3	10	0.1	10	0.04
3	10	0.3	10	0.08
3	10	0.67	10	0.22
3	10	0.8	10	0.29
1.86	10	0.1	10	0.04
1.86	10	0.3	10	0.10
1.86	10	0.67	10	0.31
1.86	10	0.8	10	0.42
1.00	10	0.1	10	0.05
1.00	10	0.3	10	0.14
1.00	10	0.67	10	0.49
1.00	10	0.8	10	0.63
3	50	0.1	10	0.06

3	50	0.3	10	0.22
3	50	0.67	10	0.75
3	50	0.8	10	0.88
1.86	50	0.1	10	0.07
1.86	50	0.3	10	0.31
1.86	50	0.67	10	0.91
1.86	50	0.8	10	0.98
1.00	50	0.1	10	0.09
1.00	50	0.3	10	0.49
1.00	50	0.67	10	0.99
1.00	50	0.8	10	0.99
3	10	0.1	40	0.04
3	10	0.3	40	0.08
3	10	0.67	40	0.23
3	10	0.8	40	0.30
1.86	10	0.1	40	0.04
1.86	10	0.3	40	0.10
1.86	10	0.67	40	0.33
1.86	10	0.8	40	0.45
1.00	10	0.1	40	0.05
1.00	10	0.3	40	0.15
1.00	10	0.67	40	0.54
1.00	10	0.8	40	0.69
3	50	0.1	40	0.06
3	50	0.3	40	0.23
3	50	0.67	40	0.77
3	50	0.8	40	0.90
1.86	50	0.1	40	0.07
1.86	50	0.3	40	0.34
1.86	50	0.67	40	0.93
1.86	50	0.8	40	0.98
1.00	50	0.1	40	0.10
1.00	50	0.3	40	0.54
1.00	50	0.67	40	0.99
1.00	50	0.8	40	0.99
3	55	0.67	25	0.81
1.86	34	0.67	25	0.80

Example Meta-Analytic Approach

Meta-analysis is a technique used to estimate the mean and variance of a group of studies in an attempt to determine population effects (Field and Gillett, 2010). In this case, we are looking to determine the effects of using CBT-I as a treatment for depression.

Original List of articles to be included:

In-person and telehealth CBT-I, RCT Design:

1. Ashworth, 2015
2. Carney, 2017
3. Manber, 2008
4. Manber, 2016
5. Pigeon, 2017
6. Watanabe, 2011
7. Christensen, 2016
8. Batterham, 2017*
9. Blom, 2015
10. Blom, 2017*

* indicates a follow-up time period of a previous study

Relevant information about these studies:

Study	Active or sham control?	Antidepressants?	Duration	In-person or telehealth?	Notes
Ashworth 2015	Active (In-person vs telehealth)	Antidepressants	8 weeks	Compared	Compares CBT-I to CBT-I
Carney 2017	Active (antidepressants)	Antidepressants and None	8 weeks	In-person	
Manber 2008	Sham (quasi-desensitization control)	Antidepressants	9 weeks	In-person	
Manber 2016	Sham (quasi-desensitization)	Antidepressants	16 weeks	In-person	

	control)				
Pigeon 2017	Sham (sleep hygiene)	?	4 weeks	Combined	
Watanabe 2011	Active (TAU)	Antidepressants	4 weeks	In-person	
Christensen 2016	Sham (placebo online program)	1 % of sample	6 weeks	Telehealth	
Batterham 2017*	Sham (placebo online program)	1% (No)	6 weeks	Telehealth	Follow-up data
Blom 2015	Active (online CBT-D)		9 weeks	Telehealth	
Blom 2017*	Active (online CBT-D)		9 weeks	Telehealth	

Since effect sizes would vary considerably depending on the control group (e.g. sham versus active), we will choose one to use to complete this meta-analysis, and compare CBT-I to the sham treatments. Additionally, as we are looking at pre- to post-treatment values, we must exclude the results of the Batterham 2017 study, which look at follow-up data of an already included study. Thus, a total of 4 studies will be included in this meta-analysis exercise.

As a note – at this point, it must be pointed out that the estimates used earlier in the power analysis calculation were overly optimistic, and thus this meta-analysis is even less powered than anticipated.

4 included studies:

Study	n	Duration	Modality	Effect Size (CBT-I vs sham), Cohen's d
Manber 2008	30	9 weeks	IP	d = 0.27
Manber 2016	150	16 weeks	IP	d = -0.07
Pigeon 2017	27	4 weeks	B	d = 0.06
Christensen 2016	1149	6 weeks	T	d = 0.69

Effect Size Calculations:

- Manber 2008: direct from the published paper
- Manber 2016: See Calculation A, below
- Pigeon 2017: See Calculation B, below
- Christensen 2016: direct from the published paper

Calculation A

From Figure 3B (approximate values):

- Baseline CBT-I HDRS-R score: 17.5 (SD 3.5)
- Baseline Control HDRS-R score: 17.5 (SD 3.1)
- Week 16 CBT-I HDRS-R score: 8 (SD 7)
- Week 16 Control HDRS-R score: 7.5 (SD 7)

Thus, the change in HDRS-R score from baseline to week 16 is 9.5 for the CBT-I group and 10 for the Control group. Carrying forward the larger of the two standard deviations, the calculation of Cohen's d is as follows:

$$d = \frac{(M_1 - M_2)}{\text{pooled SD}} = \frac{9.5 - 10}{7} = -0.07$$

Calculation B:

From paper:

- Baseline CBT-I PHQ-9 score: 16.6 (SD 5.6)
- Baseline Control PHQ-9 score: 17.5 (SD 5.6)
- post-treatment CBT-I PHQ-9 score: 11.3 (SD 6.1)
- Post-treatment control PHQ-9 score: 12.6 (SD 6.3)

Thus, the change in HDRS-R score from baseline to post-treatment is 5.3 for the CBT-I group and 4.9 for the Control group. Carrying forward the larger of the two standard deviations, the calculation of Cohen's d is as follows:

$$\text{pooled SD} = \sqrt{\left(\frac{(SD_1^2 + SD_2^2)}{2}\right)} = \sqrt{\left(\frac{(6.1^2 + 6.3^2)}{2}\right)} = \sqrt{\left(\frac{(76.9)}{2}\right)} = 6.2$$

$$d = \frac{(M_1 - M_2)}{\text{pooled SD}} = \frac{5.3 - 4.9}{6.2} = 0.06$$

Using these effect sizes, we can now complete the meta-analysis (the weighted mean of effect sizes). As previously mentioned, given that effect sizes are likely not homogeneous between studies included in this systematic review, and the authors would like to generalize the results of a meta-analysis further than very similarly conducted studies, a random-effects meta-analysis would be the appropriate choice for this analysis (Field and Gillett, 2010).

To conduct the meta-analysis using the Hunter-Schmidt method:

Estimate of population effect:

$$\begin{aligned}\bar{r} &= \frac{\Sigma n_1 r_1}{\Sigma n_1} = \frac{(30 \times 0.27) + (150 \times (-0.07)) + (27 \times 0.06) + (1149 \times 0.69)}{30 + 150 + 27 + 1149} \\ &= \frac{8.1 - 10.5 + 1.62 + 792.81}{1356} = \frac{792.03}{1356} = 0.58\end{aligned}$$

You could then estimate credibility intervals, or use Hedges and colleagues' method to calculate confidence intervals and transformed effect sizes.

Appendix 2 Power analysis calculations for the CIHR Project grant

Estimated parameters:

Power $(1 - \beta) = 0.80 / 80\%$

$z_{1-\beta} = z_{.80} = 0.84$

Significance level $(\alpha) = 0.05 / 5\%$

$z_{1-\alpha/2} = z_{.975} = 1.96$

Primary outcome: change in MADRS score from baseline to post-treatment

Estimated group difference in primary outcome (Δ) from (Lam et al., 2016) = 4.6

Estimated standard deviation (σ) from (Lam et al., 2016) = 8.7

Comparing two means for continuous variables; formula to determine required study sample size (Zlowodzki et al., 2004):

$$n_1 = n_2 = \frac{\left(2(\sigma^2) \left(z_{1-\frac{\alpha}{2}} + z_{1-\beta}\right)^2\right)}{\Delta^2}$$

$$n_1 = n_2 = \frac{(2(8.7^2)(1.96 + 0.84)^2)}{4.6^2}$$

$$n_1 = n_2 = \frac{(2(75.69)(2.8)^2)}{21.16}$$

$$n_1 = n_2 = \frac{(151.38)(7.84)}{21.16}$$

$$n_1 = n_2 = \frac{1186.8192}{21.16}$$

$$n_1 = n_2 = 56.09$$

Given our estimated parameters, we determine that we will need to enroll 56 participants per study group, for a total of 112 study participants.

Appendix 3: Contributions

Jasmyn Emily Anne Cunningham (the author) solely created the work presented in this thesis. All aspects of this thesis were prepared by the author, including but not limited to research planning and execution (including all systematic reviews), analysis, and writing (including all aspects of this thesis, and the papers and grant proposal contained herein).

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Dr. Colin Shapiro (Thesis Supervisor) – guidance, assistance, and editing of the work contained in this thesis. Dr. Shapiro is a co-author of both systematic reviews contained herein.

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Dr. Robert Levitan (Thesis Committee Member) – guidance and assistance with the planning, execution, and interpretation of the work contained in this thesis.

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