The effect of chronotherapy on depressive symptoms
Evidence-based practice

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ABSTRACT

Depression is a complex disorder involving the interaction of genetic, physiological, psychological, and environmental factors, resulting in clinical manifestations that include a variety of affective, cognitive, somatic, and behavioral symptoms. As such, individuals experiencing depressive episodes exhibit variations in sleep/wake patterns (sleep architecture, sleep disturbances) and daily mood, in addition to abnormal levels of adrenocorticotropic hormone and cortisol secretion. Such depressive episodes are also characterized by impaired attention, altered food intake, learning and memory dysfunction, psychological stress, and decreased psychomotor functioning. These alterations are collectively referred to as chronobiological disruption.

Major depressive disorder (MDD) is characterized by the presence of persistently depressed mood (low mood); loss of interest or pleasure; feelings of grief, guilt, or worthlessness; decreased energy, disturbed sleep or appetite; poor concentration; and hopelessness.

According to the Fifth Edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), depression is diagnosed when the patient presents with substantial changes in functioning lasting at least 2 weeks (mood, pleasure, social, occupational, and psychomotor function).

In 2010, the Global Burden of Disease Study concluded that depression was the second greatest cause of disability worldwide, affecting an estimated 300
million people globally.\textsuperscript{6} Similarly, the World Health Organization (WHO) reported depressive disorder as a leading cause of disability worldwide, and that the condition affects an estimated 350 million people worldwide.\textsuperscript{4} Furthermore, the global prevalence of depression is increasing, along with rates of depression-associated disability and mortality, rendering depressive disorders a major public health issue.\textsuperscript{4,7} Briley and Lépine\textsuperscript{8} reported that approximately 10-15\% of people worldwide and 3-9\% in Japan are affected by depression. Moreover, Samuels et al\textsuperscript{9} stated that depression is the most common psychiatric condition in the United States, with a prevalence as high as 18.9\%. In addition, the symptoms of depression exert a substantial impact on occupational and social functioning, potentially increasing the economic burden. Indeed, a previous study estimated that the cost of treatment is approximately $2000 per citizen.\textsuperscript{10}

Although the fundamental treatment for depression involves pharmacotherapy,\textsuperscript{11,12} many people do not seek formal treatment with anti-depressive agents\textsuperscript{13} due to the high costs and risk of side effects, which can also prevent adherence once treatment has been initiated.\textsuperscript{14} Thus, individuals with depression may seek to decrease their symptoms via complementary and alternative medicine (CAM), which may be associated with fewer side effects. Samuels et al\textsuperscript{9} reported that the use of CAM is increasing, especially in patients diagnosed with anxiety and depression. However, there is no clear definition of what constitutes CAM.\textsuperscript{15} Furthermore, the National Health Service (NHS) has stated that there is no universally accepted definition of CAM,\textsuperscript{16} which often differs among various countries.\textsuperscript{17}

However, CAM has recently been defined to encompass therapies, interventions, and products that are regarded as equal in efficacy to conventional pharmacotherapy, with increased adherence and fewer side effects.\textsuperscript{18} Such treatments are often perceived as more natural, economical, and are available without the need for a prescription. According to the National Center for Complementary and Alternative Medicine (NCCAM), CAM includes a variety of medical and health care systems, interventions, and products not considered part of conventional medicine.\textsuperscript{19}

Research has indicated that certain psychosocial therapies and interventions may be as effective as medication in treating symptoms of depression,\textsuperscript{20} such as chronotherapy. Chronotherapy involves a variety of strategies that control exposure to environmental stimuli that influence the biological clock, such as sleep deprivation (SD) or wake therapy (WT), sleep phase advance (SPA), and light and dark therapy (LT, DT).\textsuperscript{21} Several studies have reported that chronotherapy is effective in the treatment of mood and sleep disorders, including depression.\textsuperscript{22}

According to Wirz-Justice and Terman,\textsuperscript{23} chronotherapeutics refers to nonpharmaceutical treatments designed to control exposure to external environmental stimuli that act on biological rhythms. Chronotherapy interventions are based on circadian rhythms, which direct a variety of biological processes on a near-24-hour cycle.\textsuperscript{24} Circadian rhythms are responsible for generating biologic rhythms and variations in the function of physiological and biochemical processes, such as the activity of the sleep-wake cycle and emotional state.\textsuperscript{25} These rhythms drive and synchronize neurotransmitter and hormone secretion, body temperature, and day-to-day stability according to pre-programmed patterns.\textsuperscript{26,27} The suprachiasmatic nucleus (SCN) is considered the circadian pacemaker.\textsuperscript{28} and contains high concentrations of serotonin and melatonin receptors.\textsuperscript{29} Chronotherapy aims to restore the balance of these neurotransmitter systems by resynchronizing circadian rhythms.\textsuperscript{30-32} Indeed, research has indicated that such treatment exerts a positive impact on depressive symptoms.\textsuperscript{33}

Although the author was unable to find studies regarding the prevalence of depression in Jordan, Hamid\textsuperscript{34} reported that the prevalence of depression was higher than 30\% among 493 randomly selected female patients. Additional studies have reported that depression is a major public health concern in developing countries,\textsuperscript{35} suggesting that the prevalence of depression may be high in Jordan.

**Methodology. PICOT Question Structure.** Recently, mental health research has focused on the use of evidence-based practice (EBP) for the development, promotion, and management of mental health treatment.\textsuperscript{36} Cleary defined EBP as the combined use of evidence from research and clinical experiences to aid in the clinical decision-making process. Evidence-based practice provides clinicians with guidance regarding the most appropriate and effective treatment interventions,\textsuperscript{38} also, the potential contribution of 4 types of evidence in the delivery of care: research, clinical experience, patient experience, and information from the local context.\textsuperscript{39}
Essential competency for nurses today is EBP to improve quality health care and increasing provider accountability, and PICOT question is one of the first EBP processes (P = population; I = intervention or area of interest; C = comparison; O = outcomes; T = timeframe in which to accomplish the first small tests of change). The author concluded evidence question (PICOT), which is, P = depression patients and depressive episode in the course of bipolar disorder patients; I = chronotherapy; C = placebo or antidepressant; O = enhance and reduce depressive symptoms; T = 4 months of the start of the intervention. The nurse using the levels of evidence to determine the strength of research studies, assess the findings, and evaluate the evidence for potential implementation into best practice. The purpose of this EBP paper is to answer PICOT questions by reviewing the effectiveness of chronotherapeutics interventions.

Depression patients and depressive episode in the course of bipolar disorder patients, what is the effect of chronotherapy (SD, WT, SPA, LT, DT) in enhancing and reduce depressive symptoms compared with placebo within 4 months of start to intervention? Depression patients and depressive episode in the course of bipolar disorder patients, what is the effect of chronotherapy (SD, WT, SPA, LT, DT) in enhancing and reduce depressive symptoms compared with an antidepressant within 4 months of start to intervention?

Search strategy. The electronic databases that were searched were as follows: EBSCO, PUBMED, MEDLINE, CINAHL, the PILOTS database, the Cochrane Library and Ovid database from 2007 to 2015 and some websites, such as the World Health Organization, American Psychiatric Association, National Health Service, National Center for Complementary and Alternative Medicine, American Academy of Sleep Medicine, and Chicago Psychiatry Associates, with the following combination of keywords: major depression, depression, chronotherapy, light therapy, sleep deprivation, sleep phase advance, and triple chronotherapy.

Literature review. Somatic therapy for the treatment of depression includes both pharmacological and psychological interventions, or techniques designed to manipulate the stimuli received by the patient, such as chronotherapy. Chronotherapy encompasses a variety of interventions such as SD and SPA, which manipulate the sleep/wake rhythm and LT/DT which alter exposure to the light/dark cycle. Research has increasingly focused on the use of these techniques in clinical practice as a result of their efficacy, rapidity of action, lack of side effects, low risk, and low cost. Furthermore, the combined use of multiple chronotherapeutic interventions or in conjunction with conventional psychiatric treatments may result long-lasting therapeutic effects. Moreover, increased use of these techniques in psychiatric settings may shorten hospitalization, increase the rate of recovery, and reduce the need for prescription changes. Here, we present an overview of the literature concerning light therapy, sleep deprivation, and triple chronotherapy.

Light therapy. In 2005, the American Psychiatric Association concluded that bright light therapy (BLT) can be used as a first-line treatment for seasonal affective disorder (SAD) and MDD. As this treatment is based on neurobiological principles, it has recently been established as the treatment of choice for SAD. Furthermore, studies have indicated that light exerts an anti-depressant effect in patients with non-seasonal depression. According to a report by the American Academy of Sleep Medicine (AASM), exposing the eyes to safe levels of intense, bright light for brief durations at strategic times of day synchronizes the body’s internal clock. Further research has indicated that the onset of depression can be prevented by modifying the color and intensity of light. The application of bright white light during the day has been shown to influence vision and the perception of the surrounding space.

Most studies utilizing BLT have involved exposure to white light with an intensity of 2,000-10,000 lux, with exposure time varying between 30-120 minutes per day. The duration of exposure is based on therapeutic responses at 2–4 weeks. Although exposure typically occurs in the morning, evening exposure is sometimes utilized to produce phase advances or phase delays. One randomized crossover study aimed to determine the efficacy of BLT in 28 adolescents (14-17 years old) with mild depressive disorder diagnosed based on DSM-IV criteria. In this study, the participants were divided into either a BLT (2,500 Lux) or placebo (50 lux) group. One group received placebo treatment for one hour each day for one week, followed by BLT for one week, while the opposite schedule was used for the other group. Beck's Depression Inventory (BDI) was used to assess depressive symptoms. The author reported significant improvements in BDI scores following BLT, with no
significant adverse reactions. Additional studies have suggested that BLT is effective in the treatment of older adults with MDD. One study involving 89 patients age 60 or older sought to compare the efficacy of exposure to pale blue light (7500 lux) (BLT group) and dim red light (50 lux) (placebo group). The intervention consisted of 3 weeks of treatment for 1 hour each day in the early morning, following which the BLT group exhibited improvements in mood, sleep efficiency, and melatonin levels.

Hizli et al further compared the effects of BLT monotherapy and combined BLT and fluoxetine-Selective Serotonin Reuptake Inhibitor (SSRI) therapy on symptoms of depression, circadian rhythms, and sleep quality in 15 participants with depression (age: 18-65 years). Participants of this study were diagnosed with depression using the Structured Clinical Interview for DSM-IV and subsequently divided into 2 groups. The first group of 7 patients received 10,000 lux of BLT for 30 minutes each day, for 7 days (drug-free patients). The second group of 8 patients received both BLT and fluoxetine therapy. Following BLT, patients of the drug-free group reported decreased severity of depressive symptoms on the Hamilton Depression Rating Scale (HAM-D), BDI, and Morningness-Eveningness Questionnaire (MEQ). Furthermore, positive effects on mood disturbance and sleep quality, as measured using the Profile of Mood States (POMS) and Pittsburgh Sleep Quality Index (PSQI), respectively, were observed in the drug-free group. However, no significant benefit of fluoxetine was observed in the combined-treatment group.

Sleep deprivation. Sleep deprivation (SD), also referred to as WT, is a chronotherapeutic intervention first described in the 1970s that involves remaining awake for long periods to reduce depressive symptoms. Responses are typically observed within 24-28 hours. Many studies on SD have supported its efficacy in quickly reducing depressive symptoms, with benefits observed in approximately 40-60% of patients. Although the mechanism of action remains unknown, the effects of SD are likely associated with alterations in the circadian system. Casher et al further suggested that SD increases levels various neurotransmitters including serotonin, dopamine, and norepinephrine.

Previous studies regarding SD have often utilized a 3-day schedule, delaying bedtime by 2 hours and requiring participants to remain awake for up to 36 hours. Such studies have reported that this technique may be effective in preventing relapse. Although the effects of SD are rapid, these effects are relatively short lasting, and relapse may occur following recovery of sleep. Vigilance (brain arousal) declines without stimulation from the external environment. Thus, this model provides a simple explanation for the effects of SD therapy in patients with affective disorders, as patients with depression often experience increased tiredness. Sleep deprivation (SD) may promote a state of hypervigilance, thereby reducing autoregulatory behavior. Moreover, Hegerl et al reported that affective disorders may have a pathogenetic role in the regulation of vigilance. Additional research has revealed that symptoms of withdrawal and sensation avoidance in MDD are autoregulatory reactions to a hyper stable regulation of vigilance and hyperarousal.

Martiny et al studied the effects of a one-week intervention phase during 9 weeks of WT in individuals receiving inpatient treatment for MDD. The authors investigated combined use of WT, LT, and sleep time stabilization (36 patients) compared with exercise therapy (38 patients), reporting a significant antidepressant and mood-enhancing effective of WT combined with LT and sleep time stabilization relative to exercise therapy.

Triple chronotherapy. Early studies on triple chronotherapy involving combined use of BLT, SD, and SPA have suggested that such therapy may produce rapid improvements in depressive symptoms. Despite these encouraging results, few studies have examined the effects of triple chronotherapy, as this field has just begun to emerge. Moscovici and Kotler examined the effects of a chronobiologic multistage intervention (CMI) in a study involving 12 patients with moderate-to-severe depression. The CMI was comprised of LT, SD, and SPA and was associated with significant improvements in depressive symptoms, which were maintained 30 days following the intervention. Furthermore, Sahlem et al explored the impact of triple chronotherapy intervention in 10 patients with depression experiencing acute suicidal ideation. Patients underwent SD for 33-36 hours, followed by SPA for 3 nights, with 4 BLT sessions of 30 minutes each morning. The results of this study indicated that the CMI produced significant improvements in depressive symptoms and mood. Wu et al further concluded that chronotherapy consisting of LT, SD, and SPA is effective...
Choronotherapy and depressive symptoms ... Khalifeh

Table 1 - Summary of the literature review included in this study.

<table>
<thead>
<tr>
<th>Authors &amp; year of publication</th>
<th>Objective</th>
<th>Design &amp; Intervention</th>
<th>Number of sample and setting</th>
<th>Results and tool</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Niederhofer &amp; von Klitzing50</td>
<td>To show a major improvement in mood and sleep among volunteers receiving 1 week bright light in contrast to placebo</td>
<td>Randomized crossover trial</td>
<td>14, 14</td>
<td>A significant improvement of BDI scores between treatment and placebo groups.</td>
<td>Level 2</td>
</tr>
<tr>
<td>Lieverse et al51</td>
<td>To determine the effectiveness of BLT in elderly patients with MDD</td>
<td>Double blind, placebo controlled randomized control trial</td>
<td>42, 47</td>
<td>BLT group shown enhanced and improved in mood, sleep efficiency and increased melatonin level</td>
<td>Level 2</td>
</tr>
<tr>
<td>Hizli Sayar et al52</td>
<td>To compare the effects BLT alone or in conjunction with fluoxetine (SSRI), on the severity of depression, daily rhythm, the mood disorder, and the quality of sleep in patients who suffer from non-seasonal depression</td>
<td>Randomized control trial</td>
<td>7, 8</td>
<td>BLT is effective with regard to the severity of depression, circadian rhythms, mood disturbance, and sleep quality, in nonseasonal depression and not showed supportive results of used fluoxetine with BLT on any evaluation scale</td>
<td>Level 2</td>
</tr>
<tr>
<td>Martiny et al60</td>
<td>To inquiry into, if the combination of WT, LT, and sleep time stabilization effect and prevent deterioration of depressive symptoms between at the end of the series of WT</td>
<td>Posttest randomized controlled trials</td>
<td>36, 38</td>
<td>A significant impact in WT in conjunction with LT and a positive in mood from exercise therapy</td>
<td>Level 2</td>
</tr>
<tr>
<td>Moscovici &amp; Kotler33</td>
<td>To investigate the effectiveness of the CMI on depression</td>
<td>Quasi experimental (one group pretest and posttest design)</td>
<td>12</td>
<td>Affect dramatically improve symptoms of depression and maintain for a period of 30 days after the intervention of the study</td>
<td>Level 3</td>
</tr>
<tr>
<td>Sahlem et al63</td>
<td>To identify the impact of triple chronotherapy intervention on depression patients with acute concurrent suicidality and on mood</td>
<td>Quasi experimental (one group pretest and posttest design)</td>
<td>10</td>
<td>The result was reduced and improved depressive symptoms and mood and the interventions were functional and accepted in suicidal and depressed patients.</td>
<td>Level 3</td>
</tr>
<tr>
<td>Wu et al56</td>
<td>To evaluate the effectiveness of the combination of three circadian-related treatments (SD, BL, SPA) as adjunctive treatment to lithium and antidepressants</td>
<td>Randomized controlled trials (pretestposttest equivalent group)</td>
<td>32, 17</td>
<td>Significant decreases in depression in the CAT versus medication patients over a 7-week period</td>
<td>Level 2</td>
</tr>
<tr>
<td>Echizenya et al61</td>
<td>To investigate the effect of combined chronotherapy on drug-resistant depression</td>
<td>Quasi experimental (one group pretestposttest design)</td>
<td>13</td>
<td>Significant improvements in depressive symptoms in HAMD17, SDS, and VAS</td>
<td>Level 3</td>
</tr>
</tbody>
</table>

BDI - beck depression inventory, BLT - bright light therapy, MDD - major depression disorder, HAM-D - hamilton depression scale, SSRI - selective serotonin reuptake inhibitors, MEQ - morningness-eveningness questionnaire, POMS - profile of mood states survey, PSQI - pittsburgh sleep quality index, WT - wake therapy, LT - light therapy, CMI - chronobiologic multistage intervention, SD - sleep deprivation, SPA - sleep phase advance, MADRS - montgomery-asberg depression rating scale, VAS - visual analogue scale, MUSC - Medical University of South Carolina, IOP - Institute of Psychiatry, CSSRS - Columbia Suicide Severity Rating Scale, YMRS - Young Mania Rating Scale, IDSSR - inventory of depressive symptoms-self report, PHQ-9 - Patient Health Questionaire-9, ESS - Epworth Sleepiness scale, SS - Scale for Suicidal Ideation, UCI - University of California Irvine, UCSD - University of San Diego, CAT - chronotherapeutic augmentation treatments, SDS - Zung Self-Rating Depression Scale, BL - bright light
when combined with pharmacological treatment (sertraline and lithium) in patients with bipolar disorder experiencing depressive episodes. In this study, 49 patients were divided into a chronotherapeutic augmentation treatment (CAT) group (32 patients) and a medication-only group (17 patients). Patients of the CAT group exhibited significant responses by day 2 of treatment, as well as improvements in depressive symptoms, over the 7-week intervention. Echizenya et al. conducted a study involving 13 participants receiving inpatient treatment for drug-resistant major depressive episodes. A 6-day combined chronotherapy protocol including one day of total SD followed by SPA and LT for 5 days was employed. Significant and rapid improvement in depressive symptoms and increases in mood were maintained over 3 weeks, without evidence of relapse or side effects.

Discussion. Several studies have concluded that chronotherapy exerts a positive effect on depressive symptoms. The studies discussed in this literature review are summarized in Table 1. Most studies in this literature review were double-blind RCTs, which are considered to provide level 2 evidence. Most of these studies recruited and divided patients randomly into 2 groups. The results of these studies provide satisfactory answers to the PICOT questions for SD or WT, SPA, LT, and DT.

The effect of chronotherapy in enhancing and reducing depressive symptoms compared with placebo treatments within 4 months of initiation is addressed by the first PICOT question. Our review revealed that LT is effective at reducing depressive symptoms, improving mood, and enhancing sleep efficiency in patients with depression when compared with placebo treatment. Furthermore, enhancements in these effects are observed when WT is combined with LT, and when triple chronotherapy (LT, SD, SPA) is utilized. The effect of chronotherapy in enhancing and reducing depressive symptoms compared with an antidepressant within 4 months of initiation is addressed by the second PICOT question. Our review revealed that BLT monotherapy more significantly improved the severity of depression, mood disturbance, and sleep quality than fluoxetine combined with BLT. Furthermore, we observed that CAT involving LT, SD, and SPA with medication resulted in improvements in depressive symptoms relative to chronotherapy alone.

Recommendations and implications. Recent guidelines provided by the American Psychiatric Association, World Health Organization, National Health Service, National Center for Complementary and Alternative Medicine, American Academy of Sleep Medicine, and Chicago Psychiatry Associates recommend the use of chronotherapy as a first-line treatment for depressive disorders in patients who refuse, resist, or cannot tolerate medication, or for whom medications may be contraindicated, as in a case of antepartum depression. Based on the present literature review, the author recommends the use of chronotherapy for the treatment of depressive symptoms, which appear to be effective and associated with few adverse effects relative to other treatments. However, future studies on chronotherapy should increase sample size, use new light devices, and more thoroughly compare combined use of SD and SPA to triple chronotherapy. Furthermore, as no studies regarding the use of chronotherapy in Jordan were identified, the author recommends that future studies focus on the use of such treatment in Jordan, given the global prevalence of depression. Our findings indicate that chronotherapy should be emphasized at the educational, research, and clinical levels. Educational and research systems should focus on the integration of chronotherapy methods. Although early studies have been published, further studies regarding chronotherapy in Jordan are required. In the clinical field, the use of this therapy may improve the quality of care, decrease hospitalization, and increase social functioning. As such, chronotherapy should be applied in psychiatric hospitals and clinics throughout Jordan.

The studies reviewed in this paper consist of randomized clinical trials and quasi-experimental studies involving 2 to 3 variables published from 2007 to 2015. These studies have several notable strengths, as follows: manipulation present, ethical implication available, high power and credibility, low selection bias, clearly identified control group and interventions, appropriate experimental design for evaluating the hypothesis, conducted in a natural setting, high external validity, clear conceptual framework, operationally and conceptually defined for dependent and independent variables, adequate background information, mention of the instrument's reliability, and validity. However, several limitations were also noted as follows: small sample size, no mention of the instrument's reliability, and validity.
reliability and validity, operationally and conceptually undefined dependent and independent variables; lack of clear theoretical and conceptual framework; non-random assignment, low internal validity, no inference regarding cause and effect; no control group; unclear application of theoretical framework; focus on an open study rather than a placebo-controlled study, unequal duration of treatment among patients; bias towards lower scores in “last hour” time window relative to those from longer time windows; lack of a control group, inclusion of patients with both unipolar and bipolar depression, and lack of standardized therapeutic drug regimens.

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References

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