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THE VALUE OF CHRONOTHERAPY IN DEPRESSION: A SYSTEMATIC REVIEW

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THE VALUE OF CHRONOTHERAPY IN DEPRESSION: A SYSTEMATIC REVIEW

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Table List

Abbreviations (Alphabetic Order)

BLT – Bright Light Therapy

HDRS – Hamilton Depression Rating Scale

TSD – Total Sleep Deprivation

Resumo

Introdução: A depressão é uma patologia frequente na população e está associada a elevadas taxas de incapacidade, faltando opções terapêuticas de atuação rápida para o seu tratamento. A cronoterapia é um procedimento não invasivo que reduz os sintomas depressivos mais precocemente do que os fármacos antidepressivos convencionais, mas a sua eficácia não está ainda estabelecida. O objetivo desta revisão foi avaliar a eficácia da cronoterapia na redução de sintomas depressivos a curto e longo prazo.

Métodos: Realizámos uma pesquisa na literatura em três bases de dados *online*: *PubMed*, *Web Of Science* e *Science Direct*, usando o algoritmo de pesquisa: "*chronotherapy AND* (*'depressive disorder' OR 'depression' OR 'bipolar disorder' OR 'mood disorder'*)". Incluímos 12 estudos que recrutaram um total de 562 doentes com Distúrbio Depressivo Major ou um episódio depressivo na Perturbação Bipolar.

Resultados: Os doze estudos incluídos usaram diferentes procedimentos de cronoterapia combinada. Foram administradas combinações variadas de privação de sono total, terapia de luz, avanço da fase de sono, privação de sono parcial e privação de ondas de sono lentas. Foram utilizados grupos de controlo em quatro estudos, e nos restantes oito utilizaram-se apenas grupos de intervenção. Os sintomas depressivos foram avaliados usando exclusivamente escalas baseadas em entrevistas. A maioria dos estudos utilizou versões adaptadas da *Hamilton Depression Rating Scale*, fazendo avaliações antes e após a intervenção, e estabelecendo critérios de resposta, tendo-se verificado uma redução significativa dos sintomas depressivos em todos os estudos. Para além disto, nos grupos de doentes em que foi usada cronoterapia verificou-se uma resposta sustentada superior àquela obtida nos grupos de controlo, com taxas de resposta e remissão mais altas nos grupos de cronoterapia no fim do follow-up, que variou entre 7 e 29 semanas.

Discussão: A cronoterapia atua em 24-48h e mostra evidências de sustentabilidade, mas ainda necessitamos de otimização dos procedimentos e a seleção criteriosa dos doentes é instrumental para obter o máximo benefício possível para o doente, já que a resposta à intervenção varia de acordo com a resistência à terapêutica farmacológica e doença de base. São necessários estudos adicionais com grandes amostras de maneira a formar grupos com elevada significância estatística e permitir a criação de grupos de controlo, bem como a avaliação de marcadores biológicos, no sentido de aumentar a evidência da utilização de cronoterapia em doentes deprimidos.

Palavras-chave: Cronoterapia; depressão; distúrbio depressivo major; doença bipolar; privação de sono; sintomas depressivos.

Abstract

Introduction: Depression is a major concern for world health and fast-acting therapeutic options for its treatment are lacking. Chronotherapy has emerged as a safe non-invasive procedure that ameliorates depressive symptoms faster than conventional antidepressant drugs, but its value requires further validation. The aim of this review was to assess the short and long-term effectiveness of chronotherapy interventions in depression.

Methods: We conducted a literature search on three online databases: *PubMed, Web Of Science* and *Science Direct*, using the search algorithm: "chronotherapy AND ('depressive disorder' OR 'depression' OR 'bipolar disorder' OR 'mood disorder')". We included twelve studies that recruited a total of 562 patients with Major Depressive Disorder or a depressive episode in Bipolar Disorder.

Results: The twelve included studies used distinct combined chronotherapeutic procedures. The trials administered different combinations of total sleep deprivation, light therapy, sleep phase advance, partial sleep deprivation and slow wave deprivation. Control groups were included in four studies, whereas the remaining eight used only intervention groups. Depressive symptoms were evaluated using exclusively interview-based rating scales. Most studies used adapted versions of the Hamilton Depression Rating Scale, administering it before and after intervention, and defined response criteria. A significant reduction in depressive symptoms was found in all of the twelve studies. Additionally, chronotherapeutic groups showed a superior sustained response throughout the studies, obtaining higher response and remission rates in the chronotherapy groups at the end of follow-up, which ranged from 7 to 29 weeks.

Discussion: Research shows that chronotherapy induces a rapid (24-48h) and sustained decrease in depressive symptoms. These results support the introduction of combined

chronotherapy in the treatment of depression. However, optimization of the procedures and careful selection of patients is needed in order to ensure maximum benefit, given that response can be influenced by drug resistance and previous disease. Future research should focus on concomitant biological measures and biomarkers in order to strengthen the accumulating evidence towards the effectiveness of chronotherapy.

Key words: Bipolar disorder; chronotherapy; depression; depressive symptoms; major depressive disorder; sleep deprivation.

Introduction

Depression affects 322 million people worldwide (4.4% of the world's population). Prevalence has increased 18.4% between 2005 and 2015, proportionally to the world's population growth. It is more common in females (5.1%) than in males (3.6%) (1). Depression's etiology, similarly to other mood disorders, is not fully understood, but it is known to be complex and multifactorial, involving neurotransmitter changes, neuroendocrine and neuroimmune regulation or brain structure abnormalities (2).

Remission occurs approximately after 5 to 7 weeks of treatment using pharmacotherapy and cognitive therapy in an effective regimen, but 33% of patients do not achieve remission and continue showing depressive symptoms, such as anxiety, insomnia, lack of concentration and other residual symptoms (3). For those who do achieve remission, there is a 50% probability of relapse during follow-up (4). For those who relapse, 65% do not seek medical care and carry on their depression for a median duration of 13 weeks. (5). The 5-7 week delay in therapeutic response is linked with early dropout (6) and increased suicidal risk (7). Furthermore, antidepressant medication is often related with side-effects and interactions with other medications that the patient may be prescribed (8). Even electroconvulsive therapy, which is currently the most dependable and effective tool in treatment resistant depression, still takes 2 to 3 weeks to exhibit therapeutic benefits (9). These inconveniences have led the industry to look for fast acting and safe pharmaceutical alternatives for the treatment of depression, but these novel drugs are not yet ready for clinical use (10). In summary, currently there are no commonly used treatments that rapidly treat depression (9) and the need for an alternative with a rapid onset of action and high safety is emergent (10).

Chronobiology studies biological rhythms, analyzing the effects of time on biological events and internal biological clocks. This field has been greatly developed in the past

decades. Many circadian rhythms are controlled by the suprachiasmatic nucleus (SCN) of the anterior hypothalamus, such as the sleep-wake cycle, core body temperature, mood, and psychomotor performance (11). The SCN can respond to and be influenced by external environmental cues, such as temperature, food intake and the day/night cycle. Circadian rhythm disruptions are related with mood disorders and depression, and currently sleep-wake disruptions are part of the diagnostic criteria for Major Depressive Disorder. Previous studies point to circadian rhythm disturbances, such as phase advance in hormonal rhythms (12), and it has been shown that selective serotonin reuptake inhibitors accelerate these rhythms (13). BLT in the early morning induces phase advances, which can ameliorate depressive symptoms (12).

Sleep deprivation has shown anti-depressive properties, reducing depressive symptoms, especially in Major Depressive Disorder and depressive episodes in Bipolar Disorder. The response is noticeable very shortly after the deprivation (within 24-48 hours). However, there is still a concern for relapse following sleep deprivation, which has led researchers to simultaneously use other chronotherapeutic interventions, namely Bright Light Therapy (BLT) and Sleep Phase Advance (SPA) (14). A Triple Chronotherapy protocol has been used in recent studies, comprising of a single Total Sleep Deprivation (TSD) night followed by a 3-day SPA and 3 or 5 days of BLT (9,15,16). Researchers have also used another protocol, which consists of three TSD cycles (36h of sleep deprivation, followed by a sleep recovery night, and BLT during the TSD night and in the morning after recovery sleep) (17–23).

The aim of this systematic review is to assess whether chronobiological interventions are capable of achieving a significant and sustained response in patients diagnosed with Major Depressive Disorder or Bipolar Disorder.

Methods

Search strategy

A systematic search was performed on three online databases: *PubMed, Web Of Science* and *Science Direct*, using the search algorithm: "chronotherapy AND ('depressive disorder' OR 'depression' OR 'bipolar disorder' OR 'mood disorder')". The authors identified 245 articles, and 210 remained after removing duplicates. Titles and abstracts were appraised and, according to previously established inclusion and exclusion criteria, 19 articles were selected for full text analysis. After this assessment, seven studies were excluded: two did not assess depressive symptoms following chronotherapy intervention, three were designed as case reports, one was a review and one was written in French. The remaining 12 studies met the inclusion criteria and were included in this review. The search procedure is summarized in a flow chart (Fig.1).

Eligibility Criteria

We considered studies regardless of publishing date. They were further analyzed if they met the following inclusion criteria: (1) empirical quantitative studies (2) articles written in English (3) studies in humans (4) population diagnosed with major depressive disorder or bipolar disorder in a depressive phase (5) at least one chronotherapy intervention regarding depression management (6) having a standardized assessment of depressive symptoms before and after the intervention. We excluded reviews, case reports, and opinion articles.

Quality assessment

An adapted version of the Newcastle-Ottawa Quality Assessment Scale was used to evaluate the quality of the included studies. This scale uses a "star system" to rate the studies in three categories: high, moderate and low quality. The score is attributed concerning the

following criteria: the selection of the study groups, the comparability of cohorts on the basis of the design, the assessment of outcome and the adequacy of the follow up. The authors attributed one star to studies that fulfill each one of the following criteria: the exposed cohort is truly or somewhat representative of the psychiatric population with a diagnose of depression; the non-exposed cohort was drawn from the same community as the exposed cohort; the initial depression diagnose was made through a secure record or a validated method; follow-up for >3 weeks; complete follow-up (all subjects accounted for) or description of those lost. Two stars were attributed to studies that controlled for confounders, such as sociodemographic and illness variables (Table 1).

Data Analysis

In order to establish the effectiveness of chronotherapeutic interventions in depression, we extracted the following data from the studies: year, author, country, sample size~~,~~ duration and follow up time, depressive symptoms assessment, and a description of relevant results.

Fig. 1 Flow chart illustrating the search procedure.

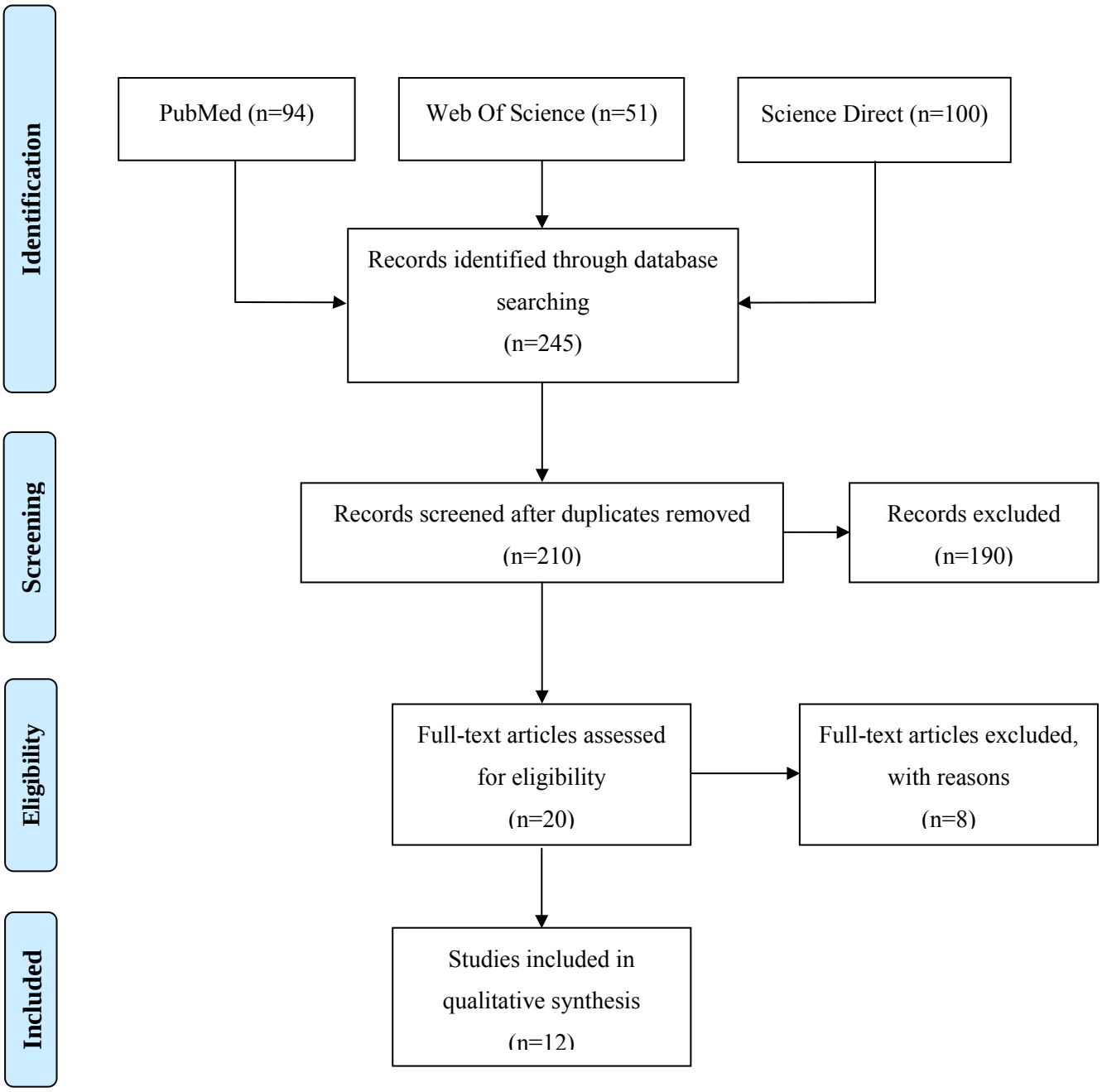

Table 1 Quality ratings for the reviewed studies on the basis of the Newcastle-Ottawa quality assessment scale (adapted)

	Selection			Comparability	Outcome			Total Score
	Representativeness of the Exposed Cohort	**Selection of the Non-Exposed Cohort**	**Ascertainment of exposure**	**Control for confounders**	**Assessment of outcome**	**Follow up period after intervention**	**Adequacy of follow up**	
Kragh et al, 2017, Denmark	Somewhat representative of the psychiatric population *	Drawn from the same community as the exposed cohort *	Structured interview *	Study controls for sociodemographic variables, somatic conditions, depression state, self-efficacy and social function. **	Independent assessment *	8 weeks *	Description provided of those lost *	8
Martini et al, 2012, Denmark	Somewhat representative of the psychiatric population *	Drawn from the same community as the exposed cohort *	Secure record *	Controls for sociodemographic and illness variables. **	Independent assessment *	20 weeks *	Complete follow up *	8
Martini et al, 2015, Denmark	Somewhat representative of the psychiatric population *	Drawn from the same community as the exposed cohort *	Structured interview *	Study controls for sociodemographic and illness variables. **	Independent assessment *	29 weeks *	Description provided of those lost *	8
Wu et al, 2009, USA	Somewhat representative of the psychiatric population *	Drawn from the same community as the exposed cohort *	Secure record *	Controls for sociodemographic and illness variables. **	Independent assessment *	7 weeks *	Description provided of those lost *	7
Benedetti et al, 2013, Italy	Somewhat representative of the psychiatric population *	N/A	Secure record *	Controls for sociodemographic and illness variables. **	Independent assessment *	4 weeks *	Description provided of those lost *	6
Moscovici et al, 2009, Israel	Selected group of patients	N/A	Secure record *	Controls for age. *	Independent assessment *	4 weeks *	Complete follow-up *	5
Suzuki et al, 2016, Italy	Somewhat representative of the psychiatric population *	N/A	Structured interview *	Study controls for sociodemographic and illness variables. **	Independent assessment *	-	N/A	5
Benedetti et al, 2008, Italy	Selected group of patients	N/A	Secure record *	Controls for sociodemographic and illness variables. **	Independent assessment *	-	N/A	4
Benedetti et al, 2009, Italy	Selected group of inpatients	N/A	Secure record *	Controls for sociodemographic and illness variables. **	Independent assessment *	-	N/A	4
Echizenya et al, 2013, Japan	Selected group of patients	N/A	Structured interview *	Study controls for sociodemographic and illness variables. **	Independent assessment *	-	N/A	4
Landsness et al, 2011, USA	Selected group of patients	N/A	Secure record *	Controls for sociodemographic and illness variables. **	Independent assessment *	-	N/A	4
Sahlem et al, 2014, USA	Selected group of patients	N/A	Structured interview *	Study controls for sociodemographic and illness variables. **	Independent assessment *	-	N/A	4

Total score – 0-8. 0-3 – low quality; 4-5 – moderate quality; 6-8 high quality

N/A not applicable

Results

The authors analyze the results of interview-based rating scales administered during clinical trials in order to determine the procedures' effect in depressive symptoms (Table 2).

Kragh, *et al*. 2017

Kragh *et al*. (17) conducted a randomized controlled trial which recruited hospitalized patients diagnosed with moderate to severe depression, for a nine-week follow-up period. The patients were divided into two groups: the control group received standard treatment for depression, whereas the chronotherapy group was submitted to TSD, consisting of three 36-hour awake periods in the first week, and BLT daily, for the whole duration of the study. Depressive symptoms were assessed weekly using the 17 item Hamilton Depression Rating Scale (HDRS-17) and the 6 item Hamilton Depression Rating Scale (HDRS-6). Response was defined as a 50% reduction or more from baseline on the HDRS-17 and remission was defined as a score of <8 in HDRS-17. There was a significant improvement in the HDRS-17 score in both groups from baseline (mean HDRS-17 scores of 22.9 in the chronotherapy group and 22.5 in the control group) to week nine (mean HDRS-17 scores of 14.0 in the chronotherapy group and 13.0 in the control group). In the first week, there was a significantly higher reduction in depressive symptoms in the chronotherapy group (HDRS-17 score 17.39), compared to the control group (HDRS-17 score 20.19). However, the study revealed no statistically significant differences between groups in weeks two to nine, which shows that the antidepressant effect initially attained with the combined chronotherapeutic intervention, could not be sustained.

Martiny *et al.*, 2012, 2015

Martiny *et al,* conducted a randomized controlled trial in 75 patients with a diagnosis of Major Depressive Disorder. Patients were followed for 29 weeks. At the beginning of the trial, patients were given pharmacological treatment and were allocated to either a chronotherapeutic intervention (TSD, BLT and sleep time stabilization) or to a group with a daily exercise program.

The first 9 weeks are reported in Martiny *et al,* 2012 (19). The study aimed to determine whether a chronotherapeutic intervention combined with duloxetine treatment could induce a rapid and sustained reduction in depressive symptoms. Patients were evaluated every week for 9 weeks, using the HDRS-17, HDRS-6 and Hamilton Melancholia Scale (MES). Response was defined as a 50% reduction or more from baseline on the HDRS, and remission was defined as a score of <8 in HDRS. At baseline, there was a mean HDRS-17 score of 23.9 for the chronotherapy group and 22.3 for the control group. Both groups responded effectively to treatment, however the authors found significantly higher remission and response rates in the chronotherapy group versus the exercise group, with 41.4% response and 23.9% remission rates in the chronotherapy group, and 12.8% response and 5.4% remission rates in the exercise group. ($p=0.003$ and $p=0.004$, respectively) in week 2. These superior response and remission rates were sustained for the whole study period, showing a 71.4% response and 45.6% remission rates in the chronotherapy group, while the exercise group obtained 47.3% response and 23.1% remission rates at endpoint.

In 2015, the authors reported the last 20 weeks (follow up phase) to assess whether the additional effect of chronotherapy in depressive symptoms could be maintained with continued use of BLT and Sleep Time Stabilization (STS) (18). Depressive symptoms were assessed at baseline and every 4 weeks thereafter, using the HDRS-17, HDRS-6 and MES scales. Response was defined as a 50% reduction or more from baseline on the HDRS and

remission was defined as a score of <8 in HDRS. The study showed high remission rates in both groups, with statistically significant higher remission rates (61.9%) in the chronotherapy group compared with the exercise group (37.9%) at endpoint (p=0.01). However, there was no significant difference in endpoint response rates between the groups (74.6% in the chronotherapy group versus 64.4% in the exercise group, p=0.22). Mean scores on HDRS-17 revealed a significantly higher reduction in depressive symptoms in the chronotherapy group (mean HDRS score of 7.5) compared with the exercise group (mean HDRS score of 10.1) (p=0.02).

Wu *et al*, 2009

Wu *et al.* conducted a 7 week randomized controlled trial, selecting 49 patients who met criteria for Bipolar Disorder with a depressive episode (16). The patients were randomly divided in two groups: a medication-only group and a group with a chronotherapeutic augmentation treatment. All patients were started on lithium 1 week prior to the sleep deprivation night. Furthermore, sertraline was administered to every patient (intolerant patients were given an alternative antidepressant). The chronotherapy group was administered one TSD night, followed by 3 nights of SPA and BLT. For depressive symptoms' assessment, the authors used the HDRS-19 scale daily in the first week, and weekly thereafter. Response rate was defined as a 50% decrease in HDRS ratings, and remission included response plus an HDRS rating ≤7 at the end of the follow-up. At baseline, the chronotherapy group showed a mean HDRS-17 score of 19.0 and the control group showed a mean HDRS-17 score of 18.5. Results showed a significant decrease in depressive symptoms in the chronotherapy group versus the medication group in every assessment except for day 6, and a significantly higher response rate in the chronotherapy group in weeks 1 and 7, showing 63% response rate in the chronotherapy group, non-specified in the control group. Significant differences in depression

scores (HDRS) occurred as early as day 2 (11.2 vs 15.1 in the chronotherapy vs control groups) and were sustained for 7 weeks (scores of 10.1 in the chronotherapy group and 15.2 in the control group at the end of 7 weeks).

Benedetti *et al*, 2013

Benedetti *et al.* (23) gathered 141 participants diagnosed with a major depressive episode without psychotic symptoms in the course of Bipolar Disorder. The clinical trial lasted for 6 days, however, the patients were followed for an additional month. The patients' data was divided into 4 groups, according to previous history of suicide attempts and response to treatment. Patients who had been taking lithium continued it, and the others started taking it together with the chronotherapeutic intervention. Every patient was administered 3 consecutive TSD cycles (36h awake, with recovery night sleep on the following nights, BLT at 03h00 in the TSD night and 30 minutes after awakening in the morning after recovery sleep, for 30 minutes). Data was collected using the HDRS-21, on days 0, 1, 2 and 6. The baseline HDRS score was 23.76 for responders with positive history of attempted suicide, 21.60 for non-responders with positive history of attempted suicide, 23.27 for responders with positive negative history of attempted suicide and 23.59 for non-responders with negative history of attempted suicide. Response was defined as a 50% reduction or more from baseline on the HDRS. There was a significant response rate to treatment (70.1%). Ongoing treatment with lithium conferred an advantage comparing to newly started lithium, but with similar final scores. There was a 21% relapse rate in the following 4 weeks which lowers the success rate to 55.3% of patients achieving a sustained response.

Moscovici *et al*, 2009

In this pilot study (24), the authors included a set of 12 patients with moderate to severe depression. Exclusion criteria included the use of antidepressant drugs in the 5 weeks prior to the intervention, and no antidepressants were administered during the trial. The authors designed a chronobiologic multistage intervention, including four days of partial sleep deprivation, dawn simulation, BLT and SPA. The researchers used the HDRS-21 and Montgomery-Asberg Depression Clinician Rating Scale (MADRS) scales in order to evaluate depressive symptoms. Response was defined as a 50% reduction or more from baseline on the HDRS and MADRS, partial response was defined as a reduction greater than 25% but smaller than 50% and remission was defined as a score of <8 in HDRS and <13 in MADRS. The scales were used on the day before the chronotherapy intervention, followed by a set of four consecutive daily measurements between days 1 to 4, and after a 4 week follow-up. Results showed a statistically significant improvement of depressive symptoms in every patient, in relation to the HDRS-21 scores (mean scores of 27.58 at baseline and 8.9 at endpoint, $p<0.001$) and the MADRS scores (mean scores of 29.33 at baseline and 7.33 at endpoint, $p<0.001$).

Suzuki *et al,* 2016

Suzuki *et al.* (20) studied 147 patients diagnosed with Bipolar Disorder who met the criteria for a major depressive episode, without psychotic symptoms. The patients were administered three TSD cycles (each cycle includes one sleepless night followed by one recovery sleep night), and BLT at 3 am during the sleep deprivation night and in the morning after recovery sleep. Lithium was administered to every patient, 74 patients had already been taking lithium and continued it, and 73 started it together with the chronotherapy procedure

(there was no significant difference in response rates in these two groups). None of the patients was administered any other antidepressant. Depressive symptoms were rated using a modified version of the HDRS-21 (HDRS-NOW) on days 0, 1, 2 and 6. Response was defined as a 50% reduction or more from baseline on the HDRS. Mean HDRS-21 scores were 23.9 for the whole sample at baseline. At endpoint, approximately 66% of patients responded to treatment (mean HDRS-21 scores of 8.3), showing a 50% reduction of HDRS scores.

Benedetti *et al*, 2008

Benedetti and colleagues investigated the correlation between the Glutamate and glutamine/Creatine ratio (Glx/Cr) and depressive symptoms, recruiting 19 patients diagnosed with type I Bipolar Disorder, in a depressive episode without psychotic features (22). Every patient underwent three consecutive TSD cycles (each cycle consisted of a 36h wake period, followed by a recovery sleep night), and BLT at 3h a.m. during the TSD night, and in the morning after recovery sleep. Patients were not taking any drugs besides lithium. Depressive symptoms were assessed daily for 1 week, using an adapted version of the Hamilton Depression Rating Scale (HDRS-NOW). Response was defined as a 30% reduction or more from baseline on the HDRS. Results showed a significant reduction in the HDRS, which varied from a mean score of 20.84 at baseline to 9.42 at endpoint. There was a response rate of 78.9%.

Benedetti *et al*, 2009

In this study, Benedetti *et al.* (25) recruited 39 patients diagnosed with Bipolar Disorder with a depressive episode without psychotic features. Every patient underwent three consecutive TSD cycles, which comprised a 36h period of wakefulness followed by one night of sleep recovery. They were also administered BLT at 3 am during the TSD night and in the morning after the recovery sleep night. Depressive symptoms were evaluated using the Hamilton Depression Rating Scale 21-item version (HDRS-21) on days 1, 2, 3 and 7. Clinical response was defined as a reduction of 50% in the HDRS-21 score, and was achieved by two-thirds of the patients. Patients were divided in responders and non-responders according to response to chronotherapy. Response rates were slightly higher in patients without drug resistance history (76%) than in drug resistant patients (54%). Patterns of mood change differed significantly between responders and non-responders, showing mean HDRS scores of 23.00 for responders/21.23 for non-responders at baseline, and 7.15 for responders/17.31 for non-responders at endpoint.

Echizenya *et al*, 2013

The authors studied 13 inpatients with a depressive episode in the course of Major Depressive Disorder or Bipolar Disorder. All of them were considered drug-resistant and refractory to conventional treatment. Patients received one night of TSD, followed by three days of SPA and five days of BLT, and were observed for a total of three weeks. Depressive symptoms were assessed using the Hamilton Depression Rating Scale 17-item version (HDRS-17) once a week (i.e. on days -1, 6, 13 and 20) and the Hamilton Depression Rating Scale 6-item version (HDRS-6) scales on day 1 to day 6, and. Response was defined as a 50% reduction or more from baseline on the HDRS. The study demonstrated a clinically significant

improvement of depressive symptoms among drug-resistant patients: mean HDRS-6 scores decreased from 11.62 on at baseline (day -1) to 6.25 on day 6; mean HDRS-17 scores changed from 19.77 at baseline (day -1) to 8.46 at endpoint (day 20) (15).

Landsness *et al*, 2011

Landsness and coworkers explored the role of slow wave sleep deprivation in 17 patients affected with Major Depressive Disorder, who were medication free for ≥6 months before selection. The trial comprised three overnight sessions: baseline, slow wave deprivation and recovery sleep nights. In order to perform slow wave deprivation, patients were monitored using a high density EEG during sleep, such that whenever a slow wave was visually detected, an auditory tone would be delivered to the patient, suppressing slow waves without awakening the subject. The authors used a modified version of the HDRS-17 scale, the HDRS-13, for evaluation of depressive symptoms, in a daily frequency. Results showed significant reduction in depressive symptoms according to HDRS (mean scores of 10.67 before slow wave deprivation and 7.83 in the morning after slow wave deprivation, p=0.01) (26).

Sahlem *et al*, 2014

This pilot study (9) included 10 participants with non-psychotic Major Depressive Disorder or Bipolar Disorder for a 1 week trial. Each patient underwent the same Triple Chronotherapy procedure (one night TSD, followed by a 3 day SPA, with BLT every morning). In order to assess the patients' depressive symptoms, the HDRS-17 scale was used at baseline prior to TSD, and at protocol completion on day five. Remission was defined as a

HDRS-17 score of 7 or lower, and response as a 50% drop in score from baseline. At endpoint, there was a significant decrease in depressive symptoms, with a HDRS-17 score decreasing from an average of 24.7 on day 0 to a score of 9.4 on day 5, which was higher than expected if the participants were only treated with regular pharmacotherapy and psychotherapy.

Table 2 Characteristics of the reviewed studies

Author year country	Sample Size	Follow up Period	Intervention		Depressive Symptoms' Assessment		Results
			Chrono therapy Group	Control Group	Scale	Timing	
Kragh et al, 2017, Denmark	40	9 weeks	TSD BLT Ad	Ad	HDRS-17	Weekly	In the first week, there was a significantly higher reduction in depressive symptoms in the chronotherapy group (mean HDRS-17 17.39 CTG vs 20.19 CG, p=0.04). No statistically significant differences between the two groups were found after the first week.
Martini et al, 2012, Denmark	75	9 weeks	TSD BLT STS Dul	Exercise program	HDRS-17 HDRS-6 MES	Weekly	Significantly higher response and remission rates in the chronotherapy group versus the exercise group (mean HDRS response/remission 41.4%/23.9% CTG, 12.8%/5.4% CG p=0.003 and p=0.004 respectively, in week 2). The superior response and remission rates were sustained for the whole study period. (mean HDRS response/remission 71.4%/45.6% CTG; 47.3%/23.1% CG)
Martiny et al, 2015, Denmark	75	20 weeks	TSD BLT Ad	Exercise program	HDRS-17 HDRS-6 MES	Baseline and every 4 weeks	Remission rates were high in both groups, but significantly higher in the chronotherapy group (61.9%) compared with the exercise group at endpoint (37.9%) (*p=0.01*). Response rates were not statistically different between groups. (HDRS 74.6% CTG vs. 64.4% CG, p=0.22) Mean scores on HDRS-17 showed a significantly higher reduction in depressive symptoms in the chronotherapy group (7.5 CTG vs 10.1; CG p=0.02).
Wu et al, 2009, USA	49	7 weeks	TSD BLT SPA Ad	Ad	HDRS-17	Daily in week 1 Weekly in weeks 1-7	Significant decrease in depressive symptoms in the chronotherapy group, compared to the control group, in every assessment except for day 6. Significant differences in depression scores (HDRS) occurred as early as day 2 (11.2 CTG/15.1CG and were sustained for 7 weeks (10.1 CTG/15.2 CG).
Benedetti et al, 2013, Italy	141	5 weeks	TSD BLT Lithium	N/A	HDRS-21	Days 0, 1, 2 and 6	Significant response rate (70,1%) to treatment. Ongoing treatment with lithium conferred an advantage comparing to newly started lithium, but with similar final scores. 21% relapse rate in the following 4 weeks lowers the success rate to 55,3% of patients achieving a sustained response.

Moscovici et al, 2009, Israel	12	4 weeks	PSD BLT SPA	N/A	HDRS-21 MADRS	Baseline, days 1 to 4 and at endpoint	Statistically significant improvement of depressive symptoms in every patient, in relation to the HDRS-21 scores (p<0,001) and the MADRS scores (p<0,001).
Suzuki et al, 2016, Italy	147	6 days	TSD BLT Lithium	N/A	HDRS-21	Days 0, 1, 2 and 6	Approximately 66% of patients responded to treatment, showing a 50% reduction of HDRS scores.
Benedetti et al, 2008, Italy	19	1 week	TSD BLT Lithium	N/A	HDRS-21	Daily	The chronotherapeutic treatment was associated with a statistically significant reduction of depressive symptoms (HDRS 20.84 at baseline vs. 9.42 at endpoint). Response rate of 78.9%
Benedetti et al, 2009, Italy	39	7 days	TSD BLT Ad	N/A	HDRS-21	Days 1, 2, 3 and 7	Response rate of 66%. Response rates were slightly higher in patients without drug resistance history (76%) than in drug resistant patients (54%) (p=0,30) Patterns of mood change differed significantly between responders and non-responders, with significant changes after every TSD cycle.
Echizenya et al, 2013, Japan	13	22 days	TSD SPA BLT Ad	N/A	HDRS-17 HDRS-6	Days 1 to 6, day 13 and 20	Significant decrease in depressive symptoms in every assessment (mean HDRS-6 11.62 at baseline/6.25 on day 6; mean HDRS-17 19.77 at baseline/8.46 at endpoint).
Landsness et al, 2011, USA	17	4 days	SWD	N/A	HDRS-13	Daily	Participants experienced a significant reduction in depressive symptoms according to HDRS scores (mean HDRS 10.67 pre-SWD/7.83 post-SWD, p=0,01).
Sahlem et al, 2014, USA	10	1 week	TSD SPA BLT Ad	N/A	HDRS-17	Baseline and in day 5	Significant decrease in depressive symptoms (mean HDRS 24.7 on day 0 and 9.4 on day 5).

N/A not applicable; CTG Chronotherapy group; CG Control Group BLT Bright Light Therapy; PSD Partial Sleep Deprivation; SPA Sleep Phase Advance; STS Sleep Time Stabilization; STS Sleep Time Stabilization; SWD Slow Wave Deprivation; TSD Total Sleep Deprivation; Dul Duloxetine; Ad pharmacological treatment of depression, including antidepressants and other treatment groups; MADRS Montgomery-Asberg Depression Clinician Rating Scale; MES Hamilton and Melancholia scales; HDRS-6 Hamilton Depression Rating Scale, 6 item version; HDRS-17 Hamilton Depression Rating Scale, 17 item version; HDRS-21 Hamilton Depression Rating Scale, 21 item scale.

Discussion

Multiple clinical trials using chronotherapeutic interventions have been performed over the last decade, showing that is a viable option in short and long-term treatment of depressive symptoms in Major Depressive Disorder and Bipolar Disorder. In the twelve included studies, a total of 562 patients were recruited and completed treatment and follow up. Depressive symptoms were evaluated using adapted versions of the HDRS, the MES and the MADRS.

Considering the studies analyzed in this review, those which used control groups showed the most reliable results., In the study by Martiny and colleagues (18,19), the reductions were significantly higher for the chronotherapy group than the control group, with response rates at 9 weeks of 71.4% and 47.3% and remission rates of 45.6% and 23.1%, respectively and this superiority was partially maintained for the whole 29-week follow up period, with signicantly higher remission rates for the chronotherapy group, but non-statistically significant differences in response rates between the two groups at endpoint. These results match an earlier publication by Wu *et al.* (16), which showed that the significant superiority in the chronotherapy group was sustained for 7 weeks. However, the article by Kragh and collaborators did not corroborate the long-term antidepressant effect of chronotherapy, presenting a significantly higher decrease in depressive symptoms solely in the first week of treatment. This could be due to a number of singularities in this study. For instance, most patients presented unipolar depression, previous resistance to treatment and antipsychotic medication. Research shows that patients with Bipolar Disorder tended to respond better to Chronotherapy than those with unipolar depression (27). Thus, unipolar patients improve in response to chronotherapy, but not as fast as bipolar patients, which could justify the lack of a prompt response. Regarding drug resistance, Benedetti *et al.* (28) have shown that double chronotherapy with TSD and BLT is useful in triggering a favorable

response in drug-resistant depression. This response is influenced by the same genetic functional polymorphisms that condition the efficacy of pharmacological treatment (25). Nevertheless, resistant patients showed lower response rates and were susceptible to an earlier relapse when compared with patients without a history of drug resistance. (21) Moreover, Kragh *et al.* (17) suggest that, for treatment resistant and highly medicated inpatients, chronotherapeutic procedures are not as useful when used as an adjunctive antidepressant treatment, and should be reserved to selected patients with a high chance of positive outcome. Additionally, research has shown that antipsychotic drugs could impair or abolish the effect of chronotherapy (29).

Most of the studies reviewed did not include a control group. Despite the global statistically significant decrease in depressive symptoms, these results are difficult to value since this reduction could be justified by other concurrent factors, such as hospitalization, antidepressant and mood stabilizing drugs and psychotherapy. Nevertheless, typically neither medication nor psychotherapy produce an onset of action that is as fast as the studies' descriptions (9).

With the exception of Landsness *et al.* (26), every article in this review implemented a double or triple chronotherapy scheme, combining BLT, SPA, TSD, PSD and/or STS. Regarding triple chronotherapy, Echizenya *et al.* (15) administered TSD followed by three days of SPA and five days of BLT, plus antidepressant drugs, over the course of three weeks to drug-resistant patients, observing a rapid and sustained decrease in depressive symptoms. Sahlem *et al.* (9) found that combining pharmacotherapy and triple chronotherapy, along with group psychotherapy, produces a faster and more robust improvement than what would be expected with pharmacotherapy or psychotherapy alone. In summary, these combinations, in addition with antidepressant medication, seem to add a fast acting and long-term sustainability to the antidepressant effect of medication.

In two of the reviewed studies (24,26), the researchers used slightly different and innovative approaches that yielded interesting results. Moscovici *et al.* used partial sleep deprivation instead of total sleep deprivation, combined with dawn simulation and sleep phase advance, while Landsness *et al.* applied slow wave sleep deprivation. Both studies provided satisfactory outcomes that lead us to believe that there are underexplored and understudied chronotherapeutic procedures other than those already described in current literature. In other words, there might be better ways to influence depressed patients' circadian rhythms that need to be further explored in future studies.

Chronotherapy is a safe non-invasive procedure, despite some descriptions of side-effects, including hypomania, irritability, headache, nausea, menstrual disturbances, sleepiness, fatigue (24) and panic attacks (19). In the studies reviewed, the most common side effect was transient sleepiness at different times of day. There was also a brief hypomanic switch in 6% of patients in the study by Wu *et al.* (16), which resolved within 24 hours without additional medication, as well as a 1.4% rate of switch into mania in a study by Benedetti *et al.* (30), which was also promptly resolved.

Numerous limitations were described in the studies, and the extent to which the results were biased is unknown. The most commonly described limitation was the absence of a control group in the trial, introducing the possibility of placebo-like effects and limiting the generalization of the findings. It is a challenge to design a randomized double-blind placebo-controlled trial which includes a chronotherapeutic intervention. These difficulties were described even in the studies that did include a control group, and blindness could be compromised in some cases (17). Dropout rates were noteworthy throughout the trials, and regardless of participants not differing significantly at baseline, they could have introduced bias by unmeasured variables (17). Other limitations included small sample sizes, non-standardization of the drug regimens, and the possibility of some patients taking brief

unreported naps, which has been hypothesized to change mood and sleep patterns, with controversial results (10). Furthermore, the use of different and adapted scales to evaluate depressive symptoms throughout the studies may interfere with the generalization of results, as different criteria were taken into consideration.

In conclusion, chronotherapy represents a safe, non-invasive and cost-effective alternative to antidepressant augmentation. (24) Research shows encouraging results, supporting the introduction of combined chronotherapy in the treatment of depression, and suggesting a general positive effect across the unipolar-bipolar dimensions (19). In addition, it appears to be a promising option to overcome treatment resistant depression and shorten treatment latency and duration. Nevertheless, results vary depending not only on the type of chronotherapeutic intervention, but also on interindividual variability. For instance, in a number of studies, some participants stated that they would not choose this treatment again. Therefore, careful patient selection is needed in order to ensure maximum benefit from the procedure (17).

Future studies require longer observational periods, with large samples sizes and control groups, in order to endorse the rapid and sustained decrease in depressive symptoms. Since there is still not enough insight into the underlying mechanisms of chronotherapy, future research should focus on concomitant biological measures and biomarkers, in order to strengthen the accumulating evidence towards the effectiveness of chronotherapy.

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