The Value of Chronotherapy in Depression

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INTRODUCTION

Depression is a major concern for world health. Symptom’s remission occurs after several weeks of treatment with an effective regimen, including pharmacotherapy and psychotherapy and even electroconvulsive therapy still takes 2 to 3 weeks to exhibit therapeutic benefits. The delay in therapeutic response is linked with early dropout and increased suicidal risk, however, currently we still lack fast-acting therapeutic options for depression. Therefore, chronotherapy has emerged as a safe non-invasive method that rapidly improves depressive symptoms, but its value requires further validation. Our aim was to assess the short and long-term effectiveness of chronotherapy interventions in depression.

METHODS

- Search Strategy**
We conducted a systematic review assessing studies which applied adjunctive chronotherapeutic procedures along with antidepressant drugs. We used a systematic search strategy following the PRISMA guidelines and, therefore, we identified twelve original studies that met our eligibility criteria.
- 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.
- Eligibility criteria**
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. Five out of twelve included studies scored high quality, and none of them scored low quality.

All the included studies reported a prompt and significant reduction in depressive symptoms. Altogether, chronotherapeutic groups showed higher response and remission rates at the end of follow-up.

CONCLUSION

Chronotherapy represents a safe, non-invasive and cost-effective alternative to antidepressant augmentation. Research shows encouraging results, supporting the introduction of combined chronotherapy in the treatment of depression. In addition, it appears to be a promising option to overcome treatment resistant depression and shorten treatment latency and duration. Optimization of the procedures and careful selection of patients is needed in order to ensure maximum benefit. Future research should focus on concomitant biological measures and biomarkers in order to strengthen the accumulating evidence towards the effectiveness of chronotherapy.

RESULTS

AUTHOR YEAR COUNTRY	SAMPLE SIZE	FOLLOW UP PERIOD	INTERVENTION		RESULTS
			CHRONO THERAPY GROUP	CONTROL GROUP	
Kragh <i>et al</i> , 2017, Denmark	40	9 weeks	TSD BLT Ad	Ad	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 <i>et al</i> , 2012, Denmark	75	9 weeks	TSD BLT STS Dul	Exercise program	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 <i>et al</i> , 2015, Denmark	75	20 weeks	TSD BLT Ad	Exercise program	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 <i>et al</i> , 2009, USA	49	7 weeks	TSD BLT SPA Ad	Ad	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 <i>et al</i> , 2013, Italy	141	5 weeks	TSD BLT Lithium	N/A	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 <i>et al</i> , 2009, Israel	12	4 weeks	PSD BLT SPA	N/A	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 <i>et al</i> , 2016, Italy	147	6 days	TSD BLT Lithium	N/A	Approximately 66% of patients responded to treatment, showing a 50% reduction of HDRS scores.
Benedetti <i>et al</i> , 2008, Italy	19	1 week	TSD BLT Lithium	N/A	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 <i>et al</i> , 2009, Italy	39	7 days	TSD BLT Ad	N/A	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 <i>et al</i> , 2013, Japan	13	22 days	TSD SPA BLT Ad	N/A	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 <i>et al</i> , 2011, USA	17	4 days	SWD	N/A	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 <i>et al</i> , 2014, USA	10	1 week	TSD SPA BLT Ad	N/A	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

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