1.Introduction

Bipolar depressive episodes often show unsatisfactory response to pharmacological treatments.

Chronoterapeutics give useful non-pharmacological options to treat bipolar depression, like Total Sleep Deprivation (TSD) and Light Therapy (LT). A considerable amount of subjects who undergo TSD alone experience an early relapse after recovery nights. Instead, the combination of TSD and LT leads to long lasting improvement of mood in bipolar depression (Benedetti et al., 2005).

Sleep abnormalities are a key feature of Bipolar Disorder (BD). A recent review gathered findings regarding sleep features evaluated though polysomnography in BD. In particular bipolar depressed individuals showed longer sleep onset latency, less efficient sleep, disturbed sleep continuity, a slow wave sleep (SWS) deficit; findings regarding total sleep time, REM latency and REM density were controversial (Zangani et al., 2021). One of the included studies reported also reduced N2 sleep and spindle number and density in bipolar depression in comparison with control subjects (De Maertelaer et al., 1987).

Chronoterapeutics are thought to exert their antidepressant effect through the regularization of biological rhythms, with a possible influence on the biological clock. However their effects on sleep are highly understudied. In particular there are few studies that adopted objective sleep measurement in BD. Furthermore, to our knowledge, sleep changes, after TSD and LT, have not been studied yet through

polysomnography (PSG) in BD, even though some studies explored PSG changes in unipolar depression. These studies found a decrease in REM density and in intermittent wakefulness (Murck et al, 2006), decreased sleep latency, REM latency, Stage 1 and 2 sleep and increased Stage 3 and Stage 4 sleep (Lu et al., 2014).

In our mood disorders unit, we conducted an exploratory observational study on patients undergoing TSD and subsequent LT. Patient's sleep was examined with qualitative PSG. Our first aim was to explore if chronotherapeutics could modify sleep architecture in bipolar depressed patients. Our second aim was to understand if possible changes could parallel the clinical evolution of bipolar depression.

2.Methods

Eleven bipolar inpatients (4 males and 7 females, mean age 53,82 ± 7,78) satisfying DSM-V criteria for a depressive episode were consecutively recruited in the period from 2019 to 2021 at our inpatients unit. Patients were enrolled in the observational study if they were offered treatment with TSD for their depressive episode, due to incomplete response to pharmacological treatments. Exclusion criteria were: concomitant alcohol or substance use disorder and presence of psychotic symptoms. Written informed consent was collected for the participation to the study.

Participants remained hospitalized for the whole observation time and were allowed to continue their pharmacological treatment. They were treated with 3 consecutive cycles of TSD. Each cycle was composed of a period of 36 hours awake, with patients being totally awake from

07:00 am until 7.00 pm of the following day. They were then allowed to sleep for a recovery night and the morning after started a new cycle. Patients were administered light therapy (LT) for 30 minutes (10000 lux bright white light, color temperature 4600 K) at 03:00 a.m. during the TSD night and in the morning after recovery sleep, half an hour after awakening, between 8 and 9 a.m. At the end of the 3 TSD cycles patients continued LT for 30 minutes every morning after awakening for one week.

Severity of depressive symptoms was evaluated at the beginning and at the end of the protocol through Hamilton Depression Rating Scale (HDRS). Participants were, then classified as remitters if final HDRS score was below 8. Patients underwent PSG the night before the beginning of the protocol and the night following the last LT session.

PSG was performed using BluNet wireless modules with patients sleeping in their hospital room (Bionen S.A.S, Florence). The assessment included electro-encephalography (EEG), electrooculography (EOG) and chin electromyography (EMG). Six scalp electrodes were adopted for EEG recording, to be positioned at F3, C3, O1, F4, C4, O2; plus a ground electrode at Cz, two electrodes for bi-mastoid reference, two electrodes for EOG recording, and two chin electrodes for bipolar EMG recording. Electrodes' locations on the scalp were determined using the international 10-20 system.

L.F., a psychiatrist who received specific training scored PSG recordings. Wake after sleep onset, N1, N2, N3, REM percentage, latency, total sleep time and number of awakenings were obtained from

PSG report. Subsequently, we calculated sleep efficiency and REM density. REM density was calculated separately for the first and last REM episode. This choice was done following the hypothesis that REM density would be different between a REM episode close to falling asleep and another close to wake up; therefore, we wanted to observe the, possibly different, effect of chronoterapeutics on REM density in the initial and final part of night sleep.

REM density was calculated as percentage of 3 s mini-epochs containing eye movements. Since some patients did not experience any REM stage until the last hours of sleep, we divided total sleep hours in 2 equal halves; we did not calculate REM density of the first REM stage, if there were no REM stages in the first half of the night.

Statistical analyses were performed with JASP software, 0.12.1.0 version. Differences between HDRS scores and sleep parameters at the two time-points were evaluated with Wilcoxon signed-rank test. Correlation analyses were then performed between changes in HDRS scores (Δ HDRS) and changes in sleep parameters (Δ sleep stage % , Δ sleep stage latency, Δ sleep efficiency, Δ number of awakenings, Δ REM density of the first and last REM stage) with Pearson's *r*. Statistical significance was set at *p*-value below 0.05.

3.Results

All patients clinically improved throughout the observation time and no manic switches have been observed.

Mean HDRS score was 20.27 at baseline and 4.909 one week after the end of the treatment (p<0.001). Nine out of 11 (81.82%) participants were classified as clinical remitters, showing a final HDRS below 8.

Mean sleep parameters are reported in table 1, with 3 parameters that significantly changed after TSD: N2% (percentage of N2) (p=0.042), N3% (percentage of N3) (p=0,032) and REM density of the last REM stage (p=0,032). Mean N2% grew from 46,995 % to 59,091%, mean N3% decreased from 16,545% to 10,091%, mean REM density of the last REM stage decreased from 13,576 to 8,350.

A positive correlation was found between the change in HDRS scores and the change in N3% (r=0.627, p=0.039). The correlation between HDRS score change and the change in other sleep parameter was not statistically significant. Full correlation analyses may be consulted in supplemental material.

4.Discussion

The most important finding of our study is the decrease in N3 sleep, a sleep stage of slow wave sleep (SWS). Decrease in N3 sleep was also correlated with amelioration of depressive symptoms. Previous studies found that during depression SWS is decreased (Riemann et al., 2001). Conversely, in this study, we observed a SWS reduction when depressive symptoms decreased. SWS reduction might have been induced by chronoterapeutic procedures, but it is unknown if the decrease is sustained over time. Later PSG assessment could be adopted by future studies to understand if TSD induced changes are transient or sustained.

Therefore, chronoterapeutics may have a specific effect in reducing this particular sleep stage. The importance of SWS was also noted by the group of Landsness that adopted a protocol of selective SWS deprivation for the treatment of depression (Landsness et al., 2011). They found that SWS deprivation reduced depressive symptoms and SWS dissipation correlated with depressive symptoms reduction.

Regarding the increase in N2 sleep, this finding could be a consequence of N3 reduction, considering that sleep stages percentages are proportional to each other. Nevertheless, a previous study found lower N2 sleep during bipolar depression (De Maertelaer et al., 1987). Therefore, N2 sleep might transiently decreases during bipolar depression, reverting to its normal levels, once euthymia is reached again. Hence, N2 sleep is also possibly influenced by chronobiological treatments.

Concerning REM density of the last REM stage, this parameter significantly decreased. REM density increase is considered a biomarker of bipolar depression and unipolar depression. Bipolar depressed inpatients show increased REM density compared to healthy controls and unipolar depressed patients (Gold and Sylvia, 2016). Therefore, the reduction we observed might be related to antidepressant response to chronobiological treatments.

Importantly, neither N2% nor REM density showed any correlation with depressive symptoms evolution in our sample. This may be explained by the small sample size, but it may also instead indicate that their role in antidepressant response IS not as important as N3 sleep.

Our study, has limitations that require consideration. First of all, patients received psychopharmacological medications that may have influenced EEG recordings. We chose to maintain pharmacological treatment even if we are aware that this may be a confounding factor, because it was unethical to interrupt treatments. Of note, psychopharmacological treatments remained stable between the two PSG recordings, reducing the possible bias. However, future studies with unmedicated subjects are required to confirm our findings.

Our findings also require replication on a larger sample and the comparison with a control group.

Despite limitations, we believe that our findings are of relevance as we showed, for the first time, that chronoterapeutics might lead to a different organization of sleep and that N3 sleep decrease might be a neurophysiological correlate of antidepressant response.

Sleep-wake cycle disruption is known to play a key role in BD and chronoterapeutics are thought to exert their beneficial effects through a regularization of biological rhythms. However, their effect on sleep has never been objectively assessed. This exploratory study is the first to demonstrate that chronoterapeutics can modify sleep architecture in BD.

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Table 1.

		Baseline		End of the study	
	N	**Mean**	**SD**	**Mean**	**SD**
TST	11	423.773	71.438	426.864	56.658
Wake %	11	14.009	7.899	12.364	7.961
N1 %	11	20.636	12.073	16.464	12.435
N2 %	11	46.995	7.736	59.091	11.398
N3 %	11	16.545	6.634	10.091	8.775
REM%	11	15.855	5.440	14.336	7.646
N1 latency	11	35.500	26.549	31.773	24.553
N2 latency	11	66.045	55.413	36.818	27.398
N3 latency	11	75.545	52.498	72.091	58.897
REM latency	11	185.500	104.391	247.091	115.046
N awakenings	11	9.091	3.936	9.091	6.580
Wake after sleep onset	11	67.636	34.212	60.364	42.994
SE	11	76.782	10.413	79.726	7.818
REM density – first REM stage	8	6.369	2.936	7.680	4.825
REM density – last REM stage	11	13.576	6.900	8.350	5.361

Caption table 1.

Sleep parameters at baseline and at the end of the study. SD: standard deviation; TST: total sleep time; SE: sleep efficiency. TST , Wake after sleep onset and sleep stages latencies are expressed in minutes.