Introduction and background

Bipolar disorder (BD) is a chronic, severe and disabling disease defined by depressive and (hypo) manic recurrences. Lifetime prevalence is about 1%, making BD a condition with an important social impact[1]. Sleep disorders are one of the main clinical symptoms, enough to be included among the diagnostic criteria of the DSM-5 for both depressive and manic phases [2]. Sleep disturbances, regardless of the phase of the disease, are also correlated with a greater severity course and a worse prognosis[3]. In addition, sleep seems to be implicated in the disorder's pathophysiology, especially as regards the manic phase. Mania is indeed often preceded by a reduction in the need for sleep and the ensuing sleep deprivation triggers a vicious cycle that eventually leads to the full-blown manic phase[4][5].

Although the importance of sleep in BD is well known from a clinical point of view, its monitoring within the common medical practice is not simple, particularly in manic phase. The quantification of night rest is generally carried out by the ward staff on an observational basis or by the patient himself through diaries or proper questionnaires[6]. A further possibility is actigraphic recording, a tecnique for assessing patient's sleep-wake rhythm by tracing body's movements. Unfortunately, these methods have proved to be poorly effective and lack the necessary precision[7][8]. Furthermore, none of these methods allow to evaluate the characteristics of sleep and its phases with needed accuracy .

Polysomnography (PSG) is a technique that allows a complete observation of sleep behaviour including electroencephalography (EEG), electrooculography, electromyogram, Electrocardiogram and the evaluation of respiratory movements. It is a non-invasive, safe, relatively inexpensive technique. Unlike the other methods, PSG recording allows detecting the actual sleep time and its characteristics in more detail, tracing brain activity and identifying non-REM (NREM) and REM stages[9].

A growing number of evidence suggests that sleep architecture is a major clinical marker and has a key role in the pathogenesis of mood disorders. However, over time the scientific community has focused only on depressive symptoms, identifying EEG changes in sleep mainly during Major Depression[10][11].

We suppose that this choice may derive both from the greater availability of subjects suffering from depressive syndrome compared to those in the manic phase, as well as from the lower manageability and tendency to collaborate of the latter during the PSG recordings.

Only a few studies have dealt with the description of sleep from the electroencephalographic point of view during the manic phases of Bipolar Disorder. Evidence from literature are conflicting and inconclusive: most of the studies found a reduction in total sleep (TST)[12][13][14], a reduction in REM sleep latency (REM latency), an increase in REM density [15][14][16] and variable NREM sleep changes such as increased perceptual N1 and N3 [14] or the increase of N1 and N2 percentages with reduction of N3% and N4% [16]. In addition these studies have often been conducted under ideal conditions, in most cases on drug-free patients and therefore fairly distant from those of normal clinical practice.

Conversely our study aims to investigate changes in manic patients' sleep EEG in a clinical context as real as possible, assuming a “pragmatic” point of view.

Our hypothesis is that we can objectify the variations in sleep architecture between the acute phases of disease and those of remission through EEG investigation. If this hypothesis will be confirmed, PSG performed during the BP treatment/hospitalization could represent a fundamental tool for assessing the progress of the disease and an instrumental and objective reference for therapeutic choices. Going further, the identification of EEG traits that anticipate changes in the patient's clinical course would represent a tool for more rapid, specific and targeted treatment of the manic phase.

Materials and methods

Study site and ethical considerations

The study was conducted within the Mood Disorders Clinical Unit of the Psychiatry Department of the San Raffaele Hospital in Milan. All the participants, volunteers, were informed in detail about the characteristics of the study and each participant was entitled to leave the study at any time. At the time of participation, each of the volunteers signed a written consent.

Participants

21 manic patients, 8 males and 13 females, aged between 29 and 77 years, were recruited from the patients admitted to our Clinical Unit. All patients met the following criteria: diagnosis of Bipolar Disorder, manic phase, according to DSM-5 criteria; age over 18; non-use of alcohol or substances in the two weeks before admission, no major medical illness or primary sleep disorder.

The clinical and demographic characteristics of the complete sample are described in table 1.

All patients were on psychotropic medication at the time of the study. In particular, 100% of the patients were taking hypnotic drugs, mostly benzodiazepines, since admitted to the ward. This choice is in line with the objective of regularizing the sleep-wake rhythm of patients in the manic phase and also responds to ethical needs. The patient's well-being is a priority over the possibility of having a "drug-free" sample. On this basis, a "pragmatic" approach was chosen in which scientific investigation was combined with clinical practice.

Clinical assessment:

The following clinical scales were used to score the severity of manic phase, the objective and subjective quality of the sleep and the chronotype:

- **Young Mania Rating Scale** (YMRS) (Young et al., 1978). One of the most used clinical questionnaires for the evaluation of manic symptoms. The scale is observer-rated, made up of 11 items, and evaluates the symptoms of the previous 48 hours.
- **Pittsburgh Sleep Quality Index** (PSQI) (Buysse et al., 1989). The Pittsburgh Sleep Quality Index (PSQI) is a test composed of 19 self-rated questions for the evaluation of different aspects of sleep.
- **Morningness-eveningness Questionnaire** (MEQ) (Horne, JA et al., 1976). It is a self-administered questionnaire composed of 19 items for the evaluation of the circadian rhythm.

YMRS and PSQI were administered for each night of PSG recording while MEQ only once, before the first PSG registration.

Instrumental assessment

Polysomnography (PSG): PSG were recorded for each subject with BIONEN BluNet® (Bionen SAS, Florence). BluNet is a lightweight, portable polysomnography composed of an EXG module, a PSG module, two inductive belts. The EXG module was connected to six scalp electrodes 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. Proper signal acquisition was tested on the spot via the proprietary application. The patient was instructed not to displace any electrode, ask the nursing staff if they needed any help, and go to bed at their usual bedtime. The appliance was removed on the following morning after the patient's spontaneous awakening. Data from the PSG were processed (elaborated /

filtered) and read via Polysmith® software (Neurotronics, Inc., Gainesville, FL). Several psychiatrists with specific training have scored each record independently in order to have a more reliable and objective evaluation of the PSG recordings. Two polysomnographic recordings were made: the first at the entrance to the ward while the second three weeks after the first recording .

Data relating to drug therapy, YMRS and PSQI scores, related subgroups, and the main polysomnographic variables recorded in each night are summarized in Table 2.

Data processing

In order to assess whether specific aspects of manic symptoms were related to the polysomnographic characteristics of sleep, the YMRS Items scores were divided into subscales. Three subscales have been identified: a first subgroup, “sleep”, consisting of only item 4 of the scale; the “hypermotor activity” subgroup given by the algebraic sum of items 1,2,3,5,6,7,10 of the scale; a last group of "psychotic features" consisting of items 8,9,11 on the Young Mania Rating Scale.

In order to evaluate a possible correlation between polysomnographic parameters and clinical response, the "Delta values" (Δ) of clinical scores (YMRS) were calculated as differences between scores at the two timepoints, normalized. The scores were calculated as follows: $\Delta_{YMRS} = ((YMRS_{T0} - YMRS_{T1}) / YMRS_{T0})*100$. In the same way, Δ were created for each subgroup of Young's scale for Mania ("Sleep", "Hypermotor Activity", "Psychotic Features").

Based on MEQ scores and in order to assess whether there were clinical or electroencephalographic features related to circadian rhythm, patients were divided into "Morning Type" (score 59 or above), "Evening Type" (score 41 or below) and "Intermediate Type" (score between 42 and 58).

Statistical analysis

The data were analyzed using Microsoft Excel® and the open-source statistical software JASP®. The results were processed and statistically analyzed using the following tests: Chi-square test used was for the comparison of categorical variables, paired-samples t-test was used for comparison of continuous variables, correlation between changes in YMRS scores and changes in sleep parameters were performed (Spearman's rho). Statistical level of significance was set at 0.05.

Results

21 patients were enrolled and EEG recorded at the admission. Of these patients, only 17 recordings at the time of discharge are available. Two patients decided to stop participating in the study after the first recording while in the remaining two cases the data was unreadable due to technical problems. For the statistical analysis, only the 17 subjects who completed both registrations were considered.

The mean scores of the YMRS scales has decreased from the first to the second recording night showing an improvement in the manic symptomatology that involves all the subgroups of symptoms identified (See Table 4).

Comparing the two recordings, the one at the entrance and the one near the discharge, increases in the average values of TST (Total Sleep Time) and SE (Sleep Efficiency) emerge while the values of wake percentage (WAKE%) and the number of awakenings decrease, testifying to a greater continuity and

effectiveness of sleep. The subjective perception of sleep also improves with the consequent reduction of the average scores on the PSQI scales.

From the sleep architectural point of view, in the second recording we find an increase in REM sleep percentage (+5,63%), REM density (+0,56) and a reduction in REM latency (-26,49 min). The N2 and N3 stages remain substantially unchanged in percentage (N2: +0,19 %; N3:-0.23%) while the N1 stage is reduced (-6.85%).

Paired Sample T test was used to assess whether there was a significant change in sleep parameters and clinical scores between the two recordings, the results are shown in Table 3 and 4. Wilcoxon signed-rank test showed a significant difference in the percentage of REM sleep % ($p = 0.01$) and in SE% ($p = 0.013$), all other changes were not significant.

A correlation analysis (Spearman's rho) was also performed between "Delta values" (Δ_{YMRS} and subgroups) of clinical indicators e PSG parameters (N1, N2, N3, REM, N1 lat, N2 lat, N3 lat, REM lat, REM density, TST) at first timepoint (acute phase of illness), in order to verify if there were predictive polysomnographic characteristics of the clinical response. Clinical scores at the entrance and near discharge from ward (YMRS and subtypes) were also correlated to the matching PSG parameters. A negative correlation was found between total sleep time (TST) and Young's score for Mania (YMRS) at the second timepoint. All further correlations were found to be non significant, results available on request or supplementary results.

Based on MEQ scores, 12 (57%) patients were found to belong to the "morning type", 4 (19%) to the "intermediate type" and 5 (23%) to the "evening type". The analyses conducted did not reveal significant differences in clinical or EEG parameters among the 3 patient groups.

Discussion

Our study aimed to monitor the sleep of bipolar patients in manic phase using PSG, in a natural clinical setting and at two specific time points, admittance into the ward (most acute phase) and near discharge (after clinical treatment). The distinctive manic symptoms (i.e. restlessness, poor insight and cooperation) make this kind of study particularly difficult, especially considering the severity of the symptoms of the patients enrolled (see Tables 2 and 4). However, in the absence of a less invasive device for sleep monitoring, PSG appears to be the only tool that can provide objective evidence on the duration and characteristics of sleep.

From the clinical point of view, the patients underwent a general and significant improvement in symptoms, as highlighted by the difference in scores on the YMRS scale between the first and second recording. From the EEG point of view, between the first and second recording there was a significant increase in the amount of total sleep (TST), its continuity (reduction of WAKE% and number of awakenings) and above all an increase in REM sleep percentage (see Table 3). These results are partly reflected in the few previous studies: as in the works of Hudson and Linkowski [15][13] the sleep of the manic patient in the acute phase appears disturbed and less efficient. However, while Hudson [15][14] noted an increase in REM density, this does not happen in our study. Instead, a new data emerges, namely a reduction in REM sleep percentage in the acute manic phase compared to the resolution phase of the symptomatology. A mirror result to studies on Major Depression [11][10]. If this result were confirmed, the suggestive hypothesis that the characteristics of REM sleep somehow reflect the clinical characteristics of the two polarities of mood could be put forward.

Nevertheless , the correlation analyses between changes in clinical parameters and changes in sleep structure were not significant. Similarly, it doesn't seem to be a direct relationship between psychopathological manifestations of manic phase and polysomnographic features. None of the subsets of Young's scale for Mania ("sleep", "hypermotor activity", "psychotic features") seem to be individually related to characteristics or their progression over time. A possible explanation is that the EEG changes of manic bipolar patients sleep

do not reside only in each stage of sleep and its percentage in the overall night, but also in their cyclical alternation with the other stages. In this sense, a larger sample of patients would allow to identify a possible hypnographic pattern of sleep in bipolar patients' manic phase.

Overall, what emerges from this study is that the significant clinical improvement of patients runs parallel to the significant changes of specific sleep EEG parameters, in particular TST, SE and REM% (See Table 3).

To deepen this aspect, a correlation analysis was conducted between the average scores of the YMRS scales relating to the second timepoint (from which item 4, relating to sleep, was subtracted) with the parameter relating to the total sleep time of the second recording. The analysis shows how, once the acute phase is overcome, the improvement in sleep is significantly correlated to the reduction in the intensity of the other symptoms measured by the Young scale ("hypermotor activity" score + "psychotic features" score). This data seems consistent with the study by Galynker and colleagues [17] in which it is shown that the attenuation of manic symptoms follows an improvement in sleep. However, it should be specified that, although the predictive value of the TST parameter on the clinical performance of patients is already intuitable from our study, this will have to be confirmed by further studies, with the aid of multiple recordings (and intermediate timepoints). Overall, our result, albeit initial, suggests that for the treatment of a manic episode the first goal could be to regulate the sleep-wake rhythm.

The study encountered several limitations: first of all, the sample's smallness and subsequent age heterogeneity. As mentioned above, studies of this type are difficult to carry out. The trouble in recruiting and monitoring the patient's sleep in the manic episode, with the current tools, is understandable. However, technological advances are rapid and we hope that new monitoring systems, such as wearable devices, will reach a degree of precision comparable to polysomnography and greater tolerability than PSG. This could allow a study on larger and longer samples, with the further possibility of a follow-up that makes it possible to evaluate the clinical trend and sleep parameters over the medium-long term.

A further criticism can be addressed to the pharmacological treatment of patients. All the patients enrolled have taken pharmacological treatment since entering the ward and this has varied according to the clinical indications, between the first and second registration. We know that most psychotropic drugs can modify brain electroencephalography and hence the polysomnographic characteristics of sleep. However, as previously stated, the intent of the study was not simply to evaluate the electrophysiological features of sleep in pathological conditions but rather to assess whether, in a clinical setting, the regularization of chronobiological rhythms, even through the use of pharmacological intervention was associated by a clinical improvement of all psychopathological manifestations. In addition to ensuring the precise quantification of variations in sleep time, PSG has allowed us to ascertain that the overall enhancement associated with a specific improvement in the sleep-wake rhythm, with greater duration, effectiveness and continuity. This data is also accompanied by an increase in the percentage of REM sleep which, whether dependent on drug therapy or not, follows the clinical improvement of patients.

What emerges overall is that sleep intervention could be the priority clinical goal and sleep monitoring through PSG recording helps to have a quantifiable and reproducible measurement of the true change in sleep-wake parameters during the manic phase. While currently representing the most realistic and precise assessment of sleep characteristics, PSG is not always well tolerated by patients, particularly during the manic episodes of bipolar disorder. It would be consequently be desirable the development of more manageable technologies, that make it possible a routine sleep monitoring as indicator for evaluating the trend of the manic phase and thereby its treatment.

Bibliography

1. Cloutier M, Greene M, Guerin A, Touya M, Wu E (2018) The economic burden of bipolar I disorder in the United States in 2015. J Affect Disord 226:45–51

2. American Psychiatric Association (2013) Diagnostic and Statistical Manual of Mental Disorders. https://doi.org/10.1176/appi.books.9780890425596

3. Eidelman P, Talbot LS, Gruber J, Hairston I, Harvey AG (2010) Sleep architecture as correlate and predictor of symptoms and impairment in inter-episode bipolar disorder: Taking on the challenge of medication effects. J Sleep Res 19:516–524

4. Barbini B, Bertelli S, Colombo C, Smeraldi E (1996) Sleep loss, a possible factor in augmenting manic episode. Psychiatry Res 65:121–125

5. Wehr TA (1989) Sleep loss: A preventable cause of mania and other excited states. In: J. Clin. Psychiatry. pp 8–16

6. Zangani C, Casetta C, Saunders AS, Donati F, Maggioni E, D'Agostino A (2020) Sleep abnormalities across different clinical stages of Bipolar Disorder: A review of EEG studies. Neurosci Biobehav Rev 118:247–257

7. Geoffroy PA, Scott J, Boudebesse C, Lajnef M, Henry C, Leboyer M, Bellivier F, Etain B (2015) Sleep in patients with remitted bipolar disorders: A meta-analysis of actigraphy studies. Acta Psychiatr Scand 131:89–99

8. De Crescenzo F, Economou A, Sharpley AL, Gormez A, Quested DJ (2017) Actigraphic features of bipolar disorder: A systematic review and meta-analysis. Sleep Med Rev 33:58–69

9. Rundo JV, Downey III R (2019) Polysomnography. Handb Clin Neurol 160:381–392

10. Benca RM, Obermeyer WH, Thisted RA, Gillin JC (1992) Sleep and Psychiatric Disorders: A Meta-analysis. Arch Gen Psychiatry 49:651–668

11. Baglioni C, Nanovska S, Regen W, Spiegelhalder K, Feige B, Nissen C, Reynolds CF, Riemann D (2016) Sleep and mental disorders: A meta-analysis of polysomnographic research. Psychol Bull 142:969–990

12. Mendels J, Hawkins DR (1971) Longitudinal Sleep Study in Hypomania. Arch Gen Psychiatry 25:274–277

13. Linkowski P, Kerkhofs M, Rielaert C, Mendlewicz J (1986) Sleep during mania in manic-depressive males. Eur Arch Psychiatry Neurol Sci 235:339–341

14. Hudson JI, Lipinski JF, Keck PE, Aizley HG, Vuckovic A, Zierk KC, Pope HG (1993) Polysomnographic characteristics of schizophrenia in comparison with mania and depression. Biol Psychiatry 34:191–193

15. Hudson JI, Lipinski JF, Frankenburg FR, Grochocinski VJ, Kupfer DJ (1988) Electroencephalographic Sleep in Mania. Arch Gen Psychiatry 45:267–273

16. Asaad T, Sabry W, Rabie M, El-Rassas H (2016) Polysomnographic characteristics of bipolar hypomanic patients: Comparison with unipolar depressed patients. J Affect Disord 191:274–279

Table 1. Demographic and Clinical Characteristics of 21 Manic Patients	
	Patients (N = 21)
Age (Years, DS)	52.4 (14.5)
Gender	8 M, 13 F
Education (Years, DS)	11 (4.1)
Onset (Years, DS)	31.1 (12.3)
Smoke (N,%)	13 (61.9%)
Alcohol (N,%) *	4 (19%)
Drug (N,%) *	2 (9.5%)
Attempted Suicide (N,%)	5 (23.8%)
Familiarity (N,%)	12 (57.1%)
Onset (Year, DS)	31.2 (12.4)
Prev. Depressive Episodes (N, DS)	7.6 (8.7)
Prev. Maniac Epsodes (N, DS)	6.8 (7.2)
MEQ score (N, DS)	54.3 (14.1)
* Total episodes, excluding 2 weeks prior to study participation. N: number; DS: standard deviation; %: percent; MEQ: Morningness - eveningness questionnaire (score at the entrance)	

Table 2: Drug therapy, Mean values of YMRS and PSQI score and PSG variables at the two timepoints

	First Night (n = 17)	Second Night (n = 17)
Drugs (Frequency; %)		
Lithium	16 (76.2%)	16 (76.2%)
Other Mood Stabilizers	9 (42.9%)	9 (42.9%)
Benzodiazepines	17 (100%)	17 (100%)
Antipsychotics	9 (42.9%)	5 (29.4%)
Questionnaires (Mean, DS)		
YMRS	26.0 (5.52)	9.00 (5.72)
YMRS "Psychomotor"	17.58 (4.61)	6.64 (4.44)
YMRS "Sleep"	2.29 (0.84)	0.7 (0.68)
YMRS "Psychosis"	6.23 (3.58)	1.65 (1.66)
PSQI	5.23 (2.81)	3.76 (2.79)
Sleep Continuity (Mean, DS)		
TST	360.82 (93.13)	417.76 (76.01)
WAKE %	15.53 (14.89)	12.01 (10.18)
Awakenings	6.4 (5.28)	5.82 (4.08)
Wake after sleep onset	72.5 (76.96)	50.82 (43.41)
Wake after persistent sleep	67.47 (62.68)	47.85 (36.61)
SE %	76.03 (19.57)	87.27 (10.40)
Sleep Architecture and REM Measures (Mean, DS)		
N1%	25.56 (17.76)	18.71 (15.1)
N2%	49.98 (14.74)	50.17 (11.6)
N3%	18.10 (12.39)	17.87 (10.16)
REM%	6.34 (7.5)	11.97 (7.06)
N1 latency	16.35 (18.91)	22.84 (62.17)
N2 latency	25.64 (33.80)	19.47 (19.98)
N3 latency	49.69 (40.59)	39.52 (27.64)
REM latency	125.89 (131.2)	99.44 (87.87)
REM density	4.06 (2.55)	4.62 (4.37)
REM density (1st period)	3.67 (2.09)	4.01 (3.96)
SD	2.34 (1.94)	2.35 (1.95)

YMRS: Young Mania Rating Scale; PSQI: Pittsburgh Sleep Quality Index
REM: Rapid eye movement; SE: Sleep Efficiency; TST: Total Sleep Time

Table 3: Comparison between the polysomnographic variables of the two recordings.

Measure	Night 1	Night 2	W	df	p
TST	360.82 (93.13)	417.76 (76.01)	33,000		0.042
N1%	25.56 (17.76)	18.71 (15.1)	117,000		0.057
N2%	49.98 (14.74)	50.17 (11.6)	77,500		0.981
N3%	18.10 (12.39)	17.87 (10.16)	67,000		0.979
REM%	6.34 (7.5)	11.97 (7.06)	18,000		0.010
SE %	76.03 (19.57)	87.27 (10.40)	25,000		0.013
REM Density	4.06 (2.55)	4.62 (4.37)	15,000		0.742
REM Latency	125.88 (131.20)	99.44 (87.87)	71,000		0.897

Note. Wilcoxon signed-rank test.
REM: Rapid eye movement; SE: Sleep Efficiency; TST: Total Sleep Time

Table 4: Comparison between YMRS (and subscales) score at the two timepoints

Measure	Night 1	Night 2	W	df	p
YMRS	26.0 (5.52)	9.00 (5.72)	153,000		<.001
YMRS "hypermotor activity"	17.58 (4.61)	6.64 (4.44)	150,000		<.001
YMRS "Sleep"	2.29 (0.84)	0.7 (0.68)	120,000		<.001
YMRS "Psychotic Features"	6.23 (3.58)	1.65 (1.66)	120,000		<.001
PSQI	5.23 (2.81)	3.76 (2.79)	105,500		0.010

Note. Wilcoxon signed-rank test.
REM: Rapid eye movement; SE: Sleep Efficiency; TST: Total Sleep Time

Table 5: Correlation (Spearman's Rho) between TST and YMRS* at the second timepoint.

TST (Second night)	YMRS* (Second Night)	Spearman's rho	p
417.7 (76,01)	8.29 (5.18)	-0.416	0.048

Note. * Item 4 (relating to sleep) was excluded from the score on the YMRS scale.
All tests one-tailed, for negative correlation.
REM: Rapid eye movement; SE: Sleep Efficiency; TST: Total Sleep Time