Journal of Affective Disorders 299 (2022) 596–603

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

Insomnia symptoms are associated with impaired resilience in bipolar disorder: Potential links with early life stressors may affect mood features and suicidal risk

Laura Palagini [a,b,*], Mario Miniati [a], Donatella Marazziti [a], Christian Franceschini [c], Luigi Zerbinati [b], Luigi Grassi [b], Verinder Sharma [d], Dieter Riemann [e]

[a] Department of Clinical and Experimental Medicine, Psychiatric Section, University of Pisa, Azienda Ospedaliera Universitaria Pisana (AUOP), Pisa, Italy
[b] Psychiatric Clinic, Department of Neuroscience and Rehabilitation, Institute of Psychiatry, University of Ferrara, Via Fossato Mortara 64, Ferrara 44121, Italy
[c] Department of Medicine and Surgery, University of Parma, Parma, Italy
[d] Department of Psychiatry, University of Western Ontario, London, Ontario, Canada
[e] Department of Clinical Psychology and Psychophysiology/ Sleep Medicine, Center for Mental Disorders, University of Freiburg, Freiburg, Germany

ARTICLE INFO

Keywords:
Bipolar disorder
Early life stress
Resilience
Mood symptoms
Insomnia
Suicidal risk

ABSTRACT

Aim: The study aimed to investigate resilience and its association with early exposure to stressful events on the clinical manifestations of bipolar disorders (BDs), such as severity of mood symptoms, suicidal ideation and behaviors focusing on the possible role of insomnia symptoms.
Method: A sample of 188 adult participants with BD of type I or II were assessed during depressed phase using the Structural Clinical Interview for DSM-5 (SCID-5), the Beck Depression Inventory-II (BDI-II), the Young Mania Rating Scale (YMRS), the Early Trauma Inventory Self Report-Short Form (ETISR-SF), Resilience Scale for Adults (RSA), the Insomnia Severity Index (ISI) and the Scale for Suicide Ideation (SSI). Participants with or without clinically significant insomnia were compared and we carried out correlations, regression and mediation analyses.
Results: Participants with insomnia showed a greater severity of depressive symptoms as well as of suicidal risk, early life stressors and lower level of resilience. Insomnia symptoms mediated the association between early life stress and low resilience, between low resilience in planning future and depressive symptoms ($Z = 2.17$, $p = 0.029$) and low resilience and suicidal risk ($Z = 3.05$, $p = 0.0002$)
Conclusion: Insomnia may be related to the severity of BDs, to higher early life stressors and lower level of resilience. Assessing and targeting insomnia symptoms may potentially promote resilience in BDs in response to early life stressful events. These results should be interpreted in light of several limitations including the cross-sectional design affecting causal interpretations.

1. Introduction

Bipolar disorders (BDs) are complex illnesses possibly resulting from the interaction of genetic, physiological, psychological, and environmental factors (Vieta et al., 2018). The different combinations of these factors may lead to a spectrum of clinical manifestations that may include elevated mood such as mania or hypomania and depressed mood that often co-occur with high variability and magnitude among patients (American Psychiatric Association, 2013).

Bipolar disorders are among the most prevalent and the most likely to be recurrent, chronic and disabling psychiatric conditions (Vieta et al., 2018; Miller and Black, 2020; Tondo et al., 2020) leading to global burdens of disease in terms of disability, morbidity, premature mortality (Delgado, 2015; Hayes et al., 2015; Morton et al., 2018; Pinto et al., 2020), and to a significant suicidal risk (Miller and Black, 2020; Tondo et al., 2020). The understanding of the mechanisms involved in the development and maintenance of BDs should thus be considered as a priority to identify potential early markers that could help in improving treatment strategies. Within this framework insomnia might be such a potentially modifiable early marker in BDs (Palagini et al., 2019a). In

* Corresponding author at: Psychiatric Clinic, Department of Neuroscience and Rehabilitation, Institute of Psychiatry, University of Ferrara, Via Fossato Mortara 64, Ferrara 44121, Italy.
E-mail addresses: lpalagini@tiscali.it, laura.palagini@unife.it (L. Palagini).

https://doi.org/10.1016/j.jad.2021.12.042
Received 26 July 2021; Received in revised form 1 December 2021; Accepted 18 December 2021
Available online 21 December 2021

particular, insomnia likely plays a triggering role in the onset and maintenance of BD. Not only circadian sleep alterations are frequent in BD as it has been shown in the last few years (Kanady et al., 2015; Geoffroy et al., 2015), but also insomnia symptoms may interest BDs across their entire course (Kanady et al., 2015; Geoffroy et al., 2015; Palagini et al., 2019a, 2019b) as many as 80–100% of people during the depressive episode, 30–35% during manic and mixed episodes, and 45–55% during the inter-episodic phase suffer from it (Ng et al., 2015; Geoffroy et al., 2015; Kanady et al., 2015; Cretu et al., 2016). Moreover, it is also a risk factor for BDs, as it may trigger them, as it has been shown to increase the risk of new onset mood episodes as well relapse or recurrence of the disorder, while also being one of the most frequent residual symptoms (Ritter et al., 2011; Rumble et al., 2015; Pigeon et al., 2017; Palagini et al., 2019a, 2019b, 2019c; Hertenstein et al., 2019). In addition, insomnia has been related to BD severity, to emotional hyper-reactivity or impulsivity, and to increased suicidality (Ng et al., 2015; Geoffroy et al., 2015; Rumble et al., 2015; Boudebesse and Henry, 2012; Etain et al., 2017; Palagini et al., 2019c). Insomnia might play a key role in BDs by potentially dysregulating the systems involved in mood and emotion regulation, including stress and inflammatory systems (for an overview see: Palagini et al., 2019a). In particular, insomnia, is considered a disorder of the "hyperarousal" with central and peripheral hyper-activation of the stress system, in turn, resulting in stress system sensitization and overload which may affect stress-risk vulnerability dimension with detrimental effect on resilience (Riemann et al., 2010, Palagini et al., 2018; 2019a, 2019b, 2019c). Recently, targeting insomnia has been demonstrated to promote resilience and mental health (Cheng et al., 2021) and to favorably impact on the trajectory of mood disorders (Asarnow and Mamber, 2019; Bei et al., 2018).

Resilience is a modifiable stress-risk dimension evolving process that is influenced by a variety of genetic, epigenetic, developmental, psychological, and environmental factors that determines an individual's capacity to adapt successfully to stressful events (Rutter, 2012; Capanna et al., 2015). Factors composing resilience regards characteristics and resources of the individual and external factors such as supportive family environment and external social networks that support and reinforce (Capanna et al., 2015). Greater resilience and has been related to less depressive symptomatology (Wermelinger, et al. 2017) and may be a protective factor against suicidal risk (Youssef et al., 2013; Liu et al., 2014). On the other hand, low resilience has been related to a dysregulation in emotions and stress response involved in psychopathological process of mental disorders including bipolar disorders (Choi et al., 2015; Mizuno et al., 2016; Angeler et al., 2018), to emotional impulsivity, internalized stigma, poorer cognitive functions, reduced quality of life in BDs (Choi et al., 2015; Lee et al., 2017; Deng et al., 2018; Post et al., 2018; Nunes and Rocha, 2021) and increased suicidal risk in particular psychiatric population (Roy et al., 2007). Despite these evidences (Germain and Dretsch, 2016; Palagini et al., 2018; Cheng et al., 2021), to date no studies have examined the association between insomnia symptoms and levels of resilience in BDs.

Among the factors, affecting resilience in BDs early life stressors may play a role (Roy et al., 2011; Kesebir et al., 2015). Early life stressors, including abnormal maternal care, maltreatment, abuse and violence, malnutrition, poor social conditions, and traumatic events during either the pre- or postnatal periods (for an overview see: Heim et al., 2018), through epigenetic mechanisms, would lead to permanent changes in the biological regulation of stress system, and would predispose individuals to mental illnesses later on (Jaworska-Andryszewska and Rybakowski, 2019; Targum and Nemeroff, 2019). Although this association is probably not specific to BDs, it may represent an early marker both for triggering these pathological conditions and its long-term clinical manifestations (Aas et al., 2016;Agnew-Blais and Danese, 2016; Jaworska-Andryszewska and Rybakowski, 2019). Interestingly, early life stressors have been demonstrated to alter sleep regulation leading to life-long/later-life insomnia (for an overview see Palagini et al., 2014, 2015; Lo Martire et al., 2019) and, via sleep alterations, contributing to the clinical pictures of BD during adulthood (Aas et al., 2016; Palagini et al., 2019a, 2019b, 2021; Lo Martire et al., 2019).

In any case, little is known about the associations among resilience, insomnia symptoms, exposure to early life stressors, and the clinical manifestations of BDs. Within this framework identifying insomnia symptoms as a target for therapeutic intervention in BDs should be of importance, as by enhancing stress resilience in at-risk populations could possibly prevent the onset of stress-induced psychopathology (Faye et al., 2018), and by targeting insomnia we might potentially target stress risk vulnerability dimension leading to implementation of resilience in response to early life stress in bipolar disorders.

In this context of a paucity of available information, we aimed to study how these factors might be interrelated and collectively associated with mood features and suicidal risk in a population of patients suffering from BD type I (BD I) or type II (BD II) during the depressed phases, with and without clinically significant insomnia symptoms. Since we hypothesized that insomnia symptoms could act as a mediator in the relationship among early life stress, impaired resilience and the clinical features of BDs, we also explored the potential processes underling the relationship between these variables by conducting mediation analyses.

2. Methods

2.1. Subjects

A consecutive series of inpatients hospitalized at the psychiatric ward of the Azienda Ospedaliero-Universitaria Pisana (AUOP, University of Pisa, Italy), with a diagnosis of depressive episode, BD of type I (BDI) or II (BDII), according to the Diagnostic and Statistical Manual of Mental Disorders criteria (DSM-5, American Psychiatric Association, 2013), were included in the present study. Inclusion criteria were participants with (1) a current diagnosis of major depressive episode with or without mixed features in the context of BDI or BDII, (2) between 18 and 65 years of age, and (3) who provided informed consent to participate in the study.

The exclusion criteria were: (1) a current or lifetime diagnosis of substance use disorder, (2) a current depressive episode with psychotic features, (3) other subtypes of BDs (i.e. not other specified), (4) a cognitive impairment, as assessed with the Mini Mental State Evaluation with a cut-off score <24 (for the Italian version Measso et al., 1993).

The current study was a cross-sectional observational study approved by the local ethical committee as a part of an ongoing main research plan aimed at characterizing insomnia and chrono-biological rhythms in several types of mood disorders. The study conformed to the Declaration of Helsinki and all participants provided written informed consent prior to being enrolled in the study.

2.1.1. Clinical assessment

All participants were evaluated with a set of questionnaires including the Structured Clinical Interview for DSM-5 (SCID-5) (First et al., 2017) to assess the presence of current or lifetime psychiatric diagnoses, the Italian version of Resilience Scale for Adults (RSA) (Hjemdal et al., 2006; Capanna et al., 2015), the Italian version of the Early Trauma Inventory Self Report-Short Form (ETISR-SF) (Bremner et al., 2007; Pietrini et al., 2010) to assess early life stress, Insomnia Severity Index to evaluate insomnia symptoms (Morin, 1993; Castronovo et al., 2016), the Scale for Suicide Ideation (SSI) to evaluate suicidal ideation and preparatory behaviors (Beck et al., 1996; Conti, 1999). According to previous studies on insomnia symptoms a score of ≥ 8 has been used as a cut off threshold for clinically significant insomnia symptoms (Morin, 1993).

The Beck Depression Inventory- II (BDI-II) (Beck et al., 1996) was used to evaluate depressive symptoms, mixed features were diagnosed using the SCID-5 (First et al., 2017), and manic symptoms were evaluated with the Young Mania Rating Scale (YMRS) (Young et al., 1978). All the participants also completed clinical report forms that included

current pharmacological treatments.

2.1.2. Assessment scales

Resilience Scale for Adults -RSA is a 33 item self-report scale for adults to measure six resilience factors and a total score (Hjemdal et al., 2006). Participants answer on a 7-point semantic differential scale in which each item has a positive and a negative attribute at each end of the scale continuum. Scores vary between 33 and 231, with higher scores indicating higher levels of resilience. The scale consists of 6 subscales measuring individual's characteristics in: (1) Perception of Self: concerning the confidence in own abilities, self-confidence, self-efficacy (for example "No matter what happens I always find a solution") (2) Planned Future: concerning the ability to plan ahead and formulate clear goals (for example " my projects for the future are easy to realize") (3) Social Competence concerning individual's own perception of social competence, (for example "It is important for me to be flexible in social circumstances") (4) Structured Style: concerning goal oriented, planning ability, organization of own time, routine oriented (for example" Rules and regular routines make my daily life easier") and external factors such as (5) Family Cohesion: concerning shared values, cohesion, loyalty, mutual appreciation, (for example "There are strong bonds in my family"), (6) Social Resources: concerning social support (for example "I always have someone who can help me when needed"). For the Italian version see Capanna et al. (2015).

The ETISR-SF is used for the assessment of physical, emotional and sexual abuse, as well as general traumatic experiences that occurred before the age of 18 (Bremner et al., 2007). It consists of 27 items and each of the items is answered "yes" (coded as 1) or "no" (coded as 0). It is divided into four dimensions: (1) general trauma (e.g. parental loss), physical, emotional and sexual abuses. Its validity and reliability have proved in different languages, including Italian, and different samples of subjects including in mood disorders (Bremner et al., 2007; Pietrini et al., 2010).

The ISI Index is a 7-item self-report questionnaire with a two-week recall period. The total score ranges from 0 to 28. For the purposes of this study, according to the ISI authors' recommendations, an ISI score of $\geq$8 indicated insomnia symptoms. The ISI has been validated in a previous Italian sample (Castronovo et al., 2016).

The SSI is a clinician-rating scale and is presented in a semi-structured interview format (Beck et al., 1996). It consists of 19 items that evaluate three dimensions of suicide ideation: active suicidal desire, specific plans for suicide, and passive suicidal desire at the time of the evaluation. Each item is rated on a 3-point scale from 0 to 2 (Beck et al., 1996; Conti, 1999).

The Beck Depression Inventory-II is a self-report 21-question inventory to assess depressive symptoms with a two-week recall period. The total score ranges from 0 to 63. A BDI-II total score of $>$ 13 is indicative of depressive symptoms (Beck et al., 1996; Ghisi et al., 2006).

The (YMRS) (Young et al., 1978; Palma et al., 1999): it is commonly employed to assess manic symptoms over the previous 48 h. A YMRS total score of $>$ 7 is indicative of hypomanic/manic symptoms (Young et al., 1978, Palma et al., 1999).

2.2. Statistical analysis

The statistical analyses were performed using SPSS 22.0 for Windows. Results were expressed as mean $\pm$ standard deviation (SD) and/or percent values. The Shapiro Wilk Test was used to check the normality of the variables. Differences in means between participants with clinically significant insomnia symptoms ISI total score of $\geq$8 and participants with non-clinically significant insomnia ISI total score$<$8 were assessed by Student *t*-tests for normally distributed variables, or the Mann-Whitney U/Wilcoxon Test for non-normally distributed variables. Categorical variables were analyzed via the Chi-Squared Test. Correlations between continuous variables were tested using the Spearman rho correlation for non-normally distributed variables and using Pearson correlations index for normally distributed variables in order to select which variable to include in the sequent regression analyses. Statistically significant variables were included in linear and multiple regression models with depressive/manic symptoms and suicidal ideation and behavior as dependent variables while taking into account, current pharmacological treatments and illness duration. All the multiple regression models were checked for multicollinearity. A variable was excluded from the model if it had a variance inflation factor greater than 10 and a condition number greater than 100 in the Eigenvalues of Centered Correlations. A mediation analysis using the Sobel test (Sobel, 1982) was performed in order to study the potential processes that may underlie the relationships between these variables. Variables included in the mediation analyses were those significantly correlated to depressive symptoms, manic symptoms and suicidal ideation and behaviors in the linear and multiple regression models. All pathways of the mediation were tested

3. Results

3.1. Descriptive statistics and comparative analyses

Twenty-three, out of the total 230 patients were excluded due to comorbid substance use disorder or concomitant psychotic features, and 19 were excluded due to incomplete questionnaires. Of the 188 patients evaluated, 81 (43.0%) participants were females, mean age 46.4 $\pm$ 13 years, 92 (48.9%) met the inclusion/exclusion criteria for BDI and 96 (51.15) for BDII, 101(44.1%) with mixed features. No patient met criteria for a formal lifetime or current post-traumatic stress disorder (PTSD), but 51(27.15) met criteria for other anxiety disorders, of whom 30 participants for panic disorder and 21 for generalized anxiety disorder. One hundred and eighteen subjects showed clinically significant insomnia symptoms (ISI$\geq$ 8) [47.4 $\pm$ 13.1years, 52, 44% female gender].

Patients with clinically significant insomnia symptoms were more frequently to have mixed features (Table 1) and they showed greater severity of depressive symptoms of suicidal ideation and plans.

In particular, they showed lower score ($<$0.001) in the rating scale measuring resilience (RSA) and in the subscales measuring planned future and structured style. They also showed higher scores on the rating scale measuring early life stress (ETISR) (Table 1). No differences were found in terms of current pharmacological therapy including drugs prescribed according to international guidelines for insomnia treatment

3.2. Correlations among variables

Results of Spearman's correlation for non-normally distributed variables and Pearson's correlation for normally distributed variables are shown in Table 2. It is evident that depressive symptoms were correlated with insomnia symptoms, early life tress and negatively with the components of resilience regarding the capacity to plan future, while manic symptoms were related to insomnia symptoms (see Table 2 for details).

Passive suicidal ideation was significantly positively related to depressive symptoms ($p < 0.001$), insomnia symptoms ($p < 0.001$), early life stress ($p < 0.05$), and with low resilience in the total score ($p < 0.05$). Active suicidal ideation was significantly positively related to passive suicidal ideation ($p < 0.001$), depressive and insomnia symptoms ($p < 0.001$, $p < 0.05$), early life stress and with low resilience in the total score ($p < 0.05$, $p < 0.05$),and in particular in planning future or structuring style ($p < 0.001$, $p < 0.05$). Suicidal plans were significantly positively related to depressive symptoms ($p < 0.001$), insomnia symptoms ($p < 0.05$), early-life stress ($p < 0.05$) and to low resilience in the capacity to planning future ($p < 0.001$). Total SSI score was significantly positively related to depressive ($p < 0.001$) and insomnia symptoms ($p < 0.001$), early-life stress ($p < 0.001$), to low resilience in the total score ($p < 0.001$) and the capacity to planning future ($p < 0.05$).

Table 1
Demographic and psychometric variables.

	Patients with Bipolar Disorder Depressive episode (N°=188)	**Patients with clinically significant insomnia** ISI≥8 (N°=118)	**Patients with non clinically significant insomnia** ISI<8 (N°=70)	**t or χ2** (df=2)	*p*
Age (years) (*m*±SD)	46.4 ± 13	47.4 ± 13.1	44.5 ± 13.2	0.14	0.143
Gender (female) N°(%)	81 (43.0)	52(44.0)	29(41.4)	0.03	0.555
Living alone N°(%)	43 (22.8)	25(21.1)	18 (25.7)	1.43	0.168
Divorced or not married N°(%)	102(54.2)	58(49.1)	44(62.8)	0.38	0.149
Unemployment N°(%)	25(13.2)	18(15.2)	8(11.4)	0.14	0.425
Illness duration (years) (*m*±SD)	18.4 ± 11.5	19±12.6	17.9 ± 11.6	0.75	0.453
Bipolar disorder I vs II N° (%)	92 (48.9)	58 (49.0)	28 (40.0)	*4.38	**0.036**
Mixed features N(%)	101(44.1)	78 (75.6)	33(29.0)	4.89	**0.022**
Anxiety comorbidity N (%)	51(27.1)	33 (27.9)	18(25.7)	0.01	0.524
Insomnia symptoms ISI tot (*m*±SD)	10.5 ± 6.4	14. ±4.9	4.1 ± 2.3	15.6	**<0.001**
Resilience scale RSA tot (*m*±SD)	87.3 ± 14.0	84.1 ± 13.7	95.1 ± 9.3	-4.95	**<0.001**
Perception of Self -RSA	13.1 ± 4.7	12.7 ± 3.2	13.1 ± 4.3	0.55	0.559
Planned Future -RSA	16.1 ± 8.5	14.2 ± 8.6	18.3 ± 7.7	-2.06	**0.041**
Social Competence- RSA	14.7 ± 6.1	14.5 ± 5.2	15.2 ± 7.6	-0.70	0.483
Structured Style -RSA	13.6 ± 5.0	12.9 ± 3.9	15.2 ± 6.6	-2.49	**0.014**
Family Cohesion- RSA	12.1 ± 3.7	12.1 ± 3.9	12.0 ± 4.7	0.118	0.906
Social Resources -RSA	14.6 ± 3.9	14.1 ± 4.5	14.9 ± 4.5	0.136	0.578
Early life stress-ETI tot (*m*±SD)	6.9 ± 5.1	7.5 ± 5.3	4.3 ± 3.5	2.52	**0.011**
SSI total (*m*±SD)	7.2 ± 6.5	7.7 ± 4.2	4.7 ± 2.3	2.75	**0.007**
Passive suicidal desire	3.1 ± 3.0	4.1 ± 2.	2.9 ± 2.6	3.36	**0.001**
Active suicidal desire	2.8 ± 3.8	3.5 ± 3.3	1.6 ± 1.8	3.04	**0.001**
Plans for suicide	0.6 ± 1.2	1.1 ± 1.3	0.45±1.19	2.01	**0.049**
Mood symptom scales					
BDI-II total score (*m*±SD)	22.6 ± 12.1	24.1 ± 12	19.2 ± 12	2.33	**0.021**
YMRS total score (*m*±SD)	8.5 ± 6.3	8.6 ± 6.7	6.9 ± 5.5	1.75	0.080
Current drug treatments	N° (%)	N° (%)	N° (%)		
Antidepressants	109(92.3)	74(62.7)	35(50.0)	1.03	0.145
Mood stabilizers	173(92.0)	112(94.2)	61(87.1)	1.04	0.168
Lithium	79 (66.9)	53(44.9)	26(37.1)	0.57	0.248
Benzodiazepines	108(57.4)	70(59.3)	38(54.2)	0.03	0.119
Neuroleptics	58(30.8)	37(31.3)	21(30.0)	0.01	0.131
Hypnoiducing drugs	114(60.6)	67(56.7)	37(52.8)	1.62	0.055

Legend. Demographic and psychometric variables. Description of the total sample of patients with bipolar disorder type I and II depressive episode with and without mixed features and comparison between patients with clinically significant insomnia Insomnia Severity Index.ISI≥8 vs patients without clinically significant insomnia ISI<8. N°=Number,%=percentage, M: mean value, SD: Standard Deviation, ***t*** = t-test.
.*a* =**χ2:**chi square. RSA-Resilience Scale for Adults and RSA subscales Perception of Self, Planned Future, Social Competence, Structured Style, Family Cohesion, Social Resources; SSI: Scale for Suicide Ideation; ETISR-SF: Early Trauma Inventory Self Reported-Short Form. Beck Depression Inventory-II, YMRS: Young Mania Rating Scale. Significance is in bold.

Table 2
Correlations among variables in patients with bipolar disorder type I and II.

	Passive-SSI	**Active SSI**	**Plans SSI**	**SSI tot**	**BDI-II**	**YMRS**	**ETI tot**	**ISI tot**	**RSA tot**	**RSA Planned Future**	**RSA Structured Style**
Passive-SSI	1										
Active SSI	**0.75****	1									
Plans SSI	**0.52****	**0.52****	1								
SSI tot	**0.89****	**0.90****	**0.89****	1							
BDI-II	**0.28****	**0.32****	**0.17***	**0.31****	1						
YMRS	0.08	0.09	0.10	0.09	0.010	1					
ETI tot	**0.21***	**0.17***	**0.16***	**0.20****	**0.15***	0.08	1				
ISI tot	**0.27****	**0.29****	**0.19***	**0.26****	**0.27****	**0.15***	**0.29****	1			
RSA tot	**-0.28***	**-0.18***	-0.13	**-0.23****	-0.11	-0.03	**-0.19***	**-0.38****	1		
RSA Planned Future	-0.27	**-0.28****	**-0.17****	**-0.28***	**-0.26****	-0.07	**-0.15***	**-0.18**	**0.54****	1	
RSA Structured Style	-0.07	**-0.19***	-0.07	-0.09	-0.01	-0.12	0.01	**-0.23****	**0.64****	**0.51****	1

3.3. Linear and multiple regression analyses

Linear regression analyses showed that significant predictors of depressive symptoms were: insomnia symptoms, early life stressors, low resilience in planning future while taking into account illness duration and current pharmacological therapy. In the multiple regression model including depressive symptoms as the dependent variable, insomnia symptoms ($p = 0.022$), and low resilience in planning future remained significant ($p = 0.007$) (Table 3).

Since manic symptoms were correlated with insomnia symptoms

Table 3
Linear and multiple regression analyses on depressive symptoms, passive, active suicidal ideation and suicidal preparatory behaviors in patients with bipolar disorder type I and II.

Depressive symptoms	Univariate B (SE)	p	Multivariate B (SE)	**p**
ISI	**0.52 (0.13)**	**<0.001**	**0.33 (0.14)**	**0.022**
ETI	**0.37(0.017)**	**0.004**	0.03 (0.01)	0.980
RSA Planned Future	**-0.34 (0.10)**	**0.002**	**-0.29 (0.10)**	**0.007**
Passive suicidal ideation-SSI	Univariate B (SE)	p	Multivariate B (SE)	**p**
ISI	**0.13 (0.03)**	**<0.001**	**0.07 (0.01)**	**0.003**
BDI-II	**0.07 (0.01)**	**<0.001**	**0.07 (0.02)**	**0.002**
ETI	**0.14 (0.05)**	**0.007**	0.04 (0.05)	0.421
RSA tot	**-0.06 (0.01)**	**0.002**	**-0.04 (0.01)**	**0.039**
Active suicidal ideation-SSI	Univariate B (SE)	p	Multivariate B (SE)	p
Passive suicidal ideation	**0.096 (0.62)**	**<0.001**	**1.12 (0.66)**	**<0.001**
BDI-II	**0.10 (0.02)**	**<0.001**	0.01 (0.01)	0.526
ISI	**0.17 (0.04)**	**<0.001**	0.03 (0.04)	0.445
ETI	**0.14 (0.06)**	**0.028**	0.02 (0.04)	0.495
RSA tot	**-0.04(0.02)**	**0.032**	-0.02 (0.01)	0.110
Preparatory **behaviors -SSI**	Univariate B (SE)	p	Multivariate B (SE)	**p**
Active suicidal ideation	**0.17 (0.02)**	**<0.001**	**0.08 (0.04)**	**0.046**
Passive suicidal ideation	**0.21 (0.02)**	**<0.001**	**0.01 (0.05)**	**0.013**
BDI-II	**0.01(0.08)**	**0.030**	0.001 (0.01)	0.940
ISI	**0.04 (0.01)**	**0.012**	0.001 (0.01)	0.927
ETI	**0.04 (0.02)**	**0.042**	0.01 (0.02)	0.804
RSA Planned Future	**0.02 (0.01)**	**0.043**	-0.001 (0.01)	0.966
SSI total score	Univariate B (SE)	p	Multivariate B (SE)	**p**
BDI-II	**0.20 (0.04)**	**<0.001**	**0.14 (0.05)**	**0.022**
ISI	**0.25 (0.05)**	**0.003**	**0.19 (0.05)**	**0.033**
ETI	**0.27 (0.04)**	**0.023**	**0.14 (0.03)**	**0.043**
RSA tot	**-0.18 (0.03)**	**0.043**	**-0.12 (0.01)**	**0.022**

Legend: **Linear and multiple regression analyses on depressive symptoms, passive, active suicidal ideation and suicidal** preparatory **behaviors in patients with bipolar disorder type I and II** . Results of linear and multiple logistic regression analyses among depressive symptoms Back Depression Inventory-BDI, Passive suicidal ideation, active suicidal ideation, Preparatory behaviors -SSI Scale for Suicide Ideation and other variables in patients with bipolar disorder type I and II, depressive episode. ISI:Insomnia Severity Index, RSA-Resilience Scale for Adults, RSA subscales Planned Future, Structured Style; ETISR-SF: Early Trauma Inventory Self Reported-Short Form, *B*= unstandardized regression coefficient. S.E.: Standard Error, Significance is in bold.

only, it was impossible to construct linear of multiple regression models.

Linear regression analyses showed that significant predictors of Passive suicidal ideation were: insomnia symptoms, depressive symptoms, early life stressors, and low resilience while taking into account illness duration and current pharmacological therapy. In the multiple regression model including passive suicidal ideation as the dependent variable, insomnia symptoms ($p = 0.003$), depressive symptoms ($p = 0.002$) and low resilience ($p = 0.032$) remained significant (Table 3).

Linear regression analyses showed that significant predictors of active suicidal ideation were: passive suicidal ideation, depressive and insomnia symptoms, early life stress and low resilience in the total score while taking into account illness duration and current pharmacological therapy. In the multiple regression model including active suicidal ideation as the dependent variable, passive suicide ideation remained significant ($p < 0.001$) (Table 3).

Linear regression analyses showed that significant predictors of suicidal plans were: passive and active suicidal ideation, depressive and insomnia symptoms, early life stress and low resilience in planned future while taking into account illness duration and current pharmacological therapy. In the multiple regression model active ($p = 0.046$) and passive suicidal ideation ($p = 0.013$) remained significant (Table 3).

3.4. Mediation analyses

Results of the mediation analyses for depressive symptoms (BDI total score) highlighted that the insomnia symptoms acted as mediator between early life stress (ETI total score) and low resilience in planning future (RSA subscale planned future) ($Z = 2.10$, $p = 0.035$) and between low resilience in planning future and depressive symptoms ($Z = 2.17$, $p = 0.029$) (Fig. 1) and between early life stress and depressive symptoms ($Z = 2.92$, SE=0.007, $p = 0.003$).

For suicidal risk (SSI total score) insomnia symptoms acted as mediators between early life stress and suicidal risk ($Z = 2.14$, SE:0032, $p = 0.031$), between early life stress and low resilience (RSA total score) ($Z = 2.35$, $p = 0.018$), and between low resilience and suicidal risk ($Z = 3.05$, $p = 0.0002$) (Fig. 2). No other mediations resulted significant.

4. Discussion

Results of the present study showed that BD patients with clinically significant insomnia symptoms had not only more frequently mixed features, a greater severity of depressive symptoms, suicidal ideation and behaviors, but also experienced more frequently early life stressors and hold lower levels of resilience in particular concerning the ability in planning future, goal and routine oriented ability. Our findings demonstrated that insomnia symptoms might play a role in affecting not only the clinical picture of BDs but also levels of resilience that might contribute to mood symptoms and suicide risk as well. In addition, insomnia may play a role in the relationship among early life stressors and impaired resilience in BDs during adulthood

These data are in line with previous studies about the association between insomnia symptoms and impaired resilience (Palagini et al., 2018; Chang et al., 2020), between early life stress and impaired resilience in bipolar disorder (Roy et al., 2011; Kesebir et al., 2015) and between early life stress insomnia/sleep disturbances and bipolar disorders in adult life (for an overview see: Palagini et al., 2015; Lo Martire et al., 2019; Palagini et al., 2021). It is tempting to hypothesize that insomnia symptoms in response to early life stressors may contribute to sensitize the stress system and to affect the stress-risk vulnerability dimension impairing the cognitive resources of the individual. By affecting resilience, alterations in sleep regulation might contribute to mood symptoms and suicidal risk in BDs.

Our findings, especially our mediation analyses, confirmed that BDs are complex disorders involving the interaction of multiple variables including insomnia as a potential key factor contributing to the severity of clinical features and to impaired resilience in BDs. Along this vein, our data appear useful to inform preventive strategies in BDs by acting on insomnia symptoms. By targeting insomnia we may potentially target the stress risk vulnerability dimension leading to implementation of resilience in BDs.

In our opinion, our study represents a significant contribution in the field. Firstly, we were able to confirm that BD patients during acute depressive phases with clinically significant insomnia showed a greater severity not only of depressive symptoms, but also of suicidal ideation and plans (Bernert et al., 2015; Kanady et al., 2015;Geoffroy et al., 2015; Pigeon et al., 2017; Palagini et al., 2019a, 2020). Insomnia symptoms involved particularly BD I patients with mixed features, that are usually related to a more severe form of BDs along with a worse course of illness, higher rates of comorbid conditions and major increases of suicidal risk (Serra et al., 2019; Tondo et al., 2020). Patients with clinically significant insomnia showed higher early life stressors confirming data previously gathered in subjects with insomnia disorders (for an overview Palagini et al., 2015; Lo Martire et al., 2019). Patients with insomnia also showed lower levels of resilience in particular regarding those areas involved in the ability to plan future, to plan ahead, formulate clear goals, and to organize own time, goal and routine oriented ability. Executive dysfunction characterizing BDs may affect functional capacity, and patients' ability to formulate clear goals and complete everyday

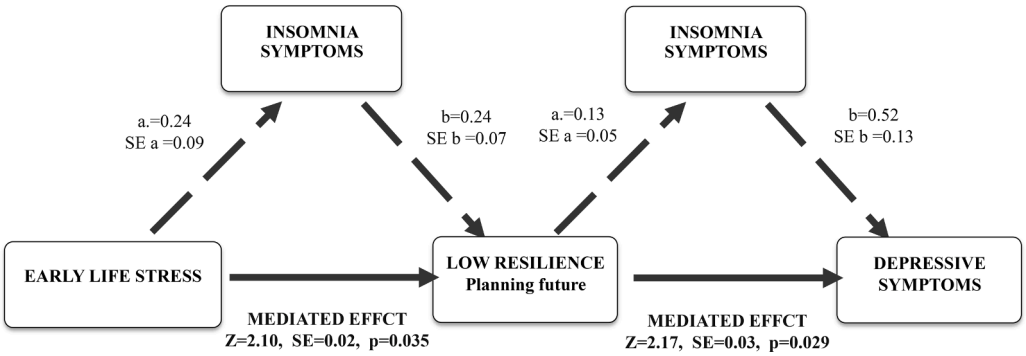

Fig. 1. Results of mediation analyses. Insomnia symptoms acted as a mediator between early life stress and low resilience in planned future (concerning the positive outlook on one's own future, sense of belief about the opportunity to succeed and the ability to plan ahead and formulate clear goals) and between low resilience in planned future and depressive symptoms.

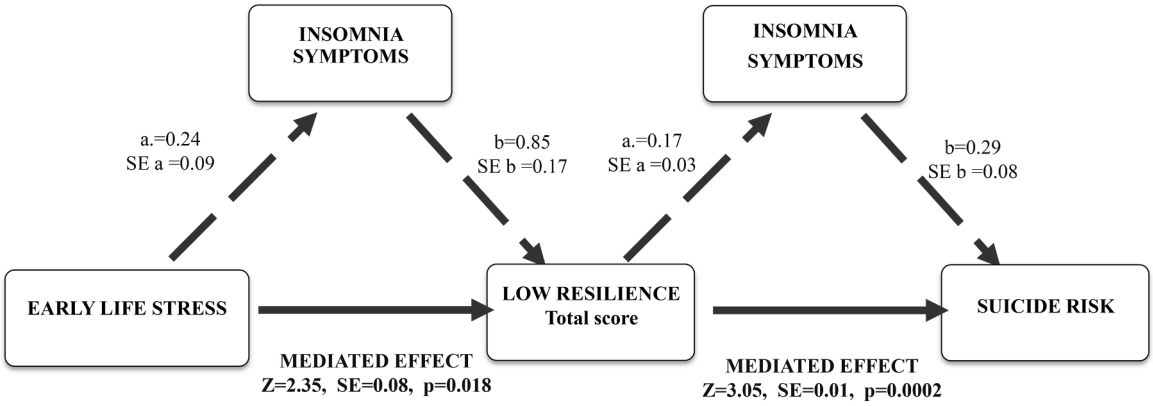

Fig. 2. Results of mediation analyses. Insomnia symptoms acted as a mediator between early life stress and low resilience and between low resilience and suicidal ideation and plans.

tasks (Cullen et al., 2016), but insomnia symptoms may contribute to it. In this framework these findings may be in line with previous different studies indicating the association between insomnia and executive dysfunctions (Ballesio et al., 2019) and low resilience and cognitive dysfunctions in BDs (Deng et al., 2018). Since executive functions are intimately associated with the integrity of the prefrontal cortex (Clark and Sahakian, 2008), it is tempting to hypothesize that insomnia, by contributing to a state of allostatic overload involving prefrontal cortex may contribute to affect neuronal circuitry underling executive regulation in BDs, in turn affecting those cognitive aspects of resilience. In addition, these findings may be in line with previous hypotheses that have pointed out the key role of daily routine disruption in BDs which, by affecting the body's ability to maintain synchronized rhythms including sleep, may favor mood episodes severity (Frank et al., 2006). In our BD patients during acute depressive phases, correlations and regression analyses revealed that insomnia symptoms, early life stress and impaired resilience might contribute to depressive symptoms and to suicidal risk, hence extending previous works in which insomnia symptoms, resilience and early life stressors, were studied separately in insomnia patients, BDs and other psychiatric disorders (Roy et al., 2011; Youssef et al., 2013; Liu et al., 2014; Kesebir et al., 2015; Germain and Dretsch, 2016; Palagini et al., 2018, 2021). By contrast, we evaluated all these factors in the same sample. It emerged that insomnia symptoms, early life stress and impaired resilience were intra-correlated, as well as they could be related to depressive symptoms, passive/active suicidal ideation suicidal behaviors.

In particular, insomnia, early life stress and low resilience in planning future were correlated with depressive symptoms, while manic symptoms were just related with insomnia symptoms. Insomnia symptoms, depressive symptoms, early life stress played a role in passive, active suicidal ideations and in suicidal preparatory behaviors. In particular low resilience in goal oriented planning future was a predictor of both passive suicidal ideation and suicidal plans.

We suggest that alterations of the sleep system in response to early life stressors (Palagini et al., 2015, 2021; Lo Martire et al., 2019) might play a key role in BDs by potentially dysregulating the stress system involved in mood and emotion regulation and favoring an allostatic overload hence impairing resilience and contributing to BD severity (for an overview see: Palagini et al., 2019a, 2019b).

Insomnia symptoms seem to act as mediator in the relationship among early life stress, low resilience in planned future and depressive symptoms, and among early life stress, low resilience and suicidal risk. Indeed, insomnia may act directly on mood symptoms, and suicidal ideation and behaviors, but it may also act throughout the mediation effect of early life stressors. As already hypothesized, we would propose that the alterations of sleep regulation would be one of the first targets of early life stressors (Lo Martire et al., 2019; Palagini et al., 2021). Early-life sleep dysregulation might sensitize the stress system through an epigenetic re-reprogramming, it may favor an allostatic overload contributing to impairing cognitive components of resilience. Despite recent interest in the relation between insomnia and suicidal risk (Pigeon, et al. 2107), the mechanism of their association has yet to be explored in great depth. Therefore, the observed association among early life stress, insomnia, low resilience and suicidal risk may be of interest. These data are in line with those showing the association between insomnia and suicidal risk (Pigeon et al., 2012), among sleep, resilience and suicide risk (Sher, 2020), insomnia and early life stressors (Palagini et al., 2019a, 2019b, 2019c), and with models sustaining the

stress vulnerability theory of suicide involving the role of early life stressors (Lutz et al., 2017) and of low resilience (Roy et al., 2011).

Our hypothesis is that alterations of sleep processes might contribute to cognitive components of resilience regarding planning future and organizing day life activities in BDs during a depressive episode, hence increasing suicidal risk. Taken together, the findings of the present study emphasize the need to assess insomnia symptoms in the clinical practice. We call for implementing it in the routine clinical evaluation of BD patients, together with the evaluation of early life stressors and resilience. A better screening of these dimensions might provide additional preventive strategies and/or improve treatments that should include cognitive behavioral therapy for insomnia (CBT-I) or pharmacological drugs for insomnia, according to recent guidelines (Riemann et al., 2010; Palagini et al., 2020, 2021). In particular, targeting insomnia symptoms may potentially modify the clinical features of BDs in response to early life stressful events and improve resilience.

4.1. Limitations

These results should be interpreted in light of several limitations including the cross-sectional design affecting causal interpretations. Consequently, longitudinal studies are needed with larger samples of patients and other types of mood disorders with psychotic symptoms, anxiety or other features of BDs, but also patients who attempted suicide to better examine the direction of risk and be able to generalize these findings. Measures of stress system activity should be included in future studies and related to insomnia symptoms in BDs. Since no differences were found among pharmacological treatments including sleep inducing treatments, it would be interesting to evaluate pharmacogenomic or other genetic profiles (Biernacka et al., 2012) of these patients and how these factors may potentially affect the individual response to sleep promoting treatments.

5. Conclusion

In conclusion, our study suggests that: (i) BD patients during a depressive phase with clinically significant insomnia show a greater severity not only of depressive symptoms and suicidal risk, but also of low resilience while also reporting higher early life stressors than those BD subjects without insomnia (ii) insomnia symptoms could be related to both depressive symptoms and manic symptoms, suicidal ideation and plans and low resilience (iii) insomnia symptoms might mediate the effect of early life stressors on resilience on mood symptoms, and suicidal ideation and behaviors. Taken together, these findings may have clinical implications for systematic screening of insomnia dimension, for prevention and early intervention strategies with appropriate therapeutic strategies for insomnia. In particular targeting insomnia symptoms may potentially modify the clinical features of BD in response to early life stressful events and enhance resilience.

Funding

None.

Declaration of Competing Interest

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. No conflict of interests to declare.

Acknowledgment

None.

References

Aas, M., Henry, C., Andreassen, O.A., Bellivier, F., Melle, I., Etain, B., 2016. The role of childhood trauma in bipolar disorders. Int. J. Bipolar Disord. 4 (1), 2.
American Psychiatric Association, 2013. Diagnostic and Statistical Manual of Mental Disorders. American Psychiatric Pub, Washington. Fifth edition (DSM-5).
Angeler, D.G., Allen, C.R., Persson, M.L., 2018. Resilience concepts in psychiatry demonstrated with bipolar disorder. Int. J. Bipolar Disord. 6 (1), 2.
Agnew-Blais, J., Danese, A., 2016. Childhood maltreatment and unfavourable clinical outcomesin bipolar disorder: a systematic review and meta-analysis. Lancet Psychiatry 3 (4), 342–349.
Asarnow, L.D., Manber, R., 2019. Cognitive behavioral therapy for insomnia in depression. Sleep Med. Clin. 14, 177–184.
Ballesio, A., Aquino, M.R.J.V., Kyle, S.D., Ferlazzo, F., Lombardo, C., 2019. Executive functions in insomnia disorder: a systematic review and exploratory meta-analysis. Front Psychol 10, 101.
Beck, A.T., Steer, R.A., Ball, R., Ranieri, W., 1996. Comparison of beck depression inventories -IA and -II in psychiatric outpatients. J. Personal. Assess. 67, 588–597.
Bei, B., Asarnow, L.D., Krystal, A., Edinger, J.D., Buysse, D.J., Manber, R., 2018. Treating insomnia in depression: insomnia related factors predict long-term depression trajectories. J. Consult. Clin. Psychol. 86, 282–293.
Bernert, R.A., Kim, J.S., Iwata, N.G., Perlis, M.L., 2015. Sleep disturbances as an evidence-based suicide risk factor. Curr. Psychiatry Rep. 17, 554.
Biernacka, J.M., McElroy, S.L., Crow, S., Sharp, A., Benitez, J., Veldic, M., Kung, S., Cunningham, J.M., Post, R.M., Mrazek, D., Frye, M.A., 2012. Pharmacogenomics of antidepressant induced mania: a review and meta-analysis of the serotonin transporter gene (5HTTLPR) association. J. Affect. Disord. 136 (1–2), 21–29.
Boudebesse, C., Henry, C., 2012. Emotional hyper-reactivity and sleep disturbances in remitted patients with bipolar disorders. Encephale 38, 173–178.
Bremner, J.D., Bolus, R., Mayer, E.A, 2007. Psychometric properties of the early trauma inventory-self report. J. Nerv. Ment. Disord. 195, 211–218.
Castronovo, V., Galbiati, A., Marelli, S., Brombin, C., Cugnata, F., Giarolli, L., Anelli, M. M., Rinaldi, F., Ferini-Strambi, L., 2016. Validation study of the Italian version of the Insomnia Severity Index (ISI). Neurol. Sci. 37, 1517–1524.
Cheng, P., Casement, M.D., Kalmbach, D.A., Castelan, A.C., Drake, C.L., 2021. Digital cognitive behavioral therapy for insomnia promotes later health resilience during the coronavirus disease 19 (COVID-19) pandemic. Sleep 44 (4), 258.
Choi, J.W., Cha, B., Jang, J., Park, C.S., Kim, B.J., Lee, C.S., Lee, S.J., 2015. Resilience and impulsivity in euthymic patients with bipolar disorder. J. Affect. Disord. 170, 172–177.
Clark, L., Sahakian, B.J, 2008. Cognitive neuroscience and brain imaging in bipolar disorder. Dialogues Clin. Neurosci. 10 (2), 153–163.
Cretu, J.B., Culver, J.L., Goffin, K.C., Shah, S., Ketter, T.A., 2016. Sleep, residual mood symptoms, and time to relapse in recovered patients with bipolar disorder. J. Affect. Disord. 190, 162–166.
Cullen, B., Ward, J., Graham, N.A., Deary, I.J., Pell, J.P., Smith, D.J., Evans, J.J, 2016. Prevalence and correlates of cognitive impairment in euthymic adults with bipolar disorder: a systematic review. J. Affect. Disord. 205, 165–181.
Delgado, M., 2015. Critique of a systematic review and meta-analysis of premature mortality in bipolar affective disorder. Acta Psychiatr. Scand. 132, 315.
Deng, M., Pan, Y., Zhou, L., Chen, X., Liu, C., Huang, X., Tao, H., Pu, W., Wu, G., Hu, X., He, Z., Xue, Z., Liu, Z., Rosenheck, R., 2018. Resilience and cognitive function in patients with schizophrenia and bipolardisorder, and healthy controls. Front. Psychiatry 9, 279.
Etain, B., Godin, O., Boudebesse, C., Aubin, V., Azorin, J.M., Bellivier, F., et al., 2017. Sleep quality and emotional reactivity cluster in bipolar disorders and impact on functioning. Eur. Psychiatry 45, 190–197.
Faye, C., Mcgowan, J.C., Denny, C.A., David, D.J., 2018. Neurobiological mechanisms of stress resilience and implications for the aged population. Curr. Neuropharmacol. 16 (3), 234–270.
First, M.B., Williams, J.B.W., Karg, R.S., Spitzer, R.L., 2017. Intervista Clinica Strutturata Per i Disturbi del DSM-5. Versione per IL Clinico. Ed. Italiana a cura Di Andrea Fossati e Serena Borroni. Raffaello Cortina Editore, Milano.
Frank, E., Gonzalez, J.M., Fagiolini, A., 2006. The importance of routine for preventing recurrence in bipolar disorder. Am. J. Psychiatry 163 (6), 981–985.
Germain, A., Dretsch, M., 2016. Sleep and resilience-a call for prevention and intervention. Sleep 39 (5), 963–965.
Geoffroy, P.A., 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.
Ghisi, M., Flebus, G.B., Montano, A., Sanavio, E., Sica, C., 2006. Beck Depression Inventory-II. Manuale italiano. Giunti Editore, Firenze.
Hayes, J.F., Miles, J., Walters, K., King, M., Osborn, D.P., 2015. A systematic review and meta-analysis of premature mortality in bipolar affective disorder. Acta Psychiatr. Scand. 131, 417–425.
Heim, C.M., Entringer, S., Buss, C., 2018. Translating basic research knowledge on the biological embedding of early-life stress into novel approaches for the developmental programming of lifelong health. Psychoneuroendocrinology S0306-4530, 30679-6.
Hertenstein, E., Feige, B., Gmeiner, T., Kienzler, C., Spiegelhalder, K., Johann, A., Jansson-Fröjmark, M., Palagini, L., Rücker, G., Riemann, D., Baglioni, C., 2019. Insomnia as a predictor of mental disorders: a systematic review and meta-analysis. Sleep Med. Rev. 43, 96–105.
Jaworska-Andryszewska, P., Rybakowski, J.K, 2019. Childhood trauma in mood disorders: neurobiological mechanisms and implications for treatment. Pharmacol. Rep. 71, 112–120.

Kanady, J.C., Soehnera, A.M., Harvey, A.G., 2015. A retrospective examination of sleep disturbance across the course of bipolar disorder. J. Sleep Disord. Ther. 4, 100193.
Lee, D., Cha, B., Park, C.S., Kim, B.J., Lee, C.S., Lee, S.J., Seo, J.Y., Cho, Y.A., Ha, J.H., Choi, J.W., 2017. Effects of resilience on quality of life in patients with bipolar disorder. J. Affect. Disord. 207, 434–441.
Liu, D.W., Fairweather-Schmidt, A.K., Roberts, R.M., Burns, R., Ansteym, K.J., 2014. Does resilience predict suicidality? A lifespan analysis. Arch. Suicide Res. 18 (4), 453–464.
Lutz, P.E., Mechawar, N., Turecki, G., 2017. Neuropathology of suicide: recent findings and future directions. Mol. Psychiatry 22 (10), 1395–1412.
Measso, G., Cavarzeran, F., Zappalà, G., 1993. Dev. Neuropsychol. 9, 77–85.
Miller, J.N., Black, D.W., 2020. Bipolar disorder and suicide: a review. Curr. Psychiatry Rep. 22, 6.
Mizuno, Y., Hofer, A., Suzuki, T., Frajo-Apor, B., Wartelsteiner, F., Kemmler, G., et al., 2016. Clinical and biological correlates of resilience in patients with schizophrenia and bipolar disorder: a cross-sectional study. Schizophr. Res. 175, 148–153. https://doi.org/10.1016/j.schres.2016.04.047.
Morin, C.M., 1993. Insomnia: Psychological Assessment and Management. Guilford Press, New York.
Morton, E., Murray, G., Michalak, E.E., Lam, R.W., Beaulieu, S., Sharma, V., Cervantes, P., Parikh, S.V., Yatham, L.N., 2018. Quality of life in bipolar disorder: towards a dynamic understanding. Psychol. Med. 48, 1111–1118.
Ng, T.H., Chung, K.F., Ho, F.Y., Yeung, W.F., Yung, K.P., Lam, T.H, 2015. Sleep-wake disturbance in inter episode bipolar disorder and high-risk individuals: a systematic review and meta-analysis. Sleep Med. Rev. 20, 46–58.
Nunes, K.G., da Rocha, N.S., 2021. Resilience in severe mental disorders: correlations to clinical measures and quality of life in hospitalized patients with major depression, bipolar disorder, and schizophrenia. Qual. Life Res. In press.
Palagini, L., Biber, K., Riemann, D., 2014. The genetics of insomnia–evidence for epigenetic mechanisms? Sleep Med. Rev. 18, 225–235.
Palagini, L., Drake, C.L., Gehrman, P., Meerlo, P., Riemann, D., 2015. Early-life origin of adult insomnia: does prenatal-early-life stress play a role? Sleep Med. 16, 446–456.
Palagini, L., Moretto, U., Novi, M., Masci, I., Caruso, D., Drake, C.L., Riemann, D., 2018. Lack of resilience is related to stress-related sleep reactivity, hyperarousal, and emotion dysregulation in insomnia disorder. J. Clin. Sleep Med. 14 (5), 759–766.
Palagini, L., Bastien, C.H., Marazziti, D., Ellis, J.G., Riemann, D., 2019a. The key role of insomnia and sleep loss in the dysregulation of multiple systems involved in mood disorders: a proposed model. J. Sleep Res. 10, 12841.
Palagini, L., Domschke, K., Benedetti, F., Foster, R.G., Wulff, K., Riemann, D., 2019b. Developmental pathways towards mood disorders in adult life: is there a role for sleep disturbances? J. Affect. Disord. 243, 121–132.
Palagini, L., Cipollone, G., Masci, I., Caruso, D., Paolilli, F., Perugi, G., Riemann, D., 2019c. Insomnia symptoms predict emotional dysregulation, impulsivity and suicidality in depressive bipolar II patients with mixed features. Compr. Psychiatry 89, 46–51.
Palagini, L., Miniati, M., Caruso, D., Massa, L., Novi, M., Pardini, F., Salarpi, G., Pini, S., Marazziti, D., Etain, B., Riemann, D., 2020. Association between affective temperaments and mood features in bipolar disorder II: the role of insomnia and chronobiological rhythms desynchronization. J. Affect. Disord. 266, 263–272.
Palagini, L., Miniati, M., Marazziti, D., Sharma, V., Riemann, D., 2021. Association among early life stress, mood features, hopelessness and suicidal risk in bipolar disorder: the potential contribution of insomnia symptoms. J. Psychiatr. Res. 135, 52–59.
Palma, A., Pancheri, P., et al., 1999. Scale di valutazione e di misura dei sintomi psichiatrici. In: Cassano GBPancheri, P., et al. (Eds.), Trattato Italiano di Psichiatria, 2nd ed. Masson Italia, Milano.
Pigeon, W.R., Pinquart, M., Conner, K., 2012. Meta-analysis of sleep disturbance and suicidal thoughts and behaviors. J. Clin. Psychiatry 73 (9), 1160–1167.
Pigeon, W.R., Bishop, T.M., Krueger, K.M, 2017. Insomnia as a precipitating factor in new onset mental illness: a systematic review of recent findings. Curr. Psychiatry Rep. 19, 44.
Pinto, J.V., Saraf, G., Kozicky, J., Beaulieu, S., Sharma, V., Parikh, S.V., Cervantes, P., Daigneault, A., Walji, N., Kauer-Sant'Anna, M., Yatham, L.N., 2020. Remission and recurrence in bipolar disorder: the data from health outcomes and patient evaluations in bipolar disorder (HOPE-BD) study. J. Affect. Disord. 268, 150–157.
Post, F., Pardeller, S., Frajo-Apor, B., Kemmler, G., Sondermann, C., Hausmann, A., Fleischhacker, W.W., Mizuno, Y., Uchida, H., Hofer, A., 2018. Quality of life in stabilized outpatients with bipolar I disorder: associations with resilience, internalized stigma, and residual symptoms. J. Affect. Disord. 238, 399–404.
Pietrini, F., Lelli, L., Verardi, A., Silvestri, C., Faravelli, C., 2010. Retrospective assessment of childhood trauma: review of the instruments. Riv. Psichiatr. 45, 7–16.
Riemann, D., Baglioni, C., Bassetti, C., Bjorvatn, B., Dolenc Groselj, L., Ellis, J.G., Espie, C.A., García-Borreguero, D., Gjerstad, M., Gonçalves, M., Hertenstein, E., Jansson-Fröjmark, M., Jennum, P.J., Leger, D., Nissen, C., Parrino, L., Paunio, T., Pevernagie, D., Verbraecken, J., Weeß, H.G., Wichniak, A., Zavalko, I., Arnardottir, E.S., Deleanu, O.C., Strazisar, B., Zoetmulder, M., Spiegelhalder, K., 2010. European guideline for the diagnosis and treatment of insomnia. J. Sleep Res. 26, 675–700.
Ritter, P.S., Marx, C., Bauer, M., Leopold, K., Pfennig, A., 2011. The role of disturbed sleep in the early recognition of bipolar disorder: a systematic review. Bipolar Disord. 13, 227–237.
Rumble, M.E., White, K.H., Benca, R.M., 2015. Sleep disturbances in mood disorders. Psychiatr. Clin. North Am. 38, 743–759.
Roy, A., Sarchiapone, M., Carli, V., 2007. Low resilience in suicide attempters: relationship to depressive symptoms. Depress. Anxiety 24 (4), 273.
Roy, A., Carli, V., Sarchiapone, M., 2011. Resilience mitigates the suicide risk associated with childhood trauma. J. Affect. Disord. 133 (3), 591–594.
Rutter, M., 2012. Resilience as a dynamic concept. Dev. Psychopathol. 24 (2), 335–344.
Serra, F., Gordon-Smith, K., Perry, A., Fraser, C., Di Florio, A., Craddock, N., Jones, I., Jones, L., 2019. Agitated depression in bipolar disorder. Bipolar Disord. 21, 547–555.
Sher, L., 2020. Sleep, resilience and suicide. Sleep Med. 66, 284–285.
Sobel, M.E., 1982. Asymptotic confidence intervals for indirect effects in structural equation models. Sociol. Methodol. 13, 290–312.
Targum, S.D., Nemeroff, C.B, 2019. The effect of early life stress on adult psychiatric disorders. Innov. Clin. Neurosci. 16 (1–2), 35–37.
Tondo, L., Vazquez, G.H., Baldessarini, R.J., 2020. Suicidal behavior associated with mixed features in major mood disorders. Psychiatr. Clin. N. Am. 43, 83–93.
Vieta, E., Berk, M., Schulze, T.G., Carvalho, A.F., Suppes, T., Calabrese, J.R., Gao, K., Miskowiak, K.W., Grande, I., 2018. Bipolar disorders. Nat. Rev. Dis. Primers 4, 18008.
Young, R.C., Biggs, J.T., Ziegler, V.E., Meyer, D.A., 1978. A rating scale for mania: reliability, validity and sensitivity. Br. J. Psychiatry 133, 429.
Youssef, N.A., Green, K.T., Beckham, J.C., Elbogen, E.B., 2013. A 3-year longitudinal study examining the effect of resilience on suicidality in veterans. Ann. Clin. Psychiatry 25 (1), 59–66.
Wermelinger Ávila, M.P., Lucchetti, A.L., Lucchetti, G., 2017. Association between depression and resilience in older adults: a systematic review and meta-analysis. Int. J. Geriatr. Psychiatry 32 (3), 237–246.