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A narrative review on insomnia and hypersomnolence within Major Depressive Disorder and bipolar disorder: A proposal for a novel psychometric protocol

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ABSTRACT

Sleep disorders have become increasingly prevalent, with many adults worldwide reporting sleep dissatisfaction. Major Depressive Disorder (MDD) and Bipolar Disorder (BD) are common conditions associated with disrupted sleep patterns such as insomnia and hypersomnolence. These sleep disorders significantly affect the progression, severity, treatment, and outcome of unipolar and bipolar depression. While there is evidence of a connection between sleep disorders and depression, it remains unclear if sleep features differ between MDD and BD. In light of this, this narrative review aims to: (1) summarize findings on common sleep disorders like insomnia and hypersomnolence, strongly linked to MDD and BD; (2) propose a novel psychometric approach to assess sleep in individuals with depressive disorders. Despite insomnia seems to be more influent in unipolar depression, while hypersomnolence in bipolar one, there is no common agreement. So, it is essential adopting a comprehensive psychometric protocol for try to fill this gap. Understanding the relationship between sleep and MDD and BD disorders are crucial for effective management and better quality of life for those affected.

1. Introduction

Sleep is a physiological process essential for human health and well-being because it plays a crucial role in several biological activities, including immune functioning, metabolism, learning, memory, behavior, and emotional regulation (Garbarino et al., 2021). Despite the

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critical role of sleep on good quality of life, sleep disorders are increasing in recent years and prospective data are not encouraging (Jawabri and Raja, 2019; Nelson et al., 2022). According to the Philips Global Sleep Survey (2019), a significant percentage of adults worldwide are not satisfied with their sleep quantity and quality. Specifically, 62% of adults report that they do not sleep as well as they would like; 67% report sleep disturbances at least once every night, whereas 44% feel that their sleep quality has worsened compared to the previous five years (Philips, 2019). Moreover, the National Sleep Foundation indicates that up to two-thirds of adults occasionally experience symptoms of insomnia at least a few nights per week, while up to 10% of adults have chronic insomnia. With regard to hypersomnolence it is difficult to determine the exact number of people affected, because the prevalence basically varies depending on the diagnostic criteria and the population studied. In fact, with the introduction of DSM-5 (APA, 2013) hypersomnolence disorder has been introduced, distinguishing it from hypersomnia disorders. In this context when we deal with hypersomnolence we refer to hypersomnolence disorder. From this perspective, it is estimated that this disorder affects less than 5% of the general population (Ohayon et al., 2017; Suni and Rehman, 2023).

The COVID-19 pandemic has had a significant impact on sleep patterns and disorders. The pandemic has brought an increased levels of stress, anxiety, and uncertainty, which can significantly affect sleep, eventually contributing to some sleep disturbances. Disruptions in daily routines, changes in work environments, and social isolation have also affected sleep schedules and quality for many individuals (Coco et al., 2021; Pérez-Carbonell et al., 2020; Varrasi, Guerrera et al., 2023). The growing number of sleep disorders in our society is also a major public health concern, mainly due to the increased risk of developing comorbid psychopathology (Hertenstein et al., 2019).

For these reasons, it is important to address sleep disorders and stimulate work towards the improvement of our sleep habits, as poor sleep can have negative effects on both mental health and physical performance, cognitive status, and overall quality of life (Carey et al., 2011; Pearson et al., 2023). In fact, people suffering from sleep disorders may be at higher risk for developing a range of health conditions, including cardiovascular diseases, metabolic disorders, immune system disorders, and cognitive impairment, particularly in elderly patients (Coco et al., 2019). Additionally, people suffering from sleep disorders are more likely to develop Major Depressive Disorder (MDD) or Bipolar Disorder (BD), anxiety disorders, post-traumatic stress disorder, social-emotional problems, and attention deficit hyperactivity disorder (Calandra et al., 2013; Soehner et al., 2014; Varrasi, Boccaccio et al., 2023). In this context, it is known that sleep disorders and depression are extremely prevalent and interconnected health issues, both affecting millions of people worldwide. Of note, sleep disorders, such as insomnia and hypersomnolence, can not only impair the quality of sleep but also increase the risk of developing depression and, at same time, they are considered among the diagnostic criteria for both MDD and BD (APA, 2013).

More in details, scientific studies have revealed compelling evidence indicating that individuals with MDD who experience insomnia tend to bear a heavier burden of illness (Joshi et al., 2023). This is reflected in heightened levels of depression severity, poor quality of life, and a greater occurrence of both medical and psychiatric conditions (Platania et al., 2020). It is worth noting that even after receiving appropriate treatment for MDD, symptoms of insomnia tend to persist among these patients (Sunderajan et al., 2010). Moreover, a strong correlation has been established between insomnia and increased severity of depression in BD (Palagini et al., 2021). Notably, sleep disturbances persist not only during the intervals between manic or depressive episodes, but also during the periods of remission in BD (Pinho et al., 2016).

Concerning hypersomnolence, a condition characterized by excessive sleepiness, patients with MDD may not experience significant challenges in falling asleep (Galušková and Šonka, 2021; Plante et al., 2019). Additionally, depressed patients with excessive daytime sleepiness (EDS), tend to exhibit more severe dysfunctional thoughts related to sleep (Cook et al., 2021). Hypersomnolence is also more commonly observed in bipolar depression compared to unipolar one, even during periods between depressive episodes. Furthermore, it is associated with long-term, severe, treatment-resistant depression (Murru et al., 2019).

Other interesting evidence highlights that also chronotype is important when we consider sleep patterns in depressive patients. It is a measure of individual differences in rest/activity or circadian timing and it has been increasingly recognized as an important correlate of mental health (Taylor and Hasler, 2018). Concerning affective disorders, some evidence found out that MDD patients were more morning-type, i.e. individuals who tend to be “early larks”, while BD had an intermediate-type, i.e. individuals who are not neither “early larks”, neither “night owls” (Serrano-Serrano et al., 2021; Urbán et al., 2011).

Despite the available evidence regarding sleep disturbances in both unipolar and bipolar depression, there is a lack of literature providing specific elements for a differential diagnosis between MDD and BD in terms of sleep features and, consequently, diagnosing sleep disorders in individuals with depression is clinically challenging. Given the current lack of consistent scientific evidence to facilitate the differential diagnosis between MDD and BD and considering that sleep disorders enhance the risk of depressive relapse, it becomes mandatory to develop new psychometric approaches that can address this knowledge gap (Guerrera, Platania, Varrasi et al., 2023; Platania et al., 2023).

For these reasons, the present narrative review aims to: (1) collect the main findings on insomnia and hypersomnolence comorbid with MDD and BD in the depressive phase; and (2) propose a novel psychometric approach to assess sleep in individuals with depressive disorders, in order to improve the diagnostic and therapeutic strategies.

2. Sleep and depression: from physiology to pathology

Persons with sleep disorders are more likely to develop psychiatric diseases, such as bipolar disorder, generalized anxiety disorder, suicidal ideation, and, especially, depressive diseases (Xu et al., 2022), as well as a number of neurological and medical disorders (Fan and Su, 2023; Joza et al., 2023). Of note, the presence and severity of a sleep disturbance is considered a clinically significant feature of depression, and, accordingly, it is listed as a diagnostic criterion for depression according to the DSM-5 (APA, 2013). Namely, individuals with depression typically describe a wide range of issues concerning sleep quantity, continuity, and quality, as well as daytime difficulties. Recent studies suggest that up to 60–90% of individuals report sleep quality complaints, particularly insomnia and hypersomnolence during a depressive episode (Hutka et al., 2021; Zhang et al., 2022).

3. Insomnia and depression

According to the DSM-5, insomnia is considered a disorder of initiating/maintaining sleep and/or non-restorative sleep, accompanied by decreased daytime functioning for at least 3 months, with a frequency of no less than 3 nights per week (APA, 2013). Population-based estimates indicate that about 33% of adults report insomnia-related symptoms, 10–15% experience associated daytime impairments, and 6–10% have symptoms that meet criteria for insomnia disorder, thus representing the most prevalent sleep disorders worldwide. Noteworthy, persistent insomnia (i.e., symptoms lasting 3 months or longer) may be a risk factor for depressive, bipolar, anxiety, and substance use disorders, as well as suicidal ideation, and it is also a frequent residual symptom after the treatment of these conditions (Fang et al., 2019; Riemann et al., 2020). Moreover, insomnia is not only a prodromal symptom, but also an independent risk factor for depression and it is also considered a core predictor of depression recurrence, even contributing to negative clinical outcomes during treatment (Li et al., 2016). Moreover, different studies support the finding that some sleep disorders, including

insomnia, increase the risk of suicidal behavior in patients with depression (Wang et al., 2019).

3.1. Insomnia and depression: investigating the common pathway through neurological markers

Some common neuromarkers of insomnia and depression have been reported. For instance, Palagini et al. (Palagini et al., 2022) (Fig. 1) highlighted common neurobiological changes between sleep loss and depression, describing and explaining the following pathways: (1) neuroinflammation, (2) activation of the stress system and (3) oxidative-stress, (4) accumulation of β-amyloid peptide, and (5) deficit of the neuroprotection mechanisms, mainly related to alterations in Brain-Derived Neurotrophic Factor (BDNF) production, as well as in kynurenine and melatonin pathways. Poor sleep quality and insomnia also results in an over-activation of the Hypothalamic-Pituitary-Adrenal (HPA)-axis and sympathetic nervous system pathways, which, together, contribute to an increased proinflammatory cytokine activity (Irwin, 2015, 2019). On this basis, it has been hypothesized that a state of chronic activation of the inflammatory system might be triggered or aggravated by insomnia and/or different conditions associated with sleep loss, eventually causing neurodegeneration (Irwin and Piber, 2018). Moreover, animal models show that sleep loss associates with measures of neuroinflammation, such as increased secretion of pro-inflammatory cytokines, increased blood–brain barrier permeability and activation of microglia (Wirz-Justice and Benedetti, 2020). The hyperactivation of the HPA-axis also causes hyperarousal, which is the key pathophysiological mechanism of insomnia (Riemann et al., 2015). It has been also hypothesized that insomnia may influence affective disorders throughout the activation of the stress system and its negative consequences on the brain, including the reduction in hippocampal and medial prefrontal cortex volume, caudate head, impaired synaptic plasticity, as well as an increase in the amygdala volume (Cantone et al., 2017; Lo Martire et al., 2020; Riemann et al., 2015) modifications resembling those described in affective disorders (Meerlo et al., 2015). In addition, the suprachiasmatic nucleus transmits a strong circadian output to the HPA axis, so that circadian sleep alterations have been considered as a stressor, since they directly alter catecholamine and cortisol release (Palagini et al., 2022).

A specific type of stress, particularly harmful to the brain, is the oxidative stress (Belcaro et al., 2018; Gulec et al., 2012). In particular, the Reactive Oxygen Species (ROS), independent molecules characterized by the presence of at least one oxygen atom and one or more unpaired electrons, such as oxygen free radicals (Jakubczyk et al., 2020), and other oxidative stress markers could be heaped in the brain during wakefulness, usually measured by d-roMs test, which measures plasma hydroperoxide levels in carr units (Belcaro et al., 2018). These findings are confirmed by the fact that sleep represents a state with an increased antioxidant activity, thus supporting a brain protection against free radicals (Besedovsky et al., 2019; Villafuerte et al., 2015).

Furthermore, insomnia, by reducing sleep duration, increasing sleep deprivation, and promoting circadian alterations, might contribute to the accumulation of neurotoxic proteins involved in neurodegenerative processes. This may occur mainly by: (1) directly impairing proteasomal degradation, (2) altering autophagy activities, (3) impairing the clearance of accumulating proteins and other molecules from the brain through the so-called “glymphatic” flow, and (4) impairing melatonin production and antioxidant defense. Overall, these pathophysiological mechanisms might lead to neurodegeneration in depression, via the impairment of the neurotoxic proteins clearance and degradation pathways (Palagini et al., 2022).

Finally, mounting evidence highlights that BDNF is strongly involved in the homeostatic regulation of sleep. BDNF expression, indeed, is decreased by psychological stressors, and this lack of neurotrophic support is involved not only in depression and other affective disorders (Rethorst et al., 2015; Schmitt et al., 2016), but also in insomnia (Furihata et al., 2020). Disruption of the sleep homeostatic process results in higher stress vulnerability, impairing BDNF levels, with negative effects on serotonin signaling, which is involved in depression as well (Palagini et al., 2022). According to this evidence, BDNF is central in the pathophysiology of stress-related depression, and is another common neurobiological marker of both depression and insomnia (Lanza et al., 2022).

Besides BDNF, poor sleep quality and insomnia are associated with an activation of the kynurenine pathway and depressive symptoms

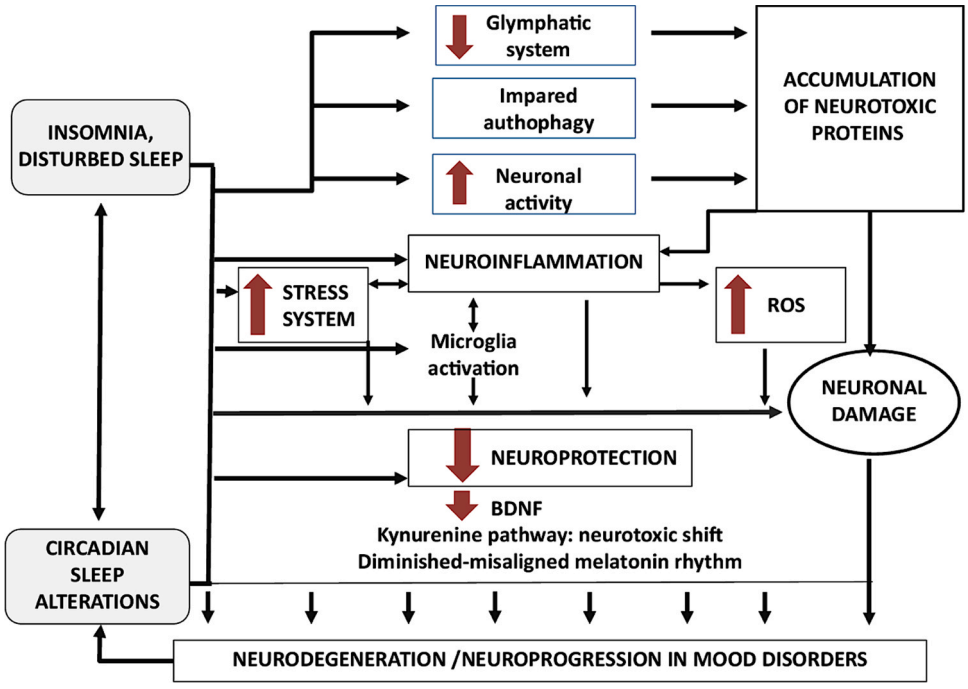

Fig. 1. A proposed model of the role of insomnia, sleep loss, and circadian sleep alterations in neurodegeneration and progression of mood disorders (Palagini et al., 2022).

severity in depression (Mukherjee et al., 2018). Similarly, alterations of melatonin and related circadian patterns have been highlighted in the contest of depression (Palagini et al., 2022).

In conclusion, neuroinflammation, activation of the stress system, failure of the anti-oxidative stress mechanisms, accumulation of β-amyloid peptide, and deficit of neuroprotective pathways related to the alterations in BDNF, kynurenine, and melatonin pathways represent key pathophysiological elements that can explain the frequent comorbidity of insomnia and depression, also supporting the bidirectionality link between these two disorders. In other words, inefficient sleep can precede depressive episodes in depression, but also depressed mood can impair normal sleep patterns (Murphy and Peterson, 2015).

3.2. Insomnia and MDD

Insomnia and MDD seem to have a strong pathophysiological correlation and clinical comorbidity.

As known, MDD is characterized by low mood, high suicide risk, and worse health-related problems than healthy people, with a worldwide prevalence around 3.5% in adults (IHME - GHDx, 2019b). Interestingly, according to the DSM-5, insomnia represents one of the diagnostic criteria for MDD, and insomnia may be considered both a causal effect for MDD (Huang et al., 2021) and a risk factor for the development and/or maintenance of MDD itself (Pandi-Perumal et al., 2020). Persistent insomnia is also linked with the occurrence of a new episode of MDD. Van Mill et al. (2010) (van Mill et al., 2010) found that insomnia and short sleep duration (≤6 h) were associated with both current and remitted MDD episodes. Although association was stronger for current than remitted episodes, the latter still had a significant impact on sleep, thus suggesting that insomnia may represent either a trait marker or a residual symptom of MDD. These results were also confirmed by Sun & Tan (Q. Sun and Tan, 2019) who highlighted that MDD patients with insomnia had a severe daytime functioning and higher REM sleep. Moreover, Sunderajan et al.(Sunderajan et al., 2010) found that MDD patients with insomnia had a greater illness burden in terms of increased depression severity, poorer quality of life, and more concurrent general medical and psychiatric illnesses. The authors highlighted also that insomnia symptoms persisted even after an adequate treatment of MDD.

Additionally, different studies have reported that people with MDD and comorbid insomnia experience a higher number of hospitalizations, inpatient stays, and relapses than depressed patients without sleep problems (O'Brien et al., 2011; Zhao et al., 2021). The same studies also demonstrated that patients with MDD and insomnia show more severe physical, mental, and psychological impairment. When the authors compared MDD with insomnia patients and MDD without insomnia patients, "excessive worry about sleep", "loss of appetite", "lack of energy", "weight loss", and "depressive mood" appeared to be more significant in the first group (Zhao et al., 2021). In brief, therefore, insomnia should be viewed as an aggravating factor for MDD.

Other authors confirmed these data, showing that MDD patients with severe insomnia have a more severe clinical presentation and poorer overall and social functioning than MDD patients without severe insomnia symptoms (O'Brien et al., 2011).

3.3. Insomnia and bipolar disorder

DSM-5 spends a separate chapter for BD and related disorders, which encompasses Bipolar Disorder I, Bipolar Disorder II, and Cyclothymic disorder. The main characteristic of these disorders is the presence of recurring manic or hypomanic episodes, that may alternate with depressive episodes. BD has a worldwide prevalence of approximately 0.68% in adults (IHME - GHDx, 2019a).

It is well known that insomnia is a typical symptom of bipolar disorder, although it may be important to provide a clarification (APA, 2013). Specifically, a reduced need for sleep stands out as a significant symptom during manic and hypomanic phases, potentially serving as a prodromal sign. Different studies found out that 69–99% of bipolar individuals report a lessened need for sleep during a manic episode. Conversely, insomnia disorder frequently manifests in the context of bipolar depression (Gold and Sylvia, 2016). Insomnia is linked with a greater depression severity in BD (Palagini et al., 2021). In addition, also during the inter-episode period, as well as in the remission phase of BD, sleep impairment is present (Pinho et al., 2016). Furthermore, insomnia seems to be the main contributor of depression in BD (Steardo et al., 2019). Suffering from insomnia and short sleep is associated with more severe symptoms of both mania and depression (Harvey et al., 2015), and this also predicts the recurrence of depressive episodes (Gershon et al., 2017).

A typical aspect of the sleep disorder in BD is that circadian rhythms appear to be disrupted not only during major affective episodes, but also during euthymic periods. In other words, an unstable circadian rhythm seems to represent the trait marker of BD (Kaplan, 2020; Roloff et al., 2022). To further support this hypothesis, in BD patients with sleep problems, melatonin levels were significantly lower than those of BD patients without sleep problems (Bradley et al., 2017).

Cretu et al.(Cretu et al., 2016) found in recovered BD patients that sleep was worse than in healthy controls, poor sleep quality correlated with residual affective symptoms, and poor sleepers, compared to good sleep quality sleepers, had earlier affective episode recurrence independent of residual affective symptoms. In addition, BD patients showed longer sleep latency and shorter sleep duration. In euthymic BD patients, also daytime functioning was worse than healthy controls. Additionally, residual symptoms of depressive mood seem to be correlated with worse sleep quality in BD patients. Kanady et al.(Kanady et al., 2015) found that the manic and depressive phases of BD were similarly characterized by hypersomnolence and insomnia; however, the inter-episode period was characterized primarily by insomnia. Additionally, the same authors assert that BD patients with evening chronotypes seem to be affected by more severe affective and sleep problems.

In BD patients, the presence of sleep problems is associated with other markers of poor course of the underlying affective disorder, including rapid cycling, anxiety, and substance use comorbidities, as well as a history of suicide attempts. In individuals with BD, poor sleep is linked to lower performance in neurocognitive assessments, which can contribute to higher rates of unemployment. Moreover, poor sleep problems in BD are associated with worse physical health, including increased weight, metabolic syndrome, and diabetes (Morton and Murray, 2020). Other findings confirm these data: Palagini et al.(Palagini et al., 2019, 2021) found that BD patients with clinically significant insomnia had more frequently mixed episodes of BD, a greater severity of depressive symptoms, suicidal ideation and behaviors, and a positive history of suicidal attempts. Moreover, some studies have found that sleep disorders, such as insomnia, also attenuate the response to pharmacotherapy in BD. On the contrary, sleep problems do not seem to affect the response to psychotherapy in the same patients (Kaplan, 2020).

Based on this evidence and the fluctuating course of BD, it has been suggested that the endogenous circadian system may play a role in the etiology, clinical manifestations, and outcome of BD (Steardo et al., 2019; Talih et al., 2018). Also, all these findings may help clinicians to better understand BD and to plan preventive strategies on insomnia and on its negative impact on BD.

In conclusion, insomnia is a common feature of both MDD and BD in the depressive phase and worsens the clinical picture and course of depression. Nevertheless, insomnia seems to be a symptom more typical of MDD, although, despite the amount of literature on insomnia and affective disorders, there is not enough knowledge yet regarding the role of insomnia in the differential diagnosis between MDD and BD. This review might be considered as a starting point for future studies to fill in this clinical and scientific gap, adopting the proposed comprehensive psychometric protocol.

4. Hypersomnolence and depression

Hypersomnolence (or EDS) is another sleep disturbance often comorbid with depression (Barateau et al., 2017). According to the DSM-5, hypersomnolence is considered as a self-reported excessive sleepiness despite a sleep period of at least 7 h. It can manifest with recurrent periods of sleep or lapses into sleep within the same day, a prolonged main sleep episode of more than 9 h per day that is non-restorative, or difficulty being fully awake after abrupt awakening. It must occur at least 3 times per week, for at least 3 months, and it should cause significant distress and decreased daytime functioning (APA, 2013). As such, hypersomnolence is a broad diagnostic term and includes symptoms of excessive quantity of sleep, deteriorated quality of wakefulness, and sleep inertia. Furthermore, persons with hypersomnolence may fall asleep rather quickly and have a good sleep efficiency (>90%), although they may have difficulty in waking up in the morning, sometimes appearing confused, combative, or ataxic. Additionally, approximately 5%− 10% of individuals who consult in sleep disorders clinics with complaints of daytime sleepiness are diagnosed with a hypersomnolence disorder (APA, 2013; Gandhi et al., 2021). Hypersomnolence complaints are higher in women, with a prevalence ranging from 9% in children to 76% in adults (Lopez et al., 2017). It can be associated with depressive disorders, especially BD (during a depressive episode) and MDD, with seasonal patterns (Plante, 2017; Sonmez et al., 2020).

A large cross-sectional study showed that MDD remained associated to EDS, even after adjustment for the use of antidepressants(Barateau et al., 2017). Hypersomnolence in depression is commonly considered as a consequence of the disorder, a concept which is in line with an altered monoamine activity. However, several associated factors may contribute to hypersomnolence in patients with depression, such as the use of psychotropic drugs, insomnia and associated nocturnal sleep disturbances (in terms of impairment in sleep architecture, with decreased slow-wave sleep duration and increased REM sleep pressure) (Lopez et al., 2017).

4.1. Hypersomnolence and MDD

As seen above, hypersomnolence is a common feature of depressive disorders. More in details, a clinical review(Gonsalvez et al., 2022) has recently reported that hypersomnolence in MDD significantly varies across age, gender, and studies, ranging from 8.9% in childhood (6- to 13-year-old children) to a rate of 75.8% in young adulthood. The frequency of hypersomnolence in MDD was higher in females and the presence of EDS predicted the onset of a MDD episode. Even during the remission phase of MDD, individuals with hypersomnolence continued to experience EDS. Moreover, MDD patients with hypersomnolence are more resistant to recognizing the resolution of their sleep disorder, even when they meet the criteria for remission(Gonsalvez et al., 2022).

An interesting finding is that depressive patients with hypersomnolence do not show reduced sleep efficiency, which, therefore, appear to be similar to that of healthy people (~85%). However, this does not exclude that MDD patients are free from difficulties in initiating or maintaining sleep, indeed they still complain of poor sleep quality (Galušková and Šonka, 2021; Plante et al., 2019). In addition, hypersomnolent depressed patients are affected by more severe dysfunctional sleep-related cognitions(Cook et al., 2021). In this context, Rethorst et al.(Rethorst et al., 2015) showed that reductions in BDNF and interleukin 1-beta (IL-1β) were related to reduced hypersomnolence, thus suggesting that BDNF and inflammatory pathways are both involved in hypersomnolence disorder. The same authors highlighted that IL-1β was believed to promote sleep, its extreme increase in inflammation appeared to have a negative effect on sleep quality. This suggests a negative feedback loop, in which sleep, inflammation, and depression interact and progressively worsen each other.

The neurobiological correlates of hypersomnolence in MDD are still unknown. Several sleep structure abnormalities have been documented in MDD, particularly in cholinergic REM sleep neurons. Subjects with MDD, indeed, show reduced REM sleep latency and increased REM density(Kaplan and Harvey, 2009). In addition, although hypersomnolence is less common than insomnia in MDD, it often represents an underestimated and undertreated clinical symptom. In fact, in cases of comorbid sleep disorders (i.e., MDD patients with both insomnia and hypersomnolence), a particularly complex clinical framework occurs, which negatively impacts the patient's social and affective life. Moreover, these patients have more lifetime depressive episodes, longer duration of the current episode, and more depression symptoms, eventually implying a more pervasive functional impairment(Zhao et al., 2021). For all these reasons, a wide and comprehensive assessment of MDD patients is necessary to better manage the multifaceted aspects of their sleep-related symptoms.

4.2. Hypersomnolence and BD

Hypersomnolence is frequently found in the depressed phase of BD spectrum disorders, with a prevalence ranging from 23% to 78%(Lopez et al., 2017), being also strongly associated with the risk of further depressive recurrences. Even in the inter-episode period, approximately 25% of euthymic BD individuals experience hypersomnolence, which is associated with a recurrence of depressive symptoms as well (Grigolon et al., 2019). In fact, hypersomnolence is more prevalent in bipolar than in unipolar depression, even during inter-episode periods, (Murru et al., 2019), during which hypersomnolence seem to be related to future depressive symptoms, independently of baseline depression severity and medication(Barateau et al., 2017). Individuals with BD, particularly in the depressive phase, have also a reduced mean activity, longer sleep duration, and a more disturbed sleep pattern(De Crescenzo et al., 2017), although the biological correlates of hypersomnolence in these patients remain unclear. Circadian rhythm disruption seems to play a pivotal role in the development and course of sleep disturbance in BD. Phase advances in melatonin secretion have also been documented in individuals with BD, although this was not fully confirmed by other studies (Kaplan and Harvey, 2009).

In conclusion, despite hypersomnolence is a frequent disturbance during depressive episodes, it has not been accurately studied yet. However, hypersomnolence seems to be even more typical of BD in the depressive phase and, accordingly, it should be better explored in order to properly assess and manage it. Further research adopting a comprehensive and valid psychometric protocol is indispensable to fill this gap.

5. Psychometric tools for the assessment of sleep disturbances

Detection of risky behaviors is essential in the primary and/or secondary prevention. In this regard, the psychometric tools are an important resource to health experts (Castellano et al., 2020). Concerning the review topic, the rich research of the past thirty years has led to a comprehensive understanding of sleep dysfunction as a complex and multifaceted condition. Indeed, the combination of the core symptoms of the sleep disorder with various neurophysiological, psychological and behavioral elements requires specific diagnostic approaches and tailored therapeutic interventions (Mollayeva et al., 2016). In light of this complexity, it is necessary to know and have at one's own disposal both objective and subjective tools to explore this intricate set of symptoms, especially in complex psychopathological pictures such as MDD and/or BD in depressive phase, in order to distinguish the different depression patterns. Although, given the current lack of consistent scientific evidence to facilitate the differential diagnosis between MDD and BD and considering that sleep disorders enhance the risk of depressive relapse, it becomes mandatory to propose and develop new psychometric strategies that can address this knowledge gap, utilizing although novel statistical methods (Guerrera, Platania, Boccaccio et al., 2023; Platania et al., 2023).

5.1. Subjective tools

In order to provide a comprehensive approach to individuals with MDD and BD, it is crucial to use not only psychometric tools to evaluate depressive symptoms but also those to assess sleep quality. However, diagnosing sleep disorders in individuals with depression is still a clinical challenge (Pinho et al., 2016).

Both subjective and objective methods are available to study sleep quality in affective disorders (see Table 1). Among the formers, a detailed clinical interview, supported by specific "self-reported" questionnaires at different levels of assessment depth, are helpful to the clinician to framework the disorders correctly. Methods such as single item scales, visual analogue scales, and sleep diaries, represent other subjective assessment methods, although they tend to assess only some of the components of the whole sleep quality. On the other hand, standardized questionnaires allow an subjective but more objective assessment of sleep than non-standardized ones, and provide a more complete evaluation of sleep quality. Since sleep disorders are multifaceted and multifactorial, the use of a single psychometric instrument may be insufficient and, therefore, a battery consisting of two or three components is recommended.

A first-line useful self-reported tool to evaluate a person's sleep habits is a sleep diary (Khan and Trotti, 2015), which is a daily record of important sleep-related information. Although not all sleep diaries are identical, they commonly include details about: bedtime and/or lights-off time; wake-up time; how long it takes to fall asleep; the number and duration of sleep interruptions; the number and duration of daytime naps; perceived sleep quality; consumption of alcohol, caffeine, and/or tobacco; daily medications used; and daily exercise performed (Suni, 2023). Overall, a sleep diary record allows the calculation of the total sleep time and helps to identify any sleep disruption or other factors that may affect sleep quality (e.g., identifying details about habits that affect sleep can show patterns that help to explain sleep problems). Information contained in a sleep diary is often more reliable and usable than a generic unstructured recollection of sleep habits. Finally, a sleep diary can increase the validity of the sleep tests by demonstrating that a person's sleep is stable in the pre-defined period leading up to the study, as well as to monitor the sleep quality perception over time (Carney et al., 2012).

Besides this tool, sleep quality and its perception can be evaluated through some psychometric instruments specifically designed to assess sleep quality. The Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989) is a self-assessment scale of sleep quality and disorders, which can be easily filled out by the subject. It consists of 19 items that result in seven component scores: (1) subjective sleep quality, (2) sleep latency, (3) sleep duration, (4) habitual sleep efficiency, (5) sleep disturbances, (6) sleep medication use, and (7) diurnal dysfunction. By discriminating between good and poor sleepers, it can provide a valid and standardized measure and feasible tool for clinicians to rapidly assess the different factors that can impair sleep quality.

The Biological Rhythms Interview of Assessment in Neuropsychiatry (BRIAN) (Moro et al., 2014) was originally validated on a sample of BD subjects to obtain an index of biological rhythm disturbance. The BRIAN is a predictor of depression severity, psychosocial functioning, and quality of life (Cudney et al., 2016). In addition, differentiation can be implemented between euthymia, unipolar, and bipolar depression, as well as mania (Duarte Faria et al., 2015). Specifically, this self-report questionnaire consists of 21 items and is referred to the last 15 days. Briefly, it asks the subject to report the frequency with which he or she experienced rhythm disturbances in different areas during that time frame. The four domains considered, which are related to circadian rhythm disturbances, are (1) sleep, (2) general activity, (3) social rhythms, and (4) eating patterns. The fifth domain (items 19–21), not included in the total score, provides a measure of the subject's chronotype. These areas, therefore, allow to consider sleep interruptions, irregularities in social rhythm, eating patterns, and abnormalities in daily domestic and work activities. Each of these domains represents a potential factor in the onset and worsening of affective episodes, psychosocial functioning, and clinical outcomes (Pinho et al., 2016). Each item is rated on a 4-point Likert scale (from "no difficulty" to "severe difficulty"), allowing for a final score to be totaled (from 18 to 72), with the higher ranges indicating the more severe subjective disruption of circadian rhythm. The BRIAN is able to differentiate across mood states of euthymia, unipolar/bipolar depression, and mania, and is an independent predictor of psychosocial functioning, severity of depression, and quality of life (Cudney et al., 2016). The BRIAN fills a gap by offering a quick, self-reported measurement of biological rhythm disruption in individuals with depression.

Different psychometric tools to assess specific sleep disorders are also validated. For insomnia, the Insomnia Severity Index (ISI) is among the most widespread used (Al Maqbali et al., 2022). ISI is a reliable and valid instrument to quantify perceived insomnia severity, both in clinical practice and in the research setting. ISI is a brief instrument that was designed to assess the severity of both nighttime and daytime components of insomnia (Morin et al., 2011). It is composed by seven items: respondents rate each element of the questionnaire using a Likert-type scale, with responses that can range from 0 to 4 (higher scores indicate more acute symptoms of insomnia). A total score of 0 to 7 indicates "no clinically significant insomnia," 8 to 14 "subthreshold insomnia," 15 to 21 "clinical insomnia (moderate severity)," and 22–28 "clinical

Table 1
Psychometric tools for evaluating Sleep Disturbances.

PSYCHOMETRIC TOOLS FOR EVALUATING SLEEP DISTURBANCES	
PYCHOMETRIC TOOL	**FUNCTION ASSESSED**
Subjective tools	
Sleep Diary	Daily record of relevant sleep-related information.
Pittsburgh Sleep Quality Index (PSQI)	Self-assessment scale of sleep quality and sleep disorders. 19 items that result in seven component scores: (1) subjective sleep quality, (2) sleep latency, (3) sleep duration, (4) habitual sleep efficiency, (5) sleep disturbances, (6) sleep medication use, and (7) diurnal dysfunction.
Biological Rhythms Interview of Assessment in Neuropsychiatry (BRIAN)	21 items that result in four domains, which are related to circadian rhythm disturbances: (1) sleep, (2) general activity, (3) social rhythms, and (4) eating patterns.
Insomnia Severity Index (ISI)	A brief instrument that was designed to assess the severity of both nighttime and daytime components of insomnia.
Epworth Sleepiness Scale (ESS)	Evaluate the occurrence of daytime sleepiness or episodes of falling asleep during participation in various activities throughout the day.
Objective Instruments	
Polysomnography (PSG)	A comprehensive monitoring system to record the different sleep stages (based on the information from EEG, electrooculogram, and electromyogram electrodes), limb movements, airflow, respiratory effort, heart rate and rhythm, oxygen saturation, and body position.
Actigraphy	Used in measuring sleep-wake states through the assessment of different sleep aspects: the total sleep time, the sleep onset latency, the wake after sleep onset, the sleep efficiency, the number of awakenings.
Multiple Sleep Latency Test (MSLT)	Used to assess excessive daytime sleepiness by measuring the time it takes for an individual to fall asleep in a peaceful daytime environment.
Maintenance of Wakefulness Test (MWT)	Used to assess the capacity to resist to a sleep onset.

insomnia (severe)."

Hypersomnolence and daytime sleepiness are well assessed and quantified by the Epworth Sleepiness Scale (ESS), which is the most used in the field. ESS is a self-administered questionnaire with eight questions. Respondents are asked to rate, on a 4-point scale (0−3), their usual chances of experience daytime sleepiness or falling asleep while engaged in eight different activities of daily living. ESS scores (the sum of the eight item scores, 0–3) can range from 0 to 24: the higher the score, the higher that person's average sleep propensity in daily life or daytime sleepiness (Johns, 1991).

5.2. Objective instruments

Objective tools are essential to quantitatively measure sleep. Polysomnography (PSG) represents the current gold standard, although difficult to perform routinely, especially in non-specialistic settings. A standard PSG recording, indeed, requires a comprehensive monitoring system to record the different sleep stages (based on the information from EEG, electrooculogram, and electromyogram electrodes), limb movements, airflow, respiratory effort, heart rate and rhythm, oxygen saturation, and body position (Rundo and Downey, 2019), among others. For these reasons, PSG is a costly procedure and requires high level of technical and medical expertise.

Alternatively, actigraphy can be used to assess measure sleep quality objectively but indirectly (through the analysis of the rest-activity pattern). Actigraphy can provide indication on: total sleep time, i.e., how long a person sleeps during the 24-hour period; sleep onset latency, i.e., how many minutes it takes a person to fall asleep for the first time since lights-out; wake after sleep onset, i.e., how many minutes the person spends awake, starting from sleep onset to the final awakening; sleep efficiency, i.e., the percentage of total time in bed truly spent asleep; and, the number of awakenings, i.e., the number of shifts from sleep to wakefulness (Khademi et al., 2019).

Another measure adopted in the study of sleep-wake rhythm is skin temperature studied from a chronobiological point of view, with particular attention to its rhythm in relation to the onset of sleep. Proximal/distal temperature is usually estimated by calculating a weighted average of nine wireless sensors placed at predefined skin locations. Specifically, the proximal one derived from five sensors placed in the infraclavicular area and mid-thigh (right and left) and on the abdomen, and the distal one from four sensors placed on the hands and feet (Longato et al., 2017; Serrano-Serrano et al., 2021).

The Multiple Sleep Latency Test (MSLT) is particularly valuable in assessing EDS by measuring the time it takes for an individual to fall asleep in a relaxing daytime environment (Arand and Bonnet, 2019). This comprehensive test requires a full day and involves four or five scheduled naps, and each subsequent nap trial begins two hours after the preceding one. Before MSLT, a full PSG sleep study is conducted to evaluate sleep quality and duration. During each nap trial, the patient lies in a relaxing, dark sleep environment, designed to maximize comfort and minimize any external factor that might influence the ability to fall asleep. in the signals recorded are the same needed to score sleep stages in PSG recordings. Following the initiation of each nap, the test measures the duration it takes to fall asleep, and the subject is awakened 15 min after falling asleep. If he/she does not fall asleep within 20 min, the nap trial is concluded.

On the other side, the maintenance of wakefulness test (MWT) is similar to MSLT, with the key difference being that the individual undergoing the test is instructed to remain awake and resist sleepiness (Chaisilprungraung et al., 2022). Typically, this is done while reclining in a comfortable chair or in bed, in a dimly lit room for a duration of 20 to 40 min. The rationale behind the MWT stems from the understanding that the capacity to resist sleep onset is more relevant to operational performance than the propensity to initiate sleep. It has been observed that the MWT can be particularly sensitive in detecting improvements in alertness following treatment of a sleep disorder. Therefore, it has been proposed that the MWT should be employed to assess and confirm that an individual's level of sleepiness is not severe enough to impede their safe functioning in operational environments.

5.3. A comprehensive assessment framework: a proposed psychometric protocol for MDD and BD

Based on the evidence available and here reviewed, there is an urgent need to propose a new psychometric protocol that can serve as a guide for researchers and clinicians in the assessment and management of sleep in patients with MDD and BD. To gain a comprehensive understanding of the intricacies of these disorders, it is crucial to employ not only psychometric tools for assessing the affective dimension but also tests that evaluate cognitive and psychosocial functioning (Gerber et al., 2023; Guerrera, Platania, Varrasi et al., 2023), which are frequently impaired in depression. Moreover, when administering these psychometric tools, the patient's complete anamnestic framework cannot be underestimated, as it is necessary to take into account any comorbidities, which play a key role in the planning of personalized pharmacological and non-pharmacological treatment. In fact, dual diagnosis is no longer the exception, but the standard. For example, the scientific literature reports data supporting the presence of substance use disorders (SUD) as a condition that makes sleep disorders more severe and complex (Miguel et al., 2023). Additionally, the inclusion of instruments to evaluate sleep problems should not be overlooked. This protocol will also aim to address the existing limitations in the current assessment methods and to provide a more comprehensive approach to the underlying psychiatric condition (see Table 2).

The rationale underlying this protocol is that an adequate management of sleep problems alongside depressive symptoms can lead to a better treatment outcome. Improving sleep quality and duration has also been associated with reduced relapse risks, enhanced response to pharmacological interventions, and improved overall functioning (Boland et al., 2020; C. Sun et al., 2023). Therefore, by incorporating sleep assessment and management into the treatment plan, clinicians can optimize the patient's outcome. In this scenario, recognizing the interplay between sleep problems and depressive symptoms allows for

Table 2
- A proposed Psychometric Protocol for MDD and BD – for research use.

PSYCHOMETRIC PROTOCOL – research use		
DOMAIN ASSESSED	**PSYCHOMETRIC TOOL**	**RATIONALE**
Affective Dimension	Hamilton Depression Rating Scale (HDRS)(Hamilton, 1960)	To evaluate the degree of severity of depressive symptomatology – clinician-evaluated
	Beck Depression Inventory (BDI-II)(Beck et al., 2011)	To evaluate degree of severity of depressive symptomatology – self-evaluated
	Geriatric Depression Scale (GDS) (Yesavage et al., 1982)	To evaluate degree of severity of depressive symptomatology in > 65 years old patients
Sleep Dimension	PSQI	To evaluate general sleep quality
	ISI	To quantify the perceived severity of insomnia
	ESS	To evaluate hypersomnolence and daytime sleepiness
	BRIAN	To assess circadian rhythm disturbances
Cognitive Dimension	Montreal Cognitive Assessment (MoCA)(Nasreddine et al., 2005)	To assess global cognitive functions, which are often impaired in depression (Guerrera, Platania, Varrasi et al., 2023)
	Frontal Assessment Battery (FAB) (Dubois et al., 2000)	To assess frontal-lobe functions, often compromised in depression (Gerber et al., 2023)
Global functioning dimension	Functioning Assessment Short Test (FAST)	To evaluate global functioning in daily-life activities

tailored treatment targeting both aspects of the disorder (i.e., MDD or BD).

6. Conclusions

Sleep disturbances are a significant clinical feature observed in both Major Depressive Disorder (MDD) and Bipolar Disorder (BD). While the link between sleep disorders and depression is widely recognized, the current lack of substantial scientific evidence regarding specific aspects for distinguishing between MDD and BD based on sleep patterns highlights the urgent need for more comprehensive clinical assessments and research studies.

Enhancing our understanding of the intricate relationship between sleep problems and depressive symptoms is crucial for tailoring more effective treatment approaches in both disorders. By recognizing the interplay between sleep disturbances and depressive symptoms, healthcare professionals can develop personalized strategies that address the unique needs of each patient.

In light of scientific literature deficiencies, a novel psychometric protocol has been proposed in order to guide clinicians in the assessment and management of sleep in patients with MDD and BD. This new multidimensional psychometric protocol has been developed to identify not only the presence/absence of some symptomatologic feature, but also the severity, pervasiveness and the degree of impairment that would characterize MDD and BD in different way. However, it is also important to consider the clinical setting in which these patients are often evaluated. One of the limitations of such an extensive psychometric protocol is the use of the patient's time and emotional and cognitive resources. Therefore, for practical purposes, a useful distinction is suggested. The proposed protocol could be better suited for scientific clinical research, where measuring numerous variables allows for a more in-depth study of the comorbidity between depressive and sleep disorders, seeking additional evidence for the differential diagnosis between MDD and BD. Conversely, a more user-friendly protocol (see Table 3) is recommended for mainly clinical use, useful in assessing the presence of depression and any impairment in sleep quality. The clinician can then decide to further investigate the diagnostic process on a case-by-case basis.

Additional research could prove valuable in identifying the key features of each test that effectively differentiate between BD and MDD depression. For instance, dedicated studies could delve into the analysis of how each subscale of subjective tests informs clinicians about the specific nature of sleep disorders in various types of depression. Currently, only a limited number of scientific studies have attempted to bridge this gap using objective measures. (Slyepchenko et al., 2019).

It is recommended that, in order to make the psychometric protocol valid and reliable, its administration must be carried out by a clinical psychologist, within a setting that puts the patient at ease and ensures confidentiality. On the methods of administration of each scale, please refer to the respective test instructions and manuals.

To establish gold standards for accurate differential diagnosis between MDD and BD, further research incorporating the proposed psychometric protocol is essential. By conducting comprehensive studies, we can not only improve the precision of diagnosis but also pave the way for more effective treatment strategies for individuals experiencing these conditions. In a timely manner, establishing a differential diagnosis can assist the clinician in planning appropriate pharmacological therapy both for depression and sleep disorders, particularly insomnia. This research endeavor holds the potential to revolutionize the field, enabling healthcare providers to deliver targeted interventions and support to those affected by MDD and BD.

Table 3
- A proposed Psychometric Protocol for MDD and BD – for clinical use.

PSYCHOMETRIC PROTOCOL – clinical use		
DOMAIN ASSESSED	**PSYCHOMETRIC TOOL**	**RATIONALE**
Affective Dimension	Hamilton Depression Rating Scale (HDRS)(Hamilton, 1960)	To evaluate the degree of severity of depressive symptomatology – clinician-evaluated
Sleep Dimension	PSQI	To evaluate general sleep quality
Cognitive Dimension	Montreal Cognitive Assessment (MoCA)(Nasreddine et al., 2005)	To assess global cognitive functions, which are often impaired in depression (Guerrera, Platania, Varrasi et al., 2023)

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Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used Hyperwrite in order to improve English in some section of the paper. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Declaration of Competing Interest

The authors declare that they have no competing interests.

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