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SHORT REPORT

Sleep disorders and depression: brief review of the literature, case report, and nonpharmacologic interventions for depression

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Antonina Luca[1]
Maria Luca[2]
Carmela Calandra[2]

[1]Department GF Ingrassia, Section of Neuroscience, [2]Department of Medical and Surgery Specialties, Psychiatry Unit, University Hospital Policlinico-Vittorio Emanuele, Catania, Sicily, Italy

Abstract: Sleep disorders are so frequently associated with depression that, in the absence of sleep complaints, a diagnosis of depression should be made with caution. Insomnia, in particular, may occur in 60%–80% of depressed patients. Depressive symptoms are important risk factors for insomnia, and depression is considered an important comorbid condition in patients with chronic insomnia of any etiology. In addition, some drugs commonly prescribed for the treatment of depression may worsen insomnia and impair full recovery from the illness. The aim of this paper is to review briefly and discuss the following topics: common sleep disturbances during depression (in particular pavor nocturnus, nightmares, hypersomnia, and insomnia); circadian sleep disturbances; and treatment of depression by manipulation of the sleep-wake rhythm (chronotherapy, light therapy, cycles of sleep, and manipulation of the sleep-wake rhythm itself). Finally, we present a case report of a 65-year-old Caucasian woman suffering from insomnia associated with depression who was successfully treated with sleep deprivation.

Keywords: sleep disorders, depression, insomnia, sleep-wake rhythm

Introduction

Sleep disorders occur frequently in patients with depression. The co-occurrence of depression and sleep disorders is so frequent that some authors have suggested that, in the absence of sleep complaints, a diagnosis of depression should be made with caution.[1] In fact, insufficient/excessive sleep, as well as dysfunctions of sleep rhythm, are likely to occur during depression. The sleep-wake cycle is regulated by two interacting processes, the circadian process and the homeostatic (or recovery) process. The former regulates the daily rhythms of the body and the brain; this is mainly due to the suprachiasmatic nucleus of the hypothalamus which provides an oscillatory pattern of activity regulating fundamental mechanisms, eg, sleep-wake activity, hormone release, and liver function. Indeed, this (circadian) process is strongly influenced by stimuli from social and environmental cues, and is "independent of wake and tiredness". In addition, circadian rhythm sleep disorders are common among depressed patients and relate to an alteration of the circadian process or to a misalignment between sleep and the 24-hour social and physical environment.[2] On the contrary, the latter (homeostatic or recovery process) is wake-dependent and regulates the drive to sleep. When sleep has been shorter than usual, there is a "sleep debt", that leads to an increase in the homeostatic drive, resulting in longer hours of deep sleep. In depression, both homeostatic and circadian rhythms are altered.[3] The most common sleep disorders in depression are pavor nocturnus, nightmares, insomnia, and hypersomnia.

Correspondence: Carmela Calandra
Department of Medical and Surgery Specialties, Psychiatry Unit of the University Hospital Policlinico-Vittorio Emanuele, Via S Sofia 78, Catania, Sicily 95100, Italy
Tel +39 09 5378 2636
Fax +39 09 5378 2636
Email c.calandra@unict.it

Pavor nocturnus (night terror episodes) is a parasomnia characterized by sudden arousal from deep sleep (polysomnographic stage 4) during which the individual may have a constricted awareness of his/her surroundings.[4] Its manifestation includes a terrified scream followed by an intense autonomic discharge, frequently associated with motor activity that is typically stereotyped, persevering, and less purposive than that of sleepwalking.[5] Night terror patients showed anxiety, depression, obsessive-compulsive tendencies, and phobia.[6] Episodes of night terror in adults are similar to the ones described in children, and seem to occur in adults with a history of psychopathology.[7]

With regard to the nightmare, the *Diagnostic and Statistical Manual for Mental Disorders, Fourth Edition, Text Revision*[8] defines it as an "extremely frightening dream" from which a person wakes up abruptly. Once awake, the individual quickly recovers orientation, preserves a detailed memory of the complicated plot of the nightmare (usually involving threats to survival, to security, or to self-esteem), and can hardly return to sleep. Nightmares occur in the general population with a prevalence of between 1%[9] to 8%.[9,10] They are more common in women and are associated with an increase in nocturnal awakenings, sleep onset insomnia, daytime memory impairment, and anxiety due to poor nocturnal sleep.[11] However, stressful experiences even occurring during childhood could influence the development of depression with sleep complaints, such as oppressive and bad dreams.[12] In addition, they can be related to the use of medications, primarily those modifying the levels of neurotransmitters in the central nervous system, such as antidepressants, narcotics, or barbiturates. Intense frightening dreams may also occur during withdrawal of drugs, such as ethanol, barbiturates, and benzodiazepines, causing rebound rapid eye movement (REM) sleep.[13]

The etiopathogenesis of nightmares is controversial, with neopsychoanalytic theories,[14,15] as well as personality,[16] evolutionary,[17,18] and neurobiologic models,[19,20] having been advanced to provide a possible explanation for these phenomena.

According to these models, dreaming represents an emotionally adaptive function (image contextualization, desomatization of feelings, mood regulation, or extinction of fear). Nightmares are widely seen to be either an intensified expression of an emotionally adaptive function or, conversely, as evidence of its breakdown. A recent study has proposed an affective network dysfunction model that integrates the tenets of many prior models suggesting that nightmares are related to problems with the fear extinction function of dreaming.[21]

Nightmares are the most common parasomnia occurring in depression, and frequently pertain the themes of masochism and poor self-image.[22] In addition, a recent meta-analysis supports an association between sleep disturbances and suicidal thoughts and behaviors.[23] A constellation of psychosocial and personality factors, baseline sleep disturbances, and comorbid anxiety symptoms may account for the residual sleep disturbances after recovery from depression.[24] Melancholic depressed patients present a high rate of nightmares, as well as middle and terminal insomnia. Indeed, feeling worse in the morning than later in the day may be related to the intervening dream content and may affect and predict suicidal tendency. Melancholia may be associated with an increased risk of suicide attempts due to repetitive and frightening dreams.[25]

Insomnia is considered a difficulty in initiating/maintaining sleep and/or nonrestorative sleep accompanied by decreased daytime functioning and persisting for at least 4 weeks.[9] The most common form of insomnia (24.4%) was difficulty maintaining sleep (middle insomnia), while difficulty initiating sleep (initial insomnia) and early morning awakening (terminal insomnia) had a prevalence of about 23%.[26] Insomnia may occur in 60%–80% of patients with major depression.[27] Depressive symptoms are important risk factors for insomnia; in fact, depression is considered an important comorbid condition in patients with chronic insomnia of any etiology, also taking into account that some drugs commonly prescribed for the treatment of depression may worsen insomnia and impair full recovery from the illness.[28] In particular, it has been demonstrated that serotonin neurons of the dorsal raphe nucleus project to the cholinergic laterodorsal and pedunculopontine tegmental areas inhibiting REM sleep;[29] consequently, REM sleep suppression has been observed in patients treated with tricyclic antidepressants,[30] selective serotonin reuptake inhibitors, and serotonin-norepinephrine reuptake inhibitors.[31] Polysomnography has indeed revealed that selective serotonin reuptake inhibitors are associated with increased awakenings after sleep onset and sleep percentage, increased sleep latency, and increased REM latency.[32] Moreover, insomnia is considered a risk factor for depression. Some studies have suggested that eating and sleep irregularities during early childhood may represent possible risk factors for depression in later life.[33] The treatment of insomnia associated with depression can be carried out with benzodiazepines and should be balanced judiciously against possible harms, including the development of dependence and proneness to accidents.[34] An important clinical problem is the high incidence of insomnia in the elderly; probably, the

pattern of polyphasic sleep is not sufficiently considered[35] in the elderly who, in wanting to pursue a monophasic sleep, demand urgent pharmacotherapy for insomnia. On the other hand, there is a positive association between sleep problems and suicidal ideation, especially in the elderly, showing further that insomnia is a risk factor for death by suicide despite recovery from other depressive symptoms.[36] In these cases, a drug-free psychoeducational intervention could represent an important and safe therapeutic approach for insomnia. A meta-analysis found moderate to large effects of behavioral treatment (ie, cognitive-behavioral therapy, relaxation, behavioral only) in sleep quality, sleep latency, and wakening after sleep onset in older individuals.[37]

Hypersomnia is characterized by excessive daytime sleepiness and daytime naps that do not result in a more refreshed or alert feeling. Hypersomnia does not include a lack of night-time sleep. Indeed, it is less common among depressed patients, but tends to be a feature of atypical depression and is more prevalent in youngsters (about 40% of depressed patients under 30 years of age and 10% of those in their 50s) and in females of all ages. Some patients experience both insomnia and hypersomnia during the same depressive episode.[38] Although hypersomnia is more prevalent in bipolar depression than in unipolar depression,[39] even during interepisode periods,[40] it occurs in approximately 30% of unipolar depressed patients[41] and is associated with long-term, severe, and treatment-resistant depression.[42] The complaint of sleepiness in hypersomnic bipolar depressed patients seems to be related to an anergic depressive condition (characterized by withdrawal, lack of interest, psychomotor retardation, and decreased energy) rather than to an increase in true sleep or REM sleep propensity.[43]

Treatment of depression by manipulation of the sleep-wake rhythm

Treatment of depression relies on so-called "somatic therapy", which includes both pharmacologic tools and manipulative interventions on the stimuli received by the subject, such as chronotherapy, light therapy, cycles of sleep, and manipulation of the sleep-wake rhythm. These interventions are readily available, and their effectiveness does not seem to be less than that of drugs.[44] Light therapy was initially developed as a treatment of choice in seasonal affective disorder,[45] antepartum depression,[46] and eating disorders.[47] Indeed, during the first week of treatment, light therapy, especially in the morning, seems to have modest antidepressant efficacy that increases when it is administered to patients who respond to sleep deprivation.[48] The effects of light depend on the time of administration. Due to the fact that the biological clock in older adults is often advanced to an earlier time, in case of difficulty in falling asleep at night and difficulty in waking up in the morning because of a delayed biological clock, bright light treatment in the morning may anticipate bedtime.[49] If in the first 15 days of treatment, medications and psychotherapy are not efficacious, treatment of sleep cycles, administered all night or partially (ie, second half of the night) produces stunning effects in just a few hours in 60% of the patients with major depression.[50] Despite the rapid action of sleep deprivation, one must not forget that the antidepressant effect is usually short, because there is often a full or partial relapse after recovery sleep or after small naps. Further, depressed patients, especially the melancholic ones who have experienced treatment of sleep cycles, are surprised by the rapidity and extent of antidepressant efficacy but are subject to rapid relapse. In order to optimize such treatment and prevent relapse, some authors recommend the association of sleep cycles every night with lithium salts or selective serotonin reuptake inhibitors.[51] The antidepressant efficacy of sleep deprivation seems to be influenced by patient characteristics, with a meta-analysis showing that the presence of baseline diurnal variation in mood contributes significantly to prediction of depression levels after total sleep deprivation.[52] The therapeutic effect of sleep deprivation is also fully enhanced by the association of this method with light therapy performed in the morning.[53] Individual genetic characteristics of the molecular mechanism of the biological clock are involved in the manifestation of mood disorders, including age at onset, risk of recurrence, response to treatment of sleep cycles, and drug treatment. Further, some authors have suggested the presence of functional associations between mood adjustment and the biological clock systems that regulate diurnal preference; in particular, it seems that evening preference might increase susceptibility to development of mood disorders.[54] These considerations lead us to think that there is an intimate connection between the neurotransmitter system (on which drug treatments act) and circadian rhythm (on which chronotherapy acts).

There is probably a bidirectional relationship between regulation of daytime affect and night-time sleep; indeed, disturbances in affect regulation during the day interfere with night-time sleep/circadian functioning. On the other hand, the effects of sleep deprivation contribute, in an escalating vicious cycle, towards difficulty in affect regulation on the following day.[55] Circadian timing in mammals is based upon the cell-autonomous clockwork located in the

suprachiasmatic nuclei of the hypothalamus. Individual cells from the suprachiasmatic nucleus and many other tissues express 24-hour molecular rhythmicity, resulting from a transcriptional-translational feedback loop. The transcription factors, CLOCK and BMAL1, form heterodimers and are bound to E-box elements in the promoters of the *Period* (*Per*) *1* and *Per2*, *Cryptochrome* (*Cry*) *1*, and *Cry2* genes. The proteins produced form complexes which, in the nucleus, interact with the CLOCK/BMAL1 complex, with repression of its transactivational activity. Post-translational events modify the timing of this negative feedback, providing a fine control over the cycle length of the molecular oscillations.[56] The integration of these oscillations, with the synchronizing effect of light, controls the secretion of melatonin, especially during the dark phase of the circadian rhythm. In fact, melatonin generally is not secreted during the day; however, not only does it increase about 2 hours before sleep onset, but it also declines in the early morning hours. Furthermore, its circadian rhythms are frequently of low amplitude in depressed patients.[57]

Shifting the focus from sleep cycles to circadian regulation, some authors have compared the levels of melatonin in pregnant depressed women versus post-partum depressed women. Compared with those who are pregnant without depression, melatonin levels decrease in pregnant depressed women during the night, whereas in post partum depressed women these levels increase, particularly in the early morning hours. However, pregnant women with a personal history of depression have earlier melatonin offset times and do not show a physiologic increase during pregnancy. These observations may be due to the less sensitive effect of estradiol or progesterone on melatonin receptors. As a result, the increase in gonadal hormones during pregnancy would increase melatonin secretion in pregnant women without depression but not in those who are depressed. On the contrary, in postpartum women, the declining levels of gonadal hormones would decrease melatonin levels in women without depression, but not in depressed ones, thus resulting in higher melatonin levels in postpartum depressed women versus healthy postpartum women.

These findings have important treatment implications. The low melatonin levels in depressed pregnant women may compromise their ability to use melatonin as a regulator of other circadian rhythms. As a result, desynchronization of circadian rhythms may predispose pregnant women to further depressive mood changes. Because melatonin treatment can alter reproductive function, light therapy would be a better strategy to synchronize circadian rhythms and thereby mitigate depression.[58] These findings complement previous studies indicating a reduced level of melatonin in women with premenstrual dysphoric disorder[59] and an increased level in women with menopausal depression.[60] Low levels of melatonin were also found in patients with schizophrenia (in both drug-free patients and after treatment with neuroleptic drugs).[61]

It would be interesting to find out the reasons for these differences between groups in the secretion of melatonin and also whether these differences are related to a different sleep time or duration. In any case, the results of these studies provide additional important information about the role that dysfunction of circadian rhythms may have in the pathophysiology of depression. In conclusion, there are reasonable grounds to study the cycles of sleep and circadian dysfunction, also taking into consideration the therapeutic potential connected with them.

Case report

A 65-year-old Caucasian woman was referred to our Psychiatry Unit for consultation. She told us that since childhood, every year in spring and in the evening towards bedtime, she suffered from mental illness with feelings of guilt about her daily activities. Awareness of the recurrence of these periods meant that, since she was young, she feared the month of April because it coincided precisely with her subjective and objective behavioral disorder. At school, she often felt so ill and impatient that one day she obtained the teacher's permission to go home before the end of the lesson. This made her feel guilty. On another occasion, again in spring, she recalled that while she was walking along the main road, she suddenly experienced a strong "sense of loss" and was nearly run over by a car. She also remembered having often felt envious of a classmate who always had lots of sweets and coins. Indeed, on one occasion, she tried to steal a few coins from her school friend because of a strong desire to buy sweets. The girl was therefore scolded by the teacher in front of the whole class and this provoked a deep sense of guilt and shame. These episodes of guilt and awkwardness in interpersonal relationships associated with depressive feelings were present every spring. Indeed, she remembered having suffered from severe pain in her eyes and having feared becoming blind; this discomfort disappeared alone after a few weeks. At the age of 40 years, the patient reported her problems to her general practitioner who prescribed paroxetine, but the patient refused it.

This peculiar pathologic phenomena continued to occur until the discomfort perceived by the patient obliged her to contact our Unit. We decided to adopt a psychoeducational

approach because of her refusal to take drugs. We advised her to get out of bed immediately, and go to a secluded area of her house and do some housework if she were to wake up in the middle of the night with negative thoughts. She usually woke up between 2 am and 4 am, and as soon as she left her bed, the negative thoughts vanished and were replaced by her household duties. After performing these activities, she was able to go to work and be productive. She returned home at 2.30 pm, and after lunch had a nap. Once she was in bed, she plunged into a deep sleep and woke up around 6.30 pm, still feeling drowsy. This feeling disappeared after about 15 minutes. In the following days, at times she would wake up during the night, while other nights she slept peacefully. In any case, whenever she woke up in the middle of the night, she performed some domestic activities.

This patient, even though she felt different from other people because of the peculiarities in her sleep-wake cycle, did not complain of any depressive symptoms. In this case the wakefulness by itself (accompanied by some goal-directed activities such as washing, cooking, and ironing) probably improved her mood. It is well known that if a patient with major depression is stimulated to be active, their mood can improve at least for a short period.[62] That said, the emerging hypothesis is that "the early morning awakening" is a form of biological remedy against depression. Hence, sleep deprivation could be a strategy to apply, especially in senile depression. In the elderly, sleep is frequently polyphasic. Finally, given that the clinical value of insomnia should not be underestimated, it would be natural to question whether the aim to treat insomnia with the objective to observe a socially agreed circadian rhythm is correct or whether insomnia should be "accepted" and considered a spontaneous expression of a biological remedy against depression.

Conclusion

The proposed clinical case report made it possible to observe how in our patient each depressive episode was characterized by middle insomnia and feelings of anxiety and worry. In the case of depression, the literature data put in evidence the therapeutic value of manipulating cycles of sleep and sleep deprivation. In our case report, the advice to get out of bed once awake and perform some housework, even though it was night-time, led to inhibition of anxiety by physical activity and defocused the issue, thereby dissolving the affective experience of crisis. Based on such experience, repeated over several years, during which the only discomfort experienced by the patient and her family was a feeling of not being "chronobiologically coordinated", it could be assumed that insomnia represents a spontaneous therapeutic trial. Rather than treating insomnia, the patient started to indulge it. This attitude is more "natural" than performing a chronotherapy with artificially imposed rhythms. Obviously, this hypothesis requires future rigorous trials.

Disclosure

The authors report no conflicts of interest in this work.

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