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Sleep Disorders in Schizophrenia. A Review of Literature

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Abstract

Up to 80% of patients with schizophrenia have suffered from sleep disorders (SD), which are normally under diagnosed and undertreated due to lack of consideration in the management of schizophrenia. The most common sleep disorders in schizophrenia are insomnia, restless leg syndrome (RLS), obstructive sleep apnea syndrome (OSAS), hypersomnia, parasomnia and circadian rhythm disorders. The relevance of insomnia should be emphasized, as it can be a prodromal signof schizophrenia, as well as an alarm sign of an incipient psychotic decompensation. Additionally, the clinical recovery of a psychotic process is usually correlated with sleep normalization. Multiple polysomnographic disturbances on sleep architecture have been found in patients with schizophrenia, including increased sleep latency, awakenings during sleep, sleep-wake cycle inversion, as well as poor sleep efficiency. These objective disturbances have been correlated to subjective poor sleep quality and other main clinical symptoms in schizophrenia.

Antipsychotics (AP) have been shown to disrupt sleep architecture, but also play a key role in the treatment of sleep disorders in schizophrenia, including a clinical improvement of insomnia, the polysomnographic correction of sleep architecture disturbances, an improvement on the patient's quality of life and functional capacity. On the contrary, antipsychotics can exacerbate comorbid sleep disorders in schizophrenia, like obstructive sleep apnea syndrome or restless leg syndrome, and exacerbate or even cause hypersomnia, obesity and cardiovascular disease, very prevalent diseases in schizophrenia.

There is evidence that sleep disorders in schizophrenia have a relevant impact on quality of life and a decisive influence on the symptoms shown in schizophrenia. Therefore, it is crucial to recognize and treat them properly. Thus, prevention, screening, diagnosis and treatment of sleep disorders should be integrated into standard clinical care in patients with schizophrenia.

Keywords: Sleep disorders and psychosis; Sleep and schizophrenia; Antipsychotic drugs and sleep disturbances

Introduction

A brief review of sleep disorders (SD) in schizophrenia has been performed in this article. The most relevant papers in medical English literature registered on PubMed (between 1990 and May/2017) have been selected using the referred keywords. Moreover, the references included on the selected articles have been examined. The main purpose has been to summarize the current recommendations about the management of SD in schizophrenia, as well as establishing the guidelines for future investigations.

Sleep has a key role on the proper function of the brain, immune, metabolic and cardiovascular systems. Between 30-80% of patients with schizophrenia suffer from insomnia or other SD, although it is rarely the main complaint [1].

SD in schizophrenia include insomnia, restless leg syndrome (RLS), obstructive sleep apnea syndrome (OSAS), hypersomnia, parasomnia and circadian rhythm disorders. All of them have a relevant influence on the symptoms and physiopathology of schizophrenia [2,3].

The physiopathological mechanisms that cause SD in these patients are unknown, although circadian rhythm and sleep homeostasis disturbances have been observed. It has been recently proved that cerebral dopaminergic pathway imbalance is related to circadian rhythm disturbances, as well as to the onset and maintenance of a psychotic decompensation in schizophrenia. This evidence suggest a firm connection between the circadian rhythm, the dopaminergic cerebral imbalance and the psychotic

process [4]. (Figure 1) shows a Light detected by the eye is relayed to the suprachiasmatic nuclei (SCN) in the hypothalamus via the retinohypothalamic tract (RHT), which uses the neurotransmitters glutamate and PACAP. Circadian rhythms are generated by a cell autonomous transcriptional–translational feedback loop (TTFL) involving a set of core clock genes. The molecular clock in the SCN synchronises circadian clocks found in tissues throughout the body, which regulate local physiology. b Sleep is the product of multiple brain regions and neurotransmitters. Abbreviations for brain regions: BF basal forebrain, DR/MR dorsal/medial raphe nucleus, LC locus coeruleus, LDT laterodorsal tegmental nuclei, LH lateral hypothalamus, LPT lateral pontine tegmentum, PPT pedunculopontine tegmental nuclei, SCN suprachiasmatic nuclei, SLD sublaterodorsal nucleus, TMN tuberomammilary nucleus, VLPO ventrolateral preoptic nuclei, vPAG ventral periaqueductal grey, vlPAG ventrolateral periaqueductal grey. Abbreviations for neurotransmitters: 5-HT serotonin, ACh acetylcholine, DA dopamine, GABA c-aminobutyric acid, Gal galanin, Glut glutamate, His histamine, NA noradrenaline, ORX orexin [5].

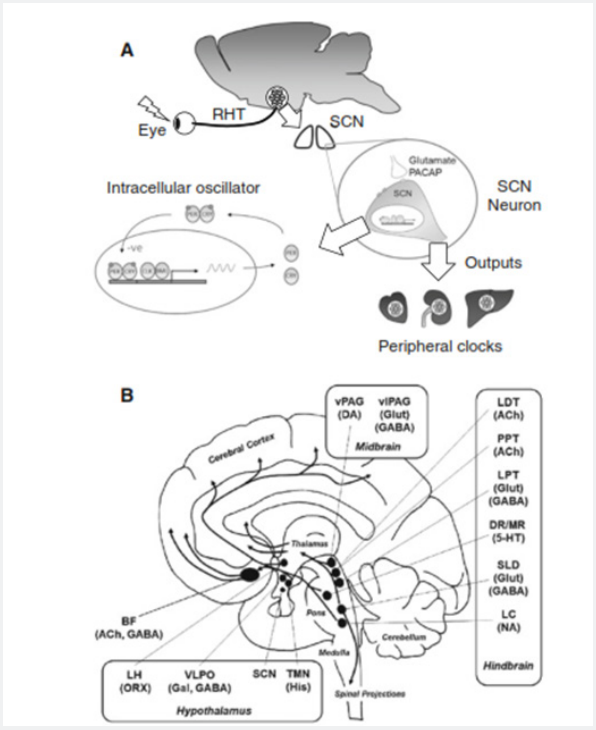

Figure 1: Schematic illustration of the mechanisms underlying circadian rhythm generation and sleep regulation.

Increased sleep latency, awakenings during sleep, sleep-wake cycle inversion, as well as poor sleep efficiency have been shown in patients with schizophrenia using polysomnography (PSG) and subjective sleep quality evaluations [3,6].

SD are regularly present on the prodromal in schizophrenia [7], usually preceding a psychotic decompensation, evincing a pathophysiological relation with the disease [8]. In fact, an acute wake-sleep cycle distortion in a patient with schizophrenia should be taken in consideration as an alarm sign of an imminent psychotic process [4,9]. Additionally, recovery from a psychotic process is usually concomitant with sleep normalization [3]. SD in schizophrenia occur both in patients treated with antipsychotic (AP) and non-treated AP patients [10].

SD have been also related to obesity and cardiovascular disease, which are very prevalent comorbid pathologies with schizophrenia [11]. Disturbance in sleep quality in schizophrenia has been related to decreased quality of life and poor life-coping strategies [12] as well as to more marked positive symptoms, immune system alterations and cognitive capacities reduction, particularly in consolidation memory.

A recent study has evidenced that chronic insomnia in patients with schizophrenia and other spectrum-related disorders is associated with more suicidal attempts [13], as well as to worse sleep quality reported by these patient's caregivers [14].

Moreover, sleep deprivation can trigger disturbances of sensoperception, paranoia and multiple neurochemical brain alterations in patients with schizophrenia [15]. Although some of these disturbances have also been described in healthy individuals with SD [16].

Alcohol and other toxic use disorders and are common comorbid disorders in schizophrenia. This can adversely influence sleep quality and trigger decompensation relapses, so that it should be systematically considered [3].

There is evidence that insomnia and chronic sleep deprivation influence directly on the pathophysiology and severity of schizophrenia. Thus, prevention, screening, diagnosis and treatment of sleep disorders should be integrated into standard clinical care in patients with schizophrenia [17].

Sleep Disorders in Schizophrenia and their Management

Insomnia

DSM-5 codes insomnia as an independent disorder, claiming the recently recognized relevance to this disorder and its management. Insomnia is the most prevalent SD in schizophrenia. Despite AP treatment, 16 to 30% of patients report persistent insomnia [18].

It can present as conciliation or maintenance insomnia, as well as a decrease in slow-wave sleep (SWS) or stages 3 and 4 of non-REM sleep [19]. As exposed below, insomnia in schizophrenia can result from multiple etiologies each of them requiring a specific therapeutic management.

Some studies suggest a relation between insomnia and clinical severity of positive and negative symptoms in schizophrenia [20]. Additionally, as previously mentioned, insomnia should always be considered as a potential prodromal sign of clinical relapse [4,7].

Due to APs adverse effects, many clinicians prescribe the lowest-effective dose in relapse-prevention. Therefore, patients

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can present some grade of psychophysical hyper activation causing insomnia. In order to treat this insomnia, it is required (1) AP dose increase; (2) AP modification to a more sedating AP; or (3) addition a sedating AP in low dose (including chlorpromazine, clozapine, olanzapine, risperidone and iloperidone). The addition of anxiolytic or hypnosedative drugs should also be considered, although precautions must be taken due to high comorbidity among schizophrenia and OSAS, alcohol and other drug abuse [3].

One of the major strategies for treating residual insomnia in schizophrenia is the use of hypnosedative APs, such as 5-HT-2 antagonists (quetiapine, olanzapine and clozapine), as monotherapy or adjuvant treatment (add-on), always taking into consideration its metabolic adverse effects, daytime drowsiness and RLS [21]. Scarce evidence on efficacy and adverse effects on SD treatment is available on zolpidem, eszopiclone and zaleplon among patients with schizophrenia. Furthermore, clinicians must consider patients with respiration sleep disorders and previous drug-use history, restricting it's administration based on clinical judgement [22].

Smoking, in general population, has been associated to insomnia and, using PSG, to longer sleep latency and reduced total sleep time [23], including awakenings to smoke in up to 50% of smokers [24]. The last surveys show that more than 60% of patients with schizophrenia are smokers [25,26]. Specific alterations in sleep-architecture in patients with schizophrenia have not been evidenced. However, smoke cessation, should always be considered in clinically stabile patients with sleep quality distortion and secondary functional impact.

Regular physical exercise has shown evidence of insomnia improvement on general population [27], being evidence in patients with schizophrenia still scant [28], though pointing to similar conclusions. A recent study has proved that patients with schizophrenia have a distorted understanding about the influence of lifestyle factors on insomnia, attributing insomnia's etiology mainly to schizophrenia [29]. Therefore, behavioral and sleep-hygiene techniques should be considered in this population.

Cognitive behavioral therapy (CBT), using cognitive, behavioral, psychoeducative and relaxation techniques, has proven efficacy in the treatment of insomnia in general population [30], as well as in patients with a psychiatric comorbid condition [31]. A recent pilot randomized controlled trial with 50 patients with schizophrenia and persistent psychotic symptoms has shown a 41% decrease in insomnia in the CBT-treated group at 12-week follow-up, proving the CBT efficacy in comparison to conventional treatment [32]. In this matter, it should be taken into consideration in regard to hypnotic drugs, their potential to generate tolerance, dependence, daytime sleepiness, cognitive undesirable effects, as well as a relapse of insomnia after treatment discontinuation, being CBT an appropriate alternative to pharmacologic treatment.

Benzodiazepines as well as non-benzodiazepine hypnotics, like zolpidem or zopiclone (acting on GABA-A receptor) are the most frequently used hypnotics in schizophrenia. Nonetheless, their use has been related to an increase in daytime sleepiness, cognitive impairments and a distortion on sleep architecture in patients with schizophrenia [33].

Suvorexant, a dual antagonist (OX1 and OX2) on orexin-receptor, has shown promising results on improving sleep onset and maintenance in patients with insomnia in general population [34]. However, it has not been yet formally studied in patients with schizophrenia.

Melatonin has proven good outcomes on small randomized controlled trials on treatment of insomnia in patients with schizophrenia [35] and a recent study showed improvement on sleep-quality perception in patients with severe mental illness and chronic benzodiazepine use treated with melatonin [36].

In a recent review an algorithmic approach to the management of insomnia in patients with schizophrenia is presented [37]. First of all, the etiology of insomnia must be precisely established, as well as its global functional impact on the patient. Therefore, it is crucial to perform a detailed sleep clinical evaluation with direct questioning, without expecting a spontaneous sleep complaint. Caregivers and bed partners usually provide relevant and objective information in the anamnesis.

Secondly, AP treatment adherence must be evaluated, considering that an optimization of schizophrenia treatment must be prioritized to beginning a new specific treatment for insomnia, as many guidelines would recommend [38]. Psychotic symptoms should always be evaluated in case of insomnia. Treatment optimization ranges from long-acting injectable AP introduction, switch to a delayed-release AP, unnecessary treatment withdrawal, etc.

On the third place, once the etiology of insomnia has been determined and schizophrenia treatment optimized, lifestyle habits should be examined: sleep hygiene, drug use, dietary habits, off-label prescription drugs use (such as herbal products). Personalized psycho education must be conducted in these cases.

On the fourth place, comorbid SD must be ruled out, namely OSAS, RLS, circadian-rhythm disorders, parasomnias or narcolepsy. Transdiagnostic approaches on SD in psychiatric population have been suggested [39] but have not yet been customized in schizophrenia.

On the fifth place, once AP treatment has been optimized and other comorbid SD ruled out, the aforementioned CBT must be considered, using a hierarchical approach, emphasizing psycho education, sleep hygiene, stimulus control therapy and finally using cognitive techniques [40]. It is fundamental to establish a regular sleep schedule and sleep restriction techniques are not recommended in these patients.

Finally, drug treatment addition should be considered, regarding as first option maintenance AP dosage increase. The use

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benzodiazepines or analogues, as well as melatonin, trazodone and other new therapies like suvorexant are other pharmacological abovementioned alternatives.

The combination of pharmacological treatment and CBT has demonstrated efficacy on managing these patients. The prior steps are exposed on (Figure 2).

Figure 2: Algorithmic approach to the management of insomnia in patients with schizophrenia [37].
Abbreviations: AP: Antipsychotic; SD: Sleep Disorders; CCT: Cognitive Behavioral Therapy.

Movement disorders during sleep

Another sleep disturbance in patients with schizophrenia treated with AP are RLS and the "periodic limb movement disorder" (PLMD). Prevalence of these disorders in patients without AP treatment has not been established. Nonetheless, considering the symptomatic response after dopamine agonist treatment, dopamine deficiency is probably related to their physiopathology. Thus, it is hypothesized that AP D2-receptor blockade may be the cause of their expression as unwanted adverse effects. In fact, case series showing a twofold prevalence of these disorders in patients with schizophrenia treated with AP in comparison to healthy controls have been reported [2,41].

Lately evidence relates certain genetic polymorphisms (CLOCK, NPAS2) with an increased susceptibility of RLS in schizophrenia [42] in patients treated with second generation APs, such as risperidone, olanzapine, quetiapine and clozapine. Not every patient treated with AP presents with these symptoms. On this basis, a polymorphism in gene BTBD9 has been suggested as a genetic risk factor [43].

Regarding the management of these syndromes, standard treatment with dopamine agonists, like ropinirole, pramipexole or rotigotine, is discouraged. Alternatively, AP change is recommended. Addition of medications such as pregabalin or gabapentin can be considered. Moreover, iron deficiency, which is a recognized risk factor on RLS development, must be examined in order to establish replacement treatment because it can cause or exacerbate RLS in patients with schizophrenia [20,44]. Recent investigations suggest using drugs targeting the glutamate system on treating RLS, although more research is needed on this matter [2].

RLS symptoms, which are clinically diagnosed, could be intensified with AP treatment, thus they may be difficult to discern from extra pyramidal symptoms [45]. For instance, AP-induced akathisia, which can also cause sleep distortion, may not be easy to distinguish from RLS, even this second syndrome has a marked circadian component being more present at evening-nighttime. In contrast to RLS, AP-induced akathisia can be treated with propranolol, benzodiazepines or anticholinergics [3].

OSAS

OSAS is a syndrome consisting on repeated upper airway obstructions during sleep, causing micro-awakenings and sleep architecture disturbance. It is defined by coexistence of compatible symptoms (daytime sleepiness as main symptom) and an increased apnea-hypopnea index (higher than 5 and assessed by PSG). It is associated to obesity and cardiovascular disease [46].

There is a high rate of respiratory disorders during sleep in patients with schizophrenia, being OSAS the most prevalent. However, OSAS prevalence has not been proven increased in schizophrenia in comparison to general population.

OSAS may cause daytime sleepiness in patients with schizophrenia treated with AP, whether directly caused or exacerbated by AP use. It affects the life quality and functioning of these patients. Obesity is the best predictor in development and detection of OSAS. Thus, AP-induced weight gain needs to be managed in order to prevent, diagnose and treat OSAS in patients with schizophrenia [47,48].

OSAS diagnosis should be posed in schizophrenia in patients with sleepiness and obesity, or those with weight gain during AP treatment. Treatment of OSAS consists mainly on weight loss through diet and physical exercise and, when symptoms persist, CPAP (Continuous Positive Airway Pressure) can be used with successful clinical outcomes and treatment adherence [3]. In patients treated with olanzapine, a marked weight loss has been shown with AP switch to aripiprazole or aripiprazole combination with olanzapine [49].

Hypersomnia

Hypersomnia is the most self-reported SD in patients with schizophrenia treated with AP, in contrast to insomnia. Among 24 to 31% of patients report daytime sleepiness [18]. Hypersomnia can be either a direct adverse effect due to AP treatment, or an OSAS symptom, which can also be directly caused or exacerbated by APs. Typical AP more related to hypersomnia include those with higher posology and lower potency, such as chlorpromazine or thioridazine. Atypical AP include clozapine, recognized as the most sedative AP, olanzapine and risperidone. In order to treating hypersomnia, AP modification, reduction in dose or dose

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fractionation are options to be considered. It must be considered that hypersomnia is closely related to the AP pharmacokinetics, pharmacodynamics and posology. Addition of aripiprazole to the clozapine maintenance AP has proven improvement on daytime sleepiness as well as a decrease in psychotic symptoms [3,50]. Aripiprazole, followed by ziprasidone and quetiapine have shown a lower rate of hypersomnia in comparison to other APs. However, there is no data about their efficacy on sleep maintenance [20].

Parasomnias

Parasomnias, such as sleepwalking or sleep-related eating disorders, occur during a partial awakening during the SWS-phase. Patients with schizophrenia present higher risk of presentation when receiving an AP prolonging SWS, such as olanzapine or the addition of lithium to an AP [3]. In fact, the use of atypical AP has been related to an increase of the sleepwalking ratio in case series of patients with schizophrenia [51].

Circadian-rhythm disorders

Circadian rhythm disorders are one of the most referred SD in schizophrenia, and are present amongst almost 50% of all patients [52], impairing their daily social and occupational functioning. Melatonin-cycle and sleep-wake cycle disorders are among the most frequent, as shown in (Figure 3), in addition to phase-delay and daytime sleepiness [19]. This suggest a biological modification in sleep circadian regulation, which can be influenced by environmental, personal and behavioral factors (for instance, too much time spent in artificial light rooms or lacking a regular activity schedule) [50] or biological factors (genetic predisposition factors in schizophrenia) [20]. These patients tend to nocturnal life, delaying going to bed time and waking up in the morning [53]. This fact could be triggered by multiple gene alteration (CLOCK; PER1; TIMELESS; CRY1), which are related to dopamine transmission pathways [54].

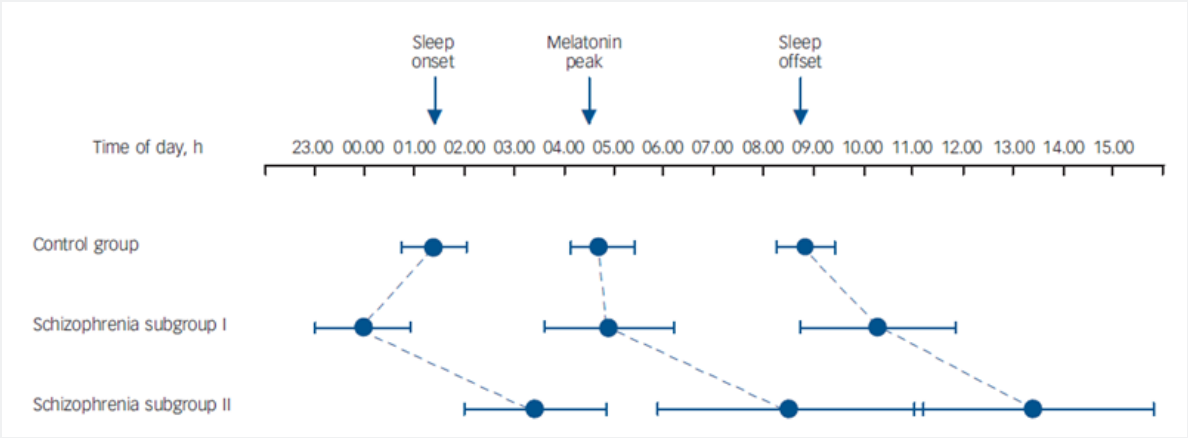

Figure 3: In this figure, the results from a study comparing the circadian rhythm and melatonin levels between patients with schizophrenia and healthy controls.

Important circadian rhythm disorders can be noted in all patients with schizophrenia in comparison to healthy controls and peak melatonin irregularity shown in one of the subgroups of patients. These alterations were maintained in spite of clinical stability and AP treatment and could not be explained by daily functioning of patients [52].

The treatment of circadian rhythm disorders depends on the specific disorder. In general, modifications in sleep hygiene can be recommended, as well as other treatments like chronotherapy, phototherapy, and according to some studies, melatonin administration [35].

Differences in SD Between AP-Treated and Treatment-Naive Patients with Schizophrenia

Conciliation and maintenance insomnia is a common symptom among patients with schizophrenia regardless of their treatment status (treated or naive) and clinical stage (acute or chronic) [6].

Many authors have proven that non-treated patients with schizophrenia, in comparison to healthy controls, have significantly more SD, such as increased sleep latency, increased number of awakenings during sleep, reduction in total sleep time and decrease in the sleep efficiency index [4,10,55].

On a similar way as treatment-naive patients, AP-treated patients, in relation to healthy controls, showed increased latency in phase 2 of sleep, increased wake-up latency after conciliation, whereas total sleep time and sleep efficiency were decreased [55]. Moreover, treatment-naive patients with schizophrenia have a more homogeneous sleep architecture than patients after AP self-discontinuation [10].

Conclusion

In this review it has been exposed, on the first place, the important comorbidity and prevalence of SD in schizophrenia [1]. The most relevant SD have been highlighted [2], emphasizing insomnia as a prodromal sign in schizophrenia [7] and potential early sign of psychotic decompensation [9] in schizophrenia. Afterwards, a specific management approach has been established on every SD, remarking the relevance on their

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different phyisiopathological etiologies regarding therapeutic options [2,3]. Finally, it has been evidenced the relation between poor sleep quality and life quality deterioration in patients with schizophrenia, correlating clinical, functional and coping capacity improvement to a good management of SD, highlighting the importance of identifying and treating SD in schizophrenia [56].

Currently, the scientific community is conferring greater relevance on the globality of schizophrenia rather than to specific isolated symptoms. Therefore, regarding patients' quality of life as main goal on the management of the disease, strategies on early identification and treatment of SD in schizophrenia should be developed. Due to the lack of validated official diagnostic and therapeutic guidelines on management of SD in schizophrenia, more studies are needed for their implementation.

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