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Abstract: ***Objective*:** Aging is a natural biological phenomenon that occurs in human beings. With increasing of age, there is an appearance of deleterious changes related to progression onto pathological conditions, including hypertension, heart disease, diabetes, hearing and vision impairments, as well as sleep disorders. It is important to recognize that some sleep disturbances reported by aged subjects include insomnia, obstructive sleep apnea, restless legs syndrome, among others. Moreover, accumulating evidence indicates that coexistence of medical issues with sleep disorders constitutes clinical challenges for treatment of comorbidities in elderly. Here, we have attempted to review and summarize the available literature that assesses the sleep disturbances in aging. In addition, we highlight the management of sleep disorders associated with aging. Due to the particular health condition of aged adults, the development of effective pharmacological interventions for sleep disorders treatment in aging is warranted.

***Methods*:** Review of studies retrieved from the PubMed.

***Results*:** The sleep-wake cycle includes abnormalities classified as sleep disorders. Comorbidity between sleep disturbances and aging-related health issues will represent a public health challenge to be addressed in the near future. Moreover, this scenario will suggest an area that requires further drug investigation and design of new pharmacological and pharmaceutical strategies to treat sleep disorders in the elderly population.

***Conclusion*:** The review highlights the sleep disturbances in aging. We focus on current knowledge in medicinal chemistry and further design of new treatments tools for managing sleep disturbances in the aged population.

Keywords: Aging, insomnia, depression, slow wave sleep, obstructive sleep apnea, REM sleep.

1. INTRODUCTION

The demographic and epidemiologic projections have indicated a growth in the elderly population worldwide in the coming years [1]. In this regard, it was estimated that subject aged ≥65 years old were 420 million in 2000 whereas that during 2000-2030, the worldwide elderly population has been projected to 973 million subjects [2-4]. These demographic transformations will represent challenges to solve geriatric-related health issues such as hypertension, arthritis, coronary heart disease, stroke and sleep disorders [5-7]. Since impairments in sleep increase in prevalence in older adults, such as insomnia, Obstructive Sleep Apnea (OSA), Restless Legs Syndrome (RLS) and others [8-

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10], the search of new drugs designed to manage these sleep disturbances it will require full attention in the near future.

Given that the increasing knowledge of sleep disorders in aging, it is indeed ambitious to describe all available evidence. Thus, based on a review of the literature available in PubMed, we first describe the basic understanding of the backbone of the sleep-wake cycle features. Next, we briefly show the aging-related sleep disorders, including insomnia, OSA, and RLS. In addition, we discuss the comorbidity in aging, including sleep disturbances with depression and dementia. Finally, we review the therapeutical approaches for sleep disorders in the elderly.

2. THE SLEEP-WAKE CYCLE: AN OVERVIEW

The sleep-wake cycle is a complex biological phenomenon that involves the interaction of multiple neurophysiological networks [11, 12]. For instance, several neuroanatomical nuclei, such as basal forebrain, hypothalamus, pons, among others, exert influence in sleep modulation [13-18]. In addition, the sleep-wake cycle is under control of several endogenous molecules such as neurotransmitters, peptides, lipids, hormones, as well as the expression of sleep-related genes [19-24]. In mammals studied so far, sleep is associated with behavioural quiescence, closed eyes, and specie-specific postural recumbence [25]. Currently, the consensus accepts that most vertebral species studied display two sleep stages: Slow wave sleep (SWS) and rapid eye movement (REM) sleep [25, 26]. In this regard, the characterization of the sleep-wake cycle includes polysomnographic traces for each state of vigilance. For instance, the electroencephalogram (EEG) signals during wakefulness (W) show rapid cortical activation and muscle activity that is recorded in the electromyogram (EMG). In regards to sleep phases, SWS shows in the EEG electrical activity such as "sleep spindles", K complex, and high-voltage slow waves whereas EMG activity is decreased. Under regular conditions, SWS progress in four different stages leading to the appearance of REM sleep, which is characterized by rapid EEG activity with low voltage and EMG abolished. The cycle of SWS-REM sleep repeats throughout the night at intervals of approximately 90-100 minutes [15].

3. THE SLEEP-WAKE DISTURBANCES

The sleep-wake cycle, as many physiological functions, displays aberrant features [27, 28]. At present, the classification of the multiple sleep disturbances is included in the *International Classification of Sleep Disorders (ICSD),* which describes the following categories:

Axis A: Contains the primary sleep diagnoses of the ICSD. The classification includes the following sections:

1. Dyssomnias; disorders that cause a complaint of either insomnia or excessive sleepiness;

2. Parasomnias; disorders that intrude into or occur during sleep and that are not primarily disorders of the states of sleep and wakefulness per se;

3. Medical or psychiatric sleep disorders; medical and psychiatric disorders that are commonly associated with sleep disturbance;

4. Proposed sleep disorders, as a response to the inclusion of new and rapid advances in sleep disorders medicine.

Axis B: Includes tests and procedures that are performed in sleep medicine, including polysomnography and the multiple sleep latency test (MSLT).

Axis C: Comprises the medical and psychiatric disorders that are not primarily sleep disorders per se.

It is worthy to mention that insomnia or excessive daytime sleepiness (EDS) are among the primary complains betwixt many patients [29, 30]. Insomnia is defined as the difficult to fall asleep and/or stay asleep across night whereas EDS is the tendency to fall asleep during daytime [31-39].

4. SLEEP DISORDERS IN AGING

As mentioned previously, the increased prevalence of aging population would account, as an additional element, for the increased rates of sleep disturbances in elderly. Future comprehensive treatments for sleep disturbances in the geriatric population should include develops of pharmacological approaches to encompass the complexity of sleep disorders [40-47].

We define aging is a natural biological process that implies an inevitable gradual degradation of most of the physiological functions leading to malfunction of diverse biological systems [48]. Amongst others, multiple health disturbances in senescence are present, such as sleep disorders [49-54], including insomnia, OSA, and RLS [54-56].

4.1. Insomnia in Aging

It has been estimated that as many as 50% of aged adults report having a hard time to fall asleep in the

night [42, 54-57]. Insomnia comprises several subtypes, including sleep onset insomnia (related with the difficulty to initiate sleep), sleep maintenance insomnia (linked with the inability to maintain sleep across the nighttime), early morning insomnia (identified with the early morning awakenings with difficulty in initiating sleep), and psychophysiological insomnia (associated with behavioral conditioned sleep troubles). Depending on the course of the sleep disturbance, insomnia can be classified as transient (lasting only a few days before or during a stressful experience), short-term (lasting a few weeks during an extended period of stress or adjustment), or chronic (enduring several months or years after a precipitating event) [58, 59]. Insomnia will represent a challenging medical scenario due to the enhancement of prevalence in the aged population. In this regard, data from the National Sleep Foundation (USA) published in 2003, The *Sleep in America* poll, which reported that 44% of aged subjects complained to have one or more of the nighttime symptoms of insomnia at least a few nights per week [60]. Similar findings have been confirmed in subsequent studies [61, 62].

4.2. Obstructive Sleep Apnea in Geriatrics

Interruptions in breathing during sleep for at least 10 s leading to intermittent, partial, and/or complete collapse of the upper airway across nighttime is the clinical feature of OSA. Central (neuronal mechanisms) and peripheral (anatomical airway abnormalities) obstructions contribute to the establishment of OSA. Because of obstruction, the consequences of any inspiratory effort provokes snoring, which in turn causes sleep fragmentation due to the continuous awakenings across nighttime. This sleep fragmentation induces sleep deprivation. Patients with OSA often report EDS as part of sleep deprivation [63]. To further complicate matters, OSA is accompanied with awakenings associated with additional sleep disturbances such as RLS [62-64].

Regarding the prevalence of OSA in elderly, the repeated cessation or attenuation of breathing (named “apneas” or “hypopneas”, respectively) affects near 60% of aged adults [64-69]. Severe health consequences of OSA have been reported such as arterial hypertension, heart attack, stroke, etc. [70-75].

4.3. Aged Subjects and Restless Legs Syndrome

The RLS is a neurological disorder characterized by an irresistible and unpleasant urge to move the limbs, which occur mostly in the night [76-78]. The prevalence of RLS increases with age. Near 10% of people in North America and Europe report the experience RLS symptoms [76-79]. The neurobiological mechanisms underlying RLS are unknown in detail. However, some evidence suggests that dysregulation of the dopaminergic system might be involved in the genesis of this disease. In this regard, it has been demonstrated that the use of a dopaminergic agonist, such as rotigotine, induces positive improvements in RLS patients [80-82]. Importantly, the study of the neurobiological origins of RLS in aged population is required. Moreover, developing drugs targeting the control RLS should differentiate motor dysfunctions observed in aged subjects with Parkinson´s disease.

4.4. Narcolepsy in Senescent Population

Narcolepsy is a life-long unhealthy condition characterized by two major symptoms, EDS and cataplexy. The degeneration of the hypocretin (also named orexin) neurons placed into the lateral hypothalamus has been suggested as the pathogenic basis of narcolepsy [83, 84]. According to the European Narcolepsy Network Study, the mean age at diagnosis of narcolepsy is 36.9 ± 17.1 years but with a range of 4-87 years [84]. Clinically, narcoleptic patients display EDS for the rest of life. Interestingly, over the years, a progressive decrease in mean sleep latency and number of sleep-onset REM sleep periods (SOREMP) in narcoleptic patients has been observed [85, 86].

The most clinically relevant examination used to diagnosis of narcolepsy is the multiple sleep latency test (MSLT). This parameter has shown a progressive increase in sleep latency and a decrease in REM sleep episodes linked with age [86, 87].

Although narcolepsy is normally described during the adolescence, recent data have suggested the putative link between hypocretin/orexin and aging-related diseases such as Alzheimer´s disease (AD) [87-90]. This area –narcolepsy in aging- is unripe and requires further research due to the limited available data. Designing age-related drugs for the treatment of narcolepsy should be considered in the coming years.

5. MEDICAL COMORBIDITY OF SLEEP DISORDERS IN OLDER ADULTS

The coexistence of medical issues with sleep disorders has long been recognized. Obesity, metabolic syndrome, depression and dementia, among many others medical issues are present with sleep disturbances in aging and these comorbidities have a negative impact on the quality of life of subjects [91-96].

5.1. Sleep Disturbances and Depression in Elderly Subjects

It has been described the relationship between depression and sleep disorders in aging, such as increased sleep onset latency, frequent awakenings across nighttime, EDS [97-100]. In addition, Almeida and Pfaff reported that 63% of geriatric patients reported sleep disturbances and they were 3.7 times more likely to develop depression [101]. Therefore, comorbidity of sleep difficulties in older adults, including depression, have been recognized [102]. Due to the enhancement in the number of geriatric population in the next decades, we will require full comprehension of the relationship between sleep disorders and depression in aging. Moreover, future drug design targeting sleep disorders in aging should consider comorbidities such as depression.

5.2. Sleep Disorders in Dementia in Aged Adults

Dementia is a mental disorder that confers memory loss, impaired reasoning, mood change, and difficulties with day-to-day activities. Data provided by the World Health Organization indicates that 47.5 million people worldwide have been diagnosed with dementia [103]. The most common forms of dementia are AD representing 70% of the referenced subjects. The mechanisms that initiate AD involves the generation and accumulation of proteins named AB and Tau, which in turn form senile plaques in the brain. Moreover, genetic mutations such as the PSEN 1 and 2, APOE4, and APP gene located in the chromosome 21 have been linked with AD genesis [104]. Regarding the relationship among sleep disorders and dementia in aged subjects, Kawada (2016) reported that geriatric patients with long sleep duration ($\geq$7 hours) displayed a risk of a decrease in cognitive performance in comparison with aged subjects with short sleep duration ($\leq$7 hours) [105]. The most common symptoms in AD include increased sleep latency, nighttime sleep fragmentation with a reduction in SWS, increased daytime napping, etc. Indeed, several findings lend support the coexistence between sleep disturbances and dementia in older adults [106-111].

5.3. Sleep Problems in Geriatric Patients with Parkinson´s Disease

On the other hand, Parkinson's disease (PD) is a progressive neurodegenerative motor disorder that affects 300 per 100,000 people [112]. Patients with PD report sleep problems, such as insomnia, EDS, RLS, OSA, sleep fragmentation, circadian rhythm disorders, REM behavior disorder [112-117].

Due to the limited understanding of the relationship between neurodegenerative disorders, such as AD or PD, with sleep disorders in aged subjects, treatment options are limited. Further studies that center on the development of novel pharmacological treatments for sleep disturbances in aged patients with neurodegenerative diseases are required.

6. THERAPEUTICAL APPROACHES FOR MANAGING SLEEP DISORDERS IN AGING

Most of the sleep problems reported in aged subjects are managed by pharmacological means [118-134]. For example, among the medications used for the treatment of insomnia in geriatric population are antidepressants, antihistamines, sedative-hypnotics, such as nonbenzodiazepines (type-1 γ-aminobutyric acid (GABA)), benzodiazepine receptor agonists (eszopiclone, zaleplon, zolpidem, zolpidem extended release) or melatonin receptor agonists (ramelteon) [118-124]. In contrast, EDS is controlled by using wake-promoting compounds, such as direct-acting sympathomimetics (phenylephrine), indirect-acting sympathomimetics (methylphenidate, amphetamine), nonsympathomimetic stimulants (caffeine, modafinil) or selective serotonin reuptake inhibitors (SSRIs) [125-129]. Regarding the therapeutic management of OSA, several tools have been used such as weight loss, surgery of the upper airway, dental appliances, and the use of Continuous Positive Airway Pressure (CPAP) which is the leading approach for treating OSA. Basically, CPAP is a bedside machine that helps a person who has OSA to breathe more easily during sleep by providing an appropriate airflow pressure through a nasal mask. This continuous airflow pressure acts as a pneumatic splint avoiding obstructive apnea by keeping the pharyngeal airway open across nighttime [135]. Lastly, OSA has been addressed with anti-inflammatory drugs, such as some intra-nasal steroids. However, these treatments are mostly given to children [136, 137]. It is our understanding that no solid evidence of using steroids inhaled through the nose may reduce symptoms of OSA in aging population.

Despite the lack of solid body of evidence of effects or drugs to manage OSA in aging, side effects of pharmacological treatments for other sleep disorders in elderly have led to include alternative treatments such as light therapy, physical activity, or cognitive behavioral therapy (sleep hygiene techniques combined with additional behavioral treatments) [138-144]. Because

these findings appear to control sleep disorders in aging, it would be interesting to study the integration of the mechanisms of action of these combined approaches (Fig. **1**).

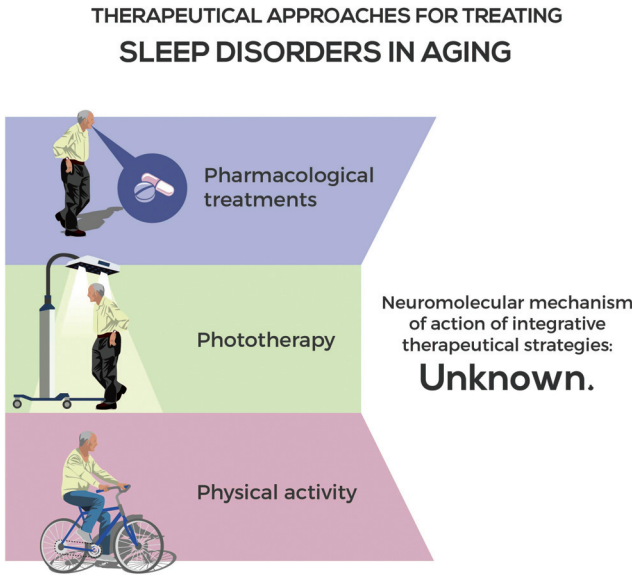

Fig. (1). Multiple therapies used to manage sleep disorders in aging. Pharmacological approaches, phototherapy and physical exercise control sleep disorders in aged population. Despite the positive outcomes from these clinical interventions, it is unknown the mechanism of action of these combined approaches.

7. DEVELOPMENTS IN MEDICINAL CHEMISTRY AND RATIONAL DRUG DESIGN FOR TREATING SLEEP DISTURBANCES IN OLDER ADULTS

With the increase in the number of aged people worldwide in the coming decades, it is important to develop novel pharmacological approaches for managing sleep disturbances in geriatric population [54-56, 62, 77-84, 145]. Besides the particular health condition of geriatric patients (hypertension, heart disease, diabetes, hearing and vision impairments, difficulty with functioning in physical and social activities, etc), when broadening drug design for sleep disturbances in elderly, it should focus on the following aspects: Firstly, differentiate in aged population tiredness and sleepiness. Fatigue is commonly reported as a feeling of exhaustion but lacks a clear definition [125, 126]. Importantly, fatigued patients not necessarily report EDS. Thus, pharmacological treatments given to manage drowsiness in the geriatric population should consider the differences among tiredness and sleepiness since both variables could have a distinct origin and might involve different mechanisms [145-147]. Secondly, recent data have shown that older subjects with EDS show cortical thickness reduction in brain regions [148, 149]. Drug design (novel bioactive compounds, analogs, in-silico drug design, combinatorial chemistry, high-throughput screening, and structure-activity relationships, among many others) should develop compounds for clinical uses for sleep-related disturbances in aged subjects but taking into account the neuroanatomical changes. Thirdly, due to the plethora of interaction between sleep disturbances and aging, new pharmacological treatments should provide comprehensive overviews of the mechanism of interaction among sleep disorders and neurological processes associated with aging. For instance, future work should help in selecting effective and efficient pharmacotherapy for OSA [150]. Fourth and last, the generation of drugs for managing sleep disturbances in geriatric adults with full positive outcomes should consider gender differences as a key element in successful therapy [151, 152].

CONCLUSION

Worldwide projective models have indicated an increase in aged population in coming years associated with an enhancement in public health issues, including sleep disorders. In this regard, the most common sleep disturbances reported by geriatric subjects include insomnia, OSA, RLS, among many others. Moreover, comorbidity between sleep disturbances and aging-related health issues would represent a clinical defiance for developing effective pharmacological treatments.

LIST OF ABBREVIATIONS

AD	=	Alzheimer´s Disease
CPAP	=	Continuous Positive Airway Pressure
EDS	=	Excessive Daytime Sleepiness
EEG	=	Electroencephalogram
EMG	=	Electromyogram
GABA	=	γ-Aminobutyric Acid
ICSD	=	International Classification of Sleep Disorders
MSLT	=	Multiple Sleep Latency Test
OSA	=	Obstructive Sleep Apnea
PD	=	Parkinson's Disease
QoL	=	Quality of Life
REM sleep	=	Rapid Eye Movement Sleep
RLS	=	Restless Legs Syndrome

SOREMPS	=	Sleep-onset REM sleep periods
SSRIs	=	Selective serotonin reuptake Inhibitors
SWS	=	Slow Wave Sleep
W	=	Wakefulness

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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