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NON-PHARMACOLOGIC MANAGEMENT OF SLEEP DISTURBANCE IN ALZHEIMER'S DISEASE

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Abstract: Sleep and wake in Alzheimer's disease (AD) are often fragmented as manifested by bouts of wakefulness at night and napping during the day. Management of sleep disturbances in AD is important because of their negative impact on both patients and caregivers. Pharmacological treatments, mainly sedative-hypnotics and antipsychotics, are often used but can be associated with significant adverse effects. Non-pharmacological treatments represent a beneficial alternative approach to the management of sleep disturbances in AD since they are associated with fewer adverse effects and their efficacy can be sustained after treatment has been completed. The aim of this article is to review non-pharmacological treatments, such as sleep hygiene, sleep restriction therapy (SRT), cognitive behavioral therapy (CBT), light therapy, and continuous positive airway pressure (CPAP), for the management of sleep/wake disturbances in AD.

Key words: Alzheimer's disease, sleep/wake, disturbances, circadian Rhythm.

Introduction

Sleep disturbance is common among Alzheimer's disease (AD) patients, with prevalences ranging from 25 to 35% (1) and is thought to contribute to caregiver burden as well as patient institutionalization (2). Sleep/wake disturbance in AD is characterized by fragmentation commonly manifested as periods of wakefulness at night and excessive napping during the day (3-5). For example, our previous work longitudinally followed sleep/wake disturbances in AD subjects and found significantly increased wake after initial sleep onset (WASO) occurring over the course of the disease (6). There have been a variety of methods used to treat this sleep disturbance. The goal of this paper will be to review various non-pharmacological approaches. First, however, we will review some key assessment issues, followed by a discussion of diagnostic criteria for sleep disturbances in AD and why pharmacological treatments are problematic in the elderly. Finally, we will turn to a discussion of non-pharmacological treatments.

Assessment issues

Sleep assessment methods include both subjective, observational measures such as clinical evaluations, sleep logs and sleep scales as well as objective, technological measures, primarily polysomnography and ambulatory actigraphy. Both subjective and objective approaches have advantages and disadvantages. For example, sleep logs are a good measure of individuals' subjective experience of their sleep. In the case of AD patients, sleep logs depend on the patient's or caregiver's ability to complete a daily diary and, given the difficulty of assessing one's own sleep, are inherently unreliable as an objective measure. Sleep scales are also dependent upon subjective ratings and observations and for the most part, are completed by others in the case of AD patients.

Polysomnography (simultaneous recording of multiple physiologic measures such as electroencepahalogram, electrooculogram, electromyogram during sleep) is considered the gold standard for objective sleep assessment. However, polysomnography requires the patient's cooperation typically for overnight in-hospital stays (usually for one or at most two nights). Furthermore, since environmental changes are often disturbing for AD patients, the experience can trigger patient agitation. Ambulatory polysomnography is available, but the equipment is more expensive than ambulatory actigraphy, takes considerable technician time to set up and score and is likely more disturbing for AD patients than less obtrusive devices such as wrist-worn actigraphs.

Actigraphy is widely used as an objective assessment method to evaluate AD patients' fragmented sleep (6, 7). Ambulatory actigraphy uses a small relatively unobtrusive device containing a piezoelectric accelerometer to record arm movement in three dimensions. For the determination of patterns of sleep/wake, the actigraph is usually worn on the non-dominant wrist over a number of consecutive 24h-periods. Using specific algorithms (8, 9) sleep/wake data are derived from patterns of activity and inactivity. Because the devices are generally well-tolerated, data can be collected for multiple nights. Thus, the actigraph can be particularly useful for generating a more complete and reliable picture of an individual's sleep/wake patterns than other methods because it can encompass the considerable night-to-night variability of disturbed sleep. However, it should be noted that actigraphy scoring algorithms require the entry of into and out of bedtimes to set the nocturnal sleep period (in AD this is usually performed by the caregiver) and that since the data are derived from movement rather than directly from brain physiology as in polysomnography, it is an indirect measure of sleep.

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Diagnostic criteria

In addition to the need for objective assessment of sleep disturbance in AD patients, diagnostic criteria are needed. An NIMH Workgroup published a set of such criteria (5). The three major requirements were:

1. The patient has a complaint (either expressed by the patient or observed by the caregiver) of insomnia and/or excessive daytime sleepiness. The insomnia may be associated with confused behavior.

2. Polysomnographic, actigraphic or structured sleep log observation (completed by the patient or a caregiver) demonstrates disturbances of the sleep/wake cycle as having at least 2 of the 4 following:

a. Increased wake after sleep onset (WASO) characterized by the number and/or length of wake episodes occurring often or long enough to affect the function or well-being of either the patient or the caregiver.
b. Decreased total sleep time (TST) with a reduction of one-fourth of the patient's total nocturnal sleep relative to their pre-morbid nocturnal sleep pattern, or when this is not known, a pattern of sleeping less than six hours during a period from 9:00 PM to 6:00AM.
c. Poor daytime wake continuity with an increase in the number and/or duration of naps during the day relative to the patient's pre-morbid daytime wakefulness and napping pattern.
d. Desynchronization of sleep/wake rhythm as reflected by altered diurnal patterns of sleep, i.e. day-night sleep ratio.

3. The sleep disturbance is associated with a diagnosis of Alzheimer's disease. The sleep disturbance was not present before the onset of the dementia and the nature and degree of the sleep disturbance can be expected to change with the stage of the disease.

In addition to meeting the diagnostic criteria, other diagnoses that may mimic a sleep disturbance in AD patients should be excluded. The following is the relevant differential diagnosis:

1. Other medical disorders especially delirium, depression, chronic pain and medication use may be present but do not account for the primary symptoms.

2. Other sleep disorders (e.g., periodic limb movement disorder, restless legs syndrome, obstructive sleep apnea syndrome), may be present but do not account for the primary symptoms. If there is a suspicion or objective documentation of a sleep disorder that does account for the primary symptoms, it should be treated first.

3. The sleep disturbance cannot be characterized as a parasomnia. Parasomnias may include behavioral manifestations of epileptiform activity or suspension of REM sleep atonia characteristic of REM Behavior Disorder (RBD).

a. RBD consists of dream-enactment behaviors, often accompanied by dream recall of frightening and/or dramatic events, and REM-specific motor activity.
b. RBD may be present in an idiopathic form or may co-occur in Parkinson's disease (PD), Lewy Body Dementia (LBD), or AD/PD overlap, if presumed nigrostriatal pathology exists.
c. If symptoms and signs compatible with such diagnoses exist in a given patient, polysomnography would be indicated to establish this differential. If polysomnography is not possible because the patient cannot tolerate it, a video recording to differentiate REM Behavior Disorder may be substituted.

Now that we have discussed assessment techniques and diagnostic criteria for an AD-related sleep disturbance, we will turn to a discussion of relevant treatments.

Treatments

Pharmacological treatments

Sedative and Hypnotic medication

Pharmaceutical treatments, including mainly sedative-hypnotics and antipsychotics, are often used to treat sleep disturbances in AD. However, they can be associated with significant adverse effects (10, 11). Both benzodiazepines and antipsychotics usually increase daytime sleepiness (12) or cause rebound insomnia (1). The more recently available benzodiazepine-like "Z-drugs", zolpidem, eszopiclone, zaleplon, have fewer adverse events but data concerning their efficacy with AD patients are limited and they also act on the benzodiazepine receptor. Use of such medications in older adults also raises concerns because of the possibility of an increased risk of falling (13).

Acetylcholinesterase Inhibitors (AChEI)

Early work suggested that nighttime sleep-related adverse events, including insomnia and nightmares, might be associated with AChEI treatment (14-16). However, recent placebo-controlled trials have tended to show maintenance of good sleep during treatment with AChEI (17-19).

Melatonin

Pineal secreted melatonin plays a key role in circadian rhythm regulation (20). Production of melatonin may be low in some older individuals (21-23), including some with AD (24). However, exogenous melatonin administration has not shown improvements of sleep/wake patterns in AD in two recent randomized controlled-trials (25, 26).

In general, pharmacological treatments may offer some short-term benefits but they have several limitations. Current pharmacotherapy has a poor side-effect profile and since their efficacy lasts only as long as the medication is taken, they are expensive. There is also the danger of drug interactions given the multiple medications taken by many older individuals. This has led researchers and clinicians to consideration of a number of non-pharmacologic treatment alternatives.

Non-pharmacological treatments

Non-pharmacological treatments have demonstrated efficacy for the management of sleep disorders in healthy young and

elderly adults. In the sections below we will define each type of therapy, its use in normal populations and then review how it has been applied to the AD population. In general the application of these treatments to AD patients has been limited with much of recent work in AD patients being done in the field of bright light treatments.

Sleep Hygiene

Sleep hygiene refers to the management of behaviors and environmental conditions thought to influence the quality of sleep (27, 28). Several studies have demonstrated that sleep hygiene education can significantly reduce wake after the onset of sleep (WASO) in normal populations (29). Sleep hygiene is often used as part of many treatment combinations and is widely used in clinical practice. However, there is no standardized package of sleep hygiene instructions and components vary from study to study. Various elements of sleep hygiene have been included in treatments for AD patients. McCurry (29, 30) trained caregivers of community-dwelling AD patients to implement sleep hygiene changes and succeeded in improving patients' sleep scheduling, napping, and walking routines.

Sleep Restriction

Excessive time spent in bed has been associated with more fragmented sleep (31). Sleep restriction therapy (SRT) has shown efficacy in improving older adults' subjective evaluations of their sleep (32, 33). Elements of SRT are often included in sleep hygiene, in cognitive behavioral treatment packages and indirectly in light therapies where scheduling of treatments can provide a certain level of sleep timing regimentation. We know of no trial of sleep restriction as an independent treatment in AD patients.

Cognitive Behavioral Therapy

Cognitive Behavioral Therapy for Insomnia (CBT-I) is in wide use in normal populations (34-37). There are several variants of CBT-I but basically it includes cognitive therapy focused on changing faulty beliefs, maladaptive cognitions and intrusive thoughts that interfere with sleep (38), in combination with various behavioral therapies applied to sleep such as stimulus control (39-41), relaxation therapy (42) and sleep restriction (31). McCurry (43) examined the use of CBT-I in AD patients. Patients followed a comprehensive behavioral program that included a sleep education component, sleep hygiene information, training in behavior management skills, increased daytime light exposure and nighttime exposure to bright light. Patients in the active condition showed greater reduction in nighttime awakenings and total time awake at night. This study illustrates how often several non-pharmacological techniques can be combined for clinical use in AD patients.

Bright Light Therapy

Many older individuals with AD have reduced exposure to bright light (44). Furthermore, lighting in nursing homes is often at low levels (45) with more demented individuals receiving less light (46). Bright light has been widely used in treating non-demented adults with Seasonal Affective Disorder (47) and less commonly for insomnia (48, 49). Yet there is no consensus regarding treatment parameters such as the timing of light exposure, light intensity, wavelength composition, and treatment duration. Several studies have examined the effects of bright light in AD patients and have found mixed results. Some studies have found beneficial effects in actigraphic-assessed rest-activity, circadian rhythms of AD patients (50, 51) but not in nocturnal sleep. Positive effects of bright light have mainly shown consolidation of nighttime sleep by lengthening the maximum nocturnal sleep bouts but not by increasing total nocturnal sleep time or decreasing daytime napping (46). On the other hand McCurry (43) found improvements in the number of nighttime awakenings and total time awake at night using a treatment package of sleep hygiene, daily walking and increased light exposure. Yet, a recent randomized, controlled-trial showed that a 10-week bright light treatment alone did not improve nighttime sleep, daytime wake, or rest-activity rhythm although light treatment plus melatonin increased daytime wake time and levels of activity (52).

Continuous Positive Airway Pressure (CPAP)

Sleep disordered breathing (SDB), including obstructive sleep apnea (OSA), has a prevalence of up to 62% in older adults (53). An apnea is characterized by a "cessation or near complete cessation (greater than 70% reduction) of airflow for a minimum of 10 seconds" (International Classification of Sleep Disorders, 2005). SDB is widespread among AD patients (54, 55) and is known to aggravate cognitive function in elderly healthy [56] and cognitively impaired people (57). Sleep apnea is also associated with sleep disturbance and daytime sleepiness (58). The prevalence of sleep apnea increases with age, especially in patients with AD (57).

In the criteria for the diagnosis of sleep disturbances in AD, we rule out SDB and other sleep disturbances as a cause of the AD-associated sleep disturbance. Nonetheless, because of its high prevalence it is likely to be found in the many AD patients with and without behavioral disturbances and some of these patients may be undergoing therapy for SDB. Continuous positive airway pressure (CPAP) treatment works by pushing air through the airway passage at pressure high enough to prevent apneas. The pressure is adjusted to the degree of patients' sleep apnea. A number of benefits have been found associated with CPAP in older adults including decreased sleep disruption from nocturia, improvements in cognitive performance and positive effects on cardiac function (59). In AD patients with SDB, CPAP has shown effectiveness in reducing subjective daytime sleepiness (60). Cooke (61) found improvement of nighttime sleep after only one night of treatment was maintained at the conclusion of 3 weeks of treatment. Furthermore, CPAP treatment has been well tolerated (62) as well as associated with improved cognitive performance in AD patients (57).

Conclusion

Non-pharmacological treatments tend to be relatively beneficial for the management of sleep disorders in AD and have several advantages over pharmacological medications:

Tolerance appears to be good and adverse events are minimal. Treatment efficacy is expected to last longer than pharmacological treatments for which positive effects stop when treatment is interrupted. Furthermore, due to increased susceptibility to adverse events among older adults with dementia, non-pharmacological treatments of sleep disorders should be considered as first-intention treatments.

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