Long-Term Care Updates

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Melatonin for sleep disturbances in patients with dementia: a literature review

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Introduction

Dementia is a term used to describe loss of memory, problem-solving, language, and cognitive abilities which interferes with daily life. While Alzheimer's is the most common form, there are many forms of dementia, such as Lewy body and vascular.[1] As of 2020, a reported 7 million people over the age of 65 had some form of dementia. If the current trend continues, this would mean 12 million people will have developed dementia by 2040. This is due more to the increase in the older population, the percent of people over 70 years of age with dementia actually decreased between 2011 and 2019. There are certain risk factors for developing dementia, women, racial/ethnic minorities, and people over 85 are at increased risk. However, more education reduces the risk. While most people with dementia do not live in a nursing home, roughly 70% of people over 70 years of age in nursing homes have some form of dementia.[2]

Melatonin is a naturally occurring hormone secreted by the pineal gland and involved in the sleep/wake cycle. Endogenous melatonin levels decrease with both age and cognitive deficits, reflected in increasing insomnia in later life and decreased levels in Alzheimer's disease (AD). This may be due to balancing of the circadian rhythm, regulation of the immune system, and antioxidant properties.[3] Sleep disturbances are a common complication with dementia. These include reduced nocturnal sleep time and daytime sleepiness, with increased sleep fragmentation and nocturnal wandering. These increase caregiver stress and may cause a person with dementia to be admitted to long-term care.[4]

There are non-pharmacologic aids for sleep disturbances caused by dementia, such as light therapy and sleep restriction.[5] In consideration of pharmacologic therapy, melatonin is a naturally occurring hormone, with few adverse effects.[4] This newsletter will consider the efficacy of melatonin on reducing sleep disturbances in dementia.

Clinical Efficacy

The first meta-analysis considered was McCleery and Sharpley (2020). This included any randomized placebo-controlled trial, which compared an active drug intended to improve sleep to placebo. At least 80% of patients in the study needed to have a diagnosed form of dementia, with sleep problems, except the exclusion of sleep apnea (considered a respiratory disorder). Primary outcomes included: total nocturnal sleep time (TNST); consolidated sleep time at night; sleep efficiency; nocturnal time awake; number of nocturnal awakenings; sleep latency; ratio of daytime sleep to night-time sleep, or of night-time sleep to total sleep over 24 hours; and adverse events. In total, they included 5 studies; 2 studies were excluded from this consultation, 1 used melatonin plus light therapy and 1 required baseline insomnia before dementia. All patients had dementia related to AD, most with moderate to severe AD. None of the trials considered how long patients slept without interruption, which is a major caregiver concern. The 3 studies considered here were considered fairly low risk for bias. In their summary of findings they found that melatonin may result in little to no difference in caregiver burden, number of nocturnal awakenings, and total nocturnal sleep time. These were low grading of recommendations assessment, development and evaluation (GRADE) evidence findings due to imprecision with wide confidence intervals (CIs) and few participants. Melatonin did not show a difference in adverse events from placebo.[4]

The second meta-analysis considered was Xu et al. (2016). This included randomized clinical trials (RCTs) with a dementia diagnosis and using melatonin versus placebo. The primary outcomes were sleep quality and cognitive function assessment using the Mini-Mental State Examination (MMSE). In total, they included 7 studies; 3 were duplicates from McCleery and Sharpley (2020), 1 included patients without dementia (without separating results), and 1 was in Chinese, all 5 were excluded from this consultation. None of their included studies showed a significant difference in adverse events between melatonin and placebo. A statistically significant prolongation of 24.36 minutes (95% CI: 3.26-45.46, $p = 0.02$) was found in TNST when melatonin was used. This was extended to 28.78 minutes ($p = 0.02$), when the treatment lasted at least 4 weeks. However, when patients with AD were separated out, the increase in TNST was no longer significant, even at 4 weeks of treatment ($p = 0.07$).[6] The clinical significance of 24-28 minutes sleep increase is also questionable, depending on individual sleep disturbances and caregiver views.[6]

Both meta-analyses attempted to correct for limitations in assessing data from non-heterogeneous study types. This was done by comparing the various studies in multiple groups, according to similarities, and reporting multiple endpoints. However, none of the studies had a large population size. Many used different ways to measure a similar endpoint and some included only patients with AD. While all cited studies claimed randomization, several were unclear as to how this was performed.[4,6]

Morales-Delgado et al. (2018) conducted a single-center randomized, double-blinded, placebo-controlled study on patients with dementia and sleep disturbances. Included patients were ≥ 65 years of age, with mild to moderate dementia, and sleep alterations. Other medications were allowed as long as they were initiated and maintained for more than eight weeks prior to the study. Patients were excluded if they had prior sleep disorders, hypersensitivity to melatonin, were using stimulants or hypnotics, or had other neuropsychiatric symptoms. Patients were then further excluded if they had less than 90% adherence during the study. In total, 31 patients were included in the data analysis. Baseline characteristics were not different between groups. The intervention was 5 mg melatonin or placebo every night for eight weeks. Blinding was achieved by computer and intervention medications were identical in appearance. The primary outcome was sleep quality per the Pittsburgh Sleep Quality Index (PSQI), which measures: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction. PSQI scores improved in both groups compared to baseline, but this could be attributed to the sleep hygiene instructions provided to all participants. Mean change from PSQI baseline in the melatonin group was -1.33 versus -1.5 in the placebo group ($p = 0.8$). Their conclusion was, melatonin 5 mg nightly was not superior to placebo in improving sleep quality in patients with mild to moderate dementia.[8]

Singer et al. (2002) performed a multicenter, randomized, placebo-controlled trial to compare two doses of melatonin on the treatment of insomnia in AD patients. Included patients were required to have a probable diagnosis of AD, nighttime sleep disturbance, a caregiver, and ability of the patient or caregiver to comply with trial protocol. A sleep disturbance was defined as an average of < 7 hours total immobile time between 2000 and 0800. Disturbances included: nighttime wandering, difficulty falling asleep, getting up (except toileting), waking the caregiver, thinking it is daytime, waking too early, and excessive daytime sleeping. Baseline characteristics were similar between groups. A total of 157 patients were enrolled. Patients were randomly assigned (blocked by study site) in a double-blind fashion (not specified) to 1 of 3 treatment arms: placebo, 2.5 mg slow-release (SR) melatonin, or 10 mg melatonin. No statistically significant differences in objective sleep measures were seen between treatment groups. Nonsignificant trends for increased nocturnal total sleep time and decreased wake after sleep onset were observed in the melatonin groups relative to placebo. TNST increased by 16 ± 54 minutes in the melatonin SR 2.5 mg arm and 13 ± 44 minutes in the melatonin 10 mg arm, compared to 3 ± 39 minutes for placebo. There was no significant difference in adverse events across the three treatment arms. Patients in the melatonin 10 mg group showed a trend toward gaining >30 minutes of TNST ($p = 0.07$).[9]

Serfaty et al. (2002) enrolled 44 patients with dementia and sleep disturbances into a randomized, double-blind, cross-over trial, comparing melatonin SR 6 mg versus placebo over 7 weeks. Inclusion criteria were: age ≥ 65 years, diagnosis of dementia, presence of sleep disturbances, and they did not live alone. Exclusions were: received ECT in the past 6 months, another axis 1 diagnosis, unable to comply with trial, severe physical problems. Of the 44 patients, 29 had AD, 8 had vascular dementia, 6 were mixed dementia, and 1 had Lewy body. Patients were randomized by computer algorithm and tablets were identical. The intervention was one week baseline data collection, then two weeks on either melatonin or placebo, followed by a one week washout period, and finally two weeks treatment with melatonin or placebo. Primary outcomes included sleep onset time, number of awakenings, TNST, and sleep efficiency. Results were only available for 25 of the 44 patients, mostly due to lack of compliance with wearing a wrist actigraphy device, used to measure sleep parameters. Missing data was entered as median baseline data, but inclusion or exclusion of this data did not alter the results. Melatonin had no effect on TNST ($p = 0.18$), number of awakenings ($p = 0.75$), or sleep efficiency ($p = 0.24$). The authors noted that there was a discrepancy between actigraphy data and caregiver reported data, which puts studies as risk of bias which rely on reported rather than recorded data. The study was underpowered, they anticipated a need of 62 patients and only used data from 25. However, the authors argue that even a correctly powered study would not have altered the results.[10]

Asayama et al. (2003) collected data from 18 patients in a double-blind, placebo-controlled, randomized trial. Included patients were inpatients to the geriatric ward of S Hospital, with diagnosed AD. Patients were allowed to continue necessary medications if they were not altered during the study period. Patients on psychotropic drugs, beta-blockers, or drugs that affect the sleep-wake cycle were given a 4 week washout from those medications before the trial began. The mean age was 79.2±6.4 years and baseline characteristics appeared similar between groups, though they were not statistically compared. The intervention was 1 week on a specified hospital schedule, 1 week of evaluation, followed by 4 weeks given placebo or melatonin 3 mg once nightly at 2030. Sleep time and activity were monitored by wrist actigraphy. The mean TNST change for placebo was -0.2 minutes and the mean TNST change for melatonin was 33.2 minutes ($p = 0.017$). The mean activity count per minute of the placebo arm was 29.8 and of the melatonin arm was -44.9 ($p = 0.014$). Daytime sleep did not show a statistically significant difference (p□0.262) between both arms.[11] Per Wang et al. (2017), this study had risk of bias due to lack of information on allocation concealment and random sequence generation, incomplete outcome data, and potential for selective reporting.[7] Blinding and allocation concealment were not specifically addressed by Asayama et al. (2003) beyond "drugs were administrated in a double blind design by randomized allocation".[11] When this study was excluded from Xu et al. (2016), the I^2 for TNST dropped from 59% to 0%.[7]

Gehrman et al. (2009) conducted a randomized, placebo-controlled trial in 41 nursing home patients with dementia. Patients were 68.3% female, average age of 82.9 years, and average time in the nursing home was 18.9 months. Patients were randomized into two groups, melatonin or placebo, and wore a wrist activity monitor. There were 3 days of baseline with no treatment, 10 days on melatonin (combined 8.5 mg immediate release and 1.5 mg extended release tablet) or placebo administered by nursing staff at 2200, then 5 days of follow-up. They hypothesized the melatonin formulation would provide a soporific effect from the immediate release and the extended release would mimic circadian rhythms. Melatonin and placebo tablets were made to look identical. The wrist device recorded activity and light exposure and was used to estimate: total sleep time, percent of time spent in bed, wake after sleep onset, number and duration of sleep bouts at night, for both night and day. "There were no significant differences in treatment effects of melatonin vs. placebo on any actigraphic sleep parameters or circadian rhythms parameters either during the day or night." One cause posed is that all patients in this study had advanced disease, to the point their neuroanatomical deterioration may have inhibited the pathways necessary for melatonin to be effective. The duration of treatment in this study was also quite short, at only 10 days.[12]

Conclusion/Recommendations

Several studies have been conducted to determine the effect of melatonin on sleep in patients with dementia. Melatonin is an appealing therapy choice due to its low rate of adverse events.[4,6,9] However, it has not been shown to improve sleep measurements significantly above placebo.[8,9,10,12] One study did demonstrate a statistically significant improvement in TSNT compared to placebo, however it had few patients, a short treatment duration, and risk of bias due to missing information on blinding and allocation.[7] Melatonin is unlikely to be harmful to patients, but it must be remembered that it is considered a supplement by the US Food and Drug Administration. It is therefore not regulated in the same way as prescription medications and potency of over-the-counter formulations may be inconsistent.[13]

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