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Treatment of Sleep Disturbance in Alzheimer's Dementia

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Introduction

Alzheimer's disease is the most common cause of dementia, affecting an estimated 5.3 million Americans, and is the sixth leading cause of death in the United States. The direct costs of caring for institutionalized patients and indirect costs of lost productivity are high. These costs are estimated at over 148 billion U.S. dollars annually (1).

Dementia is a clinical syndrome characterized by cognitive, neuropsychiatric, and functional impairments. Cognitive impairments include disturbances with memory, language, visuospatial function, perception, recognition, praxis, and the executive. Neuropsychiatric symptoms that occur in almost all dementia patients over the course of illness include disturbances in the domains of affect, perception, behavior, motivation, personality and sleep. Functional impairments include ...

Sleep disturbance is a common occurrence in dementia associated with Alzheimer's disease (AD) affecting up to 44% of patients in clinic and community-based samples(2)(3). Impairments in sleep present a background for unsupervised and potentially unsafe behaviors such as wandering and pacing, and place patients and others at risk of harm. In addition, disruption of the normal sleep process in dementia is associated with significant caregiver distress and often precipitates institutionalization into hospitals, assisted living or nursing homes contributing to the rising costs associated with dementia (4).

Significant strides in the study of sleep problems with advancing age have provided greater insights and understanding into the causes and patterns of sleep disturbance in the elderly in general and in patients with dementia specifically. The evidence for effective treatments of sleep impairments in dementia is, however, less encouraging. The aim of this systematic review was to define the current evidence-based behind treatment options for sleep disturbance in dementia.

Methods

Search Strategy and Study Selection

We conducted a comprehensive search of the scientific literature in MEDLINE and the Cochrane Central Register using Alzheimer's, dementia, and sleep disturbance as keywords. We limited the search to clinical trials, randomized controlled trials, case reports, comparative studies, controlled clinical trials and meta-analyses in humans. Our goal was to identify intervention studies which employed one or more approaches targeting sleep disturbances in dementia as either a primary or secondary measure. Studies with interventions targeting other aspects of the neuropsychiatric symptoms of dementia, but

which reported an effect on sleep as an outcome in their objective data were also included in our review.

Data Extraction

We initially grouped studies based on their intervention strategies. Within each intervention group, we separated different types of samples from where the participants were randomized or studied i.e. community based population, nursing home, inpatient etc. We also reviewed the types of sleep disturbances reported in the patients with dementia. We compared study designs and outcome measures within each intervention group and finally examined the reported effects of the intervention strategies employed on sleep disturbance.

Findings

Following our review, we found extensive literature available on the features of sleep disturbance and other neuropsychiatric symptoms associated with AD. We however found a limited number of well designed randomized controlled trials of treatment options aimed at improving sleep symptoms in AD. Several studies employed both pharmacological and non-pharmacological treatments of the neuropsychiatric symptoms of AD including sleep, but the majority did not include objective sleep assessments including PSG or actigraphy in their outcome measures. Some assessed for sleep using caregiver reports, sleep logs, rating scales and other neuropsychological instruments including the Neuropsychiatric Inventory. There were mixed results on the efficacy of treatments for insomnia in AD.

Non pharmacological interventions involving behavioral modification, stimulus control, and bright light therapy have shown a significant improvement in sleep symptoms (See Tables 6–7). Pharmacological agents have shown variability in their efficacy and safety based on the specific agents used including second generation antipsychotics, sedative-hypnotics, mood stabilizing anticonvulsants, circadian rhythm modulators, acetylcholinesterase inhibitors and alternative medicines (See Tables 1–5). Most of these agents were used to target primarily other behavioral symptoms associated with AD and for the most part, produce an effect based on their sedative properties. Although acetylcholinesterase inhibitors appear to alter sleep architecture by increasing REM sleep duration.

Discussion

Key features of disturbed sleep in dementia are sleep fragmentation with frequent nocturnal awakenings, and daytime somnolence and napping. There may be impairment with the sleep architecture in dementia including increased sleep latency, increased REM latency, less sleep efficiency, increased stage 1 NREM and decreased REM sleep (5) (6) (7) (8) (9). Other sleep disorders may be co-morbid with dementia including sleep related breathing disorders, sleep related movement disorders and essentially the spectrum of primary sleep disorders. These disorders should be treated based on recommended standards of care and appropriateness given the challenges of treating those with cognitive impairment. With regards to insomnia associated with AD, the interventions used include both pharmacological and non-pharmacological.

Non-pharmacological interventions

The non-pharmacological approaches involved decreasing the time spent in bed during the day, increased daily sunlight exposure, increased physical activity, structured bedtime routine, and decreased nighttime noise and light. In four studies, these measures showed a reduction in daytime sleepiness, a decrease in average duration and frequency of nocturnal awakenings, although one study found no significant change (10). The effects of bright light therapy (BLT) have been well studied. BLT applied at an intensity of greater than 2500 Lux

for half an hour or greater in the morning or all day shows a trend towards improved quality and duration of nocturnal sleep and reduced daytime sleepiness (11)(12)(13)(14)(15)(16)(17)(18)(19)(20). These interventions may be a good first line treatment strategy due to the relatively low risk involved with employing these interventions, in addition to the evidence in support of efficacy.

Pharmacological Interventions

There have been several medication trials of effectiveness in sleep disturbance associated with AD. The use of melatonin, a circadian rhythm modulator has shown mixed results. Other than a few individual studies reporting improved sleep duration (21) (22), melatonin has demonstrated no statistically significant differences between treatment groups or placebo. There is stronger evidence for efficacy of BLT in combination with melatonin when compared with use of melatonin alone, and in one study melatonin produced an adverse effect on mood unless combined with BLT (23). Ramelteon, acts on melatonin receptors and appears similar to melatonin in its mode of action. It is FDA approved for the treatment of insomnia in the general population and it promotes increased total sleep time in addition to shortening sleep latency. It is well tolerated and appears to lack significant adverse effects including excessive sedation and cognitive impairment that is often associated with other sedative agents (24). There is however limited data on its use in patients with AD.

On account of the importance of the effects of acetylcholine of sleep, it is pertinent to explore the possible efficacy of acetylcholinesterase inhibitors on both cognitive impairment and sleep disturbance. Although there appears to be an effect on sleep architecture, with increased REM duration using donepezil and rivastigmine (25), the overall impact of acetylcholinesterase inhibitors on sleep seems limited.

The evidence for sedative-hypnotics and second generation antipsychotics on sleep disturbance in dementia appears to be associated with sedation and attenuating the behavioral and other neuropsychiatric manifestations of dementia rather than a primary effect on sleep. However the rationale for using these agents long-term for sleep is limited given the associated risks and their adverse effect profiles including propensity for metabolic abnormalities. Sedative-hypnotic agents including benzodiazepines and non-benzodiazepines are used extensively. These agents promote sedation and also alter sleep architecture by increasing N2 Non-REM sleep. Although randomized controlled trials of their efficacy in treating insomnia in AD is limited, the non-benzodiazepines including zolpidem, zaleplon and eszopiclone appear to have a better safety profile than traditional benzodiazepines and cause less disorientation, memory loss and excess sedation with the associated risk of falls. Second generation antipsychotics are not indicated for use in patients with AD, given the risk of cardiovascular adverse events and sudden death.

There is limited evidence on the efficacy and safety of sedating antidepressants in the treatment of insomnia in AD. However, their antidepressant effects may be beneficial in cases of co-morbid affective and cognitive disturbance as insomnia may be a manifestation of either or both.

Conclusion

There are limits to the efficacy and safety of the current treatment strategies aimed at ameliorating insomnia in patients with AD. Nevertheless, several interventions have shown some modicum of efficacy and the non-pharmacological treatments expose patients to the least amount of risk in comparison to medication therapies. Further investigation and research is needed to improve the available armamentarium and subsequently improve

treatment outcomes, decrease distress experienced by both patients and care providers and increase overall level of function.

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Table 1

Melatonin

Study	Subjects	Design	Target symptom	Outcome measures	Results
(Brusco et al. 1999, 126–131)	14 patients with AD	Retrospective study for 22–35 months on 9mg of melatonin	Sleep	Structured interview and sleep logs	Improvement in sleep
(Cohen- Mansfield, Garfinkel, and Lipson 2000, 65– 76)	11 nursing home residents with mild to severe impairment	Open label clinical trial for 3 weeks on 3mg of melatonin	Agitation and sleep	Adapted nurses' ratings of sleep patterns questionnaire (NRSPQ)	Statistically significant change in daytime with less sleep. No significant change in evening and night-time sleep.
(Serfaty et al. 2002, 1120–1127)	44 patients with dementia from various samples	Randomized double blind cross over trial of slow release melatonin 6 mg	Sleep disturbance (agitated behavior and/or Wandering on at least two nights per week).	Wrist actigraphy and sleep diary	No significant effect
(Singer et al. 2003, 893–901)	157 patients from private homes and long-term care facilities	Randomized, placebo- controlled clinical trial of 2 dose of melatonin; 2.5mg slow release and 10mg and placebo	Insomnia	Wrist actigraphy	No statistical significance between treatment groups or in comparison to placebo
(Asayama et al. 2003, 334–341)	20 inpatients	Randomized, placebo- controlled clinical trial(9 control, 11 active)	Sleep, cognitive and noncognitive features of AD	ADAS MMSE CDR Actigraphy	Improved sleep duration only, ADAS cog and non cog also improved
(Gehrman et al. 2009, 166–169)	41 nursing home patients with probable AD	Randomized, double blind placebo- controlled clinical trial	Sleep and agitation	Wrist actigraphy	No significant difference between active and placebo groups

Table 2

Combined Bright Light Therapy and Melatonin

Study	Subjects	Design	Target symptom	Outcome measures	Results
(Dowling et al. 2008, 239-246)	50 Nursing home residents	Randomized clinical trial to BLT >=2500lux+ 5mg of melatonin and indoor light 150-200lux for 10 weeks	Circadian rhythm disruption	Actigraphy	Reduction in the duration of daytime sleep, increase in daytime activity, and improvement in day/night sleep ratio.
(Riemersma-van der Lek et al. 2008, 2642-2655)	189 residents of group care facility	Randomized placebo-control clinical trial to whole-day bright (+/- 1000 lux) or dim (+/- 300 lux) light and melatonin (2.5 mg) or placebo For average 15 months.	Sleep	MMSE CSDD Philadelphia Geriatric Centre Affect Rating Scale Multi Observational Scale for Elderly Subjects scale, Cohen-Mansfield Agitation Index NPI Actigraphy	Statistical Improvement in mood, reduced nocturnal restlessness and reduced sleep fragmentation Melatonin adversely affects mood unless combined with BLT

Table 3

Acetylcholinesterase inhibitors

Study	Subject sample	Study Design	Target symptoms	Outcome measures	Effect
(Markowitz et al. 2003, 602–606)	386 patients	3-month, multicenter, randomized, double-blind, placebo-controlled, flexible-dose trial of Galantamine.	Sleep	PSG NPI	No effect
(Mizuno et al. 2004, 660–665)	12 patients	Crossover intervention trial	Cognitive function and sleep	ADAS cog PSG	Significant increase in the % of REM sleep to total sleep time. Increased sleep efficiency and decreased sleep latency
(Ancoli-Israel et al. 2005, 240–245)	Sixty-three community-dwelling residents with mild to moderate AD	Randomized, 8-week, double-blind, parallel-group, multicenter, pilot comparison	sleep	Actigraphy PSG	No significant association with sleep. However, mean scores in all measures of sleep showed a tendency for minimal improvements in Galantamine-treated patients and minimal decrements in the donepezil-treated patients.
(Cooke et al. 2006, 503–511)	76 community residents	Cross sectional drug comparison of Rivastigmine, Galantamine and Donepezil	Sleep	MMSE PSG	Reduced stage 1 and increased stage 2 with Donepezil.
(Moraes et al. 2008, 677–683)	23 outpatient clinics visitors	Randomized clinical trial (11 treatment, 12 placebo)	Improved sleep and cognition	ADAS-cog PSG	AHI and oxygen saturation improved significantly after Donepezil treatment compared to baseline and placebo ($p < 0.05$). Rapid eye movement (REM) sleep duration increased after donepezil treatment ($p < 0.05$).

Table 4

Other drug therapies

Study	Subjects	Design	Target symptom	Outcome measures	Results
(Meguro et al. 2004, 61–67)	34 dementia care center residents	Randomized clinical trial with Risperidone	Behavioral and psychological symptoms of dementia.	BPSD and Visual observation	For Risperidone group, the mean daytime sleeping hours decreased by 1.2 hours, and mean nighttime sleeping hours increased by 3.8 hours.
{{}}	25 patients	7-week, open-label trial with Ziprasidone	Behavioral and psychological symptoms of dementia.	NPI	Improvement in all domains and sleep domain by 50%
(Rocca et al. 2007, 622–629)	58 outpatients	Retrospective chart review of treatments with Risperdal, Olanzapine, Quetiapine	Behavioral and psychological symptoms of dementia.	NPI	Improvement in all NPI domains

Table 5

Other treatments

Study	Subjects	Design	Target symptom	Outcome measures	Results
(Van Someren, Scherder, and Swaab 1998, 114–118)	19 nursing home residents with early AD	Randomized clinical trial with TENS	Circadian rhythm abnormalities	Actigraphy	Improvement in rest activity rhythm.
(Shinno et al. 2008, 881–885)	5 outpatient clinic visitors	Prospective interventional study with YI gan san (Japanese herb)	Behavioral and psychological symptoms of dementia.	MMSE, PSG and NPI	Improvement in sleep and symptom severity per NPI

Table 6

Behavioral and multi-faceted interventions

Study	Subjects	Design	Target symptom	Outcome measures	Results
(Alessi et al. 1999, 784–791)	29 Nursing home residents (15 intervention, 14 control). MMSE: 13.6+/-8.5, 13.1+/- 8.1	Randomized controlled trial. (Intervention: combined daytime physical activity and nighttime environmental program. Control: nighttime program alone).	Sleep and agitation	Cumulative Illness Rating Scale for Geriatrics (CIRS-G) Observational Sleep Assessment Index (OSAD), wrist actigraphy	Increase in nocturnal sleep and decrease in daytime time-in-bed.
(Alessi et al. 2005, 803–810)	118 Nursing home patients (58 in intervention and 50 in control) MMSE: 11.9+/-9.2, 10.6+/- 10.0	Randomized controlled trial (intervention: decreased daytime in-bed time, daily sunlight exposure, increased physical activity, structured bedtime routine, and decreased nighttime noise and light) for 5 days.	Sleep	wrist actigraphy (nighttime sleep) and structured behavioral observations	Significant decrease in daytime sleeping and decrease in average duration of nocturnal awakenings.
(McCurry et al. 2005, 793–802)	Thirty-six community-dwelling patients with AD (17 intervention, 19 control).	Randomized controlled trial. (Intervention: disease education, exercise and daytime light exposure with the use of a light box)	Sleep	Wrist actigraphy and Pittsburgh Sleep Quality Index	Significant reductions in number of nocturnal awakenings, total time awake at night.
(Ouslander et al. 2006, 38–47)	173 Nursing home patients. Immediate intervention (77 in the intervention group and 96 in the control group). Delayed intervention (83 in the delayed-intervention phase from initial control group).	Controlled clinical trial (daytime physical activity, evening bright light exposure, consistent bedtime routine, reduced sleep disruption and reduced nighttime noise.	Sleep	Wrist actigraphy	No significant findings between intervention and control groups
(Martin et al. 2007, 67–72)	100 Nursing home patients (54 intervention, 46 control). MMSE: 11.4+/-9.4, 10.4+/- 10.3	Randomized controlled trial (exposure to outdoor bright light, reduced daytime in-bed time, structured physical activity, bedtime routine, and reduced nighttime noise and light).	Sleep	Wrist actigraphy	Improved rest/activity rhythm with >active phase

Table 7

Bright Light Therapy

Study	Subjects	Design	Target symptom	Outcome measures	Results
(Satlin et al. 1992, 1028–1032)	10 hospital patients with AD	Open trial with 1 week of evening BLT	Sleep and agitation	Activity monitor and nursing observation	Improvement in sleep-wake cycle
(Mishima et al. 1994, 1–7)	14 patients with AD and 10 controls	Prospective 2 month study with 4 week morning BLT exposure	Sleep and behavior	Observation for sleep.	Improved nocturnal sleep and reduced daytime sleep
(Van Someren et al. 1997, 955–963)	22 patients with dementia	Open trial of indirect illumination for 4 weeks	sleep	Wrist actigraphy	Improved sleep-wake rhythm
(Koyama, Matsubara, and Nakano 1999, 227–229)	6 nursing home patients with dementia	Open trial of BLT	Sleep	Sleep log	Increased nocturnal sleep and increased daytime wakefulness
(Lyketsois et al. 1999, 520–525)	15 chronic care facility residents	Randomized controlled crossover trial	Agitation with sleep and secondary outcome	Sleep log Behave –AD CSDD	BLT showed a significant improvement in nocturnal sleep from a mean of 6.4 hours/night to 8.1 hours/night 4 weeks later ($p<0.05$).
(Ancoli-Israel et al. 2002, 282–289)	77 nursing home residents with severe dementia	Randomized clinical trial to evening bright light, morning bright light, evening dim red light, and daytime sleep restriction for 10 days	Sleep	Wrist actigraphy	No change in nocturnal sleep or daytime alertness. Increasing exposure to morning bright light improved circadian rhythm activity
(Ancoli-Israel et al. 2003, 22–36)	92 nursing home residents	Randomized clinical trial to morning BLT, morning red dim light and evening BLT	Sleep improvement	Actigraphy	Increased sleep periods.
(Fetveit, Skjerve, and Bjorvatn 2003, 520–526)	11 nursing home residents	Open trial	Sleep improvement	Actigraphy	Less nocturnal awakening and improved sleep efficiency
(Skjerve et al. 2004, 343–347)	10 institutionalized patients	Open clinical trial	Improvement in sleep and behavior	Actigraphy	Phase advance
(Dowling et al. 2005, 221–236)	46 residents in long-term care facilities	Randomized, placebo- controlled, clinical trial of BLT for 10 weeks	Nighttime sleep, and the rest-activity rhythm.	Wrist actigraphy	Some stabilization in those with aberrant rest activity rhythm
(Fetveit and Bjorvatn 2005, 420–423)	11 nursing home patients with dementia	Open trial with 2 weeks and BLT and 16 week post- treatment follow up	Daytime sleep	Wrist actigraphy and nursing staff observation	Significant reduction of daytime sleep ($P=0.042$)
(Sloane et al. 2007, 1524–1533)	66 patients in inpatient and residential care facility	Crossover intervention trial	Night time sleep	Actigraphy and observation.	Improved total night time sleep, phase advance and inconsistent daytime sleep.