Treatment options for sundowning in patients with dementia

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ABSTRACT

Objective. To review the evidence for the pharmacologic and non-pharmacologic management of sundowning in patients with dementia.
Methods. Databases were searched using the terms sundown, circadian, chronobiological, biological clock, elderly, aged, geriatric, and senior. Studies selected for inclusion assessed potential interventions for the treatment of sundowning or nocturnal agitation.
Results. A total of thirteen individual studies and two systematic reviews were evaluated. Study design and outcomes varied, but many measured sleep and nocturnal agitation. Non-pharmacologic interventions that may be of benefit include bright light therapy, music therapy, and aromatherapy. Pharmacologic therapies generally provided minimal benefit and were associated with safety concerns. Supportive evidence was found for the use of melatonin and antipsychotics. Evidence for antidepressants, donepezil, and dronabinol was weaker. Supportive evidence for the use of benzodiazepines was not found and thus cannot be recommended in elderly patients as they are more susceptible to their adverse effects.
Conclusion. The number of studies on the management of sundowning is limited and the quality of evidence supporting its treatment is weak. Non-pharmacologic interventions are first line due to safety. Pharmacologic agents are recommended as second line treatment options, in particular antipsychotics and melatonin.

KEYWORDS

Sundowning, treatment, dementia

INTRODUCTION

Reports indicate that up to 90% of nursing home residents with dementia will suffer from behavioral and psychological symptoms of dementia (BPSD).[1,2] The sundown syndrome or nocturnal delirium, commonly referred to as *sundowning*,[3] is a form of BPSD which can affect between 10% to 25% of institutionalized residents[4-6] and 66% of community dwelling patients with various types of dementias.[7] Sundowning (SD) refers to a clinically observed behavior characterized by worsening of agitation in the evening or nocturnal hours,[8,9] but it is not a formal psychiatric diagnosis in the Diagnostic and Statistical Manual of Mental Disorders. The lack of a consistent definition and criteria for diagnosis may contribute to the challenging and conflicting interpretation of research findings, particularly treatment outcomes. In addition, there is no specific discussion of SD in major treatment guidelines for dementia.[10,11]

In patients with Alzheimer disease (AD), SD has been found to be a predictor of functional decline, and caregiver stress.[7,12] In addition, patients exhibiting SD may be at increased risk of being exposed to benzodiazepines and antipsychotics, consequently experiencing the adverse effects associated with these agents, such as confusion, impaired cognition, or excessive sedation.[13] Several proposed mechanisms have been hypothesized to contribute to SD, including disruptions in circadian rhythm, sleep disturbances, and environmental factors.[3,14,15] A summary of the evidence for the treatment of SD, extracted from a literature search of Medline, Embase, International Pharmaceutical Abstracts and Scopus from inception through February 2014, is provided. A review of BPSD is beyond the scope of this article and has previously been published.[16]

A total of twelve studies and cases and four systematic reviews (SRs) were reviewed.

PHARMACOLOGIC THERAPY

Melatonin

Melatonin is a natural hormone secreted by the pineal gland in response to darkness, and is controlled by the suprachiasmatic nucleus (SCN) located in the hypothalamus. Patients with dementia and disturbed sleep-wake cycle are reported to have decreased or dysregulated melatonin levels.[17] Abnormalities in the SCN in this patient population are possibly related to the development of SD behavior. Melatonin affects sleep regulation, immune function, mood and behavior, and has antioxidant actions.[18,19] Evidence for melatonin use in dementia has been studied in several double-blind randomized controlled trials (RCTs). De Jonghe *et al.* have published a SR that includes four RCTs comparing melatonin to placebo for the treatment of SD and aggressive behavior.[20] Melatonin dosages varied from 1.5 mg to 10 mg, in a variety of sustained or immediate release formulations. The dosing times in the studies included bedtime, one-hour before bedtime,[21,22] at 8:30 p.m.,[23] or 10:00 p.m.[24] Dosing times were selected so as to not advance the sleep-wake cycle and to align exogenous melatonin administration with estimated endogenous secretion. Treatment duration ranged from 10 days to 8 weeks. These studies were predominantly performed in nursing homes and provided mixed results, with only one RCT indicating improvement with melatonin therapy, as measured by the Alzheimer's Disease Assessment Scale noncognitive subscale (ADAS-NONCOG) that assesses behavior items such as increased motor activity, delusions, and pacing. Adverse effects in all the reviewed studies were similar to placebo with the exception of one study that found a decreased severity of adverse effects in the melatonin group.[21] Melatonin given alone has demonstrated worsened withdrawn behavior and affect scores, but this effect was attenuated when administered with bright light therapy.[22] A recent SR was published only in abstract form reviewed 17 studies of melatonin, with doses between 3-10 mg for a duration of 10 days to 35 months. They found that the longest studies showed the most improvement, with a decrease in agitation behaviors. They recommend a trial of melatonin at a dose of 6 mg with at least 4-month follow-up to improve sundowning.[25] Since melatonin products may not be subject to prescription regulations, depending on jurisdiction, health care professionals should use a product that has been licensed or meets acceptable standards for pharmaceutical integrity.

Antipsychotics

Antipsychotics (APs) are commonly prescribed for agitation and psychosis in patients with dementia, and are suggested treatment options in guidelines on the treatment of dementia.[10,11,26] APs have shown modest effectiveness in short-term trials for aggression in patients with dementia.[27, 28] Evidence of severe adverse effects include increased risk of death, cerebrovascular accidents, and myocardial infarction.[29-32] The concerns of potential harm of APs in patients with dementia resulted in a U.S. FDA black box warning in 2005.[33] Meguro ***et al.*** in an open-label, uncontrolled study, examined a group of wandering patients (n=34) with AD in a nursing home.[34] Wandering patients had to show behavior consistent with leaving their rooms and becoming lost in the home as well

as having positive scores on the Behavioral Pathology in Alzheimer's Disease (BEHAVE-AD) Activity Disturbances, Aggressiveness, or Diurnal Rhythm Disturbance subscales. The wanderers were then randomized to risperidone 1 mg/day or no risperidone for one month. Mean daytime sleep hours decreased by 1.2 hours, and nighttime sleeping hours increased by 3.8 hours in the risperidone group as compared to the no risperidone group (***P***< 0.05). There were no reported adverse events. The response to risperidone is likely biased given the uncontrolled and open nature of this study. A double-blind, placebo-controlled, crossover study, assessed a mean chlorpromazine dosage of 137 mg/day in fifty female patients with dementia.[35] Patients received placebo or chlorpromazine for three weeks then were crossed over to the other group. Ward nurses assessed behaviors. A statistically significant improvement in agitation, over-activity, resistiveness, and noisiness was noted in the chlorpromazine group. Insomnia was assessed, and found to be not significant, suggesting no improvement in SD. Gotestam *et al.* performed an eight-week, double-blind trial of haloperidol (0.5 to 1 mg/day) and zuclopenthixol (5 to 10 mg/day) in 47 patients with dementia.[36] Sleep was assessed in two of the rating scales, both of which are rarely used today. The haloperidol group showed significantly better ratings for sleep on both scales, whereas the zuclopenthixol group significantly improved sleep ratings on one of the rating scales. During the 8-week study, seven patients did not complete the study (three deaths, two discontinued the study drug in the first 2 weeks due to severe adverse effects, and two had intercurrent illness). Because of potential adverse effects, and their limited evidence with marginal benefit, antipsychotics therapy should undergo a careful risk versus benefit assessment, and should be considered after non-pharmacologic therapies.

Acetylcholinesterase Inhibitors

Acetylcholinesterase inhibitors (ACIs) are commonly prescribed for patients with dementia to slow the progression of cognitive decline. There is some evidence from animal studies that cholinergic activity may impact the circadian rhythm.[37,38] No studies could be found regarding ACIs and SD. However, a case report describes improvement in SD in a 71-year-old man, clinically diagnosed with probable Lewy body dementia, who underwent a seven day washout of his current psychotropic drugs and was started on donepezil 5 mg daily.[39] During the washout period, some improvement was noted in his parkinsonism, but no changes in agitation. Improvement in a number of behavioral rating scales was noted at 10 days and up to 14 weeks of treatment. These results are preliminary as the behavioral problems may not have been due to SD, but may have been a result of discontinuing psychotropic medications, which may have been contributing to sedation. There is also contradictory evidence indicating that ACIs may worsen nocturnal agitation by worsening insomnia.[40,41]

Antidepressants

Using the sedative properties of antidepressants has been suggested for the management of sleep disturbances. Tariot *et al.* performed a trial in seven patients of tranylcypromine at a dose of 10 to 40 mg daily (mean tolerated dose 16 mg) over a period of four weeks in patients with dementia but without a diagnosis of major depressive disorder. There was no improvement in sleep as measured by nursing staff, who observed subjects hourly. In addition, all patients experienced orthostatic hypotension.[42] As pointed out by the authors, the study limitations included an inability to guarantee blind assessment of patients and the subjective assessment of sleep by nursing staff.

Benzodiazepines

No studies could be found evaluating benzodiazepines for SD in patients with dementia. These medications should be avoided as they can cause confusion and increase the risk of falls in the elderly.[3]

Cannabinoids

Dronabinol (delta-9-tetrahydrocannabinol) is a CB_1 receptor agonist. CB_1 receptors have been shown to mediate important brain functions, such as nociception, cognition, motor activity, and mood. A preliminary open-label study of six inpatients with dementia and nighttime agitation studied the effects of dronabinol 2.5 mg given at 7 p.m. daily for two weeks on the primary nocturnal motor activity measured by actigraphy.[43] Secondary outcome measures were NPI total score and subscore. Patients were continued on regular psychiatric medications and were allowed to take additional sedatives if required. All subjects experienced a statistically significant reduction in nocturnal motor activity at two weeks. A randomized, placebo-controlled, double-blind crossover trial studied dronabinol 2.5 mg PO given at 7 p.m. versus placebo in two male patients with probable Alzheimer's dementia.[44] The trial duration was 4 weeks in length. Agitation and circadian rhythm disturbances were continuously assessed using wrist actigraphy. All medications were left unchanged. However, lorazepam or pipamperone were permitted and used sporadically for acute disturbances or for sleep. Both patients experienced declines in nocturnal

activity and strengthened circadian rhythms. This effect lasted up to three weeks for one of the patients, and one week for the other patient. No severe adverse effects occurred during the trial. Given the small sample sizes and the fact that dronabinol may have negative effects on elderly patient's cognition and function that was not assessed in these studies, the current evidence does not support its use.

NON-PHARMACOLOGIC THERAPY

Physical Activity/Socialization

Daytime physical activity has been associated with better rest-activity rhythm.[45] Increasing daytime physical activity in patients with dementia may improve sleep. Nursing home patients with dementia, age > 70 years old, mild-moderate dementia and able to walk with or without a walker were randomly assigned to an experimental or control group.[46] The experimental group walked for 30 minutes at a self-selected speed with a student, while the control group received a social visit by a student, both of which took place inside the nursing home. Interventions occurred 5 times per week over 6 weeks duration. There were no differences noted in sleep disturbances. No adverse effects were reported.

Music Therapy

Music therapy (MT) includes the use of musical experiences and a trained music therapist to create relationships with patients with the goal of improving health.[47] A SR found that music therapy did show an improvement in sundowning, but this review has only been published in abstract form to date.[25] Two small trials of 56 and 45 patients with dementia were conducted. Patients with dementia residing in nursing homes received MT provided by trained music therapists. The MT groups received up to 12 sessions (30 minutes per session) and the control group underwent standard care (e.g., educational or entertainment activities). In the first study there was a statistically significant improvement in NPI scores in the MT group. Statistically significant improvements in the assessed NPI behaviors included anxiety, agitation, irritability and nighttime behavior disturbances.[48] In the second study, there was a statistically significant improvement in disruptiveness, but not agitation as measure by the CMAI.[49] No adverse effects were reported. None of these studies were blinded at any level. The implementation of MT may be challenging as it is dependent on the availability of trained music therapists.

Bright Light Therapy

Bright light therapy (BLT) refers to visible light that is usually administered from a light box, or alternatively dawn-dusk simulation, and can vary in intensity, duration, and timing.[50] It is thought that degenerative changes in the SCN, which is worse in people with dementia, contribute to circadian rhythm disturbances.[51] It is hypothesized, based on animal studies, that BLT may improve age-associated disturbances in circadian sleep-wake rhythm, by positively stimulating SCN neurons. A 2009 SR has examined the benefits of light therapy for dementia, and discusses the impact on measures of behavioral disturbances or psychiatric disturbances.[52] Five RCT assessed behavioral disturbances using a variety of scales. BLT > 2500 lux from a light box, administered daily for a mean of 92 minutes had no effect on behavioral disturbances in the evening assessments following 10 days of treatment,[53] or after one year of treatment.[22] The combination of overhead light and melatonin significantly improved scores on the CMAI over a period of 3.5 years.[24] In this study no serious adverse effects were noted. The most common adverse events were drowsiness and irritability. A recent SR published in abstract only, reviewed 12 studies on bright light therapy, and found that exposure in the morning and afternoon improved sundowning syndrome.[2] A single center RCT of 48 nursing home patients with dementia, randomized participants to daily BLT (light box with 10000 lux) or standard fluorescent tube light at 100 lux for two hours between 10 a.m. and noon for two weeks. Ninety percent of patients could tolerate light exposure for a minimum of ninety minutes per day. There was no difference on rating scales between groups.[54] BLT appears to be well tolerated but has uncertain benefit for improving agitation. The optimal dose, administration method and whether it should be used in conjunction with melatonin therapy remains unclear.

Aromatherapy

Aromatherapy uses essential oils to benefit a person's well-being. Lavender oil's (*Lavandula angustifolia)* proposed therapeutic mechanism is due to its sedative effects following inhalation.[55] An updated Cochrane review has examined the evidence for aromatherapy in dementia, of studies using a variety of compounds (e.g, 10% Melissa essential oil & base oil; cypress, lime, and eucalyptus essential oils in lotion; and lavender oil).[56] Of the four included RCTs, two studies peripherally address SD behavior, although this is not explicitly stated. A single blind RCT of 21 inpatients with dementia compared 3 interventions' impact on behavior disturbances: (1) lavender oil applied topically through massage, (2) lavender in a diffuser plus conversation, and (3) massage

only.[57] Treatments were administered twice weekly, and participants continued on their regular medications. Behaviors were recorded using a video camera during 4 one-hour periods. There was no overall statistical difference between treatment groups. However, aromatherapy plus massage showed a statistically significant reduction in motor behaviors between the hours of 3-4 p.m., which the authors suggest, could represent a reduction in agitation.

One additional study of note, the data of which were not available to be included in the Cochrane meta-analysis, showed benefit in nighttime behaviors with aromatherapy. Lin *et al.* conducted a cross-over randomized study of 70 residents with dementia living in nursing homes.[58] The effects of lavender oil as compared with sunflower oil (placebo) aromatized for one-hour overnight were assessed using the Chinese versions of the CMAI, and NPI. Participants were randomly assigned to a therapy for 3 weeks, then received a wash out period of 2 weeks, then followed by the other therapy for three weeks. The authors reported a statistically significant decrease in nighttime behaviors. No dropouts, adverse effects or changes in psychotropic medications occurred during the study. However, it has also been reported that aromatized lavender oil worsened agitation in one patient with severe dementia in a placebo-controlled trial.[59] In view of these controversial findings, a consultation with a qualified aromatherapist may be warranted.[11]

CONCLUSION

Further studies on the management of SD are required to inform clinicians about optimal treatments. Studies should focus on the time of day of behaviors, and the response to therapies at specific hours.[60] Studies should also be longer than a few weeks, and should be optimally designed with randomization and a control group. Based on the limited and conflicting evidence, it is difficult to directly compare therapies for the management of SD. There is limited evidence supporting non-pharmacologic interventions. Clinicians may want to trial MT or BLT. Further research is required to determine if aromatherapy or physical activity result in reduced SD. Studies involving non-pharmacologic therapy show minimal safety concerns, but the duration of treatment, cost, and impact require further research.

Pharmacologic therapy is associated with safety concerns, but these are minimal in the studies with melatonin. In addition, melatonin has modest evidence and could be prescribed to spare patients of the potential adverse effects of APs or who have not responded to other therapies. Other drug therapies such as dronabinol may be effective but further long-term safety data are required. APs have some evidence to support their use, but safety concerns generally outweigh the benefits for this class of medications.

Given the evidence, we suggest clinicians consider therapies least likely to cause harm and consider all the potential treatment options when selecting therapy for the treatment of SD in patients with dementia.

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