

“SUNDOWNING” AND OTHER TEMPORALLY ASSOCIATED AGITATION STATES IN DEMENTIA PATIENTS

David Bachman¹ and Peter Rabins²

¹*Department of Neurosciences, Medical University of South Carolina, Charleston, South Carolina 29425; email: bachmadl@musc.edu*

²*Department of Psychiatry and Behavioral Sciences, Johns Hopkins School of Medicine, Baltimore, Maryland 21287; email: pvrabins@jhmi.edu*

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■ **Abstract** The behavioral and neuropsychiatric symptoms of dementia and Alzheimer's disease have become an increasingly important focus of clinical research. These symptoms also pose a tremendous challenge to families and caregivers. The late afternoon/evening exacerbation of behavioral symptoms in dementia has been recognized by clinicians for >60 years. Researchers have utilized a variety of increasingly sophisticated tools to examine the circadian, hormonal, physiological, and epidemiological correlations with sundowning behavior. Although treatment remains largely empirical, an improved understanding of the complex relationships that drive sundowning behavior should lead to more effective therapies in the future.

DEFINITIONAL ISSUES

The clinical phenomenon of disruptive behavior worsening in the late afternoon or evening among dementia patients or elderly institutionalized patients has been reported in the medical literature for more than 60 years (1). Terms used to describe this phenomenon include sundowning, sundowning syndrome, and nocturnal delirium (2). Typical research definitions of sundowning have included “delirium and agitation” within one hour of darkness (1) or “the appearance or exacerbation of behavioral disturbances associated with the afternoon and/or evening hours” (3). The inclusion of the entire night under the banner of “sundowning” by some clinicians has broadened the scope of this disorder to include all disruptive sleep disorders among dementia patients. For instance, the American Sleep Disorders Association considers sundowning to include “the sleep disturbance that is characterized by nocturnal wandering and confusion” (4). This failure to arrive at a consensus definition has led Yesavage et al. (5) to refer to sundowning as an “ill-defined behavioral syndrome subsuming many different kinds of behavior. . .” (p 134). Bliwise (6) has also recently critiqued the concept of sundowning. He hypothesizes

that sundowning is a composite of behaviors, including travel behavior, loud vocalizations, wandering, maladaptive behaviors, and physical aggression. Each of these behaviors may have its own unique temporal profile, but with all of them clustering in the late afternoon or early evening.

Despite the general inclusion of sundowning in neurologic, psychiatric, and nursing textbooks as a legitimate clinical condition, the research literature is divided on the existence and/or prevalence of this syndrome. This is due, at least in part, to the variations in definition referred to above. Other differences in definition further contribute to contradictory research findings. Some studies have included cognitively intact elderly institutionalized individuals (2, 7), but most restrict the definition to individuals with identified brain disease. Studies also vary by setting, a likely contributor to the variation in reported prevalence rates and precipitants. Another source of variation is the instruments and methods used to collect data. These include caregiver questionnaires (8–10), measures of “as necessary” medication use (11), retrospective chart review (12), and wrist-worn computer devices that measure restlessness as reflected in increased motor activity (3, 13).

Some investigators have found no clinical evidence for the existence of sundowning. For example, Bliwise & Lee (14) found minimal evidence that agitation was worse nocturnally or near sunset in a systematic study of behavioral observations of nursing home residents. They concluded that disruptive behaviors occur throughout the day but have greater impact on staff in the evening. Studies using caregiver questionnaires have likewise found little evidence for increased behavioral disruption in the evening (8–10). Martin et al. (15), using computerized models, found that peak agitation was actually in mid-afternoon.

However, other investigators have identified a tendency for some patients to exhibit a peak in disruptive behaviors during the later afternoon or evening hours, a pattern consistent with the concept of sundowning. Even though these investigators reported variability in the peak time of behavioral disruption, they all described maximal behavioral disruption some time in the later afternoon or evening (1, 7, 16–22). Taken together, the evidence suggests that some patients with dementia do show a diurnal pattern in agitated behavior with worsening in the afternoon or early evening. This pattern supports the existence of a sundowning-type phenomenon in some individuals.

PREVALENCE

Reported prevalence rates for sundowning cover a wide range. Rates among patients with Alzheimer’s disease (AD) or dementia range from 2.4% to 66% (15, 23, 24), whereas prevalence in a general nursing home population has been reported to be 13% (7). Rates of sundowning among patients with severe dementia are particularly high (3). The highest prevalence rate for sundowning (66%) has been reported among dementia patients living at home (24). However, because the studies

of prevalence in home and institutional environments use different methods and do not control for disease characteristics, valid comparative data are unavailable.

It is unknown whether rates of sundowning vary by subtype of dementia because most studies have been carried out among patients with AD or among patients described as demented but without a specific diagnosis. Differential rates are plausible, however, because early AD is characterized by decreased time in stage 3 and 4 non-REM sleep and increased nighttime wakefulness. Further, as the disease progresses, REM sleep is progressively lost (25). Although the sleep changes in AD are significant, evidence suggests that disruption of sleep is actually worse in Parkinson's disease (25, 26) and that disruptive nocturnal behaviors are more common among Parkinson disease patients than AD patients (26). Patients with Lewy body disease also have more overall sleep disturbance, more movements while asleep, and more abnormal daytime sleepiness than patients with AD (27). On the other hand, patients with subcortical infarcts and frontotemporal dementia (28) exhibit less disruption of nighttime sleep (26, 29). Although disruption of nighttime sleep does not necessarily equate increased risk of sundowning, these studies suggest that sundowning is not simply a nonspecific symptom of dementia but may result from specific pathophysiologic abnormalities that interfere with normal circadian and behavioral regulation.

ETIOLOGY

A number of theories have been proposed to explain the clinical phenomenon of sundowning. Unmet physical or psychological needs at night are one plausible cause of nighttime worsening of behavior. For instance, Cohen-Mansfield et al. (30) suggested that screaming at night may arise as a response to social isolation. Alternatively, sundowning may represent a maladaptive response to fatigue (31). The high prevalence of wandering or restlessness in sundowning has suggested to some that it represents an unmet need that is nonspecific (7, 12).

The plausibility of sleep disorder as a contributor to nighttime worsening of behavior is supported by the increased risk of sleep disorders, including sleep apnea, in patients with AD (6, 25). It has been suggested that sleep disturbance in AD may be multifactorial and include sleep disordered breathing, disrupted chronobiology, and increased daytime napping (6). Patients with Parkinson's disease and Lewy body disease also have been found to have significantly disturbed nighttime sleep (27, 29). However, this hypothesis is undermined by the finding (32) that sleep disordered breathing in AD is associated with daytime behavior disorder but not evening or night agitation, and by the finding (3) that sundowning and sleep disturbance are unrelated. Thus, the contribution of disturbed nighttime sleep to disruptive daytime or early evening behavior disorder in dementia is yet to be clarified.

More recent studies have focused on the potential role of disordered circadian rhythm as an important contributing factor to sundowning in dementia. There is

evidence of the existence of a circadian rhythm for agitated behaviors in many AD patients that peaks late in the day, although the precise time, relationship to true sunset, relationship to sleep, and other disease characteristics are unclear (5, 7, 33). Compared to healthy elderly, severe AD patients do have a greater percentage of total daily motor activity at night, a less strictly circadian motor activity rhythm, and later acrophases (time of peak values) of both motor activity and body temperature rhythms (13). However, a companion study by the same group found that patients with severe dementia had less diurnal motor activity and a higher percentage of nocturnal activity than controls. In addition, sundowning patients tended to have a more chaotic temperature rhythm that had little relationship to the motor activity record. These changes are consistent with the existence of circadian rhythm abnormalities that progressively worsen with cognitive and functional deterioration (34).

One study has found that patients with dementia are exposed to inadequate amounts of light during the day (35), an environmental factor that could exacerbate underlying circadian rhythm disturbances. It is this theory that forms the rationale for light therapy in dementia (discussed below).

The suprachiasmatic nucleus (SCN) of the hypothalamus plays a central role in circadian rhythm control in mammals by producing an alerting signal during normal wake time and a sleep-inducing signal during normal sleep time (36). This is largely responsible for sleep and wake pressures (37). In view of the significant changes in sleep and wake architecture described above, it is not surprising that investigators have found evidence of pathologic changes in the SCN at autopsy in patients with AD (38, 39). Evidence for a relationship between AD pathology and circadian rhythm disturbance has recently been strengthened by studies in transgenic AD mouse models. Aged PDAPP transgenic mice exhibit pronounced sleep deficits in REM and non-REM sleep as well as deficits in circadian distribution of sleep-wake states (40). These mice also demonstrate increased amounts of wakefulness and decreased amounts of REM and non-REM sleep similar to sleep architecture changes described in patients with AD. Interestingly, these mouse models exhibit these changes in sleep architecture prior to the deposition of beta amyloid plaques, a finding that implicates abnormal cholinergic function as a plausible cause. Another group of investigators has reported that the APP23 transgenic mouse model of AD demonstrates increased motor activity during the second half of the active phase, especially at ages 6 months and 12 months; this suggests a possible analogy to human sundowning behavior (41, 42).

Associated Adverse Outcomes

With a prevalence of sundowning as high as 66% among patients living at home, sundowning behavior and fragmented sleep may increase caregiver stress (24). Not surprisingly, caregiver stress and burnout may increase the likelihood of institutionalization for the patient (43, 44).

Potential Environmental Contributors

The term sundowning implies that diminishing or diminished light/illumination is an etiology of temporally associated agitation, but evidence for this is modest (35). If diminishing light is a risk factor or generating factor for agitation, its effects are probably magnified by the high prevalence of visual and hearing impairments in older individuals, and exacerbated even further by the dementia-associated impairments in vision (agnosia) and language (aphasia) that limit the ability to decipher what is in the environment. Thus, one theoretical contributor to early evening agitation is the natural loss of light magnified by sensory and cognitive impairments. However, data demonstrating such relationships have not been reported. Nevertheless, as we discuss below, this possibility has shaped the environmental interventions that are recommended.

Another potential environmental contributor to early evening agitation is the lower number of evening- and night-shift staff in institutions, or lessened availability of home caregivers at that time of day. This could result in unmet care needs (e.g., less frequent toileting or changing of continence materials), which would increase agitation and restlessness. Low caregiver availability would also diminish the amount of structured stimulation for patients, which would lead to boredom and a consequent increase in random activity or agitation. In this mechanism, it is the loss of effective environmental stimulation that results in the temporally associated behavior disorder. Both lower number of staff for physical care and diminished caregiver stimulation are examples of unmet needs.

Other Potential Etiologic Factors

Besides changes in activity level specifically linked to circadian rhythms, we believe other etiologies are plausible in some cases. For example, afternoon fatigue might result from high levels of activity earlier in the day. The resulting afternoon or evening fatigue would then lead to increased irritability and agitation.

Also, diurnal mood variation, a pattern of mood variability in which a person's worst mood and best mood vary in a predictable fashion, is a symptom of major depression and might explain some cases of sundowning. In major depression, mood is most commonly worse in the morning and better in the early evening, but the opposite pattern occurs as well. This could lead to a temporally recurring change in activity and agitation that indicates the presence of major depression. For this to be the explanatory mechanism, other symptoms of major depression—such as early morning awakening, diminished appetite, sad appearance, and self-reported low mood—should also be present. However, these signs and symptoms can be difficult to elicit in persons with dementia; their identification often requires careful questioning by the clinician.

Specific interactions with other individuals might also be a trigger for temporally associated agitation. For example, individuals with dementia might become upset by visitors who appear strange to them or by visitors who are seeing other residents

of the facility. Because visiting hours are time-regulated, this reactive distress might appear to have a temporal association.

Medical factors can also contribute to temporally associated agitation. Some diseases in which pain is prominent have a predictable variation in pain intensity. For example, arthritis is often worse early in the morning. Agitation can be a response to temporal variation in pain. It can also be a side effect of medication or the wearing-off of medication. Some drugs induce restlessness or akathisia (e.g., antipsychotics); some worsen cognition (e.g., through anticholinergic side effects) or movement abnormalities, such as dyskinesias secondary to on-off phenomena in Parkinson's disease.

TREATMENT

It is not our intent to provide a comprehensive review of the assessment and treatment of sleep disorders in general. However, some similar principles apply in the approach to sundowning. Factors contributing to sleep problems in the elderly may include inadequate exposure to sunlight, pain due to arthritis and malignancy, organ system disorders (e.g., congestive heart failure, angina, asthma, chronic obstructive pulmonary disease, gastroesophageal reflux, incontinence, benign prostatic hypertrophy), depression and anxiety, and medication effects. For all of these reasons, a careful history and physical examination is indicated prior to the initiation of pharmacotherapy in the treatment of sundowning.

Environmental Treatments

Because it has been difficult to empirically establish the validity of temporally associated agitation syndromes, there are very few intervention trials that support the efficacy of specific therapies. However, the clinical observation of temporally associated agitation has led to the development of recommended intervention strategies. There appears to be some consensus on these strategies despite the weakness of the data supporting their efficacy (45).

STRUCTURED ACTIVITY Many observers (e.g., 45, 47) suggest that engaging individuals in planned ongoing activity diminishes the likelihood of agitation. It follows that if there is a temporal pattern to agitation then scheduling the activities at the usual times of agitation, or at times prior to its emergence, might well diminish it. These activities should be designed so that patients can engage in them despite their impairments.

REDIRECTION, REASSURANCE, AND DISTRACTION Interacting with an agitated individual in the hope of decreasing the agitation is a therapeutic skill that can be learned. Reassuring patients that the caregiver is in control of the situation, redirecting their attention away from stressing or upsetting events, and then engaging

them in another activity seems to help. If these interventions diminish agitation once it has occurred, it is likely that their inclusion in a structured activity program will help prevent episodes of agitation.

Several of the plausible environmental contributors to temporally associated agitation can be addressed. Providing adequate light, making sure that noise levels are not overwhelming or distracting, minimizing noise from visitors, and minimizing unnecessary noise (e.g., loud speakers, banging of dishes, loud staff conversation) are easy measures to initiate and might diminish agitation (45, 47).

MEETING PHYSICAL NEEDS If agitation is increased by unattended incontinence, constipation, undertreated pain, or some other physical need, it is obvious that developing a treatment plan will help diminish agitation. If exacerbation of pain or on-off dyskinesias are contributing, alterations in medication schedule or switching to a longer-acting medication might diminish the symptoms.

LIGHT THERAPY The one environmental modification that has been subjected to empirical study is light therapy. The Cochrane meta-analysis (46), a review of the published literature on this treatment for dementia, did not demonstrate the effectiveness of specific light therapy.

Pharmacologic Treatments

HYPNOTICS/BENZODIAZEPINES In general, benzodiazepines are not considered a good choice to treat sundowning. They are reported to cause a paradoxical increase in disinhibition and confusion in some individuals and are associated with an increased risk of falls in the elderly (47). One hypnotic that may have some benefit in the treatment of sundowning is zolpidem. A single double-blind study of zolpidem at 20 mg/night demonstrated improved sleep on nurses' ratings (48). There are also case reports of zolpidem improving wandering and sleep in patients with dementia and Parkinson's disease (49, 50). However, zolpidem may increase the risk of falls (51) and induce agitation (52).

ANTIPSYCHOTIC NEUROLEPTICS Antipsychotics are probably the class of medications most widely used to treat symptoms of sundowning. When sample case vignettes were presented to 145 family physicians and 14 neuropsychiatrists in Lower Saxony, Germany, >40% considered neuroleptics to be the drugs of choice (53). Antipsychotics exhibit modest effects on agitation in severe dementia in general with a 15%–20% effect size over placebo. About 20%–30% of patients may experience some sedation, which may be useful in facilitating sleep (54). One study supports the use of antipsychotics to treat sleep disturbances and nighttime maladaptive behaviors in nursing home residents with severe dementia even when there is only a modest effect on daytime agitation. Ruth et al. (55) reported that global behavioral scores remained stable or improved in most patients after discontinuation of antipsychotic medications for four weeks, but actigraphy revealed

decreased sleep efficiency and increased night activity with increased restlessness. In general, there is limited information available on the use of antipsychotics in severe dementia.

Atypical antipsychotics, as a class, have a better side-effect profile than older typical antipsychotics (47). Risperidone, an agent usually included in the class, has been shown to decrease aggressiveness and wandering and increase nighttime sleeping hours in one study (56) and to reduce nocturnal agitation in nursing home patients in another (57). Because comparative data are minimal, it is unknown if risperidone offers any advantage over any other atypical antipsychotics. However, a recent FDA review has resulted in a “black box” warning because of associations between the use of these drugs in subjects with dementia and increased mortality. Therefore, these agents should be prescribed cautiously for patients with dementia.

MELATONIN As noted above, circadian rhythm abnormalities in dementia, perhaps related to sundowning behavior, have been linked to abnormalities in the SCN. Rhythmic nocturnal melatonin secretion is directly generated by the circadian clock located in the SCN (58). Because several studies suggest that melatonin is physiologically either low or dysregulated in AD (59–64), melatonin administration has been proposed as a treatment for circadian-related behavioral problems such as sundowning.

In a MEDLINE search from 1990 to 2000, Olde Rikker & Rigaud (65) found only 12 studies with empirical treatment data for melatonin in the elderly. The 6 open-label or retrospective case studies demonstrated a trend toward improved sleep quality and decreased sundowning. Among the 6 double-blind controlled trials with objective measurements of sleep quality, 4 studies demonstrated decreased sleep latency and 3 studies found improvement in measures of sleep quality (sleep efficiency, total sleep time, and wake time during sleep) but no improvement in subjective sleep quality.

More recent studies of melatonin use specifically in dementia suggest that melatonin improves sleep quality, reduces sundowning behavior, decreases sleep latency, and decreases nocturnal activity (58, 66–68). However, using actigraphic measurements, Singer et al. (69) found no benefit of two doses of melatonin to treat insomnia in a double-blind placebo-controlled study of 36 centers with 156 nursing home subjects.

ACETYLCHOLINESTERASE INHIBITORS (AChIs) AChIs are the standard of care in the treatment of mild to moderate AD in the United States, but there is disagreement about their benefit in moderate to severe disease and in the treatment of behavioral symptoms such as sundowning. Because AChIs can increase vivid dreaming and nightmares, they might plausibly worsen insomnia or nocturnal agitation in patients with dementia (70, 71).

Rates of insomnia from donepezil, the most widely prescribed AChI in the United States, are reported as high as 10% (72). Insomnia rates may be lower with galantamine and rivastigmine (73, 74). Postmarketing surveillance data found that

sedative-hypnotic use in patients with AD on donepezil (9.78%) was twice that of AD patients not on donepezil (3.93%) (75), but the adverse effects on sleep reported with donepezil can be ameliorated simply by lengthening the time period before increasing the dose or by switching to morning dosing (76). In one study, once-a-day morning dosing with donepezil increased sleep efficiency and shortened sleep latency (77).

Data available on other AChIs and sundowning behavior are limited. Some investigators have reported decreased dreaming behavior in Lewy body disease patients on rivastigmine (78, 79). Data from three randomized double-blind trials of galantamine versus placebo in AD found no increase in insomnia/sleep problems and nightmares/dreams but no decrease in sleep problems (80). A subsample of subjects was studied using the Pittsburg Sleep Quality Index; no differences were found in sleep measures between the galantamine and placebo (81).

NMDA (N-METHYL D-ASPARTIC ACID) ANTAGONISTS Memantine has recently been approved in the United States to treat moderate to severe AD either as monotherapy or in combination with AChI therapy (82), but no data are available on the treatment of sundowning-like behaviors.

FUTURE DIRECTIONS

Many issues remain to be explored. First, questions about the validity of the construct of “sundowning” necessitate further attention to its definition, and to the demonstration that a behavioral phenotype characterized by agitation at a specific time of the day can be reliably identified. Once a behavioral syndrome is documented (i.e., validated), further work on the pathophysiology and pathogenesis of the behavior can be carried out. In all likelihood, “temporally related agitation” will have multiple etiologies. If this is the case, a variety of therapeutic interventions will need to be assessed, and the efficacy of any intervention will require accurate matching of treatment with etiology. In addition, research into prevention might well decrease the incidence of the behavior and/or its severity.

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