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Review Article

Effects of Light Treatment on Sleep, Cognition, Mood, and Behavior in Alzheimer's Disease: A Systematic Review

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Keywords
Alzheimer's disease · Bright light treatment · Sleep · Cognition · Behavior

Abstract
Background: Bright light treatment is a therapeutic intervention mainly used to treat sleep and circadian disturbances in Alzheimer's disease (AD) patients. Recently, a handful of studies also focused on the effect on cognition and behavior. Conflicting findings are reported in the literature, and no definite conclusions have been drawn about its specific therapeutic effect. ***Summary:*** The aim of this review is to provide a critical evaluation of available evidence in this field, highlighting the specific characteristics of effective bright light treatment. Eligible studies were required to assess at least one of the following outcome measures: sleep, cognition, mood, and/or behavior (e.g., depression, agitation). A total of 32 articles were included in this systematic review and identified as research intervention studies about light treatment in AD. The quality of the papers was evaluated based on the US Preventive Service Task Force guidelines. ***Key Messages:*** Overall, the current literature suggests that the effects of light treatment in AD patients are mixed and may be influenced by several factors, but with a general trend toward a positive effect. Bright light seems to be a promising intervention treatment without significant adverse effects; therefore, further well-designed randomized controlled trials are needed taking into account the highlighted recommendations.

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Introduction

Alzheimer's disease (AD) is the most frequent cause of dementia in the elderly [1] and AD patients may present with sleep disturbances and dysfunction of circadian rhythms [2]. These abnormalities might also occur in normal aging, although they are more frequent and pronounced in older adults with dementia [3]. Various forms of dementia, such as vascular dementia or dementia with Lewy bodies, are associated with different types of sleep and circadian disturbances. In AD, 44% of patients are affected by a sleep disorder and, differently from other forms of neurodegenerative disorders, the prevalence and severity of this disturbance increase with AD severity [3]. Previous studies highlighted a bidirectional relationship between AD pathology, especially amyloid-β plaque accumulation, and sleep disturbances [4]. The neurobiological bases of circadian disturbances were previously related to neuronal loss in the suprachiasmatic nucleus (SCN) [5, 6].

Postmortem studies in AD, besides the well-known neurodegenerative features of the brain, also highlighted retinal and optic nerve tissue pathology [7, 8]. In particular, histological studies reported degeneration of the inner retina with loss of retinal ganglion cells (RGCs) and depletion of related axons in the optic nerve [7, 9]. These findings were more recently confirmed in cohorts of patients studied in vivo with optical coherence tomography showing a thinning of the retinal nerve fiber layer thickness [10–13]. The specific vulnerability of the inner retina to AD pathology is further supported by the finding of β-amyloid deposits in the retina of AD patients [14–16], recently demonstrated also in vivo in AD patients [17]. Moreover, La Morgia et al. [18] showed that these β-amyloid deposits are evident within and around a specific subpopulation of RGCs, the melanopsin RGCs (mRGCs) that represent 1–2% of all RGCs. The loss of these cells was evident even with a normal RGC count, supporting a specific AD pathology affecting mRGCs. The mRGCs, by expressing the photopigment melanopsin, are intrinsically photosensitive and operate as the photoreceptors entraining circadian rhythms to light/dark cycles [19, 20]. Ambient light information is, in fact, sent to the brain by mRGCs through the retinohypothalamic tract, projecting to the SCN of the hypothalamus [21, 22]. When compared to age-matched controls, AD patients had a greater loss of mRGCs, and the remaining mRGCs exhibited a decreased dendritic diameter and abnormal morphology, suggesting functional impairment of the surviving cells in their ability to fully transmit the light information from the retina to SCN [18, 23, 24].

Considering the key role of mRGCs on circadian rhythms and sleep, these cells are particularly relevant to be potentially exploited for therapeutic options using light. Besides the reduced sensitivity to the effect of light on the central nervous system, AD patients also experience a reduction in general sensory input and less exposure to bright environmental light. These aspects may also have an impact on patient's mood and cognition, contributing to the development of behavioral disturbances, depression, and general cognitive dysfunction [25–27].

Since the early 1990s, several researchers have examined the effectiveness of bright light therapy (BLT) in dementia patients. The majority of these studies focused on the effects of light on sleep and circadian rhythms. However, a handful of researchers also studied the effects on cognition, mood, and behavior. Due to the heterogeneity of light treatment (e.g., type of intervention, duration, light intensity) and the heterogeneity of the studied populations (e.g., underlying diagnosis, stage of disease, sample sizes), conflicting findings have been reported [28–31].

The aim of this systematic review is to describe the current state of knowledge in this field, exploring the effect of light treatment on sleep, cognition, mood, and behavior in AD. The specific characteristics of successful treatments will be described in detail, providing recommendations for future research.

Dement Geriatr Cogn Disord 2018;46:371–384
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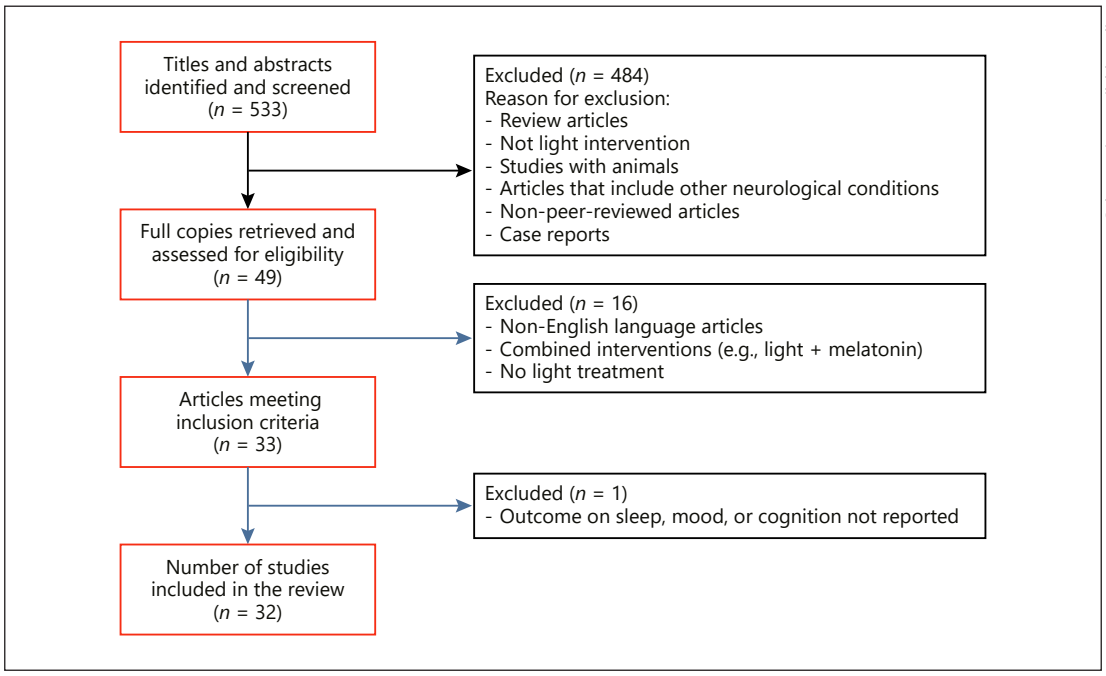

Fig. 1. Flow chart of the study selection process.

Methods

Search Strategy

The objectives and search strategy were established using the Population, Intervention, Comparator, Outcome (PICO) scheme [32]. An online literature search of PubMed and Web of Science using the terms ("light treatment" OR "light therapy" OR "bright light") AND ("Alzheimer" OR "Dementia") AND ("cognition" OR "memory" OR "attention" OR "sleep" OR "circadian rhythms" OR "mood" OR "depression" OR "agitation") was undertaken for all articles published until May 2017 (see Appendix). Using the reference lists of the retrieved articles, additional papers were identified. Previous systematic reviews on this topic and references from the review papers were also examined.

Inclusion/Exclusion Criteria

Eligible studies were required to assess at least one of the following outcome measures: sleep, cognition, mood, and/or behavior (e.g., depression, agitation). The abstracts or complete reports were reviewed to exclude articles according to the following exclusion criteria: (1) not light intervention, (2) review articles, (3) studies that included patients with other neurological conditions, (4) animal studies, (5) non-peer-reviewed articles, (6) non-English language articles, (7) case reports. A total of 32 articles were fully analyzed with the aim of characterizing the specificity and duration of the light interventions, the disease severity, and all those factors that could influence the outcome measures. The included articles were published between 1992 and 2017.

Quality Assessment

The quality of the scientific evidence provided by these articles was classified, and an overall recommendation for the efficacy of this intervention was provided based on the US Preventive Service Task Force guidelines [33]: Level I, Evidence obtained from properly designed randomized controlled trial; Level II-1, Evidence obtained from well-designed controlled trials without randomization; Level II-2, Evidence obtained from well-designed cohort or case-control analytical studies, preferably from more than one center or research group; Level II-3, Evidence obtained from multiple time series studies with or without the intervention; Level III, Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees (Table 1).

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Results

Identification and Selection of Studies

The literature search process is described in Figure 1. Overall, we reviewed 533 studies, including overlapping search results from different databases. A total of 484 publications were excluded according to the defined exclusion criteria, and a total of 49 papers were retrieved and assessed for eligibility. On initial evaluation, 16 articles were excluded because they included combined interventions (e.g., light therapy and melatonin) or were not written in English. A closer analysis of the remaining 33 full articles showed that one of them did not report any outcome measure, and therefore it was excluded. A total of 32 articles were included in this review and identified as research intervention studies of light treatment in AD. Sleep, circadian rhythms, cognition, mood, and behavior were used as outcome measures. Detailed information is given in Table 1 and described below.

Effect on Sleep and Circadian Rhythms

In total, 25 studies examined the effect of light treatment on sleep and circadian rhythms, and most of these used actigraphic measurements, specifically Interdaily stability (IS), Intradaily variability (IV), and Relative amplitude (RA), as outcome measures.

Although there was significant heterogeneity in the type of light treatment, duration of each intervention, and time of light exposure, most of these studies reported beneficial effects.

Ancoli-Israel et al. [34] compared bright light during morning versus bright light during evening and dim light during morning for 10 days. They found a lengthening of the maximum sleep bouts during night only in the first two conditions, highlighting that both morning and evening bright light resulted in more consolidated sleep at night [34]. Furthermore, in another study, the same authors showed that increasing exposure to morning bright light delayed the acrophase of the activity rhythm and made the circadian rhythms more robust [35].

Figueiro et al. [36, 37] also obtained an improvement in sleep parameters (e.g., increased total sleep time and sleep efficiency) using a tailored lighting intervention with bright light, from 6 or 8 am to 6 pm, in a group of patients diagnosed with AD and related dementia; however, these authors did not show any effect on the IS and IV parameters. Similar results were also found by Sloane et al. [38] who, after a tailored lighting intervention, did not find any significant changes in the actigraph measures (i.e., IS and IV scores); light stimulation levels achieved in this study seem to have some effect on sleep pattern, albeit minor and not statistically significant.

Differently, van Someren et al. [39] demonstrated that patients with AD and related dementia, after 4 weeks of bright light intervention, showed increased IS, which quantifies the synchronization to the 24-h light-dark cycle, and decreased IV, indicating a decreased rhythm fragmentation. These improvements indicate a more stable organization of the circadian rest-activity rhythm; however, no significant changes were found in the amplitude of the rhythm. Rest-activity recordings were also reported by Fontana Gasio et al. [40] who showed no significant changes of circadian stability or amplitude characteristics of the rest-activity cycle (i.e., IS, IV, RA); however, the dawn-dusk simulation group tended to have shortened "sleep latency," longer "sleep duration," more nocturnal immobility, and less nocturnal activity than the dim red control group. The average intensity of daytime light received by these patients was low (<300 lux, and usually much lower); therefore, probably not sufficient to produce measurable actigraphic changes.

Fetveit et al. [41, 42] demonstrated that morning bright light treatment administered for 2 weeks clearly improved sleep efficiency (from 73 to 86%), reducing also daytime sleep and waking time within nocturnal sleep by nearly 2 h. Interestingly, the authors showed that sleep efficiency remained significantly higher than the pretreatment 4 weeks after treatment termi-

Table 1. Summary table of reviewed articles

First author [Ref.], year	Study quality [32]	Participants	Intervention	Duration and frequency [follow-up]	Outcome measures: tools
Ancoli-Israel [35], 2002	Level I	*n* = 77 patients (48 F) with moderate and severe dementia *Intervention group:* (1) *n* = 11; (2) *n* =10; (3) *n* = 12 *Control group: n* = 13	*Intervention:* (1) Evening bright light (2) Morning bright light (3) Daytime sleep restriction *Control*: Dim red light	10 days for all conditions (1) 2 h a day (2) 2 h a day (3) Monitored 6 h *Control*: 2 h a day [follow-up: no]	*Sleep and circadian rhythms:* Actillume, a wrist-mounted device
Ancoli-Israel [34], 2003	Level I	*n* = 92 patients (63 F) with probable or possible AD *Intervention group:* (1) *n* = 31; (2) *n* = 30 *Control group: n* = 31	*Intervention:* (1) Evening bright light (2) Morning bright light *Control*: Dim red light	10 days (2 h a day) [follow-up: no]	*Sleep and circadian rhythms:* Actillume, a wrist-mounted device
Ancoli-Israel [55], 2003	Level I	*n* = 92 patients (63 F) with probable or possible AD *Intervention group:* (1) *n* = 25; (2) *n* = 23 *Control group: n* = 23	*Intervention:* (1) Evening bright light (2) Morning bright light *Control*: Dim red light	10 days (2 h a day) [follow-up: no]	*Behavior*: CMAI; ABRS
Barrick [56], 2010	Level II-2	*n* = 66 patients (31 F) with mild, moderate, severe, and very severe dementia [crossover design]	*Intervention:* (1) Evening bright light (2) Morning bright light; (3) All Day bright light *Control*: Standard light	3 weeks for all conditions (1) 4 h a day (2) 4 h a day (3) 13 h a day *Control:* baseline condition [follow-up: no]	*Behavior*: CMAI; observational method
Burns [48], 2009	Level I	*n* = 48 patients with moderate and severe dementia (32 F) *Intervention group: n* = 22 *Control group: n* = 26	*Intervention*: Morning bright light *Control*: Standard light	2 weeks (2 h a day) [follow-up: 4 weeks after treatment]	*Sleep*: Actigraph and sleep charts *Cognition*: MMSE *Mood*: CSDD; MOUSEPAD *Behavior*: CMAI; CRBRS
Dowling [44], 2005	Level I	*n* = 46 patients (36 F) with severe AD *Intervention group: n* = 29 *Control group: n* = 17	*Intervention*: Morning bright light or afternoon bright light *Control*: Usual indoor light	10 weeks (5 days a week for 1 h a day) [follow-up: no]	*Sleep and circadian rhythms:* Actigraph
Dowling [45], 2005	Level I	*n* = 70 patients (57 F) with severe AD *Intervention group:* (1) *n* = 29; (2) *n* = 24 *Control group n* = 17	*Intervention:* (1) Morning bright light (2) Afternoon bright light *Control*: Usual indoor light	10 weeks (5 days a week for 1 h a day) [follow-up: no]	*Sleep and circadian rhythms:* Actigraph
Dowling [57], 2007	Level I	*n* = 70 patients (57 F) with severe AD *Intervention group:* (1) *n* = 29; (2) *n* = 24 *Control group: n* = 17	*Intervention:* (1) Morning bright light (2) Afternoon bright light *Control*: Usual indoor light	10 weeks (5 days a week for 1 h a day) [follow-up: no]	*Behavior*: NPI

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Table 1 (continued)

First author [Ref.], year	Study quality [32]	Participants	Intervention	Duration and frequency [follow-up]	Outcome measures: tools
Fetveit [41], 2003	Level II-1	*n* = 11 patients (10 F) with moderate and severe dementia [*control group*: no]	*Intervention:* Morning bright light *Control*: No control group	2 weeks (2 h a day) [follow-up: no]	*Sleep and circadian rhythms:* Actigraph; nursing staff observations (questionnaire)
Fetveit [43], 2004	Level II-1	*n* = 11 patients (10 F) with moderate and severe dementia [*control group*: no]	*Intervention:* Morning bright light *Control*: No control group	2 weeks (2 h a day) [follow-up: 4, 8, 12, and 16 weeks after treatment]	*Sleep and circadian rhythms:* Actigraph
Fetveit [42], 2005	Level II-1	*n* = 11 patients (10 F) with moderate and severe dementia [*control group*: no]	*Intervention:* Morning bright light *Control*: No control group	2 weeks (2 h a day) [follow-up: 4, 8, 12, and 16 weeks after treatment]	*Sleep and circadian rhythms:* Actigraph; nursing staff diary
Figueiro [36], 2014	Level II-1	*n* = 14 patients (9 F) with mild and moderate dementia [*control group*: not specified]	*Intervention:* "Bluish-white" light *Control*: No intervention	4 weeks (10 h a day) [follow-up: 4 weeks after treatment]	*Sleep*: PSQI *Mood*: CSDD *Behavior*: CMAI
Figueiro [37], 2015	Level II-1	*Intervention group:* *n* = 35 patients (9 F) with mild and moderate dementia; 34 healthy caregivers (27 F) [*control group*: no]	*Intervention:* "Bluish-white" light *Control*: No control group	4 weeks (10 h a day) [follow-up: 4 weeks after treatment]	*Sleep*: PSQI; actigraph; sleep diary *Mood*: CSDD; GDS
Fontana Gasio [40], 2003	Level II-2	*n* = 13 patients with mild, moderate and severe dementia *Intervention group: n*= 9 *Control group: n*= 4	*Intervention:* Dawn-dusk simulation *Control*: Dim red light	3 weeks (post-dawn signal: on for 15 min; pre-dusk signal: on for 45 min) [follow-up: no]	*Sleep and circadian rhythm:* Actigraph and "sleep" variables *Cognition*: MMSE *Mood*: GDS *Behavior*: NPI
Graf [51], 2001	Level I	*n* = 23 patients with mild, moderate, and severe dementia *Intervention group: n* = 13 *Control group: n* = 10	*Intervention:* Evening bright light *Control*: Dim light	10 days (2 h a day) [follow-up: no]	*Sleep and circadian rhythm:* Nocturnal body temperature using a recording device *Cognition*: MMSE
Hickman [59], 2007	Level II-2	*n* = 66 patients (31 F) with mild, moderate, severe, and very severe dementia [crossover design]	*Intervention:* (1) Evening bright light (2) Morning bright light (3) All day bright light *Control:* Standard light	3 weeks for all conditions (1) 4 h a day (2) 4 h a day (3) 13 h a day *Control:* baseline condition [follow-up: no]	*Mood*: CSDD
Koyama [49], 1999	Level II-2	*n* = 6 patients with dementia (level not specified) *Intervention group:* (1) *n* = 3; (2) *n* = 3 [*control group*: no]	*Intervention:* (1) Early morning bright light (2) Late morning bright light *Control*: no control group	Duration: (minimum 30 days; maximum 96 days) (1) 2 h a day (2) 1 h a day [follow-up: no]	*Sleep and circadian rhythms:* Nursing staff observations

Dementia and Geriatric Cognitive Disorders
Dement Geriatr Cogn Disord 2018;46:371–384
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Table 1 (continued)

First author [Ref.], year	Study quality [32]	Participants	Intervention	Duration and frequency [follow-up]	Outcome measures: tools
Lovell [53], 1995	Level II-2	*n* = 6 patients (5 F) with severe dementia [*control group*: no]	*Intervention:* Morning bright light *Control*: No control group	10 days (2 h a day) repeated twice [follow-up: no]	*Behavior*: ABRS
Lyketsos [50], 1999	Level I	*n* = 8 patients with dementia (mean MMSE 6.4±6.8) [crossover design]	*Intervention:* Morning bright light *Control*: Dim light therapy	4 weeks (1 h a day) [follow-up: no]	*Sleep*: Mean hours of nocturnal sleep *Mood*: CSDD *Behavior*: Behave-AD
Mishima [54], 1994	Level II-2	*n* = 14 patients with moderate and severe dementia *Control group:* 10 elderly people	*Intervention:* Morning bright light *Control*: Dim light therapy	4 weeks (2 h a day) [follow-up: no]	*Sleep and circadian rhythms*: Serum melatonin levels; nursing staff diary *Behavior:* Nursing staff diary
Mishima [61], 1998	Level I	*n* = 10 AD patients (6 F) and 12 VD (7 F) patients with moderate and severe dementia [crossover design]	*Intervention:* Morning bright light *Control*: Dim light therapy	2 weeks (2 h a day) [follow-up: no]	*Sleep and circadian rhythms:* Actigraph
Most [65], 2010	Level I	*n* = 72 patients with probable AD, MCI, or SMC	*Intervention:* Light box (active condition) *Control*: Light box (placebo condition)	2 years (1 h a day) [follow-up: every 6 months up to 2 years]	*Sleep and circadian rhythm:* Actigraph; skin temperature; saliva cortisol profile *Mood*: GDS
Onega [58], 2016	Level I	*n* = 60 (43 F) patients with mild, moderate, and severe dementia *Intervention group n* = 30 *Control group n* = 30	*Intervention:* Bright light (active condition) *Control*: Low-intensity light (placebo condition)	8 weeks (1 h a day) [follow-up: no]	*Mood*: DSAOA; DMAS-17; CSDD *Behavior*: CMAI-F; CMAI-D; PAS; BARS
Riemersma-van der Lek [52], 2008	Level I	*n* = 189 patients (170 F) *Intervention group:* (1) *n* = 49; (2) *n* = 46; (3) *n* = 49 *Control group: n* = 45	*Intervention:* (1) Bright light (2) Melatonin (3) Bright light + melatonin *Control*: Inactive light	6 weeks (9 h a day) [follow-up: every 6 months up to 3.5 years]	*Sleep*: Actigraph *Cognition*: MMSE *Mood*: CSDD; PGCARS; PGCM *Behavior*: CMAI; NPI; MOSES
Satlin [27], 1992	Level II-1	*n* = 10 patients (1 F) with moderate and severe dementia [*control group*: no]	*Intervention:* Evening bright light (light box) *Control*: No control group	1 week (2 h a day) [follow-up: no]	*Sleep and circadian rhythms*: Piezoelectric activity monitor; ratings of sleep-wakefulness *Behavior:* Clinical ratings of agitation; use of restraints
Schindler [60], 2002	Level II-2	*n* = 5 patients with mild dementia [*control group*: no]	*Intervention:* Bright light *Control*: No control group	2 weeks (2 h a day) [follow-up: no]	*Behavior*: observation of delusional state and agitation

Dementia and Geriatric Cognitive Disorders
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Table 1 (continued)

First author [Ref.], year	Study quality [32]	Participants	Intervention	Duration and frequency [follow-up]	Outcome measures: tools
Sekiguchi [62], 2017	Level II-2	*n* = 17 patients (6 F) with mild, moderate, and severe dementia: *n* = 8 AD; *n* = 4 VD; *n* = 5 DLB [*control group*: no]	*Intervention:* Morning bright light *Control*: No control group	2 weeks (1 h a day) [follow-up: no]	*Sleep:* NPI-NH score (sleep)
Skjerve [47], 2004	Level II-2	*n* = 10 patients (3 F) with severe dementia [*control group*: no]	*Intervention:* Morning bright light *Control*: No control group	4 weeks (45 min a day) [follow-up: no]	*Sleep and circadian rhythms*: Actigraph; SWD *Behavior:* CMAI; BEHAVE-AD
Sloane [64], 2007	Level II-2	*n* = 66 patients (31 F) with mild, moderate, severe, and very severe dementia [crossover design]	*Intervention:* (1) Evening bright light (2) Morning bright light (3) All Day bright light *Control:* Standard light	3 weeks for all conditions (1) 4 h a day (2) 4 h a day (3) 13 h a day *Control:* baseline condition [follow-up: no]	*Sleep and circadian rhythms*: Actigraph *Behavior:* CSDD; PHQ-9
Sloane [38], 2015	Level I	*n* = 17 patients with mild, moderate, severe, and very severe dementia; *n* = 17 healthy controls (caregivers) [crossover design]	*Intervention:* Blue-white light (active condition) *Control*: Yellow-white light (placebo condition)	6 weeks (during all day) [follow-up: no]	*Sleep and circadian rhythms*: Actigraph; PSQI; MOS; Epworth Sleepiness Scale. *Mood:* CSDD; PHQ-9 QOL-AD (only used with dementia patients) CHS and ZBI (only used with caregivers)
Van Someren [39], 1997	Level II-2	*n* = 22 patients in total (15 F) *n* = 16 with probable AD; *n* = 3 with multi-infarct dementia; *n* = 2 dementia associated with alcoholism; *n* = 1 normal pressure hydrocephalus [*control group*: no]	*Intervention:* Morning bright light *Control*: No control group	4 weeks (during all day) [follow-up: no]	*Sleep and circadian rhythms*: Actigraph
Yamadera [46], 2000	Level II-3	*n* = 27 patients (16 F): *n* =10 questionably and mildly demented; *n* = 17 moderately and severely demented) [*control group*: no]	*Intervention:* Morning bright light *Control*: No control group	4 weeks (2 h a day) [follow-up: no]	*Sleep and circadian rhythm:* Actigraph *Cognition*: MMSE, CDR

CMAI, Cohen-Mansfield Agitation Inventory; ABRS, Agitated Behavior Rating Scale; CSDD, Cornell Scale for Depression in Dementia; MOUSEPAD, Manchester and Oxford Universities Scale for the Psychological Assessment of Dementia; CRBRS, Crichton Royal Behavior Rating Scale; NPI, Neuropsychiatric Inventory; PSQI, Pittsburgh Sleep Quality Index; GDS, Geriatric Depression Scale; DSAOA, Depressive Symptom Assessment for Older Adults; DMAS-17, Dementia Mood Assessment Scale-17; PAS, Pittsburgh Agitation Scale; BARS, Brief Agitation Rating Scale; PGCARS, Philadelphia Geriatric Centre Affect Rating Scale; PGCM, Philadelphia Geriatric Centre Morale Scale; MOSES, Multi Observational Scale for Elderly Subjects; SWD, Scale for Sleep-Wake Disturbances; MOS, Medical Outcomes Study sleep scale; PHQ-9, Patient Health Questionnaire-9; QOL-AD, Quality of Life-AD; CHS, Caregiving Hassles Scale; ZBI, Zarit Burden Interview; CDR, Clinical Dementia Rating.

Dement Geriatr Cogn Disord 2018;46:371–384
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nation, and sleep onset latency was significantly reduced up until 12 weeks posttreatment [43].

Conflicting findings were described by Dowling et al. [44, 45] demonstrating that 1 h of bright light, administered to institutionalized subjects with AD (mean age 84 years) for 10 weeks either in the morning or afternoon, did not lead to overall improvement in measures of sleep-wake and rest-activity compared to a control group that received usual indoor light. Only a trend toward significance in amplitude and in the rest-activity acrophase with improvement in the experimental group and worsening in the control group was found. However, no significant differences were found in variables derived from the nonparametric circadian rhythm analyses (i.e., IS, IV, or RA). According to the authors, the possible explanation for the lack of efficacy of this treatment is the old age of all participants and the severity of dementia (mean Mini-Mental State Examination [MMSE] score = 7). Subjects respond to light differently across the lifespan, and the severity of dementia may have also led to a weak sensitivity to the light exposure [46].

Furthermore, also Skjerve et al. [47] did not find significant differences on the variables IS, IV, or RA after a short bright light treatment; in this study, the authors concluded that the short treatment period (i.e., 4 weeks) was not sufficient to influence the circadian rhythm in severely demented patients. Another possible relevant factor influencing the response to light treatment is the season of the year. Burns et al. [48], applying bright light from 10 am to 12 pm in a group of people with dementia, found beneficial effects on sleep, which were more marked during winter than during summer. Specifically, they suggest that light must be turned on not earlier than the autumn equinox, when the external light cues are compromised, and turned off not later than the spring equinox.

Overall, previous findings suggest that the effects of light treatment on sleep and circadian rhythms in people with dementia are mixed and may be influenced by several factors, but with a general trend toward a positive effect of light therapy on sleep [49, 50]. Since light treatment does not have significant adverse effects, the development of studies with bigger samples and longer follow-up periods is warranted in order to generalize these results and verify whether the effects on sleep persist over time.

Effect on Cognition

The effect of light treatment on cognition was evaluated in 5 studies. Burns et al. [48] compared standard fluorescent tube light with morning bright light treatment. Fontana Gasio et al. [40] compared dawn-dusk simulation with "placebo" dim red light. Graf et al. [51] compared evening bright light with dim light. Yamadera et al. [46] explored the effects of BLT in a group of Alzheimer-type dementia patients. Finally, Riemersma-van der Lek et al. [52] compared all day bright light with dim light and monitored their patients up to 3.5 years. All these studies found modest positive effects on cognition, and one of them also showed that these improvements were maintained over time [52]. However, these studies presented the limitation that the only outcome measure used to monitor patients' cognitive status was the MMSE, a basic, and relatively insensitive screening test. Further studies with a more extensive range of cognitive tests and aimed to explore different cognitive abilities are needed to confirm these preliminary results and to define the specificity of these improvements.

Effect on Mood and Behavior

In total, 19 studies explored the effect of light treatment on mood and/or behavior disorders (e.g., depression, agitation, aggression). Some of these studies showed that, in people with dementia, BLT might have some effect on reducing agitation [48, 53, 54]; this behavior improvement is more marked in winter when the external light cues are compro-

Dement Geriatr Cogn Disord 2018;46:371–384
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mised [48]. As for the effects on sleep, also the severity of the disease might have an influence on the light treatment effects.

Ancoli-Israel et al. [55] showed that, in a group of severe AD patients, morning bright light delayed the acrophase of the agitation rhythm by over 1.5 h, but the overall agitation was not ameliorated. Since the SCN of patients with severe AD is likely to be more degenerated, and the circadian activity rhythms deteriorate as the disease progresses, it is still possible that patients with mild or moderate AD would benefit from light treatment more than those with severe AD. For example, Figueiro et al. [37] treated a group of 35 patients with mild or moderate dementia for 4 weeks with a tailored lighting intervention and, differently from previous studies, they showed a significant reduction of depressive symptoms. Barrick et al. [56] showed that ambient bright light is not effective in reducing agitation in institutionalized persons with dementia and may exacerbate this behavioral symptom in severely demented patients. Another study that described a light treatment in nursing home residents with AD showed small changes in neuropsychiatric behaviors (e.g., aggression, depression, eating disorders); however, the authors concluded that the magnitude of these changes do not represent clinically significant findings [57]. Onega et al. [58] showed that bright light exposure was associated with significant improvement in depression and agitation, while participants receiving low-intensity light displayed no significant changes or higher levels of depression and agitation. Their findings support the use of bright light exposure to reduce depression and agitation in dementia patients. Other authors showed that BLT is beneficial in some patients with dementia by decreasing depressive or agitation symptoms but may worsen symptoms in others [59, 60]. The negative effects for some participants and all these conflicting findings suggest that high-intensity ambient lighting should be tailored on an individual basis taking into account different variables.

Discussion

BLT is a therapeutic intervention mainly used to treat sleep and circadian disturbances in AD patients. Recently, a handful of studies also focused on the effect of BLT on improving cognition and reducing depression and agitational behavior in patients with dementia. However, conflicting findings have been reported in the literature, and no definite conclusions have been drawn about its specific therapeutic effect. This systematic review aimed at describing the status of the field and shedding light on the specific characteristics of successful bright light treatments.

The heterogeneity of disease severity and the age of participants seem to have an influence on the light treatment effects [44, 45]. Patients with mild to moderate AD, with more intact SCNs, showed greater response to light in comparison to patients with severe AD [46]. Other studies in severely demented patients showed that ambient bright light, instead of inducing improvements, might sometimes exacerbate their behavioral symptoms [56]. Bright light effects could vary with the severity of the disease but also with the type of dementia; Mishima et al. [61] showed a significant improvement after BLT in patients with vascular dementia, but not in patients with AD. More recently, also Sekiguchi et al. [62] showed different results in different dementia patients, suggesting that BLT is more effective in patients with mild-moderate AD. Considering this body of evidence, we suggest that mild and moderate AD patients might benefit more from BLT than patients with severe dementia. One of the limitations of the current literature in this field is the absence of an accurate dementia diagnosis and clinical characterization in the majority of the studies. Moreover, most of the studies analyzing the effects of BLT in AD patients included cases based only on a clinical diagnosis

Dement Geriatr Cogn Disord 2018;46:371–384
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of AD without any supportive diagnostic criteria (e.g., CSF or PET-amyloid) [63], and this might represent a potential confounding factor.

Furthermore, day length is a powerful factor in influencing seasonal and daily activity and circadian rhythms. In fact, successful BLT studies showed more marked beneficial effects during winter, when the external light cues are compromised, than during summer [48, 37]. Therefore, it is suggested that to obtain more beneficial effects, light must be turned on no earlier than the autumn equinox, and turned off not later than the spring equinox [48]. To minimize the potential bias from differences in daylight exposure, some authors recommended equally distributing treatment and placebo conditions across seasons [56, 64]. Another relevant aspect is the setting in which the light intervention is delivered and the modality of light exposure. Patients living at home may still be mobile and can have activities outside the house, while those living in nursing homes have fewer opportunities to spend time outdoors. Therefore, a lighting intervention in a more controlled environment, such as nursing homes, will give the opportunity to receive the lighting intervention in a homogenously lighted and controlled environment and therefore may be more effective than the same intervention at home [37].

Regarding the type of light exposure, previous studies showed mood and behavior improvement (e.g., reduced agitation) using "light boxes" [65, 27]. Often, in these cases research staff attended the intervention, actively keeping the participants seated in front of the light. These social exchanges could have independently improved study participant agitation [56]. Therefore, other modalities of light treatment, which provide target exposure levels without adding a potentially confounding staff effect, may represents a more valid method to explore the effects of bright light treatments. Moreover, most of the studies used white bright light sources without controlling for wavelength. Given that AD patients when compared to age-matched control have a greater loss of mRGCs and these cells are particularly sensitive to monochromatic blue light (at 470 nm) [66], the use of more selective wavelength would be more appropriate in tailoring light effectiveness on sleep and cognition in these patients.

Further, it should be highlighted that the nonsignificant results reported in some studies may be due to small sample sizes and to the heterogeneity of patient groups, leading to insufficient power for detecting differences; randomized control trials with larger samples are needed to confirm these preliminary results. In addition to all of the above recommendations, a wider range of outcome measures including brain structural and functional changes and extensive cognitive assessments are also needed to better define the specificity of light treatment effects. Moreover, since many of these patients are also experiencing age-related eye diseases including glaucoma, the exclusion of ocular pathologies with a complete neuro-phthalmological evaluation possibly interfering with light treatment must be considered. Finally, none of the studies measured in a quantitative way the ambient and outdoor light exposure using appropriate light sensors, and this might represent a possible confounding factor in evaluating the effectiveness of BLT.

BLT has also been considered one of the first-line treatments for seasonal affective disorder, yet a growing body of literature supports its use in other neuropsychiatric conditions including nonseasonal depression [67]. However, unlike administering BLT as monotherapy, studies that administered BLT as adjunct to antidepressant medications have failed to find evidence of efficacy [68]. Although still questionable in nonseasonal types of depression, many studies have reported it to be an effective treatment option for bipolar depression [67]. BLT seems to be effective also in improving both disordered-eating behavior and mood acutely, although the timing of symptom response and the duration of treatment effects remain unclear [69].

Overall, bright light seems to be a promising intervention treatment, and it does not have significant adverse effects; therefore, further well-designed randomized controlled trials are needed, and all of the above recommendations should be taken into account when designing appropriate interventions for ameliorating sleep and circadian rhythms in AD.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors have no conflicts of interest to declare.

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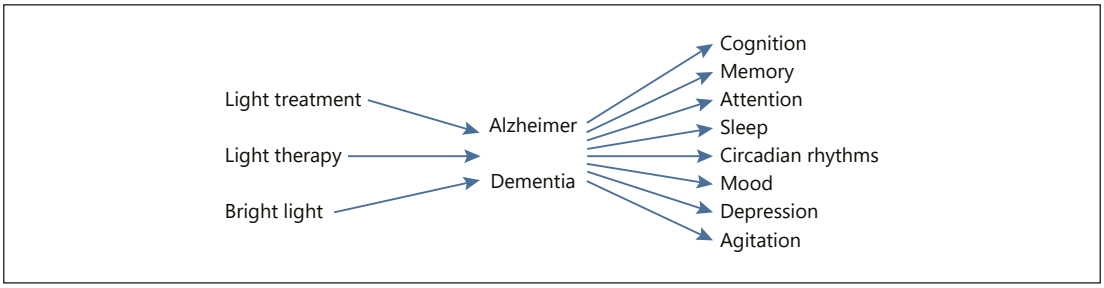
Appendix

Search Strategy



Color version available online

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