Journal of Alzheimer's Disease xx (20xx) x–xx
DOI 10.3233/JAD-200478
IOS Press

Fiat Lux: The Light Became Therapy. An Overview on the Bright Light Therapy in Alzheimer's Disease Sleep Disorders

Ilaria Roccaro and Daniela Smirni*
Department of Psychology, Educational Science and Human Movement, University of Palermo, Palermo, Italy

Accepted 2 June 2020

Abstract.
Background: A system of photosensitive retinal ganglion cells provides 'non-visual' information on the circadian sequences of light to the suprachiasmatic nucleus (SCN), which, as the 'master clock', synchronizes the chronobiological mechanisms of all the biological clocks. Damage to SCN structure alters circadian behavioral and hormonal rhythms and interferes with a regular sleep-wake pattern. Several studies have shown that, in aging and in Alzheimer's disease (AD), circadian rhythms change their synchronization with the environment and behavior loses sync with light.
Objective: The current overview aims to examine research studies showing the effect of bright light therapy (BLT) on sleep disorders and sleep-wake patterns in AD.
Methods: A literature search was conducted, taking into consideration the relevant studies over the last 20 years. Fifteen studies have been thorough: seven followed an environmental-architectural approach and eight followed a treatment devices approach.
Results: Studies agree in considering BLT as a promising non-pharmacological intervention to compensate for circadian rhythm alterations and they support the need for standardized protocols that allow a comparison between multicenter studies.
Conclusion: Interestingly, in an attempt to contain the spread of the COVID-19 pandemic, health authorities have forced the population to stay home. Therefore, AD people are not currently able to enjoy exposure to sunlight. It is predictable that they may experience an exacerbation of circadian disturbances and that the BLT can be an effective response to prevent such exacerbation.

Keywords: Alzheimer's disease, biological clocks, bright light therapy, circadian rhythms, light boxes, retinal ganglion cells, sleep disorder, suprachiasmatic nucleus

ORCID ID 0000-0002-4410-2047

INTRODUCTION

In the biblical story, in the beginning of time, 'lux facta est' and everything is born and lives in the light. The creative work primarily provided a rhythm, the light following the darkness. Such rhythm shapes the temporal frame of the life, since the prehistorical times, not only of our ancestors but also everything that is living in the universe. Light and dark alternate, shaping the regular pattern of day and night, and the great seasonal cycles. Every single vital function and every single element of living organism respond to the temporal sequence of light and dark.

Therefore, all living organisms have developed a set of 'biological clocks', as survival endogenous timing device, to ensure the basic vital functions, in relation to day and night, the individual seasons and all phenomena referring to environmental, temporal

*Correspondence to: Daniela Smirni, viale delle Scienze, Ed.15, 90128, Palermo, Italy. Tel.: +39 0 9123897748; E-mail: daniela.smirni@unipa.it.

variations [1]. Sleeping at night and being awake during the day is a typical behavior of a light-related circadian rhythm.

Light waves reach the retina, where the external world becomes an image and, through the optic nerve, as electrical signal, gets to the visual areas of the brain to become knowledge and perception. While cones and rods allow visualization of the world, both under low intensity light levels (nocturnal or scotopic vision through rod cells) or high intensity light levels (diurnal or photopic vision through cone cells), a system of intrinsically photosensitive retinal ganglion cells, through their sensitive pigment melanopsin, provides information on the circadian sequences and rhythms of light [2, 3]. Such retinal ganglion cells are unable to see the object world, like cones and rods. Their function is rather collecting 'non-visual' information on ambient 'circadian' light and transmitting to a hypothalamic neuronal structure, the suprachiasmatic nucleus (SCN), which, as the 'master clock', synchronizes the chronobiological mechanisms of all the other peripheral biological clocks [4].

These biological measuring devices of time, through hormonal and neural signals, drive and modulate the daily expression of vital homeostatic functions, sleep, blood pressure, body temperature, and neurohormone secretion [5, 6]. Melatonin and cortisol, for example, are synthesized and suppressed over the course of about 24 hours, driving the sleep/wake rhythm.

Damage to SCN structures alters circadian behavioral and hormonal endogenous rhythms and interferes with a regular sleep-wake pattern. Conversely, even in a completely blind animal, the light results in day-night cycles and, even in a dark cave, SCN records circadian rhythms regardless of environmental clues [7]. Therefore, circadian rhythms are rooted both in genetic heritage and in external environment. Light and dark are the most powerful external cues. They, as 'zeitgebers' or 'synchronizers', can activate or deactivate genes synchronizing the molecular structure of biological clocks with the 24-hour light-dark cycle and the 12-month cycle and providing timing of the internal clocks along with a set of external signals such as weather, social interaction, or eating patterns [8].

Environmental light and darkness and dysfunctional circadian patterns may impact on various conditions such as jet lag and night shift work, and may support or increase a variety of pathologies such as sleep disorders, diabetes, depression, and seasonal affective disorder [9]. In seasonal depression, for example, patients experience an increase in depression during the winter, resulting in resolution in the spring. Similarly, many depressed patients show a daily pattern of symptoms, the most serious occurring in the morning. In addition, suicide rates show diurnal and seasonal variations, with an increase proportional to the amount of sunlight intensity [10].

In healthy elderly, circadian rhythms change their amplitude and the synchronization with the environment [11]. Similarly, the number of retinal ganglion cells and their activity as well as the quantity and synthesis of the main peptides, showing a circadian rhythm in the SCN, decrease [12]. Postmortem studies on aging, dementia, and depression showed impaired functioning of the SCN which could be a basic cause of sleep rhythm disorders [13].

In AD patients, a degeneration process of the retinal ganglion cells and a loss of functionality of the suprachiasmatic nuclei results in a distortion of the biological clock and sleep-wake patterns [14, 15]. Circadian rhythms are altered, behavior loses sync with light and dark, and hormones, such as melatonin and cortisol, alter their synthesis activity or suppression. Reduction of melatonin in the cerebrospinal fluid and the loss of the diurnal rhythm of melatonin has been documented, even in preclinical stages, probably due to a defect in the retino-hypothalamic tract or in the connections between the pineal gland and the SCN [16]. Therefore, increasing dementia severity, sleep-wake rhythm disturbances increase. In addition, patients with dementia experience reduced exposure to sunlight and to a regular light/dark rhythm as the body's primary circadian stimulus. They may be underexposed to outdoor activities and to natural light and being less likely to experience the 24-hour light-dark pattern required for circadian entrainment [17, 18]. Furthermore, the environmental lighting often does not provide comfortable light and darkness for the visual and non-visual aspects of light, to maintain a stable circadian rhythm and vital dark-induced functions, such as melatonin secretion. Sleep disturbances increase so far as to compel the family to hospitalize the patient. Therefore, the treatment of sleep-wake circadian rhythm in people with dementia appears as a crucial choice to improve both the quality life of patient and caregiver [19, 20].

On these assumptions, and in relation to the side effects of drugs for sleep disorders, non pharmacological therapeutic treatments have been developed providing for a controlled exposure to stimuli that influence biological rhythms, such as bright light therapy (BLT). Such physiological therapeutic

approach uses exposure to artificial light, greater than 2500 lux, for a specific amount of time, almost to simulate sunlight and its 'circadian' effects, hypothesizing that bright light suppresses plasma melatonin level, restores the circadian amplitude in sleep-wakefulness [21], and improves restless behavior, enhancing neuronal activity in the SCN [14]. Warm color temperatures stimulate secretion of melatonin, while cool color temperatures inhibit melatonin secretion and stimulate production of cortisol, hormone for alertness and activity during the day [22].

Several studies support the effectiveness of BLT in the treatment of seasonal affective disorder and major depression as an adjuvant to antidepressants, in sleep disorders, pre-menstrual syndrome [23, 24], non-seasonal depression, seasonal bulimia [25, 26], antepartum depression [27, 28], and postpartum depression [29, 30].

The aim of the current overview was to examine research studies over the past two decades, reporting on the effect of BLT on sleep and rhythms in AD patients, to provide a contribution to the development of standardized protocols with the BLT in AD sleep disorders.

METHODS

A literature search on the MEDLINE (PubMed), Web of Science, and ScienceDirect was conducted, taking into consideration the relevant studies over the last 20 years. In particular, the following keywords have been used: bright light therapy, Alzheimer's Disease, sleep disorder, biological clocks, light boxes. We included case reports, randomized controlled trials, and observational studies on subjects with different AD severity. References from related meta-analyses and from articles retrieved during the search were examined for additional studies.

RESULTS

After an extensive literature search, fifteen studies have been thorough. Tables 1 and 2 schematically summarize the observations shown by these studies: Table 1 shows the studies that follow the environmental-architectural approach; Table 2 shows the studies that follow the treatment devices approach. The study population were patients with dementia (mild, moderate, severe, very severe AD, vascular dementia, Lewy bodies dementia, mixed, probable AD) ranged from 13 to 189 and totaled 910. Only just under 30% of the patients were living at home, whereas just over 70% lived in care facilities. Duration of treatment were rather diversified, ranging from 2 weeks to 2 years. Equally different were the modalities of BLT administration. Two different therapeutic settings were used. A first used an environmental exposure to light by particular lighting architectural systems. A second exposed the patient to natural light or to treatment devices, such as special lamps, visors, light boxes, or other artificial light sources. Both methodological approaches reported many positive effects. Patients were receiving drug therapy, except in the study of Yamadera and colleagues [31], and in one study it is not specified [32]. The majority of the studies documented improving quality and duration of sleep [33–39], reducing symptoms of depression [34–36, 40] and agitation [33, 35, 40]. Not all studies had follow up but only about a half, and most of these documented persistence of improvements even after four weeks [33, 35, 36].

Environmental-architectural approach

Hickman and colleagues [41], analyzing the conflicting results of previous studies on small samples of depressed demented patients [42, 43], examined a larger sample (66 patients) with dementia in two different care facilities, administering a high intensity and low-glare lighting system installed in the activity and in the dining areas, in four lighting conditions: light in the morning, evening bright light, bright light throughout the day, and standard light. They delivered, for multiple 3-week periods, two different therapeutic range from 2000 to 2500 lux for the three bright light conditions and from 500 to 600 lux for the standard lighting conditions. Morning light conditions showed significant effects only in one group of patients. According to the authors, high intensity lighting in public areas may not be suitable for all patients, but it should be given to target people through environmental systems in bedrooms or apartments. Furthermore, the poor homogeneity of the results had to be attributed to the methods in diagnosing depression, and to the difficulties in the self-rating of demented subjects.

Riemersma-van der Lek and colleagues [18], in a randomized placebo-controlled, double-blind design, examined an even large sample of 189 patients with dementia living in different care facilities. They used individual or combined long-term application of two treatments: bright light and melatonin. For an average of 15 months, patients were treated randomly every

Table 1
Bright Light Therapy for sleep disorders in Alzheimer's disease: environmental-architectural approach

Study	Study design	Intervention	Administration phase	Duration	Total sample size	Age	Subjects	Drug treatment	Measures	Results	Follow-up
Hickman et al., 2007 [41]	cluster-unit crossover trial	Three lighting conditions of bright light (2000–2500 lux): morning, evening, all day. And a condition of standard light (500–600 lux)	4–13 h/day (1st condition: 7–11 a.m.; 2nd: 4–8 p.m.; 3rd: 7 a.m.–8 p.m.; 4th: 7 a.m.–8 p.m.)	multiple 3-week periods in a predetermined sequence	66	Ranged <65–80+	Dementia	Yes	*Cognition:* MDS-COGS, MMSE *Mood:* CSDD	Morning light condition decreased depressive symptoms in some patients but worsened symptoms in other	No
Riemersma-van der Lek et al., 2008 [18]	multicenter, double-blind, randomized placebo-controlled trial	Four conditions: 1st: light only (±1000 lux); 2nd: melatonin only (2.5 mg); 3rd: combination of 1st and 2nd condition; 4th: neither light (±300 lux) nor melatonin (double placebo)	8 h/day (1st condition: 10 a.m.–6 p.m.; 2nd: 1 h before bedtime; 3rd: combination of 1st and 2nd condition)	Mean of 15 months	189 : 49 (light); 46 (melatonin); 49 (their combination); 45 (double placebo)	Mean 85.8	probable AD, VaD, frontal-type dementia, DLB, PD, WKS, dementia, other pathologies	Yes	*Behavior:* MOSES, NPI-Q, CMAI *Cognition:* MMSE, *Mood:* CSDD, PGCMS, PGCARS, NI-ADL *Sleep:* Actigraphic Sleep Estimates	BLT improved circadian activity rhythm disturbances, cognitive deterioration and depressive symptoms; combined with melatonin attenuated aggressive behavior and increased sleep efficiency	Results maintained
Barrick et al., 2010 [44]	cluster-unit crossover trial	Three lighting conditions of bright light (2000–3000 lux): morning, evening; all day. (Ctr: 500–600 lux of standard light)	4–13 h/day (1st condition: 7–11 a.m.; 2nd: 4–8 p.m.; 3rd: 7 a.m.–8 p.m.; 4th: baseline condition)	3 weeks for each condition	66	n.s.	mild/ moderate or severe/very severe dementia	Yes	*Behavior:* CMAI, observational method *Cognition:* MDS-COGS, MMSE	Ambient bright light may exacerbate agitation in dementia	No
Figueiro et al., 2014 [35]	Field study	300–400 lux of a "Bluish-white" light	10–12 h/day (between 6–8 a.m. – 6 p.m.)	4 weeks	14	Mean 86.9	Mild/ moderate dementia	Yes	*Behavior*: CMAI, MDS-ADL *Mood*: CSDD *Sleep*: Daysimeter, PSQI	A lighting intervention increase sleep quality and improve behavior in patients with ADRD	Improvements about the agitation were more or less maintained

Figueiro et al., 2015 [36]	RCT	350–400 lux of a "Bluish-white" light	about 10 h/day (awakening - 6 p.m.)	4 weeks	35 (+34 cohabitating as ctr)	Mean age participants 80.8; Mean age caregivers 71.8	Mild/ moderate dementia; healthy caregivers	Yes	*Mood*: CSDD, GDS-SF *Sleep*: PSQI, Actigraph, Sleep diary, Daysimeter	The lighting intervention significantly reduced symptoms of depression in the participants with ADRD	Improvements were maintained
Sloane et al., 2015 [45]	RCT with crossover	Active condition: 300–400 lux of blue-white light; Placebo condition: 400 lux of yellow-white light	awakening - 6 p. m.	6 weeks separated by a four-week washout (during all day)	17 (+17 caregivers)	participants with dementia: ranged 65–80+; caregivers: ranged 18–60+	Mild/ moderate severe-very severe dementia; Healthy caregivers	Yes	*Cognition:* MMSE, SLUMS *Mood:* CSDD, PHQ-9, QOL-AD, CHS, ZBI *Sleep and circadian rhythms:* Actigraph, PSQI, MOS, ESS	the levels of light exposure used in this study were not sufficient to change sleep parameters in subjects with dementia.	No
van Lieshout-van Dal et al., 2019 [38]	Within subjects design	1st: biodynamic lighting (600–1100 lux); 2nd: no exposure to biodynamic lighting	1st condition and 2nd condition are intermittent during a study (1st: 3 consecutive weeks, 2nd: 3 consecutive weeks, etc.)	1 year (five subsequent days and nights in the last week of each condition)	13	Mean 74.77	Dementia	Yes	*Sleep:* Caremonitor, Bedleave and Wandering module	During exposure to biodynamic lighting the average total night-time sleep significantly increased	No

AD, Alzheimer's disease; ADRD, Alzheimer's disease and related dementias; BLT, Bright light therapy; CHS, Caregiving Hassles Scale; CMAI, Cohen-Mansfield Agitation Inventory; CSDD, Cornell Scale for Depression in Dementia; Ctr, Control; DLB, Dementia with Lewy bodies; ESS, Epworth Sleepiness Scale; GDS-SF, Geriatric Depression Scale-Short Form; MDS-ADL, Minimum Data Set Activities of Daily Living Scale; MDS-COGS, Minimum Data Set Cognition Scale; MMSE, Mini-Mental State Examination; MOS, Medical Outcomes Study; MOSES, Multi Observation Scale for Elderly Subjects; n.s., not specified; NI-ADL, Nurse-informant activities of daily living adaptation; NPI-Q, Neuropsychiatric Inventory; PD, Parkinson's disease; PGCARS, Philadelphia Geriatric Centre Affect Rating Scale; PGCMS, Philadelphia Geriatric Centre Morale Scale; PHQ-9, Patient Health Questionnaire of the PRIME-MD; PSQI, The Pittsburg Sleep Quality Index; QOL-AD, Quality of Life in Alzheimer's disease instrument; RCT, Randomized controlled trial; SLUMS, Saint Louis University Mental Status; VaD, Vascular dementia; WKS, Wernicke-Korsakoff Syndrome; ZBI, Zarit Burden Interview.

Table 2
Bright Light Therapy for sleep disorders in Alzheimer's disease: treatment devices approach

Study	Study design	Intervention	Administration phase	Duration	Total sample size	Age	Subjects	Drug treatment	Measures	Results	Follow-up
Yamadera et al., 2000 [31]	RCT	3000 lux of bright light therapy	2 h/day 9–11 a.m.	4 weeks	27	Mean 79.9	Moderate and severe dementia	No	*Cognition:* MMSE *Sleep and circadian rhythms:* Actigram, Wilcoxon rank sum test	BLT improved cognitive performance, especially in the early stages of AD, and improved circadian rhythm disturbances	No
Ancoli-Israel et al., 2002 [47]	RCT	Four treatments: 1st: evening bright light (2500 lux); 2nd: morning bright light (2500 lux); 3rd: evening dim red light (<50 lux); 4th: daytime sleep restriction	2–6 h/day (1st condition: 5:30–7:30 p.m.; 2nd: 9:30 a.m.–11:30 p.m; 3rd: 5:30–7:30 p.m; 4th: 9 a.m.–12 p.m. and 2–5 p.m.)	18 days	77	Mean 85.7	Severe dementia	Yes	*Cognition:* MMSE *Mood:* GDS *Sleep:* Actillume recorder	morning bright light condition improved circadian rhythm quality and also agitation in a small subsample	Improvements were maintained
Ancoli-Israel et al., 2003 [48]	RCT	Three treatment groups: 1st: morning bright light (2500 lux); 2nd: morning dim red light (<300 lux); 3rd: evening bright light (2500 lux)	2 h/day (1st and 2nd condition: 9:30–11:30 a.m.; 3rd: 5:30–7:30 p.m.)	10 days	92:30 (morning bright light); 31 (morning dim red light); 31 (evening bright light)	Mean 82.3	probable or possible AD	Yes	*Cognition:* MMSE *Sleep:* Actillume recorder	morning and evening light led to more consolidated sleep at night; evening light increased the quality of the rhythm of circadian activity	Improvements were maintained
Burns et al., 2009 [33]	RCT	Full spectrum BLT 10000 lux (Ctr: standard light 100 lux)	2 h/day 10–12 a.m. bright light	2 weeks	48 (of which 26 of Ctr)	Mean 83.5	moderate and severe: AD, VaD, DLB, mixed	Yes	*Behavior*: CMAI, CRBRS *Cognition*: MMSE *Mood*: CSDD, MOUSEPAD *Sleep*: Actigraph and sleep charts	Bright light therapy can have some effects in reducing agitation and improving sleep	Results maintained

McCurry et al., 2011 [39]	RCT	Three active treatments: 1st: walking; 2nd: light box (2,500 lux of full-spectrum light); 3rd: combination treatment; (Ctr: no implementing daily walking, no increasing light exposure)	1st condition: 30 mins/day; 2nd condition: 1 h/day before bedtime; 3rd condition: 1st condition + 2nd condition + individualized sleep plan	2 months	132:32 (walking); 34 (SunRay light box); 33 (combination treatment); 33 (ctr)	Mean 81	AD, probable AD	Yes	*Behavior:* number of awakenings, total sleep time. SCQ *Cognition:* MMSE *Mood:* CSDD *Sleep:* Actigraphy, SDI, SDQ	Walking, light, and combination treatment had significantly greater improvements in total wake time	Improvements were not sustained
Onega et al., 2016 [40]	RCT	1st: bright light (10000 lux); 2nd: placebo low level light of Ctr (250 lux)	for 30 min twice a day (morning sessions between 8 a.m.–12 p.m.; afternoon/evening sessions between 2–8 p.m.)	8 weeks (5 days per week)	60 (of which 30 of Ctr)	Mean 82.6	Mild/moderate and severe dementia	Yes	*Behavior:* CMAI-F, CMAI-D, PAS BARS *Cognition:* MMSE *Mood:* DSAOA, DMAS-17, CSDD	regular exposure to bright light was associated with significant improvement in levels of depression and agitation	No
Sekiguchi et al., 2017 [37]	Observational study	5000 lux of full spectrum light	1 h/day 9–10 a.m.	2 weeks	17	Ranged 64–84	AD, VaD, DLB	Yes	*Cognition:* MMSE *Sleep:* NPI-NH	BLT led to the improvement of sleep disturbance in four participants	No
Onega et al., 2018 [32]	2×2×2 mixed-model repeated-measures design	1st: bright light (10000 lux); 2nd: placebo low level light of Ctr (250 lux)	for 30 min twice a day (morning sessions between 8 a.m.–12 p.m.; afternoon/evening sessions between 2–8 p.m.)	8 weeks (5 days per week)	60 (of which 30 of Ctr)	n.s.	mild/moderate and severe dementia	n.s.	*Mood:* DSAOA, CSDD	BLT is an equally effective intervention for depression in patients with both mild/moderate and severe dementia	No

AD, Alzheimer's disease; BARS, Brief Agitation Rating Scale; BLT, Bright light therapy; CMAI, Cohen-Mansfield Agitation Inventory; CMAI-D, Cohen-Mansfield Agitation Inventory-Disruptiveness; CMAI-F, Cohen-Mansfield Agitation Inventory-Frequency; CRBRS, Crichton Royal Behavior Rating; CSDD, Cornell Scale for Depression in Dementia; Ctr, Control; DLB, Dementia with Lewy bodies; DMAS-17, Dementia Mood Assessment Scale-17 Item; DSAOA, Depressive Symptom Assessment in Older Adults; GDS, Geriatric Depression Scale; MMSE, Mini-Mental State Examination; MOUSEPAD, Manchester and Oxford Universities Scale for the Psychological Assessment of Dementia; n.s., not specified; NPI-NH, Neuropsychiatric Inventory, Nursing Home version; PAS, Pittsburgh Agitation Scale; RCT, Randomized controlled trial; SCQ, Self-Administered Comorbidity Questionnaire; SDI, Sleep Disorders Inventory; SDQ, The Sleep Disorders Questionnaire; VaD, Vascular dementia.

day, for the whole day, or with light (±1000 lux or dim ± 300 lux) from ceiling fixtures in the common living room, or with evening melatonin or light and melatonin in combination or placebo.

BLT improved circadian activity rhythm disturbances, sleeping patterns as well as cognitive performance, depression, and functional limitations in patients with moderate to severe dementia. Melatonin reduced sleep onset and increased sleep duration, but increased withdrawn behavior. Combined treatment attenuated aggressive behavior, increased sleep efficiency, and improved nocturnal restlessness. According to the authors, to suppress side effects on mood, melatonin and BLT should be used in combination.

Barrick and co-workers [44] studied the impact of BLT on agitation in 66 patients with moderate or severe dementia living in care facility. They delivered, for 20 months, 2500 lux in activity and dining areas, by an architectural lighting system, according to a design involving four ambient lighting conditions: morning bright light, evening bright light, all day bright light, and standard light. In patients with mild/moderate dementia, agitation was not reduced, but even increased in all the lighting conditions, compared to standard light, while in severe dementia a tendency to a greater agitation during morning light was observed. According to the authors, probably there is no direct link between light therapy, circadian rhythms, and agitation, but a combined treatment, such as with melatonin should be used.

Figueiro and colleagues [35], assuming that circadian system is extremely sensitive to short wavelength, examined, for 4 weeks, the effectiveness of a low-level 'bluish-white' lighting (300–400 lux) on 14 patients with moderate dementia living in long-term care facilities. Such exposure increased circadian entrainment, improving total sleep time and sleep efficiency, reducing agitation and depression and increasing phasor magnitude. Subsequently, Figueiro and co-workers [36] extended previous study investigating a larger sample (35 patients) and their caregivers living at home. The results were less compelling than those of the patients from the facilities [35, 36]. However, as in previous study, circadian entrainment and sleep efficiency significantly increased, depression significantly reduced, sleep duration increased, but it was not statistically significant. The caregivers also exhibited an increase in circadian entrainment. A seasonal effect of greater sleep efficiency and longer sleep duration was also found for caregivers (the winter months better than the summer months). According to the authors, a lighting intervention in a more controlled environment, such as care facility, may be more effective than the same intervention in the home [36].

Similarly, Sloane and co-workers [45], evaluated, in a randomized controlled trial with crossover, the impact of a blue-white light therapy on 17 pairs of patients with moderate or severe dementia living at home and their caregivers. Over six weeks, two different study conditions and a four-week washout period were applied. In the 'intervention condition', participants received blue-white light and in the 'control condition' red-yellow light. The blue-white light was supposed to stimulate the circadian system more than the yellow-white and the blue LED light box would have to stimulate the circadian system more than the red LED. In the intervention condition, 13000 K compact fluorescent light bulbs were located in table and floor lamps in the area where the patients lived for most of the day and were lit from waking up at 18:00. In addition, a light-emitting diode light box was placed in the breakfast and lunch area. In control condition, 2700 K compact fluorescent light bulbs were placed in the table and floor lamps and used during the day, while a red LED light box was used for breakfast and lunch. Blue-white light improved sleep and stress in caregivers, but not in patients with dementia. Depression, instead, improved and was more sensitive to treatment and lower levels. According to the authors, the relatively low dose may have been sufficient to target normal caregivers but not people with dementia, probably because the circadian systems of people with dementia may need more time and greater or prolonged circadian stimulation to respond to light and to reach significant effects. Actually, in a previous study, Van Someren and colleagues [46] observed positive effect of bright light on sleep parameters in people with dementia only after six months of treatment.

Recently, van Lieshout-van Dal and colleagues [38], assuming that the effect of biodynamic lighting had not been studied, investigated, for three weeks, circadian function of 13 patients with dementia living in a care facility. They placed in a common area, three special biodynamic lighting armatures, producing direct and indirect light with a high illuminance and bluish color in the morning, and lower levels in the evening, to simulate intensity, spectrum, and temporal characteristics of a natural daylight curve. Lighting level and color temperature were combined and changed gradually during the day: a light intensity from 600 lux at 8 a.m., 1100 lux from 10 a.m.

till 2 p.m. and 600 lux at 5 p.m., while color temperature bluish light, around 6500 K, in the day, and warm, around 1800 K, in the evening. Results showed positive effects on the sleeping pattern. The average frequency of night-time bed wandering, total time out of bed at night and the average frequency of daytime napping significantly decreased. Conversely, the average total night-time sleep significantly increased and the patients were more active during the day, improving their circadian rhythm. As a consequence, the treatment could also facilitate the caregivers' night care task. According to the authors, biodynamic lighting stimulates circadian entrainment because it resembles daylight curve. Therefore, it could be a non-pharmacological intervention, without any side effects, in a home situation, in patients with dementia.

Treatment devices approach

Yamadera and coworkers [31] investigated the impact of BLT on cognition and circadian rhythm of 27 Alzheimer-type dementia patients. Participants were exposed to BLT in the morning for four consecutive weeks (3000 lux, 9–11 am). Circadian rhythm and cognitive performance significantly improved in early-stage AD, while they did not improve in moderately and severely demented patients. According to the authors, moderate and severe patients might have a weaker sensitivity for light, because a more severe damage in the regulation of sleep–wake rhythm, in the SCN.

Similarly, Ancoli-Israel and co-workers [47], studied in a randomized controlled trial, 77 severely demented nursing home patients, assigned to one of four treatments: evening bright light, morning bright light, daytime sleep restriction, or evening dim red light. All patients were severe. However, a differential diagnosis between the various types of dementia was not made. Patients were exposed to 2500 lux for 2 hours. In the dim light condition, they were exposed to less than 50 lux red light from 5:30 p.m. to 7:30 p.m. Each protocol lasted 18 days. Post-treatment follow-up data were collected for 5 additional days. No significant improvements in nighttime sleep or daytime alertness, in any of the treatment groups, were found. However, morning bright light condition delayed circadian rhythms in every individual and improved circadian rhythm quality. Morning bright light also improved agitation in a small subsample. Evening bright light condition delayed the rhythm, but not significantly. Such poor results were attributed to the severity of dementia and the lack of homogeneity of the sample, where different types of dementia were considered as a single group. In addition, according to the authors, light treatment might improve sleep only in some types of dementia. Results were considered clinically favorable because it appears easier to assist patients whose circadian activity patterns are more socially acceptable. On these results, in a second trial, Ancoli-Israel and colleagues [48] studied a more homogeneous group of 92 patients with possible or probable AD living in nursing home. Results did not replicate previous study. Both morning and evening light led to more consolidated sleep at night. Moreover, evening light increased the quality of the rhythm of circadian activity. However, no improvement was found on total sleep time. Therefore, increasing light exposure during the day and evening probably has the most beneficial effect on sleep and circadian rhythms in patients with dementia. According to the authors, BLT could be the most effective non-pharmacological approach to improve sleep rhythms and circadian activity in patients with AD.

Burns and colleagues [33], underlining that agitation drugs can result in serious side effects and in increasing mortality rate in people with dementia, studied the effects of BLT on agitation and sleep disturbances in order to identify alternative treatments to drugs. They assessed the effects of BLT on agitation and sleep disorders, by a single-center randomized controlled study on 48 patients living in care facility, with moderate and severe dementia, 26 randomized to standard light, 22 to BLT. Patients were exposed daily for two weeks to full spectrum BLT 10000 lux or standard fluorescent tube light at 100 lux, for 2 hours in the morning, between 10 a.m. and noon. BLT resulted in a partial reduction of agitation and improving sleep, especially in the winter. According to the authors, BLT may be a potential alternative to drug treatment and may reduce the need for medication in agitation. The wide range of responses to BLT observed were attributed to the heterogeneity of the sample examined.

McCurry and coworkers [39], to investigate the efficacy on improving sleep disorders in dementia, studied 132 AD patients with sleep problems and their caregivers, by a randomized, controlled trial with blinded assessors. They used three different treatment approach: light exposure (1 hour/day, by a light box, approximately 2500 lux of full spectrum light before going to sleep), walking (30 continuous minutes/day), and a combination treatment (walking, light exposure, sleep education). Participants were

randomly assigned to one of three active treatments or contact control. AD patients with sleep problems benefited from walking and increased light exposure, either alone or in combination. Patients with greater adherence to walking and light exposure recommendations had significantly less total wake time and better sleep efficiency at post-test than those with lesser adherence. Sleep improvements were not sustained at six months.

Onega and co-workers [40], in a first study, assessed in the AD population the effects of bright light therapy compared to low intensity light therapy. They studied, by a randomized controlled design, 60 patients with dementia, living in a long-term facility. Participants were randomly assigned to receive either bright light, or low intensity light for eight weeks, for half an hour twice a day (morning and afternoon/evening) for 2 months. The intense light (10000 lux) elicited a significant improvement in depression and agitation, while low intensity light produced higher levels of depression and agitation or no significant change. In a second study, Onega and colleagues [32] investigated the effect of BLT in relation to the severity of the dementia. They found that bright light exposure is an equally effective intervention for depression both in mild/moderate and severe dementia. However, overall findings showed that BLT alone or with other interventions, both non-pharmacological and pharmacological, improve depression regardless of dementia severity and that patients with severe dementia are most likely to be subject to changes in circadian rhythm or sleep patterns.

In an observational study, Sekiguchi and colleagues [37], to investigate the efficacy of BLT in the different stages of cognitive decline and in the types of dementia, studied 17 patients including Alzheimer-type dementia, vascular dementia, and Lewy bodies dementia. A device for bright light (approximately 5000 lux of full spectrum light), was placed at eye level, every day, for 1 hour/day (from to 9:00 to 10:00) for 2 weeks. BLT resulted in the improvement of sleep disturbance in four AD patients (on eight) in the mild or moderate stage. However, dementia patients showed difficulty complying with the light therapy due to attention deficit, their dislike of the therapy, hyperactivity, and a tendency to wander in ward. None of the vascular dementia and Lewy bodies dementia patients improved nocturnal sleep. According to the authors, patients with vascular dementia had a higher prevalence of sleep apnea. Moreover, their poor-quality sleep may reflect the disruptive effects of the lacunes in the internal capsule, in the basal ganglia and in the periventricular white matter of the neural network leading to and from the suprachiasmatic nucleus. Similarly, sleep disorders in Lewy bodies dementia have been attributed to changes in the arousal system by pathology of the brainstem and limbic region [37]. Therefore, the BLT could be considered as an effective strategy for treating dementia, depending on the type and the severity and should be emphasized as a non-pharmacological therapy for sleep disorders and a safe form of treatment for patients with dementia.

DISCUSSION

The focus of the current overview was to examine research studies, in the two last decades, reporting on the effect of the BLT on sleep and rhythms in AD patients. All the research agrees in considering BLT as a promising non-pharmacological intervention able to compensate circadian rhythm alterations in elderly people with dementia, without any side effects. Furthermore, it can drive again patients to light's primordial rhythms connecting all living beings in a single large harmonic timeline that promoting circadian entrainment, health and well-being.

However, some research does not reach sufficient evidence to support the effectiveness of BLT in dementia. Nevertheless, they agree on the need for further research for a better understanding of the effectiveness of an accounted treatment as a 'therapy' of sleep disturbances and behavior in AD. Dementia, by its nature, is a degenerative, worsening, and progressive pathology impacting cognitive function and behavioral dimension [49, 50]. To date, however, no therapeutic technique is able to stop the degenerative process, apart from a low pharmacological repertoire acting on the most disturbing symptoms. In this picture, BLT should be framed. It is referred to as 'Therapy'. Certainly not as in a recovery meaning nor, even less, as a 'restitutio ad integrum'. However, according to the literature data, BLT could represent a significant support intervention in the aging world for an increasingly large clinical population.

Methodologically, the research reports two different treatment designs. In half of the studies, an architectural lighting approach was used, both at home and in care facilities. It simulates light-dark circadian rhythms and promoting sleep-wake patterns in an 'ecological context'. The environments in

which the patient lives permanently are illuminated according to 'circadian' criteria, for the whole day and even the darkness of the evening and night [17]. In such setting, the patient can benefit dynamically from the treatment, without any active involvement and no intentional collaboration and despite his attentional and psychomotor instability and the tendency to wander and move around in the environment.

Just one half of the research [31–33, 37, 39, 40, 47, 48] instead report on light interventions delivered through special treatment devices such as light boxes. In this condition, treatment intensity and duration may be scheduled according to the circadian phases and individual patterns of the patients in a particular daytime. However, the constant presence and supervision of the operators, to ensure patient's compliance and delivery of light therapy, is needed.

In the studies, both the two intervention designs have advantages. However, while a timed exposure to intense light by specific devices can be an effective moment of a treatment program, probably, the planning of the light in the whole environment can be seen as a fully treatment, although some studies have surprisingly documented low outcome measures or improvement only in some patient subgroups or even a disorders' exacerbation.

A greater, but not full, agreement is recorded on the day exposure timing. Studies reported inconsistent data on the difference in effectiveness of the treatment in a specific period of the day [41, 48]. Differences were found with morning versus evening exposure in the heterogeneous dementia group. Morning light delayed the acrophase and improved activity rhythmicity [47]. However, when it was considered only an AD homogeneous group, both morning and evening light resulted in more consolidated sleep at night. Moreover, evening light increased the quality of the circadian rhythm.

Overall, therefore, data seem to better support the hypothesis of a greater advantage in morning light exposure. Interestingly, in this context, 'morning', 'evening', 'day', and 'night' refers to the clock time and not to the endogenous circadian phase of the patients. Probably, the optimal time for delivering lighting depends upon an individual's circadian cycle and relation to a model rhythm that is in sync with the natural light/dark cycle. Therefore, although all-day light exposure resembles the natural light/dark pattern, in practice, choosing the best time for BLT represents a complex choice, in which multiple clinical, individual, and environmental variables interact. Probably, a study protocol that evaluates the multiplicity of variables involved could provide more conclusive data also on timing.

In clinical practice, greater agreement should be reached on the most appropriate procedures to achieve the largest therapeutic advantage. Actually, non-homogeneous criteria were used in the sample recruitment criteria, in the size sample, in the timing, intensity and duration of exposure of the single therapy session, in the overall duration of the treatment, in the period of the year of therapy. Many studies have tried various combinations of intensity and duration for best results with more intense exposure in a shorter time, assuming that for people with dementia a short intervention may favor better compliance. Therefore, future research must aim at the construction of a standardized protocol allowing a more immediate data comparison and overcoming many current inconsistencies.

Finally, a relevant outstanding issue concerns interaction between BLT and other therapeutic treatments. Using BLT and melatonin [37], light treatment alone did not result in improvement, melatonin shortened sleep latency and increased sleep duration, but increased also negative mood and withdrawn behavior, while a combination BLT and melatonin increased subject's activity levels and wake time and strengthened rest-activity rhythm [44]. Similarly, studies [32] using BLT, walking, and a combination of the two treatments provided evidence that walking, light exposure, and the combination are potentially effective treatments either alone or in combination. However, future studies should be needed to understanding to what extent improvements are due to each individual therapeutic modality, such as melatonin, or whether different 'zeitgebers' may interact to amplify their efficacy.

Interestingly, recently in an attempt to contain the spread of COVID-19 pandemic, health authorities have forced populations to stay home for an unlimited time. Therefore, people with AD are not currently able to enjoy exposure to sunlight and they may experience an exacerbation of sleep and behavioral disorders, increasing caregiver's stress; hence, the need to compensate by providing targeted indoor lighting interventions, through an environmental-architectural design or special light devices.

Such lighting interventions appear as an answer to a primary problem resulting from a degenerative process of the retinal ganglion cells and suprachiasmatic structures. Degenerative process can be amplified by the lifestyle of patients who live less outdoors and reduce the time of exposure to sunlight. The recent

restrictions due to COVID-19 further increase this reduction, although the patients who can live daily life in an adequately bright environment will feel less the effects of reduced exposition to outdoor sunlight. Therefore, BLT aims primarily to reduce the damage of the neurodegenerative process. Secondly, it may represent a compensatory intervention for the reduced exposure to sunlight related to the patient's lifestyle or to the restrictions from COVID-19 pandemic or to both conditions.

In sum, although literature data are often inconsistent, research agrees on the therapeutic potential of a non-pharmacological treatment using light as a 'zeitgeber' able of eliciting responses to improve normal circadian rhythms, in patients with AD, so that even for them... 'facta est lux', 'factumque est vespere et mane'.

DISCLOSURE STATEMENT

Authors' disclosures available online (https://www.j-alz.com/manuscript-disclosures/20-0478r1).

REFERENCES

[1] Halberg F (1969) Chronobiology. *Annu Rev Physiol* **31**, 675-726.

[2] Berson DM, Dunn FA, Takao M (2002) Phototransduction by retinal ganglion cells that set the circadian clock. *Science* **295**, 1070-1073.

[3] Hattar S, Lucas RJ, Mrosovsky N, Thompson S, Douglas RH, Hankins MW, Lem J, Biel M, Hofmann F, Foster RG (2003) Melanopsin and rod–cone photoreceptive systems account for all major accessory visual functions in mice. *Nature* **424**, 75-81.

[4] Ramkisoensing A, Meijer JH (2015) Synchronization of biological clock neurons by light and peripheral feedback systems promotes circadian rhythms and health. *Front Neurol* **6**, 128.

[5] Weaver DR (1998) The suprachiasmatic nucleus: A 25-year retrospective. *J Biol Rhythms* **13**, 100-112.

[6] Stephan FK, Zucker I (1972) Circadian rhythms in drinking behavior and locomotor activity of rats are eliminated by hypothalamic lesions (suprachiasmatic and medial preoptic nuclei/retino-hypothalamic projection). *Proc Natl Acad Sci U S A* **69**, 1583-1586.

[7] Walton JC, Weil ZM, Nelson RJ (2011) Influence of photoperiod on hormones, behavior, and immune function. *Front Neuroendocrinol* **32**, 303-319.

[8] Grandin LD, Alloy LB, Abramson LY (2006) The social zeitgeber theory, circadian rhythms, and mood disorders: Review and evaluation. *Clin Psychol Rev* **26**, 679-694.

[9] Baron KG, Reid KJ (2014) Circadian misalignment and health. *Int Rev Psychiatry* **26**, 139-154.

[10] Germain A, Kupfer DJ (2008) Circadian rhythm disturbances in depression. *Hum Psychopharmacol* **23**, 571-585.

[11] Van Someren EJW (2000) Circadian and sleep disturbances in the elderly. *Exp Gerontol* **35**, 1229-1237.

[12] Swaab DF, Grundke-Iqbal I, Iqbal K, Kremer HPH, Ravid R, Van de Nes JAP (1992) τ and ubiquitin in the human hypothalamus in aging and Alzheimer's disease. *Brain Res* **590**, 239-249.

[13] Hofman MA (2000) The human circadian clock and aging. *Chronobiol Int* **17**, 245-259.

[14] Swaab DF, Fliers E, Partiman TS (1985) The suprachiasmatic nucleus of the human brain in relation to sex, age and senile dementia. *Brain Res* **342**, 37-44.

[15] Witting W, Kwa IH, Eikelenboom P, Mirmiran M, Swaab DF (1990) Alterations in the circadian rest-activity rhythm in aging and Alzheimer's disease. *Biol Psychiatry* **27**, 563-572.

[16] Lin L, Huang Q-X, Yang S-S, Chu J, Wang J-Z, Tian Q (2013) Melatonin in Alzheimer's disease. *Int J Mol Sci* **14**, 14575-14593.

[17] White MD, Ancoli-Israel S, Wilson RR (2013) Senior living environments: Evidence-based lighting design strategies. *HERD Heal Environ Res Des J* **7**, 60-78.

[18] Riemersma-Van Der Lek RF, Swaab DF, Twisk J, Hol EM, Hoogendijk WJG, Van Someren EJW (2008) Effect of bright light and melatonin on cognitive and noncognitive function in elderly residents of group care facilities: A randomized controlled trial. *JAMA* **299**, 2642-2655.

[19] Landry GJ, Liu-Ambrose T (2014) Buying time: A rationale for examining the use of circadian rhythm and sleep interventions to delay progression of mild cognitive impairment to Alzheimer's disease. *Front Aging Neurosci* **6**, 325.

[20] Srinivasan V, Kaur C, Pandi-Perumal S, Brown GM, Cardinali DP (2011) Melatonin and its agonist ramelteon in Alzheimer's disease: Possible therapeutic value. *Int J Alzheimers Dis* **2011**, 741974.

[21] Lewy AJ, Wehr TA, Goodwin FK, Newsome DA, Markey SP (1980) Light suppresses melatonin secretion in humans. *Science* **210**, 1267-1269.

[22] LeGates TA, Fernandez DC, Hattar S (2014) Light as a central modulator of circadian rhythms, sleep and affect. *Nat Rev Neurosci* **15**, 443-454.

[23] Parry BL, Mahan AM, Mostofi N, Klauber MR, Lew GS, Gillin JC (1993) Light therapy of late luteal phase dysphoric disorder: An extended study. *Am J Psychiatry* **150**, 1417-1419.

[24] Lam RW, Carter D, Misri S, Kuan AJ, Yatham LN, Zis AP (1999) A controlled study of light therapy in women with late luteal phase dysphoric disorder. *Psychiatry Res* **86**, 185-192.

[25] Lam RW, Goldner EM, Solyom L, Remick RA (1994) A controlled study of light therapy for bulimia nervosa. *Am J Psychiatry* **151**, 744-750.

[26] Braun DL, Sunday SR, Fornari VM, Halmi KA (1999) Bright light therapy decreases winter binge frequency in women with bulimia nervosa: A double-blind, placebo-controlled study. *Compr Psychiatry* **40**, 442-448.

[27] Oren DA, Wisner KL, Spinelli M, Epperson CN, Peindl KS, Terman JS, Terman M (2002) An open trial of morning light therapy for treatment of antepartum depression. *Am J Psychiatry* **159**, 666-669.

[28] Wirz-Justice A, Bader A, Frisch U, Stieglitz R-D, Alder J, Bitzer J, Hösli I, Jazbec S, Benedetti F, Terman M, Wisner KL, Riecher-Rössler A (2011) A randomized, double-blind, placebo-controlled study of light therapy for antepartum depression. *J Clin Psychiatry* **72**, 986-993.

[29] Corral M, Kuan A, Kostaras D (2000) Bright light therapy's effect on postpartum depression. *Am J Psychiatry* **157**, 303-304.

[30] Corral M, Wardrop AA, Zhang H, Grewal AK, Patton S (2007) Morning light therapy for postpartum depression. *Arch Womens Ment Health* **10**, 221-224.

[31] Yamadera H, Ito T, Suzuki H, Asayama K, Ito R, Endo S (2000) Effects of bright light on cognitive and sleep-wake (circadian) rhythm disturbances in Alzheimer-type dementia. *Psychiatry Clin Neurosci* **54**, 352-353.

[32] Onega LL, Pierce TW, Epperly L (2018) Bright light therapy to treat depression in individuals with mild/moderate or severe dementia. *Issues Ment Health Nurs* **39**, 370-373.

[33] Burns A, Allen H, Tomenson B, Duignan D, Byrne J (2009) Bright light therapy for agitation in dementia: A randomized controlled trial. *Int Psychogeriatrics* **21**, 711-721.

[34] Most EIS, Scheltens P, Van Someren EJW (2010) Prevention of depression and sleep disturbances in elderly with memory-problems by activation of the biological clock with light - a randomized clinical trial. *Trials* **11**, 19.

[35] Figueiro MG, Plitnick BA, Lok A, Jones GE, Higgins P, Hornick TR, Rea MS (2014) Tailored lighting intervention improves measures of sleep, depression, and agitation in persons with Alzheimer's disease and related dementia living in long-term care facilities. *Clin Interv Aging* **9**, 1527.

[36] Figueiro MG, Hunter CM, Higgins PA, Hornick TR, Jones GE, Plitnick B, Brons J, Rea MS (2015) Tailored lighting intervention for persons with dementia and caregivers living at home. *Sleep Health* **1**, 322-330.

[37] Sekiguchi H, Iritani S, Fujita K (2017) Bright light therapy for sleep disturbance in dementia is most effective for mild to moderate Alzheimer's type dementia: A case series. *Psychogeriatrics* **17**, 275-281.

[38] van Lieshout-van Dal E, Snaphaan L, Bongers I (2019) Biodynamic lighting effects on the sleep pattern of people with dementia. *Build Environ* **150**, 245-253.

[39] McCurry SM, Pike KC, Vitiello MV, Logsdon RG, Larson EB, Teri L (2011) Increasing walking and bright light exposure to improve sleep in community-dwelling persons with Alzheimer's disease: Results of a randomized, controlled trial. *J Am Geriatr Soc* **59**, 1393-1402.

[40] Onega LL, Pierce TW, Epperly L (2016) Effect of bright light exposure on depression and agitation in older adults with dementia. *Issues Ment Health Nurs* **37**, 660-667.

[41] Hickman SE, Barrick AL, Williams CS, Zimmerman S, Connell BR, Preisser JS, Madeline Mitchell C, Sloane PD (2007) The effect of ambient bright light therapy on depressive symptoms in persons with dementia. *J Am Geriatr Soc* **55**, 1817-1824.

[42] Lyketsos CG, Lindell Veiel L, Baker A, Steele C (1999) A randomized, controlled trial of bright light therapy for agitated behaviors in dementia patients residing in long-term care. *Int J Geriatr Psychiatry* **14**, 520-525.

[43] Hanger MA, Ancoli-Israel S, Kripke DF, Jones DW, Almendarez L (1992) Effect of phototherapy on depression in nursing home residents. *Sleep Res* **21**, 88.

[44] Barrick AL, Sloane PD, Williams CS, Mitchell CM, Connell BR, Wood W, Hickman SE, Preisser JS, Zimmerman S (2010) Impact of ambient bright light on agitation in dementia. *Int J Geriatr Psychiatry* **25**, 1013-1021.

[45] Sloane PD, Figueiro M, Garg S, Cohen LW, Reed D, Williams CS, Preisser J, Zimmerman S (2015) Effect of home-based light treatment on persons with dementia and their caregivers. *Light Res Technol* **47**, 161-176.

[46] Van Someren EJW, Kessler A, Mirmiran M, Swaab DF (1997) Indirect bright light improves circadian rest-activity rhythm disturbances in demented patients. *Biol Psychiatry* **41**, 955-963.

[47] Ancoli-Israel S, Martin JL, Kripke DF, Marler M, Klauber MR (2002) Effect of light treatment on sleep and circadian rhythms in demented nursing home patients. *J Am Geriatr Soc* **50**, 282-289.

[48] Ancoli-Israel S, Gehrman P, Martin JL, Shochat T, Marler M, Corey-Bloom J, Levi L (2003) Increased light exposure consolidates sleep and strengthens circadian rhythms in severe Alzheimer's disease patients. *Behav Sleep Med* **1**, 22-36.

[49] Smirni D, Smirni P, Di Martino G, Cipolotti L, Oliveri M, Turriziani P (2018) Standardization and validation of a parallel form of the verbal and non-verbal recognition memory test in an Italian population sample. *Neurol Sci* **39**, 1391-1399.

[50] Smirni D, Smirni P, Di Martino G, Fontana ML, Cipolotti L, Oliveri M, Turriziani P (2019) Early detection of memory impairments in older adults: Standardization of a short version of the verbal and nonverbal Recognition Memory Test. *Neurol Sci* **40**, 97-103.