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ORIGINAL ARTICLE

The effect of bright light therapy on sleep and circadian rhythms in renal transplant recipients: a pilot randomized, multicentre wait-list controlled trial

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Conflicts of interest
There are no conflicts of interest.

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Summary

This study assessed the effect and feasibility of morning bright light therapy (BLT) on sleep, circadian rhythms, subjective feelings, depressive symptomatology and cognition in renal transplant recipients (RTx) diagnosed with sleep–wake disturbances (SWD). This pilot randomized multicentre wait-list controlled trial included 30 home-dwelling RTx randomly assigned 1:1 to either 3 weeks of BLT or a wait-list control group. Morning BLT (10 000 lux) was individually scheduled for 30 min daily for 3 weeks. Wrist actimetry (measuring sleep and circadian rhythms), validated instruments (subjective feelings and cognition) and melatonin assay (circadian timing) were used. Data were analysed via a random-intercept regression model. Of 30 RTx recipients (aged 58 ± 15, transplanted 15 ± 6 years ago), 26 completed the study. While BLT had no significant effect on circadian and sleep measures, sleep timing improved significantly. The intervention group showed a significant get-up time phase advance from baseline to intervention (+24 min) [(standardized estimates (SE): −0.23 (−0.42; −0.03)] and a small (+14 min) but significant bedtime phase advance from intervention to follow-up (SE: −0.25 (−0.41; −0.09). Improvement in subjective feelings and depressive symptomatology was observed but was not statistically significant. Bright light therapy showed preliminary indications of a beneficial effect in RTx with sleep–wake disturbances. (ClinicalTrials.gov number: NCT01256983)

Introduction

Sleep–wake disturbances (SWD) are prevalent in renal transplant recipients (RTx) [1]: 49% report poor sleep quality [2,3], 34.1% poor daytime functioning [2] and 51% daytime sleepiness [3]. Other relevant indicators of sleep issues in this population are insomnia (inability to fall asleep or to stay asleep as long as desired), with a prevalence of 8% [4], restless legs syndrome (neurological disorder) 4.5% [5] and obstructive sleep apnoea 27% [6]. Sleep issues in RTx have been hypothetically linked to medications (e.g. β-blockers [7], nonsteroidal anti-inflammatory drugs [8] and corticosteroids [9]), pre-existing sleep disorders, fear of organ rejection, deteriorating kidney function, psychosocial problems, psychiatric and neurological disturbances, diet, ageing and comorbidities (e.g. diabetes,

adiposities, heart failure, rheumatoid arthritis and cancer) [10,11]. In the general population, poor sleep is associated with cardiovascular disorders, obesity, psychiatric problems and cognitive impairment [12]. In haemodialysis patients, poor sleep accompanies a 16% higher relative risk of mortality [13].

Links between high sleep disorders prevalence in RTx and other chronic illness groups are only partially understood. However, interplays between immune factors [14,15] may worsen sleep, with circadian disruption leading, conversely, to inflammatory response deregulation [16]. Our research showed that the most frequent RTx-related sleep diagnosis is chronic insomnia (42.5%), followed by circadian rhythm sleep disturbances (20.1%; 13.4% with delayed rhythm) [1]; both diagnoses include SWD [17]. The goal of SWD treatment is to re-entrain circadian rhythms and sleep–wake timing with the 24-h light/dark cycle. As an alternative to pharmacological treatments (e.g. sleeping pills), SWD can be treated via bright light therapy (BLT) [18], that is exposure of the retina to a prescribed intensity and duration of artificial morning light (from a light box) for a prescribed time of the day [19,20]. BLT shortly after morning awakening has been shown to advance sleep timing (suppressing melatonin production with earlier bedtimes and get-up times) (Fig. 1) [21,22], thereby shortening sleep latency (time necessary to fall asleep) and increasing sleep efficiency (the time spent asleep compared with time in bed) [23]. Because the endogenous circadian period for most humans is slightly longer than 24 h [24], (i.e. roughly 12 min longer than the 24-h day–night cycle, it requires daily phase-advancing synchronization via light [24]. An additional phase advance (12 min) caused by morning BLT is therefore biologically and clinically meaningful (more information can be found in the reference of Burke *et al.*) [25].

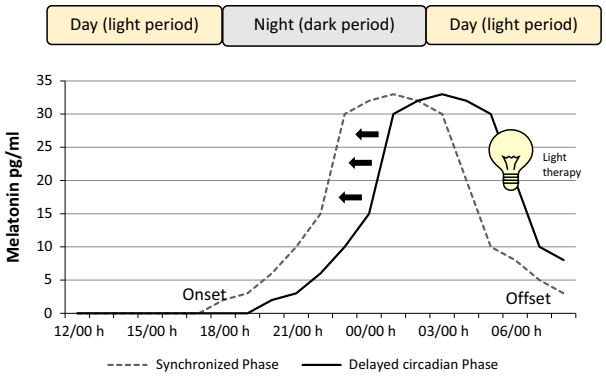

Figure 1 The diagram above shows how bright morning light affects melatonin onset and offset earlier (dotted lines), so the person can get to sleep earlier. Melatonin is a hormone excreted by the pineal gland, and its production is controlled by the circadian clock, located in the suprachiasmatic nuclei in the anterior hypothalamus. Thus, melatonin levels exhibit an endogenously controlled circadian rhythm profile. In addition, light to the retina of the eye can acutely suppress melatonin levels and phase shift melatonin rhythms, thus acting as a 'Zeitgeber' for the entrainment of the circadian timing system to the 24-h light–dark cycle from the environment [20]. In the graph, time is displayed in the *x* axis and saliva melatonin in the *y* axis.

As an established treatment for affective disorders [26], BLT has been shown to improve mood [27], depression [28,29], sleep disturbances [30] and general performance (e.g. reaction time) [31] and is a valuable treatment for SWD, particularly sleep timing problems, in the general population [32–34]. Adverse effects may include agitation, headache or nausea, but are rapidly reversible by reducing light intensity or duration [35]. Therefore, BLT can be considered a safe, reliable (especially in contrast to hypnotics) treatment for community dwelling RTx [36,37]. The purpose of this pilot study was therefore to evaluate the feasibility of implementing a daily morning BLT intervention in RTx in the community setting and to conduct a preliminary exploration of its efficacy for improving sleep characteristics. Specific aims were to (i) test the intervention's feasibility (i.e. willingness to participate in the intervention study, BLT adherence and acceptability in the RTx population), (ii) explore BLT's effects on sleep variables (sleep efficiency, sleep latency), circadian factors (sleep timing, 24-h sleep–wake behaviour, and melatonin secretion), subjective feelings and cognition.

Material and methods

Design

This pilot study used a multicentre randomized wait-list controlled design with a 1:1 randomization sequence (Fig. 2), so that everybody benefits from the intervention that is staggered over time. The intervention group completed 3 weeks of baseline measurement, followed by 3 weeks of morning BLT, then a 3 week post-treatment assessment. The baseline assessment for the control group had a 9 weeks duration, followed by 3 weeks of morning BLT. A computerized random allocation sequence was generated by an external research assistant, who also prepared the sequentially numbered opaque envelopes containing the allocation information. Until each participant opened his or her assignment package, the research team had no knowledge of allocations.

Participants, eligibility criteria and setting

Participants were recruited at the University Hospitals of Basel, Bern and Zurich and had all participated in a previously described study [1,3]. The inclusion criteria were adult RTx recipients more than 1 year post-transplant and diagnosed with SWD (sleep assessment interview in the preceding study); German speaking; on stable immunosup-

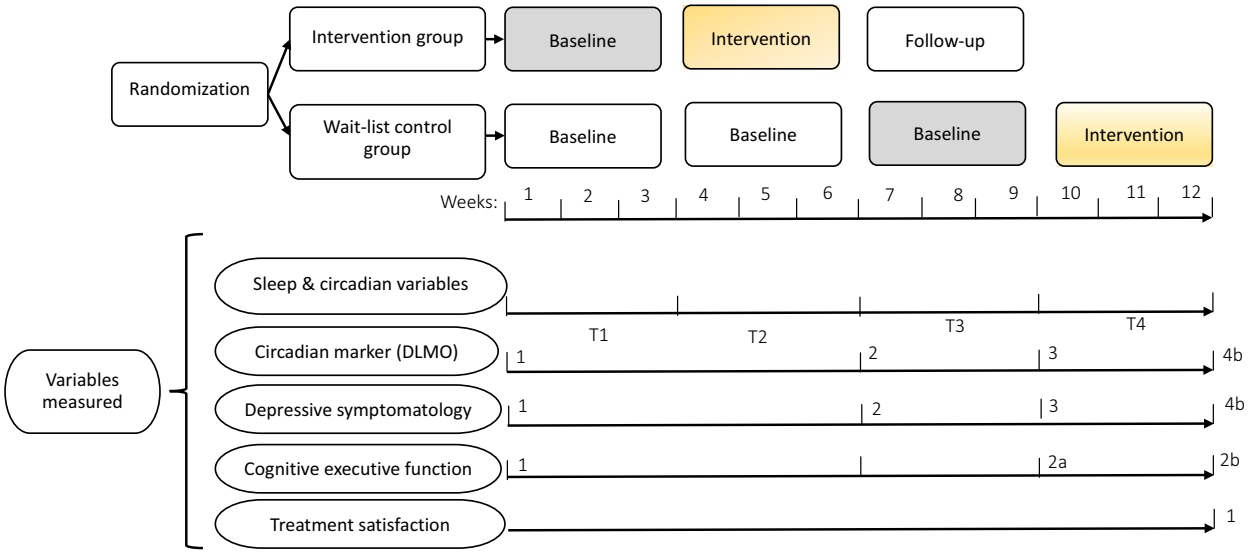

Figure 2 Randomized controlled multicentre wait-listed design including the pre–post-design for the analysis of the early and late intervention. T = time period grey and yellow boxes = analysis of the early and late intervention; Circadian and Sleep variables = measured with actimetry and diary; DLMO = dim light melatonin onset; depressive symptomatology = measured with the depression anxiety and stress scale; treatment satisfaction = measured with two questions (would you recommend light therapy to a friend and was light therapy perceived efficacious); numbers in the variables refer to the assessment times; a = measurement only for the early group; b = measurement only for late group.

pressive drugs; no signs of acute rejection; and normal ocular function (by self-report and by chart review) [38]. Exclusion criteria were acute illness or hospitalization.

Bright light therapy intervention

Morning BLT was delivered using a light box (Bright Light Energy HF 3304; Philips, Amsterdam, Netherlands) installed in each participant's home. The principal investigator (HB) instructed participants on the light box's use. To receive the appropriate dosage, at a time determined by his/her individual chronotype (measured with the morning–evening questionnaire in the preceding study, reflecting at what time of the day the individual is most active), 30 min daily for 3 weeks, the participant would sit 30–50 cm from the light box lamp, which produced 10 000 lux at eye level [1]. We allowed for a $\pm$ 1.5 h deviation from the optimum starting time (this allows for everyday life realities and light is also effective later in the morning). In the event of problems, participants were instructed to contact the research team.

Measures

Clinical characteristics

Clinical characteristics [age in years, gender, years since transplantation, BMI (kg/m^2), creatinine level (μmol/l), haemoglobin level (g/l) and medications used (including sleep drugs)] were retrieved from the participants' hospital medical charts. Comorbidity data were also extracted from patients' charts and summarized using the Charlson comorbidity index [39] (a sum of the assigned scores of the concurrent diseases: higher scores indicate greater overall morbidity). Sleep quality, daytime sleepiness and chronotype measurements were retrieved from our previous observational study data [1].

Feasibility outcomes

Feasibility was measured in relation to recruitment, attrition, number of adverse events or side effects of BLT and frequency of extra calls or visits responding to problems.

Adherence to the BLT intervention was assessed using the light sensor on the actigraph [expressed in luminance (lux/m^2)]. These data allow monitoring of both adherence to the intervention and overall individual light exposure. Nonadherence was defined as using the light box for 25% or less of the prescribed duration (as described by Michalack *et al.*) [40]. At the study's end, as proxy measures for satisfaction, the subjects were asked whether they would recommend light therapy to a friend (yes/no) and whether they felt light therapy was efficacious (yes/no).

Sleep outcomes

Sleep efficiency and sleep latency were measured with a combination actimeter/light monitor. An actimeter collects movements of the nondominant wrist at 1-min interval to provide a 24-h pattern of rest and activity, and indirectly, characteristics of sleep (sleep latency, sleep efficiency). Acti-

metry has been established as a reliable, objective method to assess SWD [41]. Participants were instructed to wear the device (Daqtometer® by Daqtix GbR, Oetzen, Germany) continuously for the entire study period [42]. To standardize the data [41], participants were provided with diaries in which to log 6 daily items: the time they went to bed, the time the lights were turned off, their perceptions of how long it took them to fall asleep, the number of times they got up during the night, the number of times they awoke and any periods the actimeter was off their wrist [43]. Daytime actimeter data gaps, normally reflecting diary-reported actimeter removal (e.g. to shower), were replaced with the average activity count for that 24-h period. If more than 3 h of data were missing for any given day, that day was excluded from further analysis. Actimetry data were analysed using SLEEP AND ACTIVITY ANALYSIS SOFTWARE 7.23V (Cambridge Neurotechnology Ltd, Cambridge, United Kingdom).

Circadian outcome

Actimetry also provided sleep timing (bedtime and get-up time) data. Bedtime was identifiable as the final activity peak before lights-out. Get-up time was defined as the first activity peak after lights-on. To determine participants' melatonin values, saliva samples were self-collected using Salivettes® (Sarstedt AG, Sevelen, Switzerland). Participants collected saliva day 1 of baseline, the final day of BLT and the final day of the study. For each 24-h collection period, participants collected and refrigerated up to five samples at 1-h intervals, starting 5 h before predicted bedtime and ending at bedtime. The sleep diary included reminders of patients' sampling days and times. Melatonin was measured via direct double-antibody radioimmunoassay (analytical sensitivity: 0.2 pg/ml) and a functional minimum detectable dose of 0.65 pg/ml (Bühlmann Laboratories AG, Allschwil, Switzerland) [44]. Saliva melatonin is normally below 3 pg/ml during daytime and up to 10 pg/ml at bedtime [45], with broad individual variability (peak values: 2–84 pg/ml) [46]. This study used the hockey-stick algorithm [47] to define and calculate dim light melatonin onset (DLMO) – the most reliable marker for circadian phase position [48].

Subjective feelings and cognitive outcomes

Depressive symptomatology was assessed via the 21-item self-report Depression, Anxiety and Stress Scale (DASS 21). Seven included items assess depressive symptoms via 4-point Likert-type scales, on which patients rate the severity and frequency of each listed state over the past week (0 = did not apply to me; 3 = applied to me very much) (Fig. 2). The resulting score can be interpreted as follows: 0–4: no depressive symptomatology; 5–6: mild; 7–10: moderate; 11–13: severe; and ≥14: extremely severe [49]. The DASS-21 has strong construct [50] and concurrent validity [51] in primary care and depressed patients [50].

Twice daily, at get-up time and before bedtime, subjective assessments of current parameters were recorded in the diary on 11-point (0–10) visual analogue scales regarding relaxation/tension, physical wellness/unwellness, alertness/drowsiness, hunger and sadness/happiness (0 = very relaxed, physically well, alert, etc.; 10 = very tense, unwell, drowsy, etc.) [52].

Executive function was measured via the Stroop colour–word interference task [53]. This task has three parts: (i) reading 74 colour words printed in black on a white background, (ii) reading 74 coloured ink printed rectangles and (iii) naming 74 colour words printed in nonmatching colours. Each part is associated with a large decrease in colour naming speed, that is 'the colour–word interference effect'. The task was administered in person or exceptionally for two patients by telephone (with the help of an instructed family member) by a research team member (days 1, 63 and 84). The three scores were combined following the task manual, resulting in one final score [54].

Data collection

The current study was approved by the relevant ethics committees of Basel, Bern and Zürich. Data were collected from December 2010 until September 2012. After providing written informed consent, participants were contacted by telephone to arrange home visits, during which the researcher explained the study details and answered any questions. At the first home visit, the participant opened the opaque allocation envelope. The actimeter was then initiated and the respective (BLT or wait-list BLT) sleep diary information explained. The researcher also provided the light box and saliva collection kit, including written and oral instructions for both. Salivette® samples were to be stored in the participant's home freezer until collected by the first author at the end of the study (visit 2). In case participants had questions or needed assistance, they were given the researcher's telephone number. At least once, on day 63, the researcher called each participant to administer the Stroop task. As a token of appreciation for their participation, at study end (visit 2), subjects received 160 Euros.

Statistical analysis

Descriptive statistics, graphs and tables were used as appropriate. Hypothesis testing for the randomized controlled trial (RCT) used linear mixed regression modelling, to which we added 'patient' as a random effect and 'group assignment', 'time point' (baseline, intervention, postintervention) and both variable's interaction term as fixed effects, using an unstructured working correlation matrix.

We also analysed the intervention data from the wait-list control group by pooling them with the data of the early-intervention group and performing a pre–post-analysis using the 3 weeks' data preceding the intervention as a baseline (for the outcome variables of bedtime, get-up time, sleep efficiency and sleep latency, depressive symptomatology, subjective feelings and cognition). Effect sizes were calculated via standardized estimates of the interaction coefficients and, for late-intervention data, the time variable. For the exploratory analysis, SPSS 19 statistics software (version 19.0.0, IBM Corporation, Armonk, New York, United States) was used, controlling for the presence of beta-blockers (BB) and acetylsalicylic acid (ASA). The mixed procedure analyses were performed using SAS 9.1.3 (SAS Institute Inc., Cary, NC, USA).

Results

Table 1 shows both groups' baseline demographics. Neither statistically nor clinically significant differences arose between groups. Of 49 patients invited to participate, 61% agreed ($N = 30$) and began the randomized controlled pilot wait-listed study, with 14 receiving the BLT intervention and 14 wait-list control intervention (attrition 6.5%). One patient from each group found the study too burdensome. Of the 26 who completed the study (Fig. 3), two were hospitalized (attrition 13%) and excluded from analysis. No extra calls or visits resulted from problems with study equipment. No adverse reactions or symptom complaints were registered. Although no technical issues were observed regarding equipment use, several participants inadvertently left their actimetry light sensors covered by their sleeves much of the time, precluding the use of light exposure data to evaluate intervention adherence. Participants' diaries indicated 100% BLT adherence. Twenty of 25 subjects (80%) reported that they would recommend BLT to a friend; however, only 13 (52%) considered it helpful for themselves.

Primary outcome – randomized trial results

Night-time sleep latency decreased slightly (−11 min) during BLT [standardized estimates (SE): −0.18 (−0.40; 0.04)] and increased again at follow-up (+18 min) [SE: 0.08 h (−0.14 h; 0.30 h)]; the control group's sleep latency decreased by 2 min from the first to the last baseline. Sleep efficiency decreased during BLT (−1.49%) [SE: 0.00 (−0.16; 0.17)]; and decreased again (−0.95%) during follow-up [SE: −0.05 (−0.21; 0.12)]; the control group's decreased by 1.18% from the first to the last baseline (all statistically nonsignificant, Table 2).

Morning BLT induced a significant phase advance for get-up time from baseline to intervention (+24 min)

Table 1. Descriptive characteristics of the sample.

	All ($N = 30$)		Intervention group ($N = 15$)		Wait-list control group ($N = 15$)	
	N	Percentage	*N*	Percentage	*N*	Percentage
Centre 1	13	43.3	6	20.0	7	23.3
Centre 2	4	13.3	2	6.6	2	6.6
Centre 3	13	43.3	7	23.3	6	20.0
Males	15	50.0	8	26.6	7	23.3
	Mean	SD	Mean	SD	Mean	SD
Age	59.63	12.65	60.72	10.33	58.54	14.91
Years since Tx	12.65	6.60	10.33	6.83	14.91	6.60
Chronotype (MEQ)	62.03	10.30	63.00	10.29	61.06	10.58
Comorbidity Index (CCI)	1.47	1.63	1.80	1.79	1.13	1.46
BMI kg/m²	25.12	5.51	24.44	3.69	25.8	6.95
Crea µmol/L	144.88	50.94	145.92	60.92	143.85	41.14
Hb g/l	123.42	11.73	122.86	14.47	124.20	7.92
Sleep quality (PSQI)	12.30	3.41	13.27	2.84	11.33	3.75
Daytime sleepiness (ESS)	7.90	3.65	7.93	4.01	7.87	3.40
	N	Percentage	*N*	Percentage	*N*	Percentage
Cyclosporin	14	46.6	5	33.3	9	60.0
Tacrolimus	12	40.0	7	46.6	5	33.3
Sirolimus/ Everolimus	2	6.6	2	13.3	0	0.0
Mycophenolate mofetil	18	60.0	9	60.0	9	60.0
Azathioprine	7	23.3	3	20.0	4	26.6
Corticosteroids	10	33.3	5	33.3	5	33.3
Statin	15	50.0	9	60.0	6	40.0
ACE	5	16.6	2	13.3	3	20.0
ARB	14	46.6	7	46.6	7	46.6
CCB	2	6.6	1	6.6	1	6.6
B-blocker	11	36.6	6	40.0	5	33.3
Diuretics	5	16.6	3	20.0	2	13.3
Anticoagulants	9	30.0	4	26.6	5	33.3
Acetylsalicine	10	33.3	5	33.3	5	33.3
Oral antidiabetics	1	3.3	0	0.0	1	6.6
Antidepressives	5	16.6	2	13.3	3	20.0
Anxiolytics	1	3.3	1	6.6	0	0.0
Antiepileptics	3	10.0	3	20.0	0	0.0
Benzodiazepine	1	3.3	0	0.0	1	6.6

SD, standard deviation; MEQ, morning eveningness questionnaire [16–52 evening type; 53–64 normal type; 65–86 morning type]; CCI, Charlson comorbidity index; PSQI, pittsburgh sleep quality index [Score >5 means poor sleep quality]; ESS, epworth sleepiness scale [Score >10 means daytime sleepiness]; BMI, body mass index; Crea, creatinine; Hb, haemoglobin; ACE, angiotensin-converting-enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium-channel blockers.

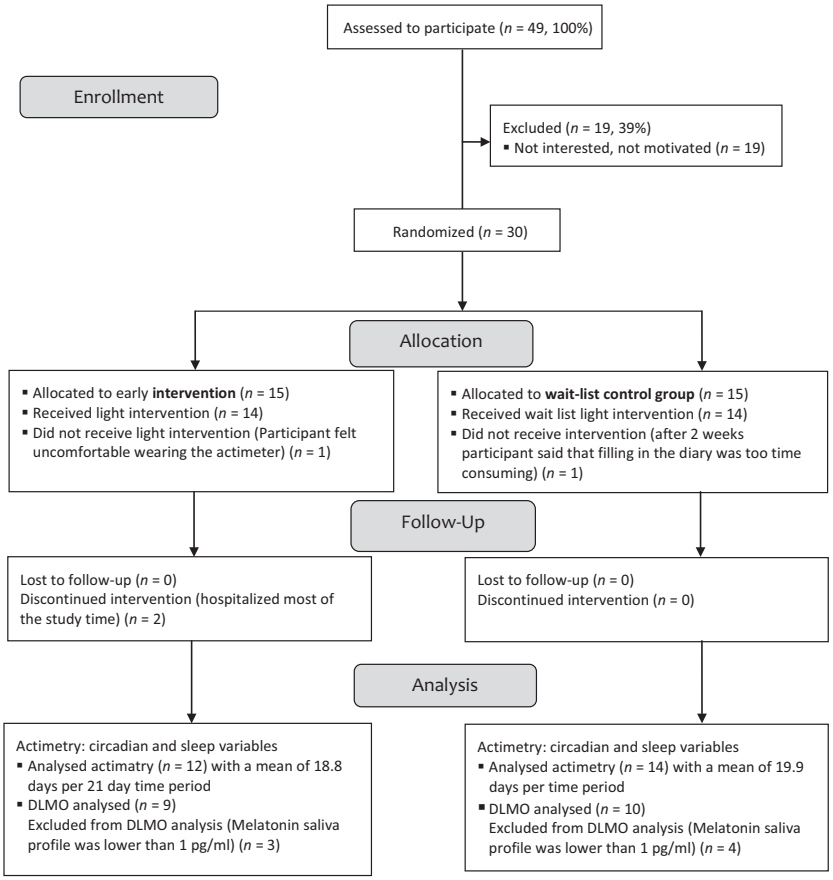

Figure 3 Flow diagram of sample.

[SE: −0.23 (−0.42; −0.03)], with a small (+14 min) but significant phase advance for bedtime from intervention to follow-up [SE: −0.25 (−0.41; −0.09)] (Table 2). Phase advances are signified by positive (+) signs and delays with negative (−) (Fig. 4). The circadian marker (DLMO) did not differ statistically for the intervention group (baseline to intervention: −13 min [SE: 0.58 (0.05; 1.11)] and intervention to follow-up: +5 min [SE: 0.47 (−0.09; 1.02)]; however, the wait-list control group, which was expected to remain stable, experienced an overall phase advance in DLMO (baseline 1 to baseline 2: +1 h 44 min). This might be explained by the fact that most melatonin values were lower than 3 pg/ml (baseline: 87.7%; follow-up: 86.8%). For 10 participants at baseline and 11 at follow-up, all values were lower than 3 pg/ml.

Bright light therapy (BLT) improved depressive symptomatology in the intervention group (baseline-intervention: 5.92–5.75 [SE: −0.28 (−0.87; 0.31)] and from intervention to follow-up: 5.75–4.08 (score >5 means depressive symptomatology), [SE: −0.52 (−1.12; 0.08)]; cognitive executive function (i.e. Stroop test results) did not change.

Results of combined early- and late-intervention data set analysis

Using all intervention data, including those from the wait-list group, we performed a pre–post-analysis. The intervention group's baseline and baseline 3 of the wait-list group were added, along with intervention data of both groups (N = 26). Morning BLT showed a significant baseline-to-intervention get-up time phase advance (+17 min) (Table 2). Other measurements showed no significant effects. Depressive symptomatology improved, although not significantly, with BLT (SE: 0.52 in Table 2). BLT improved subjective morning assessments for well-being, alertness and happiness (Table 3) and evening assessments for well-being and drowsiness.

Exploratory analysis of medication known to suppress melatonin production

To explore factors related to the high incidence of low melatonin secretion, we examined potential effects of medications. Beta-blockers (BB) and acetylsalicylic acid (ASA) are

Table 2. Comparison of outcome variables over time (sleep variables, circadian factors, depressive symptomatology and executive function).

	Wait-list control Group (wait list)			Intervention Group			SE (95% CI)		SE (95% CI)
	N	Mean	SD	*N*	Mean	SD	RCT		Pre–post-design
Sleep efficiency (%)									
N = 14									
T1	N* = 276	73	17.61	247	77.16	12.44	T1–T2	0.00 (−0.16; 0.17)	**−0.07 (−0.02; −0.15)**
T2	N* = 284	72.1	17.16	211	75.67	12.76	T2–T3	−0.05 (−0.21; 0.12)	
T3	N* = 280	71.82	17.47	217	74.72	12.4	T1–T3	−0.05 (−0.21; 0.11)	
Sleep latency (min)									
N = 14									
T1	N* = 276	33.21	0.8	277	45.35	0.81	T1–T2	−0.18 (−0.40; 0.04)	**−0.07 (−0.18; −0.04)**
T2	N* = 284	33.55	0.81	211	38.38	0.16	T2–T3	0.08 (−0.14; 0.30)	
T3	N* = 280	34.61	0.86	217	49.15	0.76	T1–T3	**0.26 (0.04; 0.48)**	
Bed time (decimal time)									
N = 14									
T1	N* = 276	22.48	1.37	248	22.98	1.78	T1–T2	−0.12 (−0.28; 0.04)	−0.10 (−0.004;0.19)
T2	N* = 284	22.6	1.49	211	22.89	2.02	T2–T3	**−0.25 (−0.41; −0.09)**	
T3	N* = 280	22.56	1.28	217	22.66	1.83	T1–T3	−0.13 (−0.29; 0.03)	
Get-up time (decimal time)									
N = 14									
T1	N* = 276	7.24	1.39	248	7.44	1.69	T1–T2	**−0.23 (−0.42; −0.03)**	**−0.21 (−0.32; −0.11)**
T2	N* = 284	7.17	1.37	211	7.03	1.79	T2–T3	**−0.22 (−0.42; −0.03)**	
T3	N* = 280	7.13	1.16	217	7.01	1.42	T1–T3	0.00 (−0.19; 0.20)	
Dim Light Melatonin Onset (decimal time)									
T1	10	22.28	4.84	9	21.71	1.29	T1–T2	**0.58 (0.05; 1.11)**	**−0.15 (−0.47; −0.16)**
T2	9	20.53	6.28	7	21.93	2.2	T2–T3	0.47 (−0.09; 1.02)	
T3	10	19.67	3.64	5	21.84	0.53	T1–T3	−0.12 (−0.68; 0.45)	
Depressive symptomatology									
T1	13	4.08	3.66	12	5.92	3.45	T1–T2	−0.28 (−0.87; 0.31)	**−0.10 (−0.40; −0.19)**
T2	13	4.69	3.17	12	5.75	3.77	T2–T3	−0.52 (−1.12; 0.08)	
T3	12	4.75	5.86	12	4.08	3.12	T1–T3	−0.24 (−0.84; 0.36)	
Executive function (seconds)									
T1	10	49.2	5.77	12	49.17	10.08			**−0.10 (−0.21; −0.41)**
T3	8	50.38	14.73	11	48.45	6.52			

N*, night; 24-h time is in decimal; SD, standard deviation; T, time; SE, standardized estimates; 95% CI = 95% confidence interval; significant results are marked in bold.

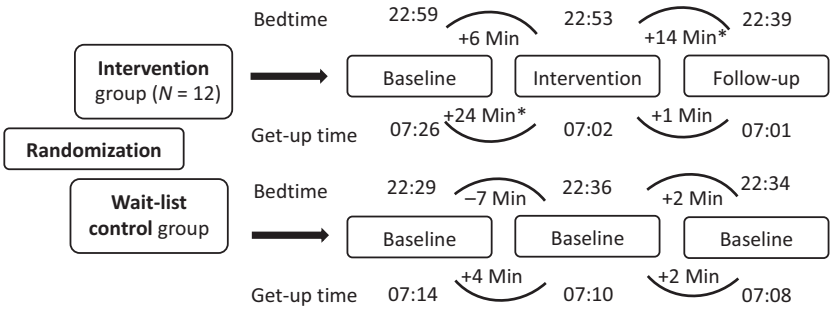

Figure 4 Bedtime and get-up time for the three measurement periods. *Significant outcome derived from Table 2 [bedtime: T2–T3: −0.25 (−0.41; −0.09 and get-up time T1–T2: −0.23 (−0.42; −0.03)]; +, phase advance; -, phase delay. This Figure is a compilation of the descriptive data and the results of the standardized estimates in Table 2. This Figure shows a 24-min phase advance in get-up time from baseline to intervention and a 14-min phase advance in bedtime from intervention to follow-up.

known to suppress melatonin [55]; however, it is unclear whether ASA inhibits melatonin secretion via prostaglandin synthesis (as is known for nonsteroidal anti-inflammatory drugs) [8]. Therefore, we hypothesized that RTx recipients taking BB and/or ASA would not show a phase advance. The exploratory subgroup analysis of the combined

Table 3. Descriptive parameters of the combined sample pre- and post-bright light therapy (BLT) intervention.

	Pre-BLT Median (25th and 75th Percentile)	Post-BLT Median (25th and 75th Percentile)	
Sleep variables			
Bedtime in hours (decimal)	22.53 (21.97;23.80)	22.97 (21.49;23.99)	Later bedtime
Get-up time in hour (decimal)	7.09 (6.47;8.03)	7.01 (6.17;7.64)	Earlier get up time
Sleep latency in minutes	21.96 (12.78;36.23)	18.18 (12.03;35.15)	↓ Sleep latency
Sleep efficiency in percentage	76.95 (69.77;82.04)	78.27 (69.93;84.85)	↑Sleep efficiency
Cognitive parameter			
Interference *t*-score in seconds	49.75 (40.5;57.5)	50.5 (42.75; 53.75)	↑Performance
Psychological parameter			
Depressive symptomatology	3.75 (1.50;8.75)	3.0 (2.0;7.38)	↓Symptomatology
Subjective feelings before bedtime			
Relaxed (0)–tense (10)	3.5 (2.00;5.00)	3.5 (2.50;5.00)	=
Physically unwell (0)–well (10)	6.5 (4.75;8.00)	7.00 4.50;8.00)	↑Well
Alert (0)–drowsy (10)	6.5 (5.00;8.50)	7.50 (5.00;8.50)	↑Drowsy
Sated (0)–hungry (10)	1.5 (0;3.00)	1.00 (1.00;2.00)	↓Hungry
Sad (0)–happy (10)	7.00 (5.50; 8.50)	7.50 (5.5;8.50)	↑Happy
Subjective feelings after waking up			
Relaxed (0)–tense (10)	3.50 (2.00;5.50)	3.00 (2.00;4.50)	↓Tense
Physically unwell (0)–well (10)	6.50 (5.00;8.00)	7.00 (4.50–8.00)	↑Well
Alert (0)–drowsy (10)	4.50 (3.00–6.50)	4.00 (2.00;7.00)	↓Drowsy
Sated (0)–hungry (10)	2.50 (1.00;4.50)	5.00 (1.50–8.00)	↑Hungry
Sad (0)–happy (10)	7.00 (5.50;8.38)	7.50 (5.00–8.00)	↑Happy

↑, more; =, no change; ↓, less (all not statistically significant).

early- and late-intervention data sets showed that in total, 17 patients were taking BB and/or ASA. Compared with these 17, those using neither BB nor ASA showed nonsignificant phase advances for both bedtime (SE: −0.08; 95% CI 0.25; 0.10) and get-up time (SE: 0.11; 95%CI −0.09; 0.31). A significant result for bedtime or get-up time, that is with a power of 80%, would require much larger samples ($N = 260$ or 182, respectively). For those taking neither BB nor ASA, sleep efficiency increased (4.9%) and sleep latency decreased (6 min), both significantly (SE: 0.42; 95%CI 0.20; 0.65 and SE: −0.28; 95%CI −0.45; −0.10, respectively), with powers of 87% for sleep efficiency and 96% for sleep latency.

Discussion

This is the first study testing the feasibility and the efficacy of 3 weeks' morning BLT for improving sleep problems in a sample of chronically ill RTx patients in a pilot RCT with wait-list design. Feasibility was high concerning attrition (13%), but low concerning recruitment (61%), highlighting this study's high labour intensity and long duration. Considering the diary logs, which were completed very precisely, BLT was feasible.

In general, our findings show an intervention effect for BLT in the desired direction. From baseline to intervention, sleep latency improved, but sleep efficiency decreased (not significantly). This loss might have resulted from the new sleep–wake pattern supported by the early-morning scheduling of BLT. The relatively small improvement in sleep latency during BLT suggest that the treatment timing and/or dosing were inadequate or that RTx have clinical problems too complex for short-term BLT [56]. The latter possibility is supported by the wide range of interindividual responses. Generally, sleep latency and sleep efficiency improve over a longer course of BLT [57]; other times, it is more likely the alleviation of depressive symptomatology that improves the sleep–wake cycle [58]. The SEs found in this study are low compared with BLT effect sizes published for seasonal affective disorders [SE: 0.84 (0.60; 1.08)], seasonal depression [SE: 0.53 (0.18; 0.89)] and adjunct treatment of depression [SE: −0.01 (−0.36; 0.34)] [28].

In view of circadian factors, we found that morning BLT phase-advanced bedtime and get-up time, but did not phase-advance DLMO. The 14-min bedtime phase advance was statistically significant and, as mentioned above, is clinically relevant. For lasting sleep improvements, BLT dosing and duration require further evaluation [59]. Our study used only a 30-min duration. And while the optimal duration is not known, at least two studies agree that increases are more effective in duration than in intensity [60,61]. Longer BLT durations can also be supplied simply by spending time outdoors, that is in moderately bright natural light. Another factor – one not measurable in this study – could be exposure to evening light, which might have neutralized the phase-advancing effect of morning BLT on bed time [31].

Depressive symptomatology, subjective feelings, well-being and alertness improved, confirming BLT's previously described benefits in other chronically ill populations [62], depressive patients [28,29] and in the general population [31]. Cognitive executive function was unaffected, but was normal at baseline compared with healthy similar age cohorts [63].

Analysis of the combined early- and late-intervention data showed only a small post-BLT phase advance for get-up time, possibly indicating that participants' close adherence to the scheduling of the intervention resulted in sleep restriction (i.e. participants had to get up to take light therapy). However, no direct bedtime impact was observable for the group as a whole.

Low baseline melatonin secretion might be another reason for the limited intervention effect. Indeed, participants' melatonin saliva values were significantly lower than in the general population. Following this argument, nebivolol or carvedilol [64] is preferred over bisoprolol (which suppresses melatonin secretion) in order for BLT to be effective; however, their cardio- and vasoactive effects have to be evaluated on an individual base. Melatonin supplementation could be considered; however, given that melatonin might interact with other drugs [65,66], caution is indicated in RTx recipients, who are known for their complex medication regimens. To our knowledge, no published study is available on melatonin supplementation in RTx recipients.

A second explanation for the subjects' low saliva melatonin profiles could be calcification of the pineal gland and melatonin pathways [67,68]. Most RTx recipients have pronounced histories of renal failure, leading to altered mineral metabolism and eventually resulting in renal osteodystrophy, soft tissue and vascular calcification. Depending on treatment adherence, calcification of the pineal gland may be more or less pronounced, resulting in reduced melatonin production.

Strengths and limitations

One clear limitation of this study was the limited number of participants; however, for a pilot RCT or pre–post-studies using actimetry and measuring melatonin profiles (with typical enrolments of 6–31 participants), a sample size of 30 is reasonable [28,69,70]. For this pilot study, we focused both on the feasibility of the intervention and on the effect, two important parameters for future research. For this reason, we used standardized estimates and no *P*-values for the descriptive data and no alpha correction has been performed in the results section. One important strength of this study was the use of saliva melatonin profiling, which led to important insights (very low values over the whole night in this patient group). To reduce study burden in future studies, we suggest limiting baseline testing to 2 weeks, with a 2-week follow-up and we also recommend 5 weeks of BLT rather than three [62]. A longer treatment showed a longer remission time, suggesting that a longer treatment time in RTx recipients prolonger the sleep–wake equilibrium [71].To measure light exposure in the prebedtime hours, the proper placement of the actimeter's integrated light sensor should be fully explained to participants.

Conclusion

This study suggests the potential benefit of BLT for RTx recipients, to synchronize their circadian rhythm with normal wake-up times, thereby alleviating sleep–wake disturbances, and to improve subjective feelings. This evidence is insufficient to prove the impact of bright light therapy, but the intervention was feasible which provides an important basis for researchers planning sleep research in transplant populations to learn from our experience.

Given the limited treatment options for RTx recipients with sleep disorders and depressive symptomatology, these benefits make BLT a promising treatment. One half hour of BLT provides light exposure comparable with that received over one half hour outdoors; therefore, clinicians are encouraged to recommend RTx recipients to go outside every morning to synchronize their internal clocks. This practice would increase alertness, reduce daytime sleepiness and support adherence to immunosuppressive medications [72].

Future larger-scale research should consider the exclusion of patients taking drugs interfering with circadian rhythm, issues such as a lack of melatonin excretion in patients on specific beta-blockers, as well as the potential benefits of longer-duration BLT. They should also consider practical suggestions on how to increase patients' time spent outdoors.

Authorship

HB, AW-J, SDG: designed the study. HB, KD: analysed the data. HB, SDG, AW-J: wrote the paper. All other co-authors reviewed and gave input. AW-J, CC, TW: contributed to chronotherapy and actigraphy/sleep methods and analyses knowledge. HB, JS, TF, RMV: were involved in the data collection process in the three centres and contributed to nephrology background knowledge.

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Transparency declaration

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