



# **BRIGHT LIGHT THERAPY IN RENAL TRANSPLANT RECIPIENTS WITH SLEEP- WAKE DISTURBANCE**

## **INAUGURALDISSERTATION**

zur

Erlangung der Würde eines Doktors der Pflegewissenschaft

vorgelegt der

Medizinischen Fakultät und der Philosophisch-Naturwissenschaftlichen Fakultät

der Universität Basel

von

Hanna Burkhalter

Aus Rüegsau und Basel, Schweiz

Basel, den 06. November 2013



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Basel, den 06. November 2013

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Basel, den 6. November 2013 (Tag der Promotion)

Dekan Prof. Dr. Christoph Beglinger

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## ACKNOWLEDGEMENTS

Research is never a one man or woman show, but teamwork expanding into a complex international net, integrating all needed personal contacts. Therefore I want to dedicate this section to all the kind individuals who were willing to help a student complete her dissertation.

First, I thank the members of my PhD committee, Prof. Dr. Sabina De Geest, Prof. Dr. Anna Wirz-Justice, Prof. Dr. Christian Cajochen, Prof. Dr. Jürg Steiger, and Prof. Dr. Terri Weaver.

Prof. Dr. Sabina De Geest not only contributed the preparation and realization of this dissertation project, she encouraged me to dive into the international society of academia via various research projects and international conferences.

The world of chronobiology was brought nearer by Prof. Dr. Christian Cajochen and Prof. Anna Wirz-Justice, who impressed me with her broad knowledge, her wisdom and her open attitude. The chronobiology team, especially Claudia Renz and Dr. Vivien Bromundt, advised me and helped me to understand how another institute works.

With his gift for communication, Prof. Dr. Jürg Steiger contributed to an excellent research setting. Initially, only two research centres were included (Basel, led by Prof. Dr. Steiger and Zürich, led by Prof. Dr. Thomas Fehr); however, the interest in sleep following renal transplantation inspired the Bern centre, led by Dr. Reto Venzin, to contribute. Each center offered excellent support; but I owe special thanks to Nicole Brun and the ambulatory outpatient clinic of Basel, to Irina Klimmeck and Denise Biemann the “freezer ladies” for the melatonin storage, to Kathrin Koch, Julia Hoffmann and the ambulatory outpatient clinic in Zürich and to Dr. Ute Eisenberger, Regula Rottermann, and René Nussbaum of University Hospital Bern.

In Philadelphia, during a one-week visit in December 2010, I first met Prof. Dr. Terri Weaver and her research team. I was impressed to see so many nurses doing research in different sleep areas with a nursing focus. This visit inspired and motivated me to choose sleep as a nursing research issue.

Secondly, I express special thanks to every member the Institute of Nursing Science team, both for their stellar work on the review process and for simply listening and encouraging me to stay on track. A special thank goes to Monika Kirsch, who has remained a dear friend through all the challenges that have confronted me through my



undergraduate and graduate work, and who is now my office mate at the INS. She has survived all the ups and downs involved in this dissertation project!

I also thank all members of the A-Team (Greet Van Malderen, Brenda Marcus, Cornelia Kern, Irene Kälin, Steffie Gehlen, Klara Remund and Michael Huber), whose excellent administrative support and budgeting made my life easier.

Third, I thank all the students (Gashi Gani, Tobias Ries, Julien Tai, Marie-Louise Daly, Amina Trevisan, Tabea Kepper, Aylin Schwarz), friends (Lea, Susanne, Sara and Simon Schweyer, Nadia Gugler, Rahel Junk, Silvia Freund, Kathryn Nilles, Armand Cachelin, Caroline Barth-Kollmer) and family members (my parents, Rosette and Ruedi Roth) who patiently helped with preparing envelopes, printing addresses, inserting data, reviewing letters and so on. You have all been a great support! I thank Chris Shultis for his constant and devoted editing of all the articles included in this dissertation.

With no reservations, I thank my beloved husband Marco, our families and friends, who have tolerated these long years of time deprivation. Special thanks are due to Susanne Helbling-Fuchs, Leta Singer, Dr. Andreas Gschwind, Renata Linder, Benj Schaffner, Dr. Hans Paul and Françoise Walliser, and Dr. Walter and Elisabeth Meili, all of whom encouraged me to discover who I am and to be all that I can be.

Finally, I thank the Nierenstiftung Schweiz - Alfred und Erika Bär-Spycher Stiftung and the International Transplant Nurse Society, who funded my research project.

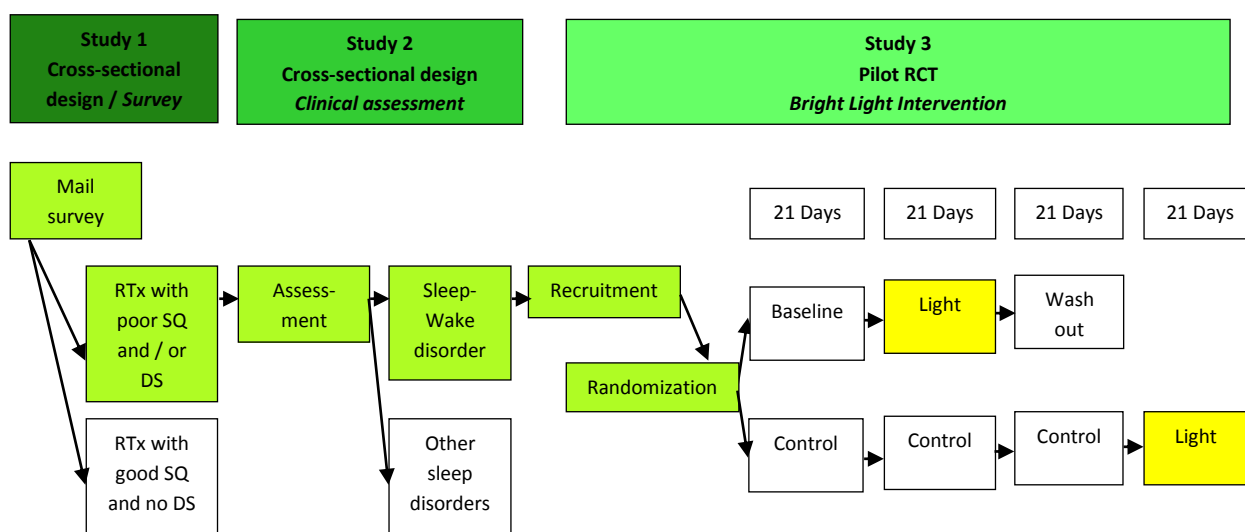
# SUMMARY

While the knowledge of sleep disorders in renal transplant recipients is severely limited, preliminary evidence shows that issues with poor sleep quality (SQ) and daytime sleepiness (DS) are highly prevalent. Non-pharmacological interventions such as light therapy, used to treat certain sleep and mood disorders, have not yet been tested as a means to improve sleep in this population. Therefore, the aims of this research program were:

- 1)
  - a) to evaluate the validity of a single-item daytime sleepiness measure integrated in the Swiss Transplant Cohort Study (STCS) (study 1; chapter 3);
  - b) to determine the prevalence of immunosuppressive non-adherence (NA) in renal transplant recipients patients (study 1; chapter 4);
  - c) to assess the association between daytime sleepiness (DS), depressive symptomatology, and non-adherence to the immunosuppressive regimen (study 1; chapter 4);
- 2) to diagnose renal transplant recipients patients with sleep disorders following the ICSD-2 classification system (study 2; chapter 5);
- 3)
  - a) to determine the prevalence and evolution of sleep quality from pre- to 2 years post-transplantation in kidney, liver, lung and heart recipients included in the Swiss Transplant Cohort study (a prospective nation-wide cohort study) (secondary data analysis of the Swiss Transplant Cohort Study; chapter 6);
  - b) to assess the impact of sleep quality on perceived health status from pre- to 2 years post-transplant (secondary data analysis of the Swiss Transplant Cohort Study; chapter 6); and
- 4) to assess the feasibility and effect size of bright light therapy in home dwelling renal transplant patients with sleep-wake disturbances (study 3; chapter 7).

Figure 1 shows the flow chart of the research project.

Figure 1: Flowchart of the research program



Legend: SQ= Sleep quality; DS = Daytime sleepiness

### STUDY 1; CHAPTER 3:

Using a cross-sectional multicenter design including a convenience sample of 926 adult renal transplant patients (36.9% female; mean age:  $58.0 \pm 12.3$  y.; mean years since transplantation:  $10.6 \pm 7.6$ ) transplanted at 3 Swiss transplant centers, we found a 65.2% prevalence of poor sleep quality and a 51% prevalence of daytime sleepiness.

Based on the ROC curve analysis, a score  $> 4$  on the Swiss Transplant Cohort Study-daytime sleepiness item indicates daytime sleepiness. The Swiss Transplant Cohort Study-daytime sleepiness content validity is high as expert reviews were unanimous. Concurrent validity is moderate (Spearman's rho,  $r_s$ : 0.531,  $p < .001$ ) and, although low, convergent validity with depression and poor sleep quality was significant ( $r_s$ : 0.235,  $p < .001$  and  $r_s$ : 0.318,  $p = .002$ , respectively). Regarding group difference validity, renal transplant recipients with moderate, severe and extremely severe depressive symptomatology scores showed, respectively, 3.4, 4.3 and 5.9 times higher odds of daytime sleepiness than those with none [Burkhalter, H., et al., *Validation of a single item to assess daytime sleepiness for the Swiss Transplant Cohort Study*. *Prog Transplant*, 2013. 23(3)].

### STUDY 1; CHAPTER 4:

Using a cross-sectional multicenter design including a convenience sample of 926 adult renal transplant recipients (36.9% female; mean age:  $58.0 \pm 12.3$  y.; mean years since transplantation  $10.6 \pm 7.6$ ) transplanted at 3 Swiss Transplant centers, we found non-adherence levels of 16% for taking, 42% for timing, and a median overall non-adherence

level of 0%. Based on the multivariate logistic regression analysis, daytime sleepiness was a significant predictor ( $p < 0.001$ ) for taking (1.09 [1.04-1.14]), timing (1.06 [1.03-1.10]) and overall non-adherence (1.09 [1.05-1.13]). The STCS-DS item yielded very similar predictive values. [Burkhalter H., et al., *Daytime sleepiness is associated with immunosuppressive non-adherence in renal transplant recipients: a cross-sectional multi-center study*. 2013. Submitted.]

#### **STUDY 2; CHAPTER 5:**

This cross-sectional study included 249 renal transplant recipients, each of whom was transplanted at one of three Swiss transplant centers. All had reported poor sleep quality and / or daytime sleepiness in the previous study (study 1). With the Survey of Sleep (SOS), a detailed self-report questionnaire, we screened for sleep and health habits, sleep history, main sleep problems and sleep disturbances. Of these 249 participants, 48 participated in an in-person interview session and 118 in a telephone interview to determine a preliminary sleep diagnosis according to the International Classification of Sleep Disorders (ICSD). Descriptive statistics were used to analyze the Survey of Sleep itself and the frequencies of sleep disorders in renal transplant recipients. The sample had a mean age of  $59.1 \pm 11.6$  years, 60.2% were male and the mean time since transplantation was  $11.1 \pm 7.0$  years. The most frequent sleep problem was difficulty staying asleep (49.4%), followed by problems falling asleep (32.1%). The most prevalent sleep disturbance was the need to urinate (62.9%), and 27% reported impaired daytime function. The interview showed that most suffered from insomnia. [Burkhalter, H., et al., *Self-reported Sleep Disturbances in Renal Transplant Recipients*. Submitted, 2013.]

#### **SECONDARY DATA ANALYSIS OF THE SWISS TRANSPLANT COHORT STUDY; CHAPTER 6)**

Sleep quality was assessed pre-transplant, then at 6, 12 and 24 months post-transplantation using a single question (see study 1) with responses ranging from 0 (very poor) to 10 (very good), where the cut-off for poor sleep quality was  $< 6$ . Random intercept regression analysis was used to identify statistically significant associations.

The study included 1076 patients (age:  $52.38 \pm 13.05$  years; 65% males; 639 kidney, 215 liver, 126 lung, 96 heart). For all groups, poor sleep quality decreased significantly from pre-transplantation (39.41%) to 12 months post-transplantation (24.75%). Liver and heart recipients had the highest prevalence of poor sleep quality pre-transplantation, while sleep quality in transplant recipients of all organs except lungs decreased to a prevalence of 22-30% at 12 months and remained constant at 24 months. Lung recipients' mean sleep quality actually increased from 22% to 42% in the final 12 months. [Burkhalter, H., Denhaerynck K., and S. De Geest, *Sleep Quality Improves from Time of Listing to 2*

*Years PostTransplant in Solid Organ Transplant Recipients: A Prospective Cohort Study.* In preparation for submission 2013.]

### **STUDY 3; CHAPTER 7:**

This was a non-blinded, randomized controlled pilot trial to study the efficacy of light therapy. Thirty home-dwelling renal transplant recipients aged  $56.9 \pm 13.5$ y, all previously screened for sleep-wake disturbances, were randomly assigned to receive either an immediate or a delayed (end of study) light therapy intervention.

The intervention process had 3 stages of 3 weeks each, during which subjects' wrist actimeter (DaQtix) data were collected for analysis of circadian rhythm and sleep parameters. The first was a baseline measurement period. For the second, additionally morning light (10'000 lux) was scheduled (according to chronotype) for 30 min daily. The final stage was for follow-up. Depressive symptomatology was assessed four times-at the beginning of the baseline period, then at the end of each 3-week stage-using the Depression, Anxiety and Stress scale (DASS) (scoring: 0-21; >4 indicates depressive symptomatology). We used a random-intercept regression model to test group-time interaction. Effect sizes reflect the interaction estimated for standardized outcome variables. For the outcome variables bedtime, get up time, sleep efficiency and sleep latency, we added a step to the analysis in which we controlled for the presence of Beta Blockers and acetylsalicylic acid, both of which are frequently taken by renal transplant patients but are known to impact levels of melatonin, which contributes to consolidated sleep.

The trial showed that light therapy induced a phase advance in bedtime of 19 min and get-up time of 22 min. The pre-post analysis showed a phase advance only in get-up time. Post-hoc analysis revealed that light therapy significantly increased sleep efficiency (Standardized Estimates (SE): 0.42) and decreased sleep latency (SE: -0.28) in renal transplant recipients taking neither beta-blockers nor acetylsalicylic acid. Light therapy improved depression and mood in the whole group without affecting selective attention. Renal transplant recipients not taking beta blockers and/or acetylsalicylic acid showed a non-significant phase advance for bedtime (Standardized Estimates (SE): -0.08) and get up time (SE: 0.11). However, sleep efficiency increased (4.9%) and sleep latency decreased (6 min) significantly for those not taking beta blockers (SE: -0.28) or acetylsalicylic acid (SE: 0.42). The power for the improvement in sleep efficiency is 87% and for sleep latency 96%. [Burkhalter, H., et al., *A Pilot Randomized Controlled Study of Light Therapy for Sleep-Wake Disturbances in Renal Transplant Recipients*, in preparation for submission, 2013.]

### **Conclusions**

This research program, which was the first to comprehensively address sleep quality aspects in renal transplant patients, generated new evidence that sleep quality and daytime sleepiness are highly prevalent throughout the transplant course in all 4 large organ transplant groups. It also established validity for the single Swiss Transplant Cohort Study daytime sleepiness (STCS DS) item, and showed that daytime sleepiness is a risk factor for immunosuppressive medication adherence in renal transplant recipients. Sleep assessment revealed that most renal transplant recipients had difficulty staying asleep, followed by problems falling back asleep. Insomnia was the most common sleep diagnosis, indicating that these patients might benefit from cognitive-behavioral sleep-wake interventions as used in general sleep medicine.

Analysis of the Swiss Transplant Cohort Study data confirmed that sleep quality improves from pre-to post-transplantation, and that poor sleep quality is predictive of overall poor health status. Finally, in the pilot randomized controlled trial, bright light therapy showed favorable outcomes on selected sleep parameters as well as improving depressive mood, and may therefore be added to sleep disorder treatment options for renal transplant recipients. The influence of beta blockers and /or non-steroidal anti-inflammatory drugs regarding sleep disorders requires further study, as does the potential use of supplementary melatonin and the classical approach of promoting sleep hygiene rules.

## Dissertation

This dissertation is organized into 9 chapters:

**Chapter 1** introduces sleep, circadian rhythms and chronotypes, and sleep-wake disturbances. The emphasis is on the theoretical underpinning driving this research project. The behavioral part of the hypothesis is based on the integrated model of behavioral prediction [1], while the sleep-wake association is based on the two-process model of sleep regulation [2] and the Spillman model [3]. The chronotherapeutic intervention of bright light therapy is based on research indicating that it safely and reliably improves the patient's sleep-wake disturbance, thereby stabilizing sleep patterns. In the final part, gaps in the scientific literature are summarized.

**Chapter 2** describes the aims of this dissertation.

**Chapter 3** presents the results of a multicenter survey study describing the prevalence of daytime sleepiness, as measured via the validated Epworth Sleepiness Scale and the Swiss

Transplant Cohort Study's newly developed daytime sleepiness item. This study addresses content validity and validity related to other variables.

**Chapter 4** presents further results of the multicenter survey study introduced in Chapter 3, describing the association between immunosuppressive drug non-adherence and daytime sleepiness. Daytime sleepiness is therefore seen as a barrier to immunosuppressive medication adherence.

**Chapter 5** summarizes the range of sleep diagnoses found in our renal transplant recipients based on a detailed questionnaire and an in-depth sleep assessment interview.

**Chapter 6** presents the prevalence and evolution of sleep quality from pre- to post-transplant in kidney, liver, lung and heart recipients included in the Swiss Transplant Cohort Study (a prospective nation-wide cohort study). Further, it shows the impact of sleep quality on perceived health status from pre- to 2 years post-transplant.

**Chapter 7** presents the feasibility and effect size of a pilot RCT of bright light therapy in renal transplant recipients with sleep-wake disturbances, analyzing sleep, circadian, psychosocial and neurocognitive parameters.

**Chapter 8** summarizes all the new results and discusses the overall research project, including future research perspectives.

## References of summary

1. Fishbein, M. and I. Ajzen, *Prediction of Behaviour*, in *Belief, Attitude, Intention, and Behavior: An Introduction to Theory and Research*. 1975, Addison-Wesley: Reading, MA p. 335-383.
2. Borbély, A.A., *A two process model of sleep regulation*. *Human Neurobiology*, 1982. 1(3): p. 195-204.
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# CHAPTER 1

## INTRODUCTION

## 1.1. Introduction

Sleep problems are a widespread and growing general health issue [1, 2], hindering daily functionality and weakening overall health [3]. In a survey of 10'132 individuals, Léger et al (2008) reported a 56% prevalence of sleeping problems in the US, 31% in Western Europe and 23% in Japan [4]. An epidemiological study summarizing studies in France between 1980 and 2009 reported that 30-50% of the adult population had at least one sleep disorder and 15 -20% had insomnia [5]. In another epidemiological study, Ohayon and Lemoine (2004) reported a 20% - 40% prevalence of insomnia symptoms in the overall population of Western Europe, with women and the elderly the most affected groups [6].

The prevalence of sleep medication use among different age groups reflect the growth of sleep disorders with age: 3.2% in subjects aged 44 years or younger, 13.3% for ages 45 - 64, 22% for ages 65 - 74, and 32% for 75 years or older [6]. Repercussions of sleep problems on daytime functioning were reported by most insomnia subjects (67%) [7]. Whether intentional or unintentional, sleep loss (being awake for over 20 hours) impairs performance comparably to a blood alcohol concentration of 0.10% [8]. About one-third of renal transplant recipients report poor sleep quality [9] and 34.1% report poor daytime functioning [9]. These are worrisome figures, as transplant recipients require full alertness for their self-care and chronic illness pathway management.

This introductory chapter will give an overview of the evidence concerning sleep-wake disorders in general as well as their particular significance to solid organ transplant recipients. This section will cover: sleep regulation (1.1), importance of sleep-wake function (1.2), general adverse effects of inadequate sleep (1.3), sleep disturbances classified in sleep medicine (1.4), measurement tools (1.5), diagnosis and treatment of sleep disorders (1.6), sleep in solid organ transplant recipients (1.7), and finally, gaps in the transplant literature with respect to sleep (1.8).

## 1.2. Introduction to sleep regulation

Sleep is defined as “a reversible state of perceptual disengagement from and unresponsiveness to the environment” [10]. Healthy sleep accounts for about one third of a person's life, i.e., ca. 8 hours per 24-hour period. However, if minimum levels of sleep quality and quantity are not met, problems arise during wakefulness (particularly in the performance of long and monotonous tasks without feedback) [11].

Sleep is divided into different stages, defined by changes in brain activity, i.e., electroencephalographic (EEG) patterns. A normal night of sleep includes 5 to 6 sleep cycles, each of which involves moving from stage 1 (light sleep) to stage 4 (deep sleep) and back again, with intervals of Rapid Eye Movement (REM) sleep. The proportion of time spent in each stage changes throughout the night. At the beginning of the night, deep sleep is prominent; in the morning hours, REM sleep lasts longer.

This study's theoretical basis is the “two process model of sleep regulation” [12], which proposes that the interaction of a sleep-wake dependent homeostatic process and a circadian process generate the timing and structure of sleep and waking [13]. The homeostatic process is often compared to an hourglass that is turned twice in 24 hours. During the day, sleep pressure accumulates until the person goes to sleep and the hourglass is turned. The longer a person is awake, the higher his sleep pressure. Independent of sleep pressure, the circadian process is genetically programmed [14], with a periodicity close to 24 hours [15], and synchronized to the environmental rhythms of day/night and light/dark [16]. This rhythm differs among individuals in terms of periodicity and phase (timing). Interindividual variations in timing are known as chronotypes [17]. Persons exhibiting extreme chronotypes are often called “larks” for the early type and “owl” for the late type. The Horne-Östberg Morningness-Eveningness Questionnaire (MEQ) [18] is commonly used to establish individual circadian phase preference. As sleep and daytime functioning are linked to the activity of the circadian clock, individual preferences for morning and evening activity have biological bases [19].

During the aging process, the proportions of the different sleep elements and stages change [20]. One very obvious change in chronotype occurs in young people entering adolescence, as they experience a delay in their circadian timing system, resulting in a tendency to stay up later and sleep in later [21]. In contrast, elderly people tend to shift to earlier chronotypes, resulting in very early wakeup and bedtimes [22] (see figure 2). Additionally, wake-time after sleep onset increases, i.e., whereas adolescents may commonly experience long periods of unbroken sleep, it is normal for an aged person to perceive (accurately) that he is often awake during the night.

Figure 2: Epidemiology of the human circadian clock

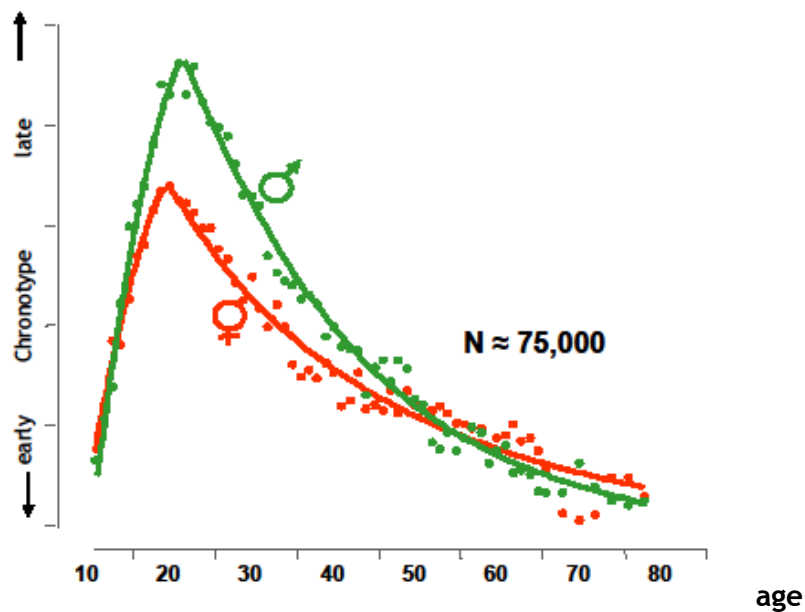


Image credit: Roenneberg, T., et al., *Epidemiology of the human circadian clock*. *Sleep Med Rev*, 2007. 11(6): p. 429-38.

### 1.3. Importance of sleep for waking functionality

#### 1.3.1. Theoretical underpinning: The two process model of sleep regulation

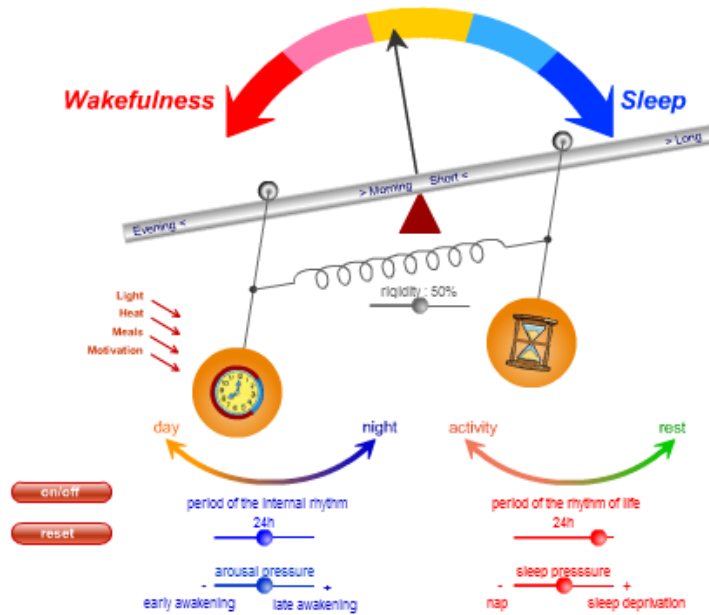
The two process model of sleep regulation (figure 3a and 3b) posits that sleep is regulated by a homeostatic process and a circadian process [23]. The homeostatic process is a quantitative need for sleep that rises while a person is awake and declines during sleep, i.e., homeostatic sleep pressure varies with prior time awake and on the characteristics of the preceding sleep. The circadian process is independent of time awake or asleep and provides time-of-day input, synchronized through the external signal of light.

Theoretically, these two processes are relatively independent; however, in real life they interact to determine timing and duration of sleep [15]. Further, both systems can be consciously overridden. For example, a week of working night shifts can temporarily reset the body's synchronized processes to keep a person awake when he would ordinarily be sleeping or vice-versa.

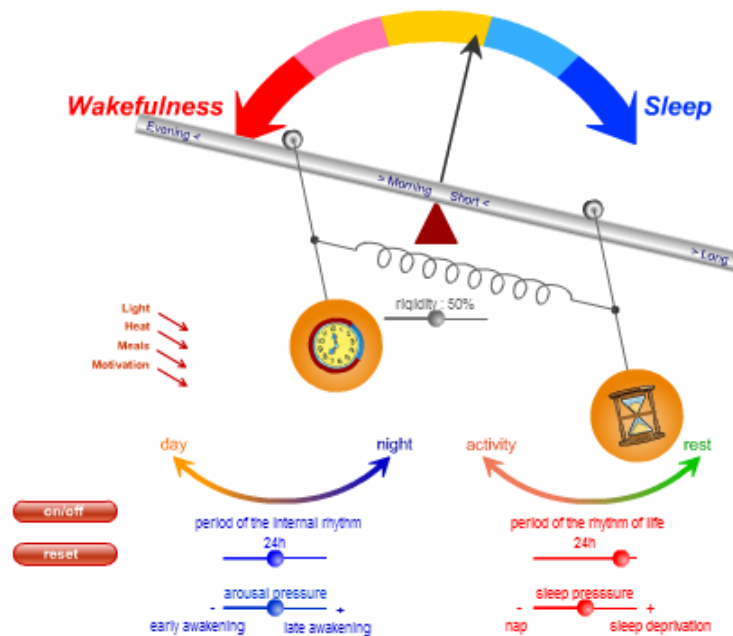
**Figure 3a:** Schematic representation of the two process model of sleep regulation. This figure represents an awake person.

Circadian  
Pendulum

Homeostatic  
Pendulum



**Figure 3b:** Schematic representation of the two process model of sleep regulation. This figure represents a sleeping person.



Images 2 & 3 credit: Double pendulum model for the regulation of sleep/wake rhythms [http://www.sommeil-mg.net/spip/Chronobiology-Have-to-sleep\\_216](http://www.sommeil-mg.net/spip/Chronobiology-Have-to-sleep_216) used with permission: Dr Guilhem Pérémarty ProSmg Association 15.07.2013

The internal master clock is situated in the suprachiasmatic nuclei of the anterior hypothalamus (figure 4). However, clock genes tick at their own endogenous circa-24 hour (i.e., circadian) frequency in every cell and organ of the body, and peripheral oscillators (middle-level timekeepers) are found in the esophagus, lungs, liver, kidneys, pancreas, spleen, thymus and skin [24]. Both the master clock and peripheral oscillators need to be synchronized by so-called Zeitgebers (external “time givers”). However, not all Zeitgebers act equally on all clocks, e.g., physical activity is a Zeitgeber for the muscles, and food is a Zeitgeber for the liver.

The most powerful Zeitgeber is light, which works with melatonin as a Zeitgeber for the internal master clock. This principle has been developed into a useful therapy to synchronize the master clock [25]. Guidelines have been published to help time bright light therapy to achieve the desired effect [26].

**Figure 4:** Location of the master clock - the suprachiasmatic nuclei

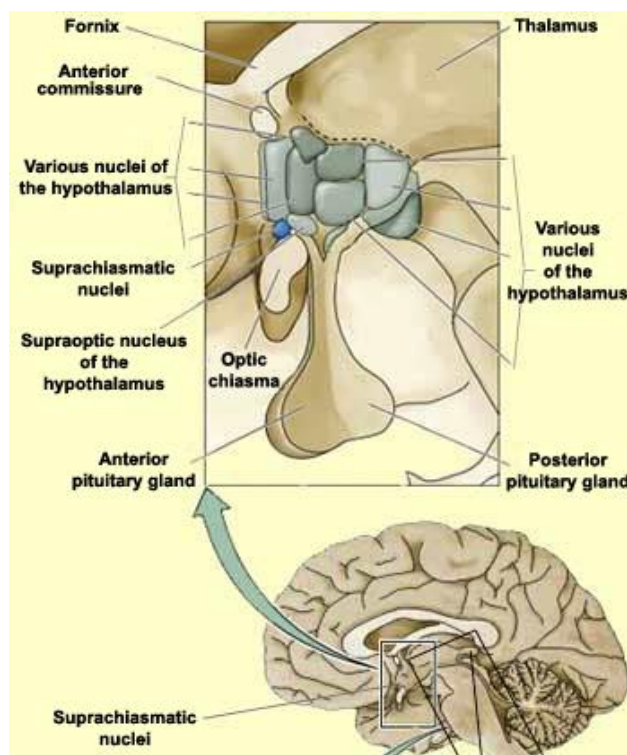


Image credit: <http://thebrain.mcgill.ca> (Copyleft)

### 1.3.2. Sleep-wake interaction

The homeostatic process is determined by individual behavior, which, in turn, is influenced by work or social constraints. To varying degrees, all humans can adapt to an irregular sleep rhythm; however, a quantitative lack of sleep (homeostatic process) or a qualitative lack of sleep (circadian process) will be perceived respectively as sleepiness or tiredness

[13, 27-29]. This can happen any time a person has been awake too long or at the wrong time of day: the homeostatic and circadian processes fall out of synchronization, resulting in sleepiness or tiredness at odd times (jet-lag or shift work are obvious examples). Thus, the sleep-disordered individual must learn to schedule sleep time to match his circadian process and his sleep need to his homeostatic process until the sleep-wake cycle is again in harmony with the external world and social requirements.

## **1.4. General adverse effects of inadequate sleep**

This section will address the main adverse effects of inadequate sleep, beginning with general impairment, then, in more detail, impacts on work (economic and safety burdens) and overall health

### **1.4.1. Human errors and public health burden caused by sleep disorders and sleep deficit in the general population**

In 2012, the American Academy of Sleep Medicine and the Sleep Research Society developed a statement to communicate the importance of sufficient sleep and circadian alignment for adult health to national health stakeholders [30]. Quantitative and / or qualitative lack of sleep creates an overwhelming and uncontrollable need to sleep, causing problems with memory and attention [31], complex thought processes, motor responses to stimuli, performance in school or on the job, emotion control [8, 32], physiological factors [33], neurobehavioral factors [34], and cognitive performance [34].

And as the number of adults sleeping less than 7 hours per night is increasing [35], so is the magnitude of the problem. Inadequate sleep duration has consequences on physiological and neurobehavioral factors that become progressively worse under chronic short sleep conditions [33]. Van Dongen et al. (2003) adds that: “chronic restriction of sleep to 6 h or less per night produces ongoing cognitive performance deficits equivalent to up to 2 nights of total sleep deprivation” (page 1) [34]. Sleep deficits seriously impair waking neurobehavioral functions (lapses in behavioral alertness) in healthy adults [34]. The obvious and notable consequence of sleep deprivation is daytime sleepiness [36].

Full-time exposure to artificial light enables us to reduce sleep time to meet the demands of a 24/7 society with long and late hours for business, commutes, or free time activities. Social jet-lag, i.e., discord between an individual’s chronotype and his socially set sleep times, results in insufficient sleep before work days and “rebound sleep” on weekends. The greater the social jet-lag, the greater the occupational hazards: sleep deficits are a societal health problem with economic impact [37]. Working around the



clock (i.e., shiftwork) is a factor for the growing rate of human error in industrial and transportation accidents [2]. The consequences of such preventable accidents (caused by poor sleep quality or daytime sleepiness) are a society-wide economic burden [38]. Shift workers (people working permanent night shifts, rotating shifts and evening shifts) are at very high risk of sleepiness due to sleep deprivation and the desynchronization of sleep and wakefulness [39]. The highest rate of industrial accidents is found among night shift workers [40] and high error rates are found among shift workers in general [41]. People with daytime sleepiness have a significantly higher accident rate [42], and adults with daytime sleepiness have cognitive and memory problems [43, 44]. Balkin et al. (2008) in their review wrote that sleep deprivation impairs the entire spectrum of mental abilities, ranging from simple psychomotor performance to executive mental functions [45]. Durmer et al. (2005) adds the aspect of neurocognitive consequences of sleep deprivation [46] and Killgore et al. (2006) the impaired decision making following sleep deprivation [47].

Perhaps the most frightening consequence of sleep loss is impaired driving [48, 49]. Being awake for over 20 hours impairs performance comparably to a blood alcohol concentration of 0.10% [8]. Driving at night or in the early to mid-afternoon further increases the risk of an accident because these are times that our internal clock is most vulnerable to sleepiness [50]. But these figures only represent the tip of a very large iceberg, as driving is only one of many tasks demanding full alertness. Our daily lives, including work performance and precise execution of essential tasks (i.e., remembering timed immunosuppressive intake) are all also affected by sleep deficits [51].

#### **1.4.2. Health problems caused by sleep disorders and sleep deficits in the general population**

Sleep disorders and sleep deficits are precipitating a growing public health burden [2, 52]. Although few articles have been published linking sleep with clinical outcomes, poor sleep is associated with poor quality of life [53], impaired resilience to stress, and vulnerability to psycho-physiological disorders [54] including depression [55, 56]. Sleep disturbances are further associated with higher risks of cardiovascular disease [57], metabolic disorders [58-62], diabetes [63], chronic inflammation [64, 65] and accelerated mortality [66-70] in the general population. Short sleep (<5hours) is associated with coronary artery calcification [71], and an increased risk of overall cardiovascular events, including myocardial infarction [72]. Finally, sleep durations of less than 6 hours or more than 8 hours have been associated with depression [73]. The best longevity rates are found among those who sleep an average of 7 hours per night [74].

Considerable evidence supports a close interaction between immune function and sleep [75]. Luyster et al. (2012) in his review summarizes that: “Sleep deprivation contributes to a number of molecular, immune, and neural changes that play a role in disease development, independent of primary sleep disorders [30]. Cytokine changes triggered by infection increase sleep drive and alter sleep architecture [76, 77]. A growing body of evidence suggests non-causal links between cytokines (molecules involved in immune responses) and excessive daytime sleepiness. Kapsimalis et al. (2007) hypothesized that these molecules play important roles both in mediating excessive daytime sleepiness because of sleep loss or insomnia, and in the pathogenesis and cardiovascular consequences of obstructive sleep apnea [78]. In their review of the topic, Palma et al. (2007) [79] concluded that sleep deprivation and the immune system influence one another bi-directionally [79]. Enough sleep keeps the immune system working properly, which in turn protects against both infection and malignancy [80].

## **1.5. Sleep disturbances as classified in sleep medicine**

The International Classification of Sleep Disorders [81] classifies sleep disorders into a total of eight categories, beginning with the six main disorder types: 1) Insomnia, 2) Sleep Related Breathing Disorders, 3) Hypersomnias, 4) Circadian Sleep-Wake Disturbances, 5) Parasomnias, and 6) Sleep Related Movement Disorders. The two remaining categories are grouped: 7) Isolated Symptoms, Apparent Normal Variants, and Unresolved Issues, and 8) Other Sleep Disorders. This dissertation will focus on insomnia and circadian sleep-wake disturbances.

### **1.5.1. Insomnia**

Skalski summarizes insomnia as "a subjective feeling of not getting enough sleep in terms of its length and quality together with its consequences, such as being unproductive and in bad mood during daytime" [82]. It can be symptomatic of primary medical illnesses, mental disorders, use or abuse of certain substances, or other sleep disorders. As an overarching term, it includes a number of more specific diagnoses: adjustment sleep disorder (associated with a specific stressor), psychophysiologic insomnia (heightened arousal and learned sleep-preventing associations), paradoxical insomnia (where subjective reports of severe sleeplessness are incongruent with the absence or minor degree of daytime impairment), insomnia due to a mental disorder (insomnia constitutes a distinct symptom); idiopathic insomnia (onset in infancy or early childhood); inadequate sleep hygiene (associated with activities that are inconsistent with optimal sleep); behavioral insomnia of childhood (resulting from inappropriate sleep associations or inadequate limit

setting); insomnia due to a drug or substance; or insomnia due to a medical condition [81]. According to the international classification of sleep disorders (ICSD-2) [81], the main symptoms are difficulties with sleep onset and sleep maintenance, or early waking, combined with deteriorating daytime functioning. One commonly used theoretical underpinning is Spielman's "3P" model [83], i.e., predisposing factors (e.g., genetics, comorbidities), precipitating factors (e.g., life stresses such as surgery, or corticosteroids against acute graft rejection [84]), and perpetuating factors (unintentionally maintained bad behaviors, such as lying in bed awoken). Precipitating factors might trigger acute insomnia; however, unless perpetuating factors come into play, the problem will disappear as these factors diminish. In the general population, depending on the definition used, prevalence rates of insomnia range from 4% to 48% [85, 86].

### 1.5.2. Circadian sleep-wake disturbances

Sleep-wake disturbances are mainly categorized under the sleep diagnoses of either circadian rhythm sleep disorders (CRSD) or insomnia. Circadian rhythms are the circa-24-hour cycle of daily physiological functions, especially sleep onset and waking times [14]. Poor sleep quality (especially difficulties with sleep onset and/or sleep maintenance) and daytime sleepiness are the main symptoms of this class of sleep disorder [87]. In the international classification of sleep disorders, circadian disorders of the sleep-wake rhythm are further specified. They may be delayed or advanced, i.e., 3 or more hours later or earlier than the desired or socially acceptable sleep and wake times. More rarely, a free-running rhythm is present, i.e., the sleep-wake rhythm is no longer synchronized to the 24-hour day and follows its endogenous genetic periodicity, which is usually somewhat longer than 24 hours. Totally blind individuals often suffer from free running circadian rhythm sleep disorders, as light cannot function as their main Zeitgeber (time giver). To synchronize them to the 24 h rhythm, they are therefore commonly treated with melatonin as the zeitgeber for darkness. Irregular sleep-wake rhythms with scarcely detectable 24-hour patterns are most common in advanced Alzheimer's dementia and occasionally in patients with Parkinsonism [88]. This deregulation results in a slow progressive change in temporal organization until death [89]. The consequences include behavioral disturbances, such as daytime agitation and nighttime restlessness [89]. Both Alzheimer's and Parkinson patients can be treated with bright light therapy [90].

Environmental and lifestyle factors such as shift work, jetlag, or social jetlag can bring on circadian rhythm sleep disorders, but a dysfunction of the circadian clock can also be responsible [87]. Affected individuals most commonly suffer from impaired social and occupational functioning, as they are tired and awake at inappropriate times for work or

social activities [87]. The late ("owl") chronotype usually accumulates a sleep debt during the week and compensates via extensive sleep duration during the weekend [91]. During the weekdays, however, late chronotypes consume more stimulants [91] and are more depressed [92, 93]. In fact, evidence is accumulating that sleeping at the wrong biological time has a depressogenic effect [94, 95].

A circadian rhythm sleep disorder is normally a stand-alone diagnosis; however, in patients presenting with symptoms of insomnia or excessive sleepiness, it can also be a differential or secondary sleep diagnosis [96]. For an accurate sleep diagnosis, a detailed sleep assessment is often necessary to rule out common morbidities related to daytime sleepiness (e.g., cardiovascular disease, metabolic disorders, mood impairment) [97]. The prevalence of circadian rhythm sleep disorders in the general population is not well characterized, but is estimated at around 1% [98, 99] in adults. Delayed circadian rhythm sleep disorders have a prevalence of 8.4% in adolescents and young adults [100].

## 1.6. Measurement tools for sleep-wake disturbances

In the following sections only measurement tools for insomnia and circadian rhythm sleep disturbances are summarized. The overview ranges from questionnaires with their psychometric properties to objective measurement tools.

### 1.6.1. Measurement tools for Insomnia

This section describes the questionnaires, assessment interviews and other tools most often used to screen and diagnose sleep disturbances. In the case of screening tools used to detect sleep disturbances, a positive result has to be followed by an in-depth questionnaire and an assessment. Further, a diagnosis of insomnia will require a sleep assessment and follow-up visits. For this diagnosis, three conditions have to be fulfilled: adequate sleep opportunity, persistent sleep difficulty, and associated daytime dysfunction. Defining the cause of a sleep-wake disturbance in insomnia patients is very complex since it is often multifactorial [81].

#### 1.6.1.1. Questionnaires used for screening

Hundreds of instruments are available for measuring aspects of sleep, however there are really no instruments to diagnose insomnia. Two of the most popular are the **Epworth Sleepiness Scale (ESS)** [101], an 8-item questionnaire based on Spielman's 3P model [83], measuring daytime sleepiness, and the **Pittsburgh Sleep Quality Index (PSQI)** [102], a 25-item questionnaire measuring poor sleep quality. Even together, these represent only part of the insomnia diagnostic, but are often used as preparatory "homework" for a sleep

assessment, and their combined range is broad enough to impede false negatives. Other questionnaires are available for very specific diagnoses (e.g., the Restless Legs questionnaire). If insomnia is already suspected, the Insomnia Severity Index can be used as a screening tool.

The Epworth Sleepiness Scale is a validated questionnaire that measures a subject's expectation of dozing, i.e., falling into a light sleep [103], in eight hypothetical situations. Response ratings range from 0 (no probability) to 3 (high probability). Scores for the eight items are summed, yielding a total dozing score between 0 and 24. An Epworth Sleepiness Scale sum score  $\geq 6$  indicates DS [101]. A score of  $\geq 10$  indicates that the subject is very sleepy and should seek medical advice [101]. Total ESS scores show high test-retest reliability ( $\rho = 0.82$ ,  $p < 0.001$ ) [104] and a high level of internal consistency (Cronbach's  $\alpha = 0.74-0.88$  in 4 separate chronically ill groups) [105]. A factor analysis of ESS item scores of 150 patients and 104 students isolated a single factor [104], and the full questionnaire has been validated for application in German-speaking populations [106].

The Pittsburgh Sleep Quality Index is a self-rated questionnaire assessing a wide variety of sleep quality related factors, including estimates of sleep duration and latency, and of the frequency and severity of specific sleep-related problems, over the previous month. Its 19 items are grouped into seven component scores, each weighted equally on a 4-point (i.e., 0-3) scale. The seven component scores are summed to yield a global PSQI score of 0-21; higher scores indicate lower sleep quality. A cut-off of  $>5$  points indicates poor sleep quality [102]. Tested as a marker for sleep disturbances in insomnia patients versus healthy controls, this cut-off showed a sensitivity of 98.7 and a specificity of 84.4 [107]. Backhaus et al. translated it into German using the back-translation method [107], after which item analysis confirmed internal consistency of the German version (Cronbach's  $\alpha$  of 0.85) [107]. The test-retest reliability for a short interval (2 days) was high for both the global and the subscale scores (0.76 to 0.92). For a longer interval (45.6  $\pm$  18 days), the test-retest reliability was low for the "sleep quality" ( $r = 0.23$ ) and "sleep disturbance" ( $r = 0.27$ ) subscores, but remained moderate to high for the global score ( $r = 0.86$ ) and four of seven subscores (reliability: 0.59 - 0.83) [107]. Sleep diaries show a high correlation with the PSQI [107] indicating good validity (evidence based on relationship to other variables) based on relation to sleep parameters [107].

The **Insomnia Severity Index (ISI)** is a screening questionnaire used to assess the nature, severity, and impact of insomnia, and to monitor treatment response in adults [108]. A self-reported questionnaire with a recall period of 2 weeks, the ISI is mostly used in studies to confirm insomnia symptoms. Its 7 items are scaled on a 5-point Likert-type scale (0=no problem, 4=very severe problem). While no German version is available, the

scoring internal consistency of the English version has a Cronbach's alpha of 0.90[108], as well as face and content validity. It is correlated with sleep diaries, polysomnography, and interviews. The cutoff score of 10 had a sensitivity of 86.1% and a specificity of 87.7% for detecting insomnia cases in the interview-assessed community sample [109].

More than one follow-up session is often necessary to exclude all similar disorders (e.g., a high score on the Epworth Sleepiness Scale could indicate insomnia, but oxygen saturation during night-time sleep must first be measured). In this context, the 9-question **Berlin Questionnaire** [110] is used to screen for sleep apnea by focusing on one very common symptom: snoring. The questionnaire is divided into three categories related to the probability of sleep apnea. Patients can be classified as high- or low-risk. The questionnaire assesses snoring severity, excessive daytime sleepiness, and history of high blood pressure or obesity, with a Cronbach's alpha of 0.86 - 0.92 for internal scoring consistency [110]. In primary care patients, using an apnea-hypopnea index of > 5 as a cutoff, its sensitivity and specificity were respectively 86% and 77%. An apnea-hypopnea index cutoff of >15.7 [111] yielded a sensitivity of 54% and a specificity of 97%. Measured concurrently with polysomnography, using a respiratory disturbance index of >5, the sensitivity and specificity of the Berlin questionnaire were respectively 68% and 49%. A respiratory disturbance index of >10 yielded a sensitivity of 62% and a specificity of 43%, and a respiratory disturbance index greater than 15.9 yielded sensitivity and specificity figures respectively of 57% and 43% [112].

#### 1.6.1.2. Sleep assessment interview

As mentioned in the introduction to this section (1.5.1), insomnia is difficult to screen with questionnaires alone; an in-depth assessment interview and clinical history are generally necessary to identify insomnia-contributing factors [113]. The temporal, quantitative and qualitative aspects of sleep, behavioral and environmental factors, symptoms of other sleep disorders, and daytime causes and consequences of disturbed sleep are key elements of the sleep history [113]. At the time of data collection for the current study, several sleep assessment questionnaires were considered, including the Holland Sleep Disorders Questionnaire (40 items) [114], the Global Sleep Assessment Questionnaire (including various questionnaires) [115], the SLEEP-50 questionnaire (50 items) [116] and the Survey of Sleep (SOS) [117]. However, of these, to our knowledge only the SOS had a German translation.

As it is a self-report questionnaire, the SOS is a helpful tool to prepare for the assessment interview. Developed at the University of Pittsburgh and later translated into German by Dr. Daniel Brunner (Somnologist at the Hirslanden center of sleep medicine), it

is commonly used to report sleep disturbances in insomnia patients [117]. It has 7 parts: (1) an overview; (2) sleep habits; (3) sleep disturbances ; (4) daytime function ; (5) health habits; (6) sleep history; and (7) medical history [118]. As the SOS is only regarded as a preparation for an interview (rather than a stand-alone data collection instrument), neither validity nor reliability results have been published for it.

### **1.6.1.3. Other tools or tests**

Normally a sleep assessment is combined with a clinical check-up. Patients can support the information gathering by providing the sleep expert with hospital records and clinical reports. The first diagnostic step is the evaluation of these documents, the preparatory questionnaire, the assessment itself and the functional analysis of the sleep complaints, all of which will narrow the field of possible diagnoses. To further facilitate this step, sleep-wake diaries could be a highly cost-effective tool both to define sleep/wake patterns and to identify behaviorally treatable patterns of sleep hygiene (section 1.6.2).

The second step, wrist actigraphy (see section 1.5.2.3), gathers continuous objective data on rest-activity patterns over many days. The actimeter is a wrist-worn device that records body movement to determine sleep patterns.

Another method of sleep data collection is polysomnography, a comprehensive diagnostic test measuring brain wave activity, eye and jaw muscle movement, leg muscle movement, nasal airflow, snoring activity, respiratory effort (chest and abdominal excursion), heart rate and oxygen saturation. As this test measures all these physiological parameters with great accuracy, the American Academy of Sleep Medicine considers it the gold standard for quantifying and qualifying sleep disorders. It can quickly test for sleep apnea or parasomnias mentioned in the sleep history [113], and is also commonly used to diagnose narcolepsy, idiopathic hypersomnia, periodic limb movement disorder, rapid eye movement behavior disorder, and sleep apnea. However, the diagnosis of insomnia and circadian rhythm sleep disorders requires several weeks and one laboratory night adds little informative value.

### **1.6.2. Measurement tools for circadian rhythm sleep disorders**

The following sections describe the most commonly used measurement tools for circadian rhythm sleep disorders. As noted in section 1.4.2, the screening instruments for these disorders are the same as for insomnia. Questionnaires and a sleep assessment help narrow the range of possible diagnoses. To qualify as a circadian problem, a disorder has to fulfill two main criteria: it must be persistent, i.e., a recurrent pattern of sleep disturbance (signaling disruption of the circadian time-keeping system or misalignment between the

endogenous circadian rhythm and the exogenous factors that affect the timing or duration of sleep); and it must lead to insomnia and / or daytime sleepiness with impairment of social, occupational or other daytime functioning tasks [81].

#### 1.6.2.1. Questionnaires used for screening

Screening for circadian misalignment requires knowledge of the subject's effective bedtime and get-up time, the environmental constraints and the chronotype. The degree of interindividual variation in circadian sleep timing indicates whether the subject's current bedtime is misaligned. The Horne-Östberg Morningness-Eveningness Questionnaire (MEQ) [18] is a commonly used measure of circadian phase preference (chronotype). This tool provides a subjective measure of interindividual variation in circadian sleep timing, ranging from the early ("lark") type to the late ("owl") type. When interventions are planned to shift the biological clock, knowing an individual's internal time is crucial, as a given clock time of application may correspond to significantly different internal times for owls and larks, thus producing unwanted results.

The Morningness-Eveningness Questionnaire consists of 19 items in 2 formats: 5-point multiple-choice (5) and 4-point multiple choice (14) with different scoring weights ranging from 0 to 6. The sum gives a score ranging from 16 to 86; scores of 41 and below indicate "evening types", scores between 42-58 indicate "intermediate types", and scores of 59 and above indicate "morning types" [119]. The internal consistency established in the general population in New Zealand was very good (Cronbach's alpha =0.83). The questionnaire's accuracy has also been measured against oral temperature curves (a measure of circadian rhythm). Morning types had a significantly earlier peak time in the circadian rhythm cycle compared to evening types. They also tended to have a higher daytime temperature and a lower post-peak temperature [18]. There are different scoring of the Morningness-Eveningness Questionnaire. With the original scoring 49.8% of the total population was classified as morning type compared to 5.6% with evening-type chronotypes [120]. In a validation study in a sample of middle-aged workers- (non-students), anyone scoring under 53 was considered an evening type, whereas anyone scoring above 64 were classed as an morning type. This reclassification resulted in 28.1% morning type, 51.7% intermediate, and 20.2% evening type [121].

Whereas the Morningness-Eveningness Questionnaire assumes a single schedule throughout the week, the Munich Chronotype one (MCTQ) takes into account different sleep timing during the week and at week-ends [22]. The MCTQ uses 13 rated items to assess individual phases of entrainment on working and work-free days. Aimed at subjects aged 6 to > 65 years, it collects clock-time data including get-up and bedtimes, the time



the subject becomes fully awake, and the lengths of sleep latency and inertia periods [122].

### 1.6.2.2. Sleep logs or diaries

The diary is an easy and very effective measure to evaluate a subject's sleep-wake pattern. Most diaries have predetermined slots or lines to insert daily bedtime, lights-out times, subjective sleep latency, rising up during the night, and wakeup time. Sleep diaries often also include simple Likert scales for subjective measures such as mood, well-being, tension, or tiredness. Diary data also assist researchers in validating, editing and interpreting actimetry measurements [123, 124]. Example shown in figure 5.

**Figure 5:** Example of a sleep diary showing entries made before bedtime (grey part) and after getting up (yellow part)(in German):

Vor dem Schlafengehen ausfüllen!																				
TAG/ DATUM	ZEIT	BEFINDEN										BEWEGUNG		NICKERCHEN		AKTIRMETER AB				
		0	1	2	3	4	5	6	7	8	9	10	von	bis	von	bis	von	bis		
MI/ 11.08. 2012	22:20	entspannt			x									angespannt	14:30	14:45	13:45	14:00	08:30	08:45
		körp. unwohl								x				körp. wohl	18:00	18:30	16:05	16:45	15:00	15:15
		wach							x					müde					21:20	21:40
		gesättigt							x					hungrig						
		schlechte Stimmung							x					sehr gute Stimmung						

Am nächsten Morgen ausfüllen!																			
ZEIT	EINSCHLAF ZEIT	NÄCHTLICHE WACHEPISODEN		AUFWACH ZEIT	AUFSTEH ZEIT	BEFINDEN													
		von	bis			0	1	2	3	4	5	6	7	8	9	10			
						entspannt													angespannt
						körp.unwohl													körp.wohl
						wach													müde
						gesättigt													hungrig
						schlechte Stimmung													sehr gute Stimmung

Image credit: Sleep diary developed by H.Burkhalter for the study described in chapter 7.

### 1.6.2.3. Actimetry

Circadian rhythms can be objectively measured through actimetry. Polysomnography is used to measure sleep parameters (e.g.: REM and non REM cycles) for single night, however cannot measure activity rhythms. Polysomnography normally measures brain electroencephalographic activity, eye movements, muscle activity or skeletal muscle activation, heart rhythm and chest movement (breathing) over one night in a sleep center

under “laboratory” conditions. Though indispensable for many sleep diagnoses, polysomnography is very expensive and time-consuming, and does not reflect the patient's normal home environment. For measuring circadian rhythms, then, the current study focused on actimetry.

The actimeter is a wristwatch-shaped device to continuously measure arm movements/unit of time. Normally it is worn on the non-dominant wrist. Actigraphy has been established as a reliable and objective method for the naturalistic study of sleep and wakefulness in a 24-hour context [124-126]. Several models of actimeter are available. In the study reported in chapter 7 we used Daqtometers (Daqtometer by Daqtix GbR, Oetzen Germany), which include an integrated light sensor [127]. The light sensor on the upper surface of the device measures the individual's light exposure during the entire measurement period. The light data helps to interpret the circadian sleep-wake rhythms, and is well suited to an intervention study involving light, i.e., to assess adherence to light therapy. In addition to wearing the device, users must keep a diary indicating any periods when they are not wearing the actimeter [128], and entering their bedtimes, wake up times, get-up times and exceptional events (e.g., parties, very cold days, or periods when the actimeter was under a sleeve). Practical parameters for the role of actigraphy in the study of sleep and circadian rhythm can be found in Littner et al. (2003) [129].

Standardized protocols exist for editing and analyzing actimetry data [130]. The stored values on the actimeter are downloaded to a personal computer, then edited with the aid of diary entries to determine adherence levels. After the editing of the raw data, the main analysis software [88] yields three figures regarding the subject's overall circadian rhythm ((1) interdaily stability (IS); (2) intradaily variability (IV); (3) relative amplitude (RA)), four focusing on sleep variables ((1) bed time, (2) get up time, (3) sleep efficiency, (4) sleep latency) and one more for light (intensity measured in Lux). IS reflects the stability of the rhythm over the full time span of interest, ranging from 0 to 1, where 1 represents perfect stability over the entire period. A low IS value indicates greater day-to-day variation. IV indicates the degree to which the rhythm is fragmented. This also ranges from 0 to 1, with higher values indicating a more disrupted sleep-wake rhythm (e.g., frequent naps, frequent night-time sleep disruptions). RA expresses the ratio between the most active 10 h period and the least active 5 h period in each 24 hour period. As with the other measures, it ranges from 0 to 1. In this case, higher values indicate better-regulated sleep-wake rhythms.

#### 1.6.2.4. Circadian phase marker- Dim light melatonin onset

Perhaps the important hormone for synchronizing sleep patterns with night and day is melatonin. It is produced by the pineal gland, with the suprachiasmatic nuclei controlling its daily cycle of synthesis and excretion [25]. Light absorbed through the retina inhibits its production, while darkness permits production. Under normal conditions, melatonin levels rise during the night and decline at dawn [131] (Figure 6). The increase in melatonin secretion in the evening correlates with an increase in sleep propensity [132]. Melatonin affects the circadian rhythm by initiating a nightly thermoregulatory cascade which decreases heat production and vasodilatation of distal skin regions, leading to heat loss, which in turn induces increased sleepiness and a decrease in core body temperature preparatory for sleep [133].

**Figure 6:** Example of an individual saliva melatonin profile

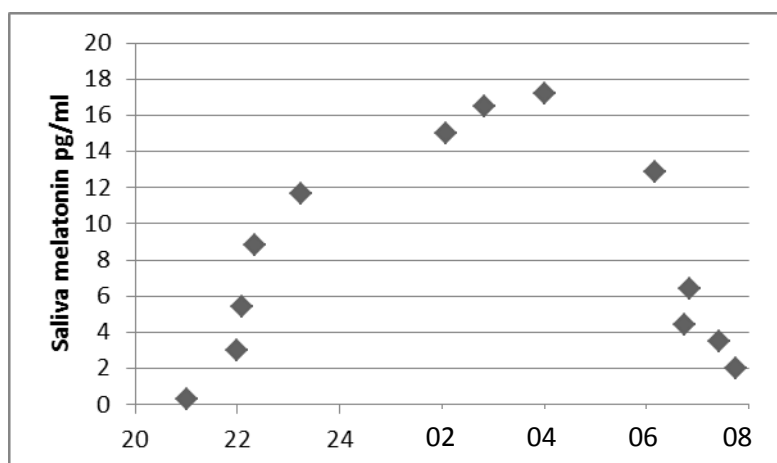


Image credit: H. Burkhalter - Saliva melatonin profile of one subject that participated in the bright light intervention study (Chapter /)

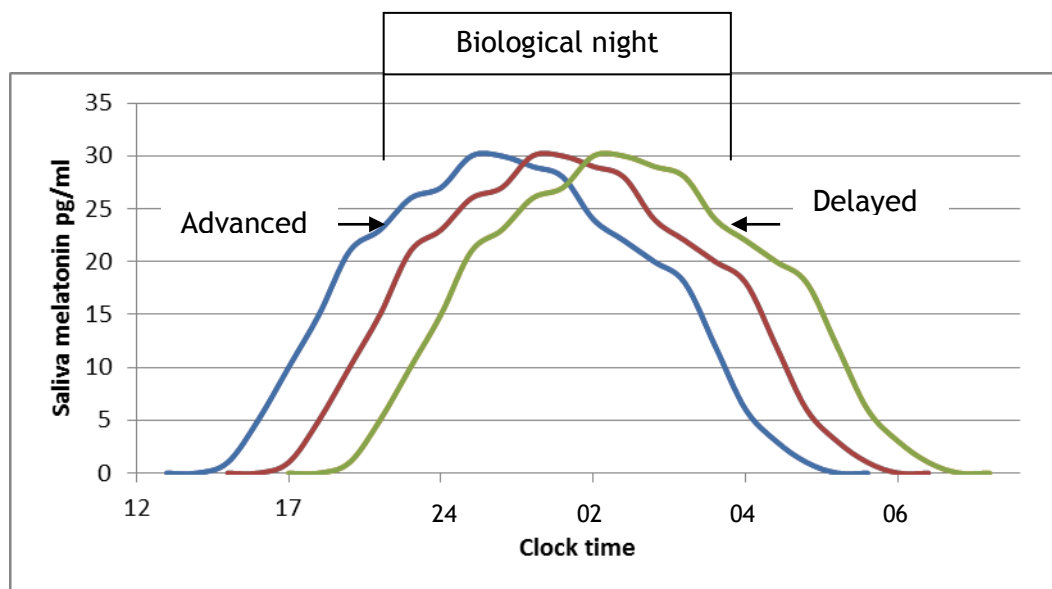
Melatonin begins to rise an hour or two before sleepiness begins, peaks in the middle of the night, and falls until about the time of awakening [134]. As Melatonin onset each evening results in a clear change from the low levels throughout the day, it is useful as a circadian marker when the entire nocturnal rhythm cannot be measured. Levels can be measured in the blood, saliva [135] and urine (melatonin metabolite 6-sulphatoxymelatonin (aMT6S)) [136]. Dim-Light Melatonin Onset (DLMO) is a standardized physiological estimate of circadian phase when samples are collected under dim light conditions [137].

Adding to its diagnostic value, empirical evidence indicates that saliva melatonin can reliably be self-collected and stored at home. For a study including 1848 patients with possible delayed sleep phase disorder, participants self-collected late afternoon and evening saliva melatonin samples at 5 consecutive one-hour intervals at home: dim-light

melatonin onset could be determined in 76.2% (n=1408) of cases [138]. To check the reliability of patient self-collection, a recent study compared 24 individuals' home-collected saliva melatonin samples with laboratory-collected samples from the same subjects the following night. Analyses indicated a significant correlation between the at-home and in-lab dim-light melatonin onset assessments [139], and dim-light melatonin onset could be determined in 80% of the self-collected sample [139]. The reasons for the unsuccessful dim-light melatonin onset measurement included very low values (<3 pg/mL), profiles where initial melatonin levels were already above the threshold of 4 pg/mL, fluctuating curves, bleeding gums or mislabeling of tubes [139].

For persons whose sleep onset is not aligned with melatonin increases, dim-light melatonin onset time is a useful measure to determine internal phase, as onset timing varies according to individual chronotype. Phase advance or phase delay with respect to normal dim-light melatonin onset times (around 9 pm) can easily be recognized through a pre-bedtime evening melatonin saliva profile. If dim-light melatonin onset is delayed, morning light exposure will normally advance it [140]. Figure 6 indicates that bright light therapy can correct problems in either direction: If dim-light melatonin onset is poorly synchronized (i.e., delayed or advanced), appropriately timed light exposure therapy can be used to correct it (Figure 7).

**Figure 7:** Highly simplified diagram of phase shifts of the circadian system



Bright light in the evening or melatonin supplementation treatment to delay the clock

Early morning bright light treatment to advance the clock or melatonin supplementation treatment in the early evening

Dim-Light Melatonin Onset is the most reliable marker for human circadian phase position, and is optimally obtained via evening blood or saliva sampling [141]. Unfortunately, the cost of assaying samples is relatively high. Dim-light melatonin onset can be calculated from hourly or half-hourly sampling. Thresholds either of 3 pg/mL or of a "3k" concentration (equal to the mean plus two standard deviations of the first three low daytime points) are commonly used [142]. Related calculations can easily be performed using the "hockey-stick" method recently developed by Danilenko et al. (2013) [143]. Figure 6 shows a saliva melatonin profile of an individual who participated in the bright light intervention study and figure 8 shows the calculated Dim-Light Melatonin Onset based on these data using the software developed by Danilenko et al. (2013).

**Figure 8:** Example of a calculated Dim-Light Melatonin Onset time based on saliva melatonin samples collected in the evening

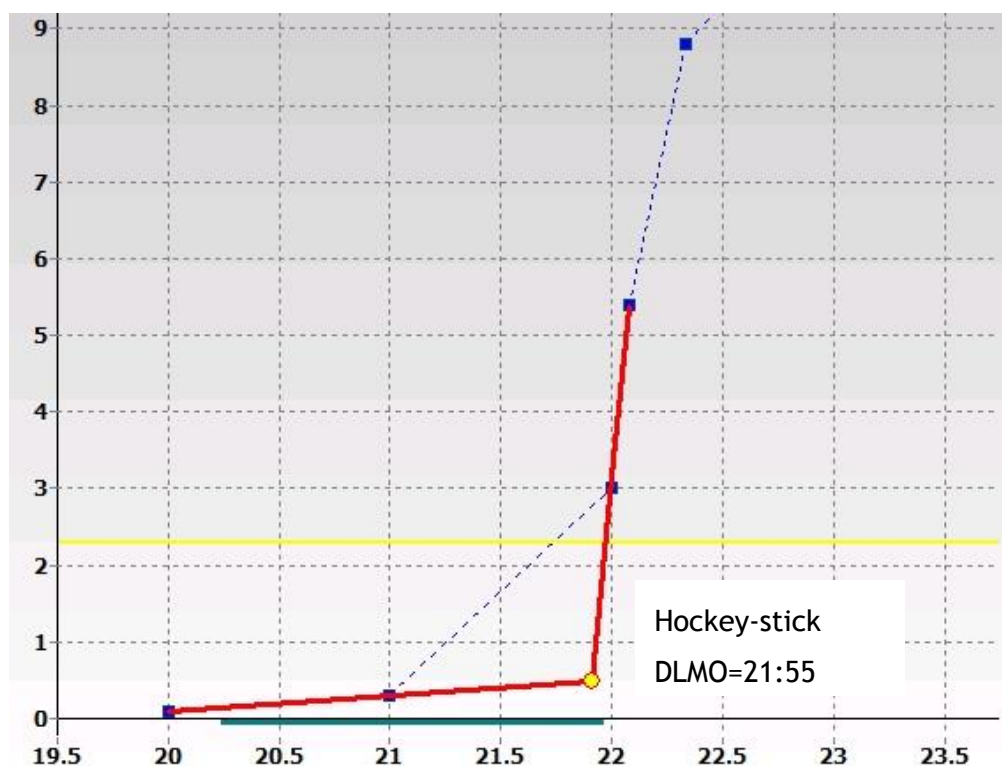


Image credit: C. Danilenko - Hockey-stick method to estimate evening dim light melatonin onset (DLMO) [143]

#### 1.6.2.5. Other measurement tools

In patients with symptoms suggestive of both a circadian rhythm sleep disorder and another primary sleep disorder, polysomnography (see section 1.5.1.3) is indicated to rule out numerous conditions; however, for reasons summarized above (see section 1.5.2.3), it is not indicated for the diagnosis of circadian rhythm sleep disorders.

## 1.7. Treatments for sleep-wake disturbances

The following section describes the main treatment for insomnia and circadian rhythm sleep disorders.

### 1.7.1. Insomnia treatment

The two main treatment classes for insomnia [113] are behavioral (e.g., cognitive behavioral therapy) [144, 145] and pharmacological (e.g., hypnotics, sedating antidepressants and antipsychotics)[146]. Buysse et al. (2013) wrote in a short report for the journal of the American medical association in his summary findings that: “Behavioral treatments should be used whenever possible, and medications should be limited to the lowest necessary dose and shortest necessary duration” [113]. Sleep medications are often used to diminish patients' worries, as most are extremely distressed about their poor sleep. Many individuals spend considerable time in bed trying to “catch up” on sleep; in this situation, a sleep drug is only helpful if administered with sleep (and eventually sleep restriction) schedules. Using the 3P model [83] as an underlying framework for insomnia, the main treatment objective is to prevent a transient insomnia from evolving into a persistent insomnia. Therefore, the vanguard of sleep intervention studies currently involve cognitive and/or behavioral treatments (sleep restriction, stimulus control therapy, relaxation based interventions, cognitive therapy and sleep hygiene education)[113].

### 1.7.2. Circadian rhythm sleep disorder treatment

Circadian phase adjustments demand appropriate treatment timing. Before embarking on any course of treatment, a questionnaire estimating the patient's chronotype is essential [147]. The most common treatment for sleep disorders is quick pharmacological relief; however, while behavioral interventions are slower, it has been suggested that they are more durable [148-150]. Especially in shift workers or frequent travelers with time zone changes, timed melatonin supplementation and /or light can speed up the phase change [151]. Behavioral therapy, such as improved sleep hygiene (See Table 1) (especially enforcement of stable sleep and wake times, together with exposure to light at the correct time of the day and avoidance of exposure at counterproductive times) is the basic approach for all patients diagnosed with circadian rhythm sleep disturbances [144]. There are hundreds of sleep hygiene rules, all of which include behavioral, environmental, dietary and exercise components.

**Table 1:** Sleep hygiene rules derived from the U.S. Department of Health and Human Services - National Institute of Health [152]:

Nr.	Sleep hygiene rule
1	Keep your internal clock set with a consistent sleep schedule
2	Exercise early during the day
3	Avoid caffeine, alcohol, nicotine, and other chemicals that Interfere with sleep
4	Avoid alcoholic drinks before bed.
5	Avoid large meals and beverages late at night.
6	Don't take naps after 3 p.m.
7	Relax before bed.
8	Take a hot bath before bed.
9	Have a good sleeping environment.
10	Have the right sunlight exposure.
11	Don't lie in bed awake. Go to bed when you are truly tired

#### 1.7.2.1. Intervention with Zeitgebers - Chronotherapeutics to normalize the circadian process

Chronotherapeutics involve controlled exposure to environmental stimuli (e.g., food intake, exercise, social cues, auditory stimuli and light [153, 154]) that influence biological rhythms and help synchronize the homeostatic and circadian processes both with one another and with the external day-night cycle. As light is the main Zeitgeber for the suprachiasmatic nucleus, bright light therapy is the main intervention against circadian imbalances [155]. When exposed to light, receptors in the retina transmit neural impulses to the suprachiasmatic nuclei-the body's master clock-and to a number of other centers responsible for sleep and wakefulness (cellular, physiological, and behavioral patterns) (figure 9).

**Figure 9:** Neurological structures, including the suprachiasmatic nuclei, which are involved in human circadian rhythm control.

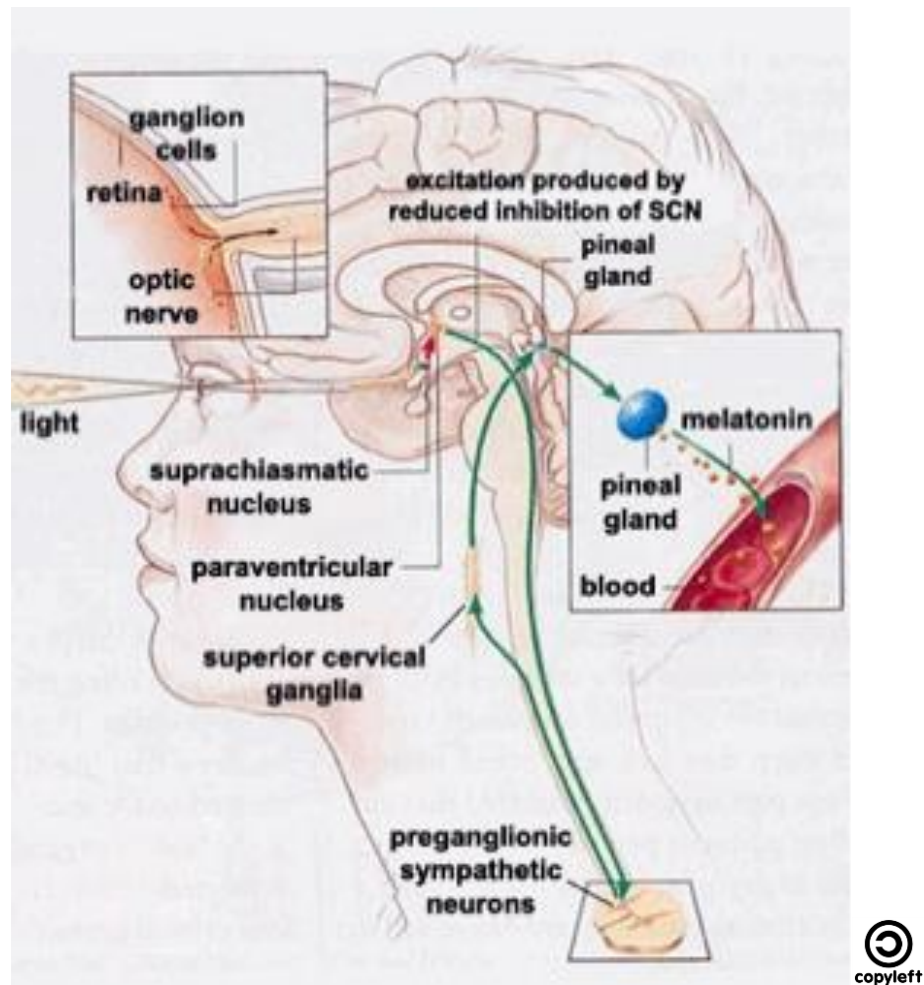


Image credit: <http://thebrain.mcgill.ca> (Copyleft)

Further interventions include dawn and dusk simulation therapies [130, 156], dark therapy or blue light blocking therapy [157, 158] and wake therapy (sleep deprivation as a rapid antidepressant) [159, 160]. Dawn and dusk simulation therapy is used while in bed, during normal sleep hours. The simulator gradually alters light levels to mimic outdoor dawn and dusk transitions. As this treatment requires minimal attention from the patient, and most of the signal is presented while the user is asleep, it is considered automatic [161]. Blue light blocking therapy in the evening can involve the patient either wearing amber colored glasses or simply avoiding blue light. (In nature, blue light is normally a characteristic of morning light. However, computer screens and televisions equipped with short wavelength (blue range) light-emitting diodes (LED) have been shown to suppress the evening rise in endogenous melatonin [162]). Finally, wake therapy uses sleep deprivation to treat patients with affective disorders. In depressed patients, the combination of light and wake therapy elicits a rapid and sustained antidepressant response [163].



### 1.7.2.2. Background and effect of bright light therapy

Bright light therapy consists of exposure to specific very bright (typically 10,000 lux), full-spectrum UV-filtered light from a light box for a beginning dose of 30 minutes [140]. When this light reaches the retina, it triggers signals to the suprachiasmatic nuclei to shift or stabilize circadian rhythms (Figure 10). As light suppresses melatonin secretion [164], night-time darkness is essential for normal melatonin production. Bright light therapy aims to stabilize the sleep phase [165] by resynchronizing a misaligned rhythm or by correcting for a lack of environmental light stimulation (e.g., for people living at higher latitudes in winter or who are housebound). Since 2005, light therapy has been indicated as the first-line treatment in seasonal and non-seasonal depression in [155, 166], i.e., in depressed patients, it is considered a viable alternative or adjunct to antidepressive medication [167, 168].

**Figure 10:** Light influence cyclic human behavior

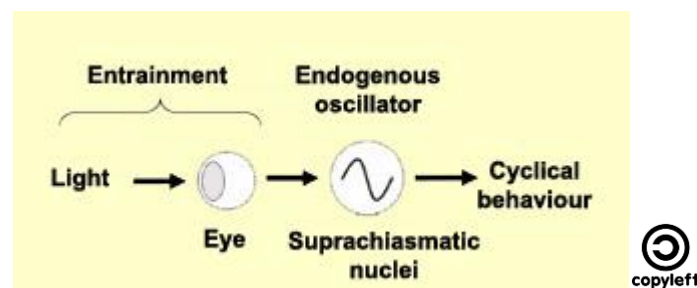


Image credit: <http://thebrain.mcgill.ca> (Copyleft)

In addition to the external influence of light, cyclical genes regulate the biological clock mechanism endogenously. When light reaches the retina, sensors activate the suprachiasmatic nuclei, which signal the pineal gland to regulate physiological and behavioral functions and cycles. The timing of light treatment must match the patient's chronotype [169] and other sleep pattern details. For example, advancing a patient's sleep phase requires bright light early in the day. To increase the positive effect for people having trouble falling asleep and getting up on time each morning, light intervention should be even earlier. Terman and Terman (2005) recommend beginning morning light treatment about 7½ hours after dim light melatonin onset [170].

In contrast to pharmacological agents, non-pharmacological interventions have little or no risk of adverse side effects [171, 172]. Side effects of light therapy overdose may include agitation, headache, or nausea. Side effects can be lessened by reducing the light dosage (intensity, duration, or both), increasing the distance between the patient and the light source (i.e., lowering the intensity), or by moving morning therapy sessions to a later time when ambient light levels are higher [173].

Apart from the circadian sleep disorders noted above, bright light therapy is useful against disturbances arising from shift work and jet-lag [174]. For shift workers [175, 176] it has demonstrated subjective improvements in work time performance tasks [144]. Some studies have even shown melatonin shifts and improvements in daytime sleep [177]. Regarding jet lag, bright light therapy can accelerate circadian synchronisation following transmeridian travel [178]. Preflight treatment with bright light therapy prior to eastward travel can be used to produce phase advances and potentially eliminate jet lag altogether [179].

Morning bright light therapy has also proved useful against a growing range of neuropsychiatric disorders. For example, it is the treatment of choice for seasonal affective disorder (SAD) [155] and has shown promising results versus non-seasonal depressive syndromes [155, 180], in major depression [181, 182], antepartum depression [183], eating disorders [184], attention deficit/ hyperactivity disorder [185], borderline personality disorder [186], Parkinson's disease [187] and Alzheimer's dementia [188].

### 1.7.3. Drug treatments for sleep disorders

Sleep drugs can provide effective symptomatic relief of sleeplessness resulting from travel across time zones or to deal with acute stress (e.g., a medical procedure, loss of a loved one, mental trauma). However, where sleep disorders are deep-rooted, medication does nothing to treat the underlying causes. Persistent sleep disorders require in-depth assessment, with the diagnosis leading the treatment approach [189].

One commonly prescribed sleep medication group is the benzodiazepines. These drugs are well-suited for anxiety disorders [190], and include 3 classes: long-, intermediate- and short- acting (time to peak action) [191]. Short-acting benzodiazepines are considered safe for the short-term management of insomnia in the elderly [192]. However, the elimination half-life can last up to 100 hours [191, 193], leaving the patient with a "hangover".

Benzodiazepine and psychopharmacological treatment aiming to interrupt acute sleeplessness following a traumatic event (e.g., surgery, transplantation) are recommended primarily to stop the progress of molecular mischief associated with the brain's reaction to traumatic stress [194]. Sleep disturbances lasting beyond this period require more comprehensive diagnostic criteria.

After the diagnosis of an anxiety disorder, a long-term low-dose benzodiazepine treatment is not considered abusive or addictive [195] as this drug was designed especially to combat this disorder. Still, the side-effects can be significant. Studies have reported

ataxia, psychomotor impairments (leading to increased incidences of falls and fractures in the elderly), cognitive impairment, withdrawal, addiction, and renal bio-accumulation [196]. In fact, many prescribers dread benzodiazepines for their adverse daytime effect (daytime sleepiness and slowdown) [197] and their risk of addiction and abuse [198]. Additionally, benzodiazepine use can lead to tolerance [198], craving (if abruptly discontinued), and strain on hepatic and renal degradation processes [199]. Finally, even after a single dose [200], benzodiazepines reduce both the nocturnal secretion of melatonin [201] and inhibit cortisol secretion [202].

Non-benzodiazepine psychoactive drugs resemble the benzodiazepines regarding effects and risks, but different chemical structures. They are mainly used to treat sleep disorders and are known to reduce sleep onset latency [203]. Some also help the user to stay asleep (e.g., Zolpidem, Estazolam). However there is a debate about the safety of these drugs, as they may increase cancer risk, especially skin cancer [204]. This detail is very important for immunosuppressed patients as immunosuppression increases the risk of actinic keratosis progression to skin cancer [205]. As solid organ transplant recipients are normally immunosuppressed, their incidence and risk of malignancy is elevated [206]. A further problem is that patients often remain on sleep drugs for months or years, increasing the risk of dependence, accidents and other adverse health effects [207].

#### **1.7.4. Melatonin supplementation for sleep disorders**

The circadian cycle-regulating hormone melatonin is secreted by the pineal gland in response to darkness. It is also available as a medication or dietary supplement. Clear evidence of benefits exists regarding its use against insomnia [208], the effects of jet lag [209], shiftwork-related difficulties [210], delayed sleep phase syndrome [211-213]. It also strengthens the immune system [214, 215], reduces free radicals in the body, functions as an anti-oxidant, may curtail metabolic syndrome [216-219] and has immunomodulation effects beneficial in cancer patients [220-224]. Melatonin or melatonin agonist medication doses are timed to increase melatonin levels 2-3 hours before bedtime [168], as this induces sleepiness [225].

Melatonin levels differ considerably between individuals [226-228]. Some studies report no gender-based differences in adult melatonin levels [226] and some do [229]; however, in children, girls' levels are significantly higher [230]. Melatonin secretion declines with age [231] and growth [226, 228]. However, the decrease between childhood and adulthood serum melatonin levels is related mainly to an increase in body size rather than to decreasing pineal secretion [228]. At every age, melatonin deficiency or disruption of its rhythm is associated with an increased prevalence of sleep disorders [232] and

sleep/wake cycles disturbances [233]. People with hormone cycle dysfunction, damaged melatonin receptors (fragile X syndrome) or disease-induced night-day rhythm reversal (Smith-Magenis Syndrome, a developmental disorder), require up to 100% melatonin supplementation [234].

In Switzerland melatonin is available only as a slow release drug of 2 mg (Circadin Retard®) [235] for the treatment of insomnia in people aged 55 and older [208]. In April 2007, Circadin was approved by the European Medicines Agency as a monotherapy for the short-term treatment of primary insomnia in patients aged 55 or older. The recommended dosage is 2mg daily, 30 minutes before bedtime for 3 months [208]. This prescription is well tolerated, with no hangover and no observed safety issues regarding concomitant therapy with antihypertensive, antidiabetic, lipid-lowering or anti-inflammatory drugs [208]. Interestingly, a 2 mg dose is roughly 80 times higher than the amount of melatonin secreted nightly by healthy adults (5 to 25 micrograms). Further, the effect of melatonin supplementation seems to persist for at least 3 months after stopping exogenous treatment [236]. Keijzer et al. (2011) wrote in the discussion section that this might be caused by tissue storage of exogenous melatonin [138].

Before a supplementation of melatonin is scheduled, the effect of evening bright light use has to be quantified and all substances and medications having interactive potential should be accounted for. Substances such as caffeine, tobacco, and alcohol can inhibit melatonin secretion [237]. Caffeine, for example, inhibits its metabolism via CYP1A2 [238]. A more complex challenge is checking all medications taken and their interaction potential. Medications known to interact with melatonin are Beta blockers and nonsteroidal anti-inflammatory drugs. Single studies have reported that melatonin may also change the efficacy of anti-coagulants (Warfarin® [239]), diabetes medications [240] and oral contraceptives [241]. Melatonin suppression by light or beta-blockers can be treated by melatonin supplementation [242, 243]. Beta blockers are known to suppress melatonin [244-246] by blocking sympathetic signaling to the pineal gland. Non-steroidal anti-inflammatory (NSAID) drugs providing analgesic, antipyretic and anti-inflammatory effects are known to inhibit the prostaglandin synthesis and suppress melatonin [247]. Further, melatonin decreases the effect of  $\alpha$ 1-adrenergic receptor agonists (methoxamine) and  $\alpha$ 2-adrenergic agonists (e.g., clonidine) by decreasing presynaptic calcium levels and inhibiting norepinephrine. Calcium channel blockers may lower melatonin levels via the activation of the voltage-dependent L-type channel (which mediates the entry of calcium ions into excitable cells) [248]. No results were found for the interaction with immunosuppressiva and steroids, however we assume a lower suppression of the immune system.

## 1.8. Sleep disturbances in solid organ transplant recipients

Firstly, this section will describe the solid organ transplantation procedure and its prevalence. It will then deal with common outcomes and the need for immunosuppressive medication. In addition it will explain the importance of considering transplant recipients as chronically ill. Then the focus will shift to sleep disorders in solid organ transplant recipients, their prevalence, associated factors and treatment options.

### 1.8.1. Introduction and prevalence of solid organ transplantation

In 2012 35 hearts, 52 lungs, 92 livers, 96 living donor kidneys and 155 cadaveric donor kidneys have been transplanted in Switzerland alone, leaving 102 heart, 122 lung, 282 liver and 1207 renal failure patients on waiting lists [249]. Transplantation involves explanting a functioning organ from a donor and implanting it in a recipient. Recipients of solid organs (i.e., heart, lung, liver and kidney) are the focus of this dissertation.

As a therapy for end-stage kidney disease, **kidney** transplantation surpasses dialysis treatment in the quality and length of life that it provides and in its cost-effectiveness [250]. Patients suffering from heart failure have only three treatment options: **heart** transplantation, heart-lung transplantation or implantation of a mechanical circulatory support device. For heart transplantation, no cost-effectiveness analysis can be applied due to the shortage of organs, and the devices available are mostly intended for temporary support only [251]. With **lung** transplantation, factors to be considered include the underlying disease, other therapies which alleviate the disease, life expectancy and quality of life with or without transplantation. For some diseases, lung transplantation shows a net benefit; careful decision making is necessary [252]. **Liver** transplantation is similar to kidney transplantation in that donors can be live or cadaveric, but the economics are very difficult to estimate, as liver allocations are based on the severity of the prospective recipient's illness (Model for End-Stage Liver Disease)[253]. In some cases, then, liver transplantation is clearly indicated; in others it is not.

For those patients who receive organs, the risks of complication from the transplantation procedure itself are very small compared to that of rejection and the side effects of the anti-rejection therapy [254], particularly immunosuppressive medications. As their name implies, these functionally suppress the immune system and therefore increase susceptibility to infectious diseases. Without them, due to differences in human leucocyte antigen haplotypes, the recipient's immune system would attack the transplanted organ, leading to rejection (tissue death) [255, 256].

The pharmacological treatment of solid organ transplant recipients is very complex. Immunosuppressive drugs are considered high-risk for the many possible pharmacokinetic and pharmacodynamic drug-drug interactions. Imprudent prescription or even over-the-counter drugs can cause acute graft rejection. Also, as most solid organ transplant recipients are taking a calcineurin inhibitor (cyclosporine, tacrolimus), which are nephrotoxic, these patients are at risk of developing renal dysfunction [257]. Standard protocols in use for renal transplant recipients typically involve three drug groups, each directed to a site in the T-cell activation or proliferation cascade which are central to the rejection process: calcineurin inhibitors (e.g., cyclosporin, tacrolimus), anti-proliferative agents (e.g., azathioprine, mycophenolate mofetil) and steroids (prednisolone) [258].

Chronic calcineurin inhibitor nephrotoxicity is associated with irreversible histological damage to the glomeruli, arterioles and tubulointerstitium [259]. Calcineurin inhibitor metabolism occurs mainly in the liver and gastrointestinal tract through the hydroxylating and demethylating actions of CYP3A4 and CYP3A5 isozymes [259]. Immunosuppressants act on the cytochrome P450 (CYP-450) system and P-glycoprotein protein transport, both of which play significant roles in the absorption, distribution and metabolism of immunosuppressants [260]. Although a broad range of variables (age, hepatic function, multiple metabolic pathways) influence patient outcomes, substrates, inhibitors, and inducers of CYP-450 isoenzymes are the main drug interaction risk for immunosuppressed recipients, [261]. The best known interactions with immunosuppressive drugs such as calcineurin-inhibitor (cyclosporine and tacrolimus) are azole antifungals, macrolide antibacterials, rifampicin, calcium channel antagonists, grapefruit juice, St John's wort and protease inhibitors [262]. Interaction with mycophenolic acids occurs via interference with the intestinal flora or by limiting drug absorption [262]. Clinically relevant immunosuppressive drug interactions require prompt identification [263].

#### **1.8.1.1. Monitoring of acute rejection**

While solid organ transplant groups have numerous organ-specific reasons for failure, the similarity of dissociation between short and long-term attrition suggests some similarities [264]. The recent decrease in acute rejection is the result of improved induction therapies and more potent immunosuppressive drugs. However, these result in more infections and elevate cancer risks. All solid organ transplant recipients treated with calcineurin inhibitors suffer from nephrotoxicity [265]-the dominant factor for chronic kidney disease-with increased morbidity and premature mortality [266]. Chronic kidney disease is highly prevalent, affecting 30% to 50% of the non-renal organ transplant population, with an annual end-stage renal disease risk of 1.5% to 2% [267]. In liver transplant recipients,

improved immunosuppression increases the risk of hepatitis C recurrence [268]. In heart transplantation, higher immunosuppression will decrease acute rejection but increase other side effects [269], though the cumulative number of moderate/severe rejections was found to have accelerate cardiac allograft vasculopathy onset [270].

At 3 and at 6 months post-transplantation, a biopsy is standard procedure in Switzerland for renal transplant recipients, to balance the immunosuppressive medication dosage against the risk of opportunistic infections. In renal transplant recipients, the Banff classification of rejection is used on graft biopsies (normal, antibody-mediated rejection, borderline changes, T-cell mediated rejection, interstitial fibrosis and tubular atrophy and other) [271]. The Banff criteria are sometimes also used for liver [272] and pancreas transplant recipients [273]. If rejection is underway, a biopsy is necessary to determine the therapy required. The classification of heart [274] and lung allograft rejection [275] is described in a consensus paper of the International Society for Heart and Lung Transplantation (ISHLT). The categories are acute rejection, chronic rejection, chronic vascular rejection and airway inflammation (for lung transplant recipients) and cellular rejection and acute antibody mediated rejection (for heart transplant recipients).

### **1.8.2. Outcome (survival) for solid organ transplant recipients**

The one-year survival rate after renal transplantation is 95% and roughly 90% at 3-5 years, with bacterial and invasive fungal infections being the primary causes of mortality in this population [276]. In the U.S., the expected one-year survival rate after liver transplantation approached 90% in 2012 [277]. This represents an astonishing improvement since 2000, when one study of a large U.S. cohort of liver transplant recipients reported an overall one-year patient survival rate of 59% [278].

As with renal transplant recipients, infections are the most common multifactorial problem for liver transplant groups [279]. In Spain's heart transplant program database, the 2012 figures for survival after heart transplantation were 77.8% at one year, 64.4% at five years, 48.9% at ten years, 35.6% at fifteen years, and 24.2% at twenty years [280]. In 2011 the Registry of the International Society for Heart and Lung Transplantation reported that, for patients surviving one year post-transplantation, the median survival period had reached 14 years [281]. Lung transplant recipients' graft survival depends strongly on avoiding infections associated with bronchiolitis obliterans syndrome (chronic allograft rejection) [282]. Based on registry data, current survival rates are 87% at 3 months, 78% at 1 year, 62% at 3 years, 50% at 5 years (the survival half-life), and 26% at 10 years. While the mortality rate is highest in the first year [283], the rates for wait-listed lung transplant

candidates has declined with the development of techniques to temporarily support acutely decompensating patients (extracorporeal membrane oxygenation)[284].

### **1.8.3. Outcome (quality of life) for solid organ transplant recipients**

In addition to survival rates, there is considerable interest in examining patient-reported outcomes of solid organ transplantation, such as symptom experience and distress, and quality of life. Symptoms are very important both to transplant recipients and to pre-transplant patients, partly because they may signal significant changes in their health [285], but also because of symptoms' impacts on overall comfort. Studies have confirmed an overall improvement in health confirmed by studies describing symptoms improvement from pre- to post-solid organ transplantation; more details are provided in the following five studies.

Approaching quality of life as a specific outcome, a cross-sectional case-control study by Reimer et al. (2002) compared 149 renal transplant recipients with 149 hemodialysis patients and 149 healthy controls. Members of the three groups were strictly matched by age and gender. Quality of life was measured with a global inventory, the Munich Quality of Life Dimension List. The analysis showed that transplant recipients and healthy controls experienced similar quality of life (6.55 respectively 6.52), and that both groups' ratings were significantly higher than those of the dialysis patients (5.63) ( $p < 0.0001$ ) [286].

In a more recent cross-sectional study, Kovacs, A.Z., et al. (2011) compared 888 renal transplant recipients with 149 hemodialysis patients regarding health related quality of life using the Kidney Disease Quality of Life Questionnaire. This study's findings were similar to those of Reimer et al.: the transplant recipients had significantly better health related quality of life scores (median 50, IQR 40) compared to the hemodialysis group (median: 35, IQR: 30) [287].

The same has been shown for liver transplant recipients. Measuring quality of life pre- and post-transplantation, Russell, et al. (2008) found that their group of 107 liver transplant recipients transplanted 1 to 39 months previously had a significant overall improvement in health related quality of life compared to pre-transplantation [288]. Their mean Short Form 36 Health Survey physical component score improved significantly from  $27 \pm 8$  to  $35 \pm 11$  and the mean Short Form 36 Health Survey mental component score improved from  $40 \pm 11$  to  $49 \pm 12$  [288].

Finally, one study compared sleep quality and quality of life at 6 and 12 months post-transplantation. Silva et al (2012) reported that, evaluated with the Short-Form Health



Survey, post-transplant quality of life was  $47.8 \pm 17.6$  at 6 months and  $46.3 \pm 16.8$  at 12 months for the physical component and  $72.8 \pm 20.6$  at 6 months and  $71.2 \pm 18$  at 12 months for the mental component [289]. For heart-lung and lung transplant recipients only post-transplant numbers are available, but indicate that both groups' health related quality of life is similar to the general population [290].

#### 1.8.3.1. Side effects of immunosuppressive drugs and symptom experience

Studies have shown that frequently occurring and distressing symptoms negatively affect organ transplant recipients' quality of life [291-294]. The post-transplant therapy regimen is very demanding, considering the risks of symptoms [295] and new comorbidities, which can include cardiovascular diseases [296], malignancies (especially skin cancer [297]) and infections [298]. Effective treatment must balance rejection prevention or control with loss of protection against an array of infectious agents and mutant cells [299]. The most common side effects of immunosuppressives are hypercholesterolemia, diabetes and nephrotoxicity. Others vary according to the immunosuppressive regimen and its dosage. High dosages of mycophenolate mofetil (MMF) and mucous membrane pemphigoid (MMP) are known to cause leukopenia and diarrhea; cyclosporine is nephrotoxic (constriction of pre-glomerular arterioles, causing hypertension), causes hyperlipidemia, hirsutism, fine tremor, increased appetite and gingival hyperplasia; tacrolimus can cause tremor and (when used in high doses) induce diabetes; Rapamune® (sirolimus) and everolimus are known to cause thrombocytopenia and hyperlipidemia. Most regimens include steroids, which are known for their side effects of nephrotoxicity, accelerated vascular disease, osteonecrosis, osteoporosis, and new-onset diabetes mellitus [299]. The one advantage of immunosuppression is a greatly decreased risk of rejection. The disadvantage is the greatly elevated risk of malignancies (especially neoplasm, the oncogenic potential of Epstein-Barr virus and human herpes virus) and infectious diseases (especially urinary tract infections) [299].

A number of studies have assessed symptom occurrence and patient distress. Since as early as 1987, research has shown that sleep-related symptoms are prevalent and/or distressing in solid organ transplant recipients. Below is a summary of the available data for symptom occurrence and distress, starting with renal, then lung, heart and finally liver transplant recipients. Unless otherwise noted, the studies were cross-sectional.

Using the Adapted Transplant Symptom Frequency and Symptom Distress Scale to gather data from **renal transplant recipients**, De Barros and Cabrita (1999) reported that the most distressing symptoms for women were painful menstruation and insomnia [300].

In that case, fatigue was ranked as the 7<sup>th</sup> most common and 9<sup>th</sup> most distressing symptom of 27 symptoms [300]. Using the Modified Transplant Symptom Occurrence and Symptom Distress Scale (45 symptoms) on a sample of 356 renal transplant patients, Koller et al. (2010) found that both sexes considered “tiredness” and “joint pain” the two most distressing and most frequently occurring symptoms [301]. Assessing symptom experience in renal transplant patients on tacrolimus-based therapy, Moons, et al. (2003) ranked sleeplessness 6<sup>th</sup> for occurrence and 10<sup>th</sup> for distress [302] out of 45 symptoms. And, Rosenberger, et al. (2005), assessing adverse symptoms of immunosuppressive medication in renal transplant recipients, ranked sleep disorders 8<sup>th</sup> for the most distressing symptom [303].

Two studies assessed symptom occurrence in **heart transplant recipients**. One placed fatigue 2<sup>nd</sup> for occurrence and 4<sup>th</sup> for distress (Lough, et al., 1987) [304]; the other accorded sleeplessness rank 5 for distress and fatigue rank 7 for occurrence (Moons et al., 1998) out of 27 symptoms [305]. Finally, a huge study including 722 solid organ transplant recipients ranked difficulty staying asleep 7<sup>th</sup> for occurrence (Hathaway et al., 2003) out of 46 symptoms [306].

Symptom occurrence in **lung transplant recipients** has twice been assessed by a research group around D.M. Lanuza. In the first study she reported fatigue as the 3<sup>rd</sup> most occurring symptom (Lanuza et al., 1999) [307]. The second study reported that, prior to lung transplantation; sleepiness was ranked 8<sup>th</sup> for symptom frequency and 9<sup>th</sup> for distress. Not feeling rested after sleep was ranked 10<sup>th</sup> for frequency, but was not considered distressing. Fatigue was ranked 3<sup>rd</sup> for both frequency and distress (Lanuza et al., 2012) [308]. After transplantation, at 9 months, sleepiness decreased significantly. Problems falling asleep significantly increased at one month post-transplantation, and not feeling rested after sleep was significantly reduced after 12 months (Lanuza et al., 2012)[308].

In a study by Drent et al. (2008) of 123 **liver transplant patients**, symptom experience was assessed using the "Modified Transplant Symptom Occurrence and Symptom Distress Scale" (29-item version). Of the symptoms associated with immunosuppression, fatigue was ranked 5<sup>th</sup> and sleeplessness was ranked 9<sup>th</sup> for women. Eighty-five percent of the women sample (n=75) reported that the fatigue occurred frequently and 89% reported that it is distressing and 69% reported that the sleeplessness occurred frequently and 92% that it is distressing. Men ranked fatigue 6<sup>th</sup> and 72% of the men sample (n=47) reported that fatigue is frequent and 76% reported that it is distressing [309].

#### **1.8.4. Factors associated with sleep in chronically ill patients**

The previous section (1.7.3) described symptoms as useful for monitoring changes in health, and cited associated studies confirming sleep-related symptoms high rankings for frequency and distress. However, sleep disorders' effects may go beyond psychological distress. In a cross sectional study by Riegel et al (2007 & 2009) including heart failure patients, daytime sleepiness has been associated with poor self-care [310, 311], and in a study by Elder et al. (2008) using data from the Dialysis Outcome and Practice Pattern Study, poor sleep quality in dialysis patients was associated with an increased risk for mortality [312].

Also, immunosuppressant drugs are not the only cause of sleep disorders in transplant recipients. Various chronic medical conditions and comorbidities have also been found to reduce sleep quality [313]. Depression, heart disease, corporal pain and memory problems have all been linked to insomnia [314], while obesity, arthritis, diabetes, lung disease, stroke and osteoporosis are associated with other sleep-related problems such as breathing pauses, snoring, daytime sleepiness, restless legs or insufficient sleep [314]. Further sleep disturbances are correlated with pain [315] and depressive symptomatology [316]. It is also known that beta-blockers [244], non-steroidal anti-inflammatory drugs [247], bronchodilators [317], corticosteroids [318], decongestants [319], neurological [320] and psychiatric medication can all cause sleep disturbances.

#### **1.8.5. Transplant patients needs to be regarded as a chronically ill persons**

Chronic diseases persist over long periods with several symptoms and of generally slow progression [321]. Chronically ill patients need ongoing medical supervision and guidance in their self-management. Transplant recipients can be regarded as chronically ill as they require a complex lifelong therapeutic regimen, have to engage in regular medication intake and need regular medical follow-up [322]. Further, a study assessing chronic kidney disease according to the guidelines set out in the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative reported that 90% of renal transplant recipients have a chronic kidney disease [323]. In addition, many have chronic kidney disease-related complications and the treatment fall below targets established for non-transplant chronic kidney disease patients [324].

Current care in Switzerland is usually delivered as part of an acute-care treatment model. Transplant patients are often cared for by multiple surgical and medical specialists (physician, nurses, dieticians...) and may suffer from a lack of consistent care [325] (i.e., lack of care coordination, lack of active follow-up to ensure optimal outcomes, failure to

follow established practice guidelines or to adequately train patients to manage their illness)[326]. A disease management approach such as a multidisciplinary clinic may be an appropriate model for the future [327]. This emphasizes the need to implement chronic illness management principles into post-transplantation follow-up care [322, 328]. The chronic care model entails more than a multidisciplinary team: indeed, the focus is not on immediate acute problems but on professional long-term tracking, treatment and follow up programs. Emerging socio-demographic, psychosocial [329], behavioral [330] and system factors in tracking and follow-up care [331] indicate important associations between these factors and transplant outcomes [264, 332-337].

One aspect of chronic illness management absent from acute care models is a regular follow-up of self-management adherence issues (e.g., dealing with symptoms, emotional impact, complex medication regimens, difficult lifestyle adjustments...). Poor self-management leads to poor healthcare outcomes, i.e., higher morbidity and mortality and further increased overall healthcare costs due to avoidable complications, hospitalizations and procedures [338]. In renal transplant recipients, 36% of graft failures are associated with medication non-adherence [339]. For this non-adherent group, immunosuppressive drugs are very unforgiving: missing more than 5% of doses significantly increases the risk of acute rejection [340]. Urquhart et al. (1998) defined forgiveness as: “the ability of a pharmaceutical to maintain therapeutic drug action in the face of occasional, variably long lapses in dosing” [341], pg.215. Forgiveness is dose-dependent, so one method of extending a pharmaceutical’s forgiveness is to increase the dose [342]. However, this would entail more side-effects, thereby damaging long-term outcomes. The clinical meaning of non-adherence is similar to that for HIV drugs [343], heart failure drugs [344] and oral anticancer drugs[345]. To summarize, it is crucial to keep the patient on track with his prescribed regimen. To emphasize the importance of long term follow-up tracking factors, a study including 249 renal transplant recipients reported that electronically monitored non-adherence was correlated with lower self-efficacy, higher self-reported non-adherence, no pillbox usage, and male gender [346]. A literature review further revealed that non-adherence resulted from the interplay of numerous influential factors (the most studied of these were socio-economic, patient-related and condition- or disease-related factors)[347]. Schmid-Mohler et al. (2010) explored non-adherence to immunosuppressive drugs based on the Integrative Model of Behavioral Prediction: in this study, including 114 renal transplant recipients, forgetfulness was the most powerful barrier against adherence [348]. Intention to adhere plays a minor role in non-adherence in renal transplant recipients. As described in subsection 1.3.1, sleep deficit is associated with daytime sleepiness and cognitive impairments, including forgetfulness. As sleep

deficiency is associated with cognitive slowing [349], it has been hypothesized that forgetfulness is one of the consequences of sleep-wake deregulation[350]. Riegel et al. (2011) reported that excessive daytime sleepiness in heart failure patients was significantly associated with poorer medication adherence [51]. However, in transplantation medicine, evidence supporting a link between non-adherence and daytime sleepiness is very limited.

### 1.8.6. Prevalence of sleep disorders in solid organ transplant recipients

Another important aspect of chronic illness management is a regular follow-up of sleep [67, 351]. A small number of studies in solid organ transplant recipients focus on sleep-related symptoms, characteristics, or diagnoses (e.g., sleep quality, insomnia, sleep apnea). There is, however, considerable variability in measurement tools and methods, leading to broad differences in the reported prevalence of sleep disorders pre- and post-transplantation. One common point is that certain underlying medical diagnoses correlate strongly with higher risks of certain sleep disorders (e.g., adiposity with sleep apnea [352]). We therefore divided the description of sleep disorders by organ. Table 1 shows various aspects of sleep as measured or assessed with a number of measurement tools. A summary of the studied sleep diagnoses follows, starting with poor sleep quality, insomnia, fatigue, sleepiness, daytime functioning, sleep-disordered breathing, and finally sleep-related movement disorders.

Table 2: Summary of the literature of sleep measurement in solid organ transplant recipients (excluding case studies and reviews).

Study	Design	Sample	Measurement	Results	Comment
Kidney			Self-report		
Sabbatini, M., et al., 2005 [353]	Cross-sectional	N = 301 renal transplant recipient N = 245 hemodialysis patients N = 169 normal control subjects	<b>Sleep Quality:</b> Pittsburgh sleep quality index (PSQI)	PSQI mean <ul style="list-style-type: none"> <li>• of renal transplant patients = <math>6.46 \pm 3.71</math></li> <li>• of hemodialysis patients = <math>8.52 \pm 3.81</math></li> <li>• of control subjects = <math>3.54 \pm 1.61</math></li> </ul> With bivariate analysis, a significant correlation was detected between total PSQI score in renal transplant recipients and their age ( $r=0.2$ , $P<0.002$ ), but no further relationship existed with cumulative time on dialysis, time after transplantation, hemoglobin, C-reactive protein, or calculated creatinine clearance; nor with doses or blood levels of cyclosporin, tacrolimus and steroids	No prevalence of sleep quality is reported
Eryilmaz, M.M., et al., 2005 [354]	Cross-sectional	N = 100 renal transplant recipients	<b>Sleep quality:</b> Pittsburgh sleep quality index <b>Depression:</b> Beck Depression Inventory <b>Education:</b> Self-report questionnaire	Prevalence of poor sleepers = 30%.  Poor sleepers were younger (mean age: 31 vs 37), less educated (mean years of education: 7.80 vs 9.55), and more depressed (mean BDI scores 13.63 vs 7.18).	Small and very young sample (mean age $36.1 \pm 11.3$ )
Kachuee, H., et al., 2007 [355]	Cross-sectional	N = 125 renal transplant recipients	<b>Sleep Quality:</b> Pittsburgh sleep quality index (PSQI) <b>Quality of life:</b> Short-Form Health Survey (SF-36) <b>Anxiety and depression:</b> Hospital Anxiety and Depression Scale <b>Sexual relation:</b> Relationship and Sexuality Scale	Prevalence of poor sleepers = 62% PSQI mean of renal transplant patients = $6.45 \pm 2.59$  Poor sleepers had higher total medical comorbidity scores ( $P=.009$ ), more bodily pain, poorer general mental health, and less physical function on SF- 36 ( $P=.02$ ), less sexual function, and more severe anxiety ( $P=.02$ ).	Very young sample (mean age $42 \pm 12$ years). Mean PSQI score is similar to Sabbatini et al 2005.

Study	Design	Sample	Measurement	Results	Comment
Burkhalter, H., et al., 2011 [9]	Cross-sectional	N = 135 renal transplant recipients; age: 51.6±11.9 years	<b>Sleep Quality:</b> Pittsburgh sleep quality index (PSQI)  <b>Sleep Quality and daytime functioning:</b> Swiss Transplant Cohort Study sleep quality and daytime functioning item	Prevalence <ul style="list-style-type: none"> <li>of poor sleepers (PSQI) = 47.4%</li> <li>of poor sleepers (STCS-SQ) = 31%.</li> <li>of poor daytime functioning = 34%.</li> </ul>	
Ameli, J., et al., 2007 [356]	case control	201 kidney transplant recipients ; 67.7% males  Group 1= end stage renal disease secondary to hypertension (n=82; mean age: 43.83±12.05; 67.1%males)  Group 2 = end stage renal disease secondary to other causes (n=119; mean age: 41.32±12.31; 68.1% males).	<b>Sleep quality:</b> Pittsburgh Sleep Quality Index (PSQI)  <b>Anxiety and depression :</b> Hospital Anxiety Depression Scale (HADS)  The groups were matched for medical comorbidities, demographic and clinical data, and symptoms of anxiety and depression	Mean of the Pittsburgh sleep quality index for renal transplant recipients with end stage renal disease <ul style="list-style-type: none"> <li>secondary to hypertension = 7.42±2.36</li> <li>secondary to other causes = 6.60±3.07 (sig. difference p=.042)</li> </ul> Mean of sleep duration scores for renal transplant recipients with end stage renal disease <ul style="list-style-type: none"> <li>secondary to hypertension = 1.22±1.12</li> <li>secondary to other causes = 0.86±1.12 (sig. difference p=.026)</li> </ul> Mean of depression for renal transplant recipients with end stage renal disease <ul style="list-style-type: none"> <li>secondary to hypertension = 8.67±2.06</li> <li>secondary to other causes = 9.30±2.32 (p= ns)</li> </ul> Mean of anxiety for renal transplant recipients with end stage renal disease <ul style="list-style-type: none"> <li>secondary to hypertension = 8.74±3.27</li> <li>secondary to other causes = 8.61±2.96 (p= ns)</li> </ul>	Pittsburgh sleep quality index score is significantly higher in renal transplant recipients with end stage renal disease secondary to hypertension compared to the other studies including all renal transplant recipients (6.46±3.71 [353] and 6.45±2.59 [355])
Rodrigue, J.R., et al., 2011 [357]	cross-sectional	N = 100 renal transplant recipients; age: 53.1±11.3, 54% males  N = 100 hemodialysis patients; age: 52.1 ± 12.2, 62% males	<b>Sleep quality :</b> Pittsburgh Sleep Quality Index (PSQI)  <b>Fatigue:</b> Profile of Mood States Fatigue subscale	Mean of the PSQI <ul style="list-style-type: none"> <li>for hemodialysis patients = 9.55±4.8</li> <li>for renal transplant patients =6.84±4.0 (p&lt; 0.001)</li> </ul> Mean of the sum score of the fatigue scale <ul style="list-style-type: none"> <li>for hemodialysis patients = 8.99±5.5</li> <li>for transplant recipients = 6.81±5.5 (p=0.02).</li> </ul> Hemodialysis patients had worse physical functioning (p = 0.008), role-physical (p =0.003), bodily pain (p = 0.05), general health (p < 0.001), vitality (p = 0.003), and social functioning (p = 0.05).	Multiple testing
Silva, D.S., et al., 2012 [289]	Longitudinal design (6 and 12 months post-transplantation)	N = 76 renal transplant recipients; 60% white; mean age 42±12 years and similar proportions of male and female subjects.	<b>Sleep Quality:</b> Pittsburgh sleep quality index (PSQI)  <b>Quality of life:</b> Short-Form Health Survey (SF-36)	Prevalence of poor sleepers <ul style="list-style-type: none"> <li>at 6 months = 36.7%</li> <li>at 12 months = 38.3% (p: ns)</li> </ul> Quality of life physical component <ul style="list-style-type: none"> <li>at 6 months = 47.8±17.6</li> <li>at 12 months = 46.3±16.8 (p: ns)</li> </ul> Quality of life mental component. <ul style="list-style-type: none"> <li>at 6 months = 72.8±20.6</li> <li>at 12 months = 71.2±18 (p: ns)</li> </ul>	Very small sample size
Kovacs, A.Z., et al., 2011 [287]	Observational cross-sectional	N = 888 renal transplant recipients; 58% males; age: 49±13  N = 187 hemodialysis patients; 60% males; age: 49±12	<b>Insomnia:</b> Athens Insomnia Scale  <b>Sleep apnea:</b> Berlin Sleep Apnoea Questionnaire  <b>Restless legs syndrome:</b> Restless legs syndrome questionnaire  <b>Quality of life:</b> HRQoL was assessed via the Kidney Disease Quality of Life Questionnaire  <b>Depression:</b> Center for Epidemiologic Studies Depression (CES-D) questionnaire	Prevalence of insomnia <ul style="list-style-type: none"> <li>in hemodialysis patients = 15%</li> <li>in renal transplant recipients = 8%</li> </ul> Prevalence of obstructive sleep apnea <ul style="list-style-type: none"> <li>in hemodialysis patients = 33%</li> <li>in renal transplant recipients = 27%</li> </ul> Prevalence of restless legs syndrome <ul style="list-style-type: none"> <li>in hemodialysis patients = 11%</li> <li>in renal transplant recipients = 5%</li> </ul> Prevalence of depression <ul style="list-style-type: none"> <li>in hemodialysis patients = 15%</li> <li>in renal transplant recipients = 11%</li> </ul> General health scores for quality of life <ul style="list-style-type: none"> <li>in hemodialysis patients = median 50, IQR 40</li> <li>in renal transplant recipients = median 35, IQR 30 (low score = better quality of life) (sig. difference p&lt; 0.001)</li> </ul>	Multiple testing
Novak, M., et al., 2006 [358]	Observational cross-sectional	N = 884 renal transplant recipients; age: 49 ± 13  N = 183 Hemodialysis patients; age: 49±13  N= 1996 general population; age: 49±12	<b>Insomnia:</b> Athens Insomnia Scale  <b>Sleep apnea:</b> Berlin Sleep Apnoea Questionnaire  <b>Restless legs syndrome:</b> Restless legs syndrome questionnaire	Prevalence of insomnia <ul style="list-style-type: none"> <li>in hemodialysis patients = 15%</li> <li>in renal transplant recipients = 8%</li> <li>in general population = 8%</li> </ul> Prevalence of at least 1 reported insomnia symptom <ul style="list-style-type: none"> <li>in hemodialysis patients = 83%</li> <li>in renal transplant recipients = 70%</li> <li>in general population = 50%</li> </ul> Prevalence of restless legs syndrome <ul style="list-style-type: none"> <li>in renal transplant recipients = 4.4%</li> </ul> Prevalence of obstructive sleep apnea <ul style="list-style-type: none"> <li>in renal transplant recipients = 8.9%</li> </ul> The prevalence of insomnia was higher for female vs. male transplant recipients (10% versus 6%; P = 0.014) and AIS scores (median, 3 [IQR: 5] versus median, 2 [IQR: 4]; p= 0.05) .  Renal transplant recipients with insomnia were	Multiple testing

Study	Design	Sample	Measurement	Results	Comment
				<p>significantly older than non-insomnia recipients (53±10 vs 48±13 p&lt;0.001)</p> <p>In the transplant population, the presence of restless legs syndrome and high risk for obstructive sleep apnea were associated with significantly higher AIS scores than the absence of these conditions (10% vs 4% p&lt;0.001 respectively 54% vs 25% p&lt;0.001)</p>	
Molnar, M.Z., et al., 2007 [359]	cross-sectional	N = 785 renal transplant recipients; mean age: 49±13; 59% males	<p><b>Restless legs syndrome:</b> Restless legs questionnaire</p> <p><b>Quality of life:</b> HRQoL was assessed by the Kidney Disease Quality of Life Questionnaire</p> <p><b>Insomnia:</b> Athens Insomnia Scale</p>	<p>Prevalence of Restless legs syndrome = 4.46%</p> <p>Patients with Restless legs syndrome were more than three times more likely to have insomnia than patients without RLS (29% vs. 9%, p=.001).</p> <p>Almost 23% of patients with RLS reported moderate or severe problems with sleep initiation, whereas only 10% of the patients without RLS had a similar complaint (p&lt;.05). Similarly, almost 20% of the patients with RLS versus 7-9% of those without it reported moderate or severe problems with sleep fragmentation and early awakening (P &lt;.05). Daytime consequences of poor sleep (impaired well-being or functioning capacity, sleepiness) were also significantly more frequently reported in patients with restless legs syndrome versus those without restless legs syndrome (p&lt;.05)</p> <p>In a multivariate negative binomial regression model, the presence of restless legs syndrome was the strongest significant predictor of insomnia (odds ratio=2.858, 95% CI=1.196-6.830; P=.018) after controlling for multiple sociodemographic and clinical variables</p>	
Molnar, M.Z., et al., 2007 [360]	Prospective study over 4 years	<p>N= 804 renal transplant recipients; Mean age: 49±13 and median time after transplantation was 54 months</p> <p>N= 38 renal transplant recipients with restless leg syndrome; age: 51±11, 61% men</p> <p>N= 766 renal transplant recipients without restless leg syndrome; age: 48±13, 59% men</p>	<p><b>Restless legs syndrome:</b> Restless legs questionnaire</p> <p><b>Mortality over 4 years</b></p>	<p>Prevalence of Restless legs syndrome in renal transplant recipients = 4.5%</p> <p>Mortality prevalence in renal transplant recipients</p> <ul style="list-style-type: none"> <li>with restless legs syndrome = 26%</li> <li>without restless legs syndrome = 11% (sig. difference p&lt; 0.01)</li> </ul> <p>Mortality at 4 years was significantly greater in patients who had restless leg syndrome at baseline: univariate hazard ratio for the presence of restless leg syndrome was 2.53 (95% confidence interval, 1.31 to 4.87). In multivariate Cox proportional hazard analysis, the presence of restless leg syndrome significantly predicted mortality (hazard ratio, 2.02; 95% confidence interval, 1.03 to 3.95) after adjustment for several covariables.</p>	
			Polysomnography		
Rodrigues, C.J.O., et al., 2010 [361]	Prospective study	N = 34 patients with end stage renal disease assessed pre- and post-transplantation, (age: 35±10.4 years, 58% male)	<p><b>Sleep disordered breathing:</b> Polysomnography</p>	<p>Prevalence of sleep disordered breathing</p> <ul style="list-style-type: none"> <li>in patients with end stage renal disease = 26.5%</li> <li>in renal transplant recipients = 21%</li> </ul> <p>Mild cases were predominant in both phases of the study, where only 3 patients before and 2 after transplantation had an apnea hypopnea index ≥15 (severe). Patients with apnea hypopnea index ≥5 prior to transplantation had a significant reduction in apnea hypopnea index (15.4±7.8 vs 4.4±4.4; p = 0.008). Considering only patients with apnea hypopnea index &lt;5 prior to transplantation, the difference was not significant (1.6±1.3 vs 2.7±4.5, p = 0.21).</p>	
Molnar, M.Z., et al., 2010 [362]	Observational cross-sectional study	<p>N = 100 renal transplant recipients; age: 51±13</p> <p>N = 50 dialysis patients who were on the transplant waiting list; age: 50±13</p>	<p><b>Sleep disordered breathing:</b> Polysomnography</p>	<p>Prevalence of obstructive sleep apnea</p> <ul style="list-style-type: none"> <li>in hemodialysis patients = 26%</li> <li>in renal transplant recipients = 25%</li> </ul> <p>Prevalence of mild apnea-hypopnea (apnea-hypopnea index [AHI] &gt; or =5/h and &lt;15/h)</p> <ul style="list-style-type: none"> <li>in hemodialysis patients = 18%</li> <li>in renal transplant recipients = 28%</li> </ul> <p>Prevalence of moderate apnea-hypopnea (AHI &gt; or =15/h and &lt;30/h)</p> <ul style="list-style-type: none"> <li>in hemodialysis patients = 11%</li> <li>in renal transplant recipients = 16%</li> </ul> <p>Prevalence of severe apnea-hypopnea (AHI &gt; or =30/h)</p> <ul style="list-style-type: none"> <li>in hemodialysis patients = 14%</li> <li>in renal transplant recipients = 10%</li> </ul> <p>Of renal transplant recipients with obstructive sleep apnea more were males, compared to non-obstructive sleep apnea recipients (80% vs. 49% p= 0.006). Further BMI (29±5 vs. 26±5 p= 0.005), neck circumference (40±3 vs. 37±4 p= 0.002) and abdominal circumference (107±12 vs. 95±15 p= 0.001) were significantly greater and average oxygen saturation during sleep (91.8±1.6 vs. 94±2.0 p= 0.001) was significantly lower.</p>	Multiple testing
Jurado-Gamez, B., et al., 2008 [363]	Prospective study	N= 9 hemodialysis patients who received transplantation (7 men and 2 women, age: 42±16.2 years, BMI 26±3.7)	<p><b>Sleep disordered breathing and sleep related moving disorders:</b> Polysomnography</p>	<p>Incidence of periodic limb movement per hour:</p> <ul style="list-style-type: none"> <li>at pre-transplantation = 36±34</li> <li>at post-transplantation = 24±20.8 (p= 0.041)</li> </ul> <p>Incidence of apnea and hypopnea episodes</p> <ul style="list-style-type: none"> <li>at pre-transplantation = 10±10.7</li> <li>at post-transplantation = 4.9±6.1 (p= 0.029)</li> </ul> <p>Incidence of dips in SaO2 ≥3% per hour of sleep</p> <ul style="list-style-type: none"> <li>at pre-transplantation = 25±26</li> <li>at post-transplantation = 12±11.2 (p= 0.010)</li> </ul> <p>Incidence of sleep apnea/hypopnea (%):</p>	Small sample size

Study	Design	Sample	Measurement	Results	Comment
				<ul style="list-style-type: none"> <li>at pre-transplantation = <math>5 \pm 6.8</math></li> <li>at post-transplantation = <math>0.7 \pm 1.1</math> (<math>p = 0.008</math>).</li> </ul> <p>Three of the 9 patients had sleep apnea/hypopnea syndrome while on hemodialysis. The sleep apnea/hypopnea syndrome disappeared in 2 cases after kidney transplantation, with an overall improvement in the number of respiratory events and nocturnal SaO<sub>2</sub>.</p>	
Beecroft, J.M., et al., 2007 [364]	Prospective study	N= 18 renal transplant recipients (11 men, 7 women), age: 27-65,	<b>Sleep disordered breathing:</b> Polysomnography	<p>Prevalence of sleep apnea</p> <ul style="list-style-type: none"> <li>at pre-transplantation = 61%</li> <li>at post-transplantation = 44%</li> </ul> <p>In three of the 11 patients (27%) with sleep apnea at pre-transplantation, their apnea hypopnea index fell from <math>20.4 \pm 15.4</math> to <math>7.2 \pm 6.8</math> events/h</p> <p>Following successful kidney transplantation, obstructive sleep apnea improved in fewer than 30% of patients with end stage renal disease. Persistent sleep apnea may contribute both to sleep-related symptoms and the risk of cardiovascular disease in this patient population.</p>	Very small sample size
Beecroft, J.M., et al., 2008 [365]	Prospective study	N= 18 renal transplant recipients (11 men, 7 women), age: 27-65,	<b>Sleep related movement disorders:</b> Polysomnography	<p>Prevalence of periodic limb movement:</p> <ul style="list-style-type: none"> <li>at pre-transplantation = 39%</li> <li>at post-transplantation = 16%</li> </ul> <p>Prevalence of restless leg syndrome</p> <ul style="list-style-type: none"> <li>at pre-transplantation = 47%</li> <li>at post-transplantation = 5%</li> </ul> <p>Pre-transplant patients with periodic limb movement were significantly older than those without (median age 54 (38-65) vs. 36 (27-57) <math>p &lt; 0.05</math>).</p> <p>Transplantation was associated with a significant reduction in periodic limb movement index in all patients (8 (0-110) events/h vs. 2 (0-80) events/h); further sleep efficiency and sleep architecture were significantly improved.</p> <p>Patients with periodic limb movement at pre-transplantation improved significantly at post-transplantation for periodic limb movement index, events/ hour (40 (24-110) vs. 14 (1-80) <math>p &lt; 0.001</math>); Periodic limb movement index arousals, events/ hour (13 (1-37) vs. 3 (0-12); <math>p &lt; 0.05</math>); total sleep time (5.1 (3.3-6.2) vs. 5.5 (4.2-6.0); <math>p &lt; 0.05</math>) and Stage 1, % total sleep time (8.1 (1.5-21.6) vs. 6.9 (2.4-20.2); <math>p &lt; 0.05</math>).</p>	Very small sample size
Fornadi, K., et al., 2012 [366]	Cross-sectional study	100 randomly selected kidney transplant patients; mean age: $51 \pm 13$ years, 43% were women.	<b>Sleep disordered breathing and sleep related moving disorders:</b> Polysomnography  <b>Insomnia:</b> Athens Insomnia Scale	<p>Prevalence of obstructive sleep apnea = 25% The percentage of men was significantly higher in the obstructive sleep apnea -positive group. Patients with obstructive sleep apnea had significantly higher BMI and hemoglobin level.</p> <p>Prevalence of periodic limb movements = 27% The percentage of diabetic patients was significantly higher among patients with periodic limb movements versus without.</p> <p>Prevalence of Insomnia =16% The serum interleukin-6 level was significantly higher in patients with insomnia. Insomniacs were older and had significantly higher Charlson Comorbidity Index compared with patients without insomnia. The usage of sleeping pills was significantly higher in insomniacs than in patients without insomnia.</p> <p>No significant difference was found in the levels of inflammatory markers between patients with versus without obstructive sleep apnea and periodic limb movements. Apnea-hypopnea index showed a significant association with white blood cell count (<math>\rho = 0.23</math>), and weak, non-significant correlation (<math>\rho &lt;  0.15 </math>) with the other inflammatory markers. Periodic Limb Movement index showed weak (<math>\rho &lt;  0.15 </math>), non-significant correlation (<math>\rho &lt;  0.15 </math>) with all markers of inflammation. The serum interleukin-6 level was significantly higher in patients with insomnia (AIS <math>\geq 10</math>) than in non-insomniacs [median (IQR): <math>3.2(2.6-5.1)</math> vs. <math>1.7(1.2-2.9)</math> ng/l; <math>P = 0.009</math>]. The levels of other inflammatory markers were similar between insomniacs and non-insomniacs.</p>	Multiple testing
Lung			Polysomnography		
Malouf, M.A., et al., 2008 [367]	Prospective study	N = 25 lung patients assessed pre-and post-transplantation	<b>Sleep disordered breathing:</b> polysomnography	<p>Prevalence of sleep disordered breathing:</p> <ul style="list-style-type: none"> <li>at pre-transplantation = 44%</li> <li>at post-transplantation = 36%</li> </ul> <p>Eleven of the 25 patients (44%) had sleep disordered breathing prior to their lung transplantation. After lung transplantation, 5 of these 11 continued to have sleep disordered breathing, 4 of whom had respiratory disturbance index scores of <math>&gt;20</math> events/hour. Four of 14 patients who previously had normal polysomnography developed new sleep disordered breathing post- lung transplantation.</p> <p>Improvement from pre-to post-transplantation:</p> <ul style="list-style-type: none"> <li>awake SaO<sub>2</sub>: <math>91.5 \pm 4.7\%</math> vs. <math>96.0 \pm 1.85\%</math>, <math>p &lt; 0.001</math></li> </ul>	<p>Lung transplantation improves oxygenation, but new-onset sleep disordered breathing may occur after the procedure.</p> <p>No BMI and no percent total sleep time with SaO<sub>2</sub> <math>\leq 90\%</math> data reported, only p value.</p>



Study	Design	Sample	Measurement	Results	Comment
				<ul style="list-style-type: none"> <li>• minimum sleep oxygen saturation (<math>p &lt; 0.004</math>)</li> <li>• percent total sleep time with <math>\text{SaO}_2 \geq 90\%</math> (<math>p &lt; 0.001</math>)</li> <li>• increase in BMI post- lung transplantation to <math>24.3 \pm 4.7</math> (<math>p &lt; 0.02</math>)</li> </ul> <p>There were no differences between pre- and post-transplantation:</p> <ul style="list-style-type: none"> <li>• in total sleep time, <math>333.7 \pm 7</math> vs <math>349. \pm 5</math> minutes (<math>p &lt; 0.9</math>)</li> <li>• sleep efficiency, <math>76.9 \pm 27</math> vs <math>77.1 \pm 10.4</math> (<math>p &lt; 0.96</math>)</li> <li>• arousal index, <math>19.9 \pm 11.6</math> vs <math>19.9 \pm 13.7</math> (<math>p &lt; 0.98</math>)</li> <li>• overall respiratory disturbance index <math>8.48 \pm 10.8</math> vs <math>11.9 \pm 18.5</math> (<math>p &lt; 0.3</math>).</li> </ul>	Small sample size
Naraine, V.S., T.D. Bradley, and L.G. Singer, 2009 [368]	cross-sectional	<p>N = 24 lung transplant recipients</p> <p>N = 9 non-sleep disordered breathing; age: <math>43.8 \pm 12.6</math>; 56% males; time since transplantation: <math>37.8 \pm 17.6</math> months</p> <p>N = 9 obstructive sleep apnea; age: <math>56.7 \pm 11.0</math>; 89% males; time since transplantation: <math>24.3 \pm 12.7</math> months</p> <p>N = 6 central sleep apnea; age: <math>52.0 \pm 8.1</math>; 50% males; time since transplantation <math>19.8 \pm 5.0</math> months</p>	<b>Sleep disordered breathing:</b> polysomnography	<p>Prevalence of sleep disordered breathing was 63% one year post-lung transplantation (obstructive sleep apnea was observed in 38% and 25% had central sleep apnea)</p> <p>Apnea-hypopnea index, event/ hour in transplant recipients</p> <ul style="list-style-type: none"> <li>• With obstructive sleep apnea (1) = <math>20.1 \pm 14.2</math></li> <li>• With central sleep apnea (2) = <math>41.1 \pm 38.1</math></li> <li>• Without sleep-disordered breathing (3) = <math>4.9 \pm 2.6</math> (1.2 vs. 3 <math>p &lt; 0.05</math>)</li> </ul> <p>Obstructive event index/ hour in transplant recipients</p> <ul style="list-style-type: none"> <li>• With obstructive sleep apnea (1) = <math>17.8 \pm 13.9</math></li> <li>• Without sleep-disordered breathing (3) = <math>3.8 \pm 2.7</math> (1 vs. 3 <math>p &lt; 0.05</math>)</li> </ul> <p>Hypopnea index/ hour in transplant recipients</p> <ul style="list-style-type: none"> <li>• With obstructive sleep apnea (1) = <math>15.0 \pm 5.3</math></li> <li>• Without sleep disordered breathing (3) = <math>4.5 \pm 2.6</math> (1 vs. 3 <math>p &lt; 0.05</math>)</li> </ul> <p>Obstructive sleep apnea patient were significantly more emphysema patients (44% vs. 0% <math>p &lt; 0.05</math>), more snoring (78% vs. 33% <math>p &lt; 0.05</math>); higher systolic blood pressure (<math>137.3 \pm 9.9</math> vs. <math>123.6 \pm 12.9</math> <math>p &lt; 0.05</math>), higher body mass index (<math>28.8 \pm 4.2</math> vs. <math>24.0 \pm 4.0</math> <math>p &lt; 0.05</math>) compared to non-sleep disordered breathing transplant recipients.</p> <p>Central sleep apnea patient were significantly treated more with Cyclosporine (100% vs. 22% <math>p &lt; 0.05</math>) and had a higher body mass index (<math>27.2 \pm 2.7</math> vs. <math>24.0 \pm 4.0</math> <math>p &lt; 0.05</math>) compared to non-sleep disordered breathing transplant recipients.</p>	Small sample size Polysomnography should be considered in lung transplant recipients if they have gained weight
Heart			Subjective measurement		
van de Beek, D., et al. 2008 [369]	retrospective cohort study	N = 313 heart transplant recipients (transplanted between 1 to 10 years ago)	<b>Sleeping disorders:</b> Data were extracted on patients „history”	<p>Prevalence of sleeping disorders = 32%</p> <p>sleeping disorders were related to baseline body mass index, with a mean body mass index of 26.8 for patients with sleeping disorders vs 24.5 for those without sleeping disorders</p>	Unclear which measurement tools were used to assess sleep.
			Polysomnography		
Brilakis, E.S., et al., 2000 [370]	Retrospective study	<p>N = 147 heart transplant recipients</p> <p>17 heart transplant recipients mean interval of 17.5 months after transplantation. Age: 50.8 years (range, 24-67 years).</p>	<p>Clinical assessment</p> <p><b>Sleep disordered breathing:</b> polysomnography</p>	<p>Prevalence of sleep apnea = 11.6% (13 had obstructive sleep apnea and 4 had mixed sleep apnea)</p> <p>The patients presented with snoring (100%), excessive daytime somnolence (65%), witnessed apneas (53%), and morning fatigue (53%). Sixteen (94%) had a mean weight gain of 10.4 kg after transplantation, although 1 lost 14.6 kg. Of the 11 patients with obstructive sleep apnea who underwent nasal continuous positive airway pressure titration, significant improvements occurred in the apnea-hypopnea index (decreased from 37.6 to 10.4; <math>p = 0.01</math>) and mean arousal index (decreased from 44.5 to 19.4; <math>p = 0.01</math>). Only 2 of the 8 patients with sleep apnea for whom nasal continuous positive airway pressure was recommended were still using it at the time of telephone follow-up.</p>	Screening instrument for apnea is unclear
Mansfield, D.R., et al. 2003 [371].	Prospective and observational cross-sectional study	<p>N = 37 heart failure patients pre-transplantation:</p> <p>N = 16 patients with central sleep apnea N = 6 patients with obstructive sleep apnea N = 15 patients with no sleep-disordered breathing</p> <p>N = 22 (6 months post-heart transplantation):</p> <p>N = 13 patients with central sleep apnea; age: <math>54 \pm 9</math>, 100% males, post-transplantation time <math>13.2 \pm 8.3</math> months N = 9 patients with no sleep-disordered breathing; age: <math>44 \pm 10</math>, 80% males, post-</p>	<b>Sleep disordered breathing:</b> polysomnography	<p>Apnea hypopnea index in heart transplant recipients</p> <ul style="list-style-type: none"> <li>• without central sleep apnea = <math>2 \pm 1</math></li> <li>• with central sleep apnea = <math>28 \pm 15</math> (<math>p &lt; 0.01</math>).</li> </ul> <p>Significant improvement from pre- to post- heart transplantation in the central sleep apnea group:</p> <ul style="list-style-type: none"> <li>• Heart rate, beats/min: <math>28 \pm 15</math> vs. <math>7 \pm 6</math>, <math>p &lt; 0.01</math>,</li> <li>• mean <math>\text{Spo}_2</math>, %: <math>94.7 \pm 1.8</math> vs. <math>96.3 \pm 1.6</math>, <math>p &lt; 0.01</math></li> </ul> <p>In the pre-transplant patients with no sleep-disordered breathing, all patients remained free of it after transplantation. Four patients from the central sleep apnea pre-transplant group acquired post-transplant obstructive sleep apnea.</p>	No prevalences are reported. The sampling strategy is not completely clear

Study	Design	Sample	Measurement	Results	Comment
		transplantation time 20.6±10.7 months			
Javaheri, S., et al., 2004 [372]	cross-sectional study	N=45 heart transplant recipients:  N = 15 no sleep disorders; age: 58±14, 87% males; time post-transplantation 25±14  N= 14 with periodic limb movement, aged 55±11, 84% males, time post-transplantation 26±14  N = 16 with sleep-related breathing disorders; age: 58±10, 94% males, time post-transplantation 30±15	<b>Sleep disordered breathing and sleep movement disorders:</b> polysomnography  <b>Quality of life:</b> Short-Form Health Survey (SF-36)	Prevalence of obstructive sleep apnea = 36% Prevalence of periodic limb movement = 33% (45% of whom had restless leg syndrome)  Body mass index was significantly higher in recipients with sleep-related breathing disorders (33±5 vs 28±3 recipients with no sleep disorders and 28±4 recipients with periodic limb movement p= 0.0008). Hypertension (prevalence in %) and systolic blood pressure (in mmHg) were also significant higher in these three groups (88% vs 27% and 50% p= 0.002) respectively (147±18 vs 122±14 and 130±14).  The physical component of the SF-36 health survey, a scale of physical morbidity, was significantly lower in cardiac transplant recipients with obstructive sleep apnea than in those without it.	
Ayik, S., et al. 2013 [373]	cross-sectional study	N=43 heart transplant recipients  N = 18 recipients without obstructive sleep apnea; age: 34.8±10.1, 77.8% males, time after transplantation 32.6±20.9  N = 25 recipients with obstructive sleep apnea; age: 49.0±12.1, 84% males, time after transplantation 48.2±33.2	<b>Sleep disordered breathing:</b> Polysomnography  <b>Daytime sleepiness:</b> Epworth Sleepiness scale	Prevalence of obstructive sleep apnea 58%  Obstructive sleep apnea patients were significantly older (34.8±10.1 vs. 49.0±12.1) and showed a greater value of body mass index (23.4±2.7 vs. 26.8±4.1) and waist circumference (88.5±13.6 vs. 102.3±13.5); further, they had higher sleepiness scores 5.5±2.6 vs. 2.6±2.8.  Obstructive sleep apnea patients had significantly more apnea hypopnea events/ hour (1.8±1.5 vs. 28.2±22.3) and more time with SaO <sub>2</sub> under 90% (min) (4.3±12.6 vs. 29.3±54.2).  The apnea-hypopnea index showed significant correlation with age, BMI, waist circumference, neck circumference, time of oxygen saturation under 90% and systolic arterial pressure  The multivariate analysis revealed obesity as a risk factor that, along with waist circumference, was an independent predictor for obstructive sleep apnea	Only 50% agreed to participate in the study.
<b>Liver</b>					
Rodrigue, J.R., et al., 2010 [374]	Observational cross-sectional study	N= 95 liver transplant recipients  N = 110 pre-transplant patients	<b>Sleep quality:</b> Pittsburgh Sleep Quality Index  <b>Fatigue :</b> Fatigue Symptom Inventory	Prevalence of poor sleep quality <ul style="list-style-type: none"> <li>In pre-transplant patients = 73%</li> <li>In liver transplanted recipients = 7%</li> </ul> Prevalence of fatigue <ul style="list-style-type: none"> <li>In pre-transplant patients = 86%</li> <li>In liver transplanted recipients = 76%</li> </ul> Correlates of pre-transplant fatigue severity were female gender (odds ratio [OR]=0.22, P=.04), higher body mass index (OR=1.07, P=.04), higher mood disturbance (OR = 1.05, P= .02), and poor sleep quality (OR = 0.26, P= .02).  Correlates of post-transplant fatigue severity were use of sleep medications in the past month (OR = 0.51, P= .02) and higher mood disturbance (OR = 1.06, P= .004).  Higher body mass index (OR=1.06, P=.05), sleep medications (OR = 0.43, P= .03), and more mood disturbance (OR = 1.04, P= .007) were predictive of poor sleep quality in pre-transplant patients, whereas higher body mass index (OR = 1.07, P= .04) and more anxious mood (OR = 1.28, P= .03) were predictive of poor sleep quality in post-transplant patients.	
van Ginneken, B.T., et al., 2010 [375]	Prospective study	70 liver transplant recipients assessed pre- and 2 years post-transplantation; age: 52.5±12.3, 44% males; time since transplantation: 6.7 ± 3.8 years	<b>Sleep quality:</b> Pittsburgh Sleep Quality Index  <b>Fatigue:</b> Severity of fatigue scale <b>Health-related daily functioning:</b> self-assessment version of the Sickness Impact Profile- 68 (SIP-68).  <b>Health-related quality of life:</b> Medical Outcomes Study Short Form-36 (SF-36)  <b>Anxiety and depression:</b> Hospital Anxiety and Depression Scale	Prevalence of poor SQ <ul style="list-style-type: none"> <li>post-transplantation = 51% (mean score 6.6 ± 4.2)</li> </ul> Prevalence of fatigue <ul style="list-style-type: none"> <li>pre-transplantation = 60%</li> <li>post-transplantation = 62%</li> </ul> Prevalence of depression <ul style="list-style-type: none"> <li>post-transplantation = 27% (mean score 5.1±4.6)</li> </ul> Prevalence of anxiety <ul style="list-style-type: none"> <li>post-transplantation = 26% (mean score 4.8±4.2)</li> </ul> Health-related quality of life [48.4±21.7 to 52.3±21.1 (p=ns)], fatigue [4.45±1.63 to 4.47±1.79 p=ns] improved from pre- to post-transplantation.  In the mixed model, fatigue was a significant predictor of daily functioning and all health-related quality of life domains (p < 0.01). Anxiety, depression, and sleep quality were significantly associated with severity of fatigue when controlled for age and sex (r = 0.30 to r = 0.60, p < 0.05).	No pre-transplant prevalence for sleep quality
Fredericks, E.M., et al., 2012 [376]	cross-sectional study	N = 47 pediatric liver transplant recipients; age: 10.9 ±4.6; time since transplantation: 6.2±3.9, 45 % males	Pediatric Quality of Life Generic Core Scales	Prevalence of: <ul style="list-style-type: none"> <li>Sleep-disordered breathing = 23%</li> <li>Restless legs syndrome = 30%</li> <li>Snorers = 17%</li> <li>Excessive daytime sleepiness= 40%</li> <li>Symptoms of inattention and hyperactivity = 45%</li> <li>Low health related quality of life = 43%</li> </ul>	Pediatric recipients

A systematic PubMed search was performed for publications on sleep in solid organ transplant recipients (1966-2013), including only English, German, French and Italian articles. We included studies if they were retrospective, prospective or cross-sectional, and reported at least a prevalence for sleep and specified the measurement tool used. Out of 737 hits, we selected 27 studies for inclusion in the summary table. The following section provides first an overview of the sleep symptom or disturbance (poor sleep quality, insomnia, fatigue, sleepiness, sleep disordered breathing, sleep related movement disorder), followed by a summary categorized by organ (kidney, lung, heart, or liver).

**Poor sleep quality** in renal transplant recipients has mainly been measured via self-report (Pittsburgh sleep quality index) (7 Studies), with prevalence ranging from 30% - 62% [9, 289, 353-357]. In heart transplant recipients, van de Beek et al. (2008) reported a prevalence of 32% for sleep disturbances assessed by chart review [369]; and two studies assessed poor sleep quality in liver transplant recipients (via the Pittsburgh Sleep Quality Index, a valid and reliable questionnaire[107]) with prevalence ranging from 51% to 77% [374, 375]. All of these studies had relatively large sample sizes, ranging from 95 to 313 transplant recipients. Poor sleep quality was associated with greater age [353], higher total medical comorbidity scores [355], more bodily pain [355], poorer general mental health [355], less physical function [355], less sexual function [355], and more severe anxiety [355].

**Insomnia** was measured in three cross-sectional studies using the Athens insomnia scale (a scale with diagnostic validity for insomnia [377]) in renal transplant recipients, revealing a prevalence of 15% [287, 358] in a sample of renal failure patients, 8% [287, 358] - 16% [366] in renal transplant recipients and 8% in the general population [358]. A higher prevalence of insomnia has been found in female than male transplant recipients [358], and renal transplant recipients with insomnia are significantly older than non-insomnia recipients ( $53 \pm 10$  vs.  $48 \pm 13$ y) [358].

**Fatigue** is not a sleep parameter [378]. Cella D. et al (1998) defined: "Fatigue is a subjective state of overwhelming, sustained exhaustion and decreased capacity for physical and mental work that is not relieved by rest". However fatigue is often associated with insomnia [113]. Fatigue was measured in an observational cross-sectional study with the Profile of Mood States Fatigue subscale (a uni-dimensional scale that measures fatigue severity) [379]. Higher scores indicate more fatigue. Rodrigue et al. (2011) reported that the mean fatigue scale sum score was  $8.99 \pm 5.5$ , significantly higher for hemodialysis patients than for transplant recipients ( $6.81 \pm 5.5$ ;  $p= 0.02$ ) [357]. Brilakis et al. (2000) in a

retrospective chart review study of heart transplant recipients reported a prevalence of 53% for fatigue at a mean interval of 17.5 months after transplantation [370]. Regarding liver patients, two studies used the Fatigue Symptom Inventory (the psychometric properties of which have been determined useful and valid [380]) to measure fatigue. The first, by Rodrigue et al. (2010), showed a fatigue prevalence of 86% in liver-insufficient patients and 76% in liver transplant recipients [374]. The other, a prospective study by van Ginneken et al. (2010), reported fatigue prevalence of 60% pre-and 62% post-liver transplantation [375]. Correlates of pre-transplant fatigue severity were female gender (OR=0.22, p=.04), higher body mass index (OR=1.07, p=.04), elevated mood disturbance levels (OR = 1.05, p= .02), and poor sleep quality (OR = 0.26, p= .02) [374]. Correlates of post-transplant fatigue severity were use of sleep medications in the past month (OR = 0.51, p= .02) and elevated mood disturbance (OR = 1.06, p= .004) [374]. In the mixed model, fatigue was a significant predictor of daily functioning and all health-related quality of life domains ( $p < 0.01$ ). Anxiety, depression, and sleep quality were significantly associated with severity of fatigue when controlled for age and sex ( $r = 0.30$  to  $r = 0.60$ ,  $p < 0.05$  [375]. As no fatigue prevalence has been reported in renal transplant recipients, no comparison is possible with this group; and no measurement tool was specified for the heart transplant study, preventing comparison with it as well. However, fatigue appears to be a highly relevant symptom in liver transplant recipients.

**Sleepiness**, measured with the Epworth Sleepiness scale (a validated questionnaire that measures a subject's expectation of dozing in eight hypothetical situations [105, 106]) showed in the study of Ayik et al. (2013) scores of  $5.5 \pm 2.6$  in heart transplant recipients with obstructive sleep apnea, and of  $2.6 \pm 2.8$  in those without it [373]. In the only other cross-sectional sleepiness study of transplantation recipients, Fredericks et al. (2012) used the Pediatric Quality of Life Generic Core Scales to gather data from pediatric liver recipients, reporting a sleepiness prevalence of 40%. The related topic of daytime functioning has been measured in just one study of renal transplant recipients. Using a developed item showing low content validity, the authors reported a 34% prevalence of poor daytime functioning (Burkhalter et al., 2012)[9].

**Sleep disordered breathing** is assessed with polysomnographic measurements of respiratory airflow, respiratory effort and peripheral pulse oximetry. Five studies have assessed sleep disordered breathing in **renal transplant recipients**. Unfortunately, as they used different inclusion and exclusion criteria, the only comparable prevalence is the 25% of obstructive sleep apnea reported by Molnar et al. (2010) and Fornadi et al. (2012) [362, 366]. Molnar et al. (2010) also reported a slightly higher prevalence (26%) in hemodialysis patients [362]. And Beecroft et al. (2007) measured the prevalence of sleep apneas

(including obstructive and central sleep apnea) at 61% pre-renal transplantation and 44% post-transplantation [364]. Including all sleep breathing disorders, Rodrigues et al. (2010) reported prevalence of 26.5% in patients with end stage renal disease and 21% in renal transplant recipients [361]. Further, a prospective study by Jurado-Gamez (2008) reported no prevalence, but presented objective parameters from pre-to post-transplantation: significant reductions in the number and duration of apnea and hypopnea episodes, in the number of dips in SaO<sub>2</sub>  $\geq$ 3% per hour of sleep, and in the percentage of time spent in apnea/hypopnea [363]. Only two studies including **lung transplant recipients** both measured sleep parameters and assessed sleep disordered breathing. Both used small sample sizes—one 25 and the other 24 participants. In the first, a prospective study, Malouf et al. (2008) reported prevalence of 44% pre-transplantation and 36% post-transplantation [367]. In the other, a cross-sectional study conducted one year post-transplantation, Naraine, Bradley and Singer reported nearly double that prevalence (63%, i.e., obstructive sleep apnea was observed in 38%, while 25% had central sleep apnea) [368]. The same study showed that obstructive sleep apnea patients were significantly more likely to be emphysema patients (44% vs. 0%), to snore more (78% vs. 33%), to have higher systolic blood pressure (137.3 $\pm$ 9.9 vs. 123.6 $\pm$ 12.9), and to have higher body mass indexes (28.8 $\pm$ 4.2 vs. 24.0 $\pm$ 4.0) compared to non-sleep disordered breathing transplant recipients [368]. Central sleep apnea patients were significantly more often treated with Cyclosporine (100% vs. 22%) and had a higher mean body mass index (27.2 $\pm$ 2.7 vs. 24.0 $\pm$ 4.0) compared to non-sleep disordered breathing transplant recipients [368]. Malouf et al. (2008) reported that 11 of their 25 patients had sleep disordered breathing prior to the lung transplantation. Of these, 5 (4 of whom had respiratory disturbance indexes >20 events/hour) continued to have sleep disordered breathing post-transplantation. Of the other 14, all of whom had previously received normal polysomnography reports, four developed new sleep disordered breathing post-transplantation [367]. Interestingly, the mean body mass index increased post-lung transplantation for the entire group to 24.3 $\pm$ 4.7 [367]. In Brilakis et al.'s (2000) retrospective study of 147 **heart transplant recipients**, the 17 with sleep apnea showed prevalence of 100% for snoring, 65% for excessive daytime somnolence, 53% for witnessed apneas and 53% for morning fatigue. Following transplantation, sixteen of these 17 experienced a mean weight gain of 10.4 kg [370]. In the total sample of 147, the retrospectively assessed apnea prevalence was 11.6% (13 with obstructive sleep apnea and 4 with mixed sleep apnea) [370]. Another prospective study including 22 heart transplant recipients assessed pre-and post-transplantation reported a significant improvement in the central sleep apnea patients regarding apnea hypopnea index (events/ hour: 28 $\pm$ 15 vs. 7 $\pm$ 6) and mean Spo<sub>2</sub> (percentage: 94.7 $\pm$ 1.8 vs. 96.3 $\pm$ 1.6) Mansfield et al.(2003) [371]. The post-transplant prevalence of obstructive sleep apnea in heart transplant recipients ranges from

36% [372] to 58% [371, 373], while a 13% prevalence is reported for central sleep apnea [371]. Pre-transplantation, the prevalence of obstructive sleep apnea is 16% [371] and of central sleep apnea, 43% [371]. In one cross-sectional study, body mass index was significantly higher in transplanted patients with sleep-related breathing disorders than in those with none (Javaheri et al., 2004) [372]. A more recent study by Ayik et al. (2013) reported that obstructive sleep apnea patients were significantly older, with a greater mean body mass index, waist circumference and higher sleepiness scores [373]. In lung [367] and in heart transplant recipients [370, 372], the weight gain reported could be associated with the increase of sleep disordered breathing prevalence [367, 370, 372, 373]. Abundant evidence links increased body mass index with increased obstructive sleep apnea [381].

**Sleep related movement disorders** were assessed with polysomnography (muscle activity or skeletal muscle activation) in 3 studies in renal and in 1 study in heart transplant recipients. Restless leg syndrome was assessed in 4 studies of renal transplant recipients via the Restless Legs Syndrome Questionnaire (a validated questionnaire that is updated yearly [382]). Jurado-Gamez et al. (2008) reported in a prospective study (N= 9) that the pre-transplantation prevalence of periodic limb movement per hour was  $36 \pm 34$  and post-transplantation  $24 \pm 20.8$  ( $p = 0.041$ ) [363]. The prevalence of periodic limb movements in renal transplant recipients ranges from 16% (Beecroft et al., 2008) [365] to 27% (Fornadi et al., 2012) [366]. In a study including 18 patients at pre-transplantation, reported a prevalence for periodic limb movements of 39% (Beecroft et al., 2008) [365]. Polysomnographic data of these 18 patients showed a prevalence of 47% pre-transplantation and 5% post-transplantation for restless leg syndrome [365]. The research group of the Institute of Behavioral Sciences at Semmelweis University in Budapest published four studies reporting the prevalence of restless legs syndrome (assessed with the Restless legs syndrome questionnaire) in renal transplant recipients. The pre-transplantation prevalence was 11% [287] and 4% to 5% post-transplantation [287, 358-360], however these prevalence appear to be based on the same sample. The mortality rate at 4 years in renal transplant recipients with restless legs syndrome is reported to be 26%; without restless leg syndrome, it is 11% (sig. difference  $p < 0.01$ ) [360]. Periodic limb movements are experienced by 33% of heart transplant recipients, 45% of whom have restless legs syndrome (Javaheri et al. 2004) [372].

The literature includes only one intervention study for sleep in solid organ transplant recipients. Gross et al. (2010) assessed the efficacy of mindfulness-based stress reduction on anxiety, depression and sleep quality. This intervention (eight weekly 2.5-

hour classes) reduced anxiety and sleep symptoms ( $P < .02$ ), with medium treatment effects (.51 and .56). Benefits were sustained over one year [383].

The following section supplies a more general discussion of sleep symptoms and sleep disturbances, classified by transplanted organ. While our literature review revealed different priorities across the solid organ transplant groups, it is clear that poor sleep quality is prevalent (30-62%) after **renal transplantation**. Some of the poor sleepers have insomnia (8%), some sleep disordered breathing (18%), some sleep movement disorders (5%) and some a combination or a less prevalent sleep disturbance. Concerning the prevalence of obstructive apnea after kidney transplantation, Sim et al. (2010) report an association with the side effects of steroid regimens, which include weight gain, obesity, abnormal fat distribution and development of metabolic syndrome [384].

As described in section 1.3.2, sleep is associated with the immune system. However, Fornadi et al. (2012) reported a lack of significant association between sleep and inflammatory markers in renal transplant recipients [366]. They found that the apnea-hypopnea index was associated with white blood cell count but had only a weak correlation with the other inflammatory markers; their Periodic Limb Movement index data showed weak correlations with all markers of inflammation; and, while the serum IL-6 level was significantly higher in patients with insomnia, the levels of other inflammatory markers were similar for both insomniacs and non-insomniacs [366].

Chronic lung allograft dysfunction, mostly manifested as bronchiolitis obliterans syndrome, is the single most severe limitation to lung recipients' long-term survival [385]. The main symptoms are airway obstruction, shortness of breath, wheezing and dry cough. These symptoms can start gradually and trigger sleep disordered breathing. In lung transplant recipients, the post-transplantation prevalence of sleep disordered breathing ranged from 15% to 63%, the prevalence of obstructive sleep apnea was 38% and that of central sleep apnea was 25%. **Lung transplantation** improves sleep disordered breathing and oxygenation. However, Malouf et al. (2008) reported that new-onset sleep disordered breathing occurred later in the post-transplant phase [367]. In addition, lung transplant recipients with sleep disordered breathing (prevalence 63%) had a higher systolic blood pressure, higher body mass index and higher arousal index compared with those who had no sleep disordered breathing condition [368]. Further, Naraine et al. (2009) reported that cyclosporine use was associated with central sleep apnea, and lung transplant recipients with obstructive sleep apnea had a greater change (pre- to post- transplant) in body mass index compared with non-sleep disordered breathing subjects [368].

Sleep disturbances are also very prevalent (32%) after **heart transplantation**. The most common diagnoses are obstructive sleep apnea (36-58%), followed by restless legs syndrome (45%) and periodic limb movement (33%). Obstructive sleep apnea adversely affects cardiac function in heart transplant recipients [386]. Weight gain since transplantation was significantly greater in recipients with obstructive sleep apnea than in those without [372]. Van de Beek et al. (2008) in a retrospective cohort study of 313 heart transplant recipients linked sleeping disorders to baseline body mass index: the mean body mass index was 26.8 for patients with sleeping disorders vs 24.5 for the patients with none [369]. Ayik et al. (2013) found that elevated body mass index is a risk factor and waist circumference an independent predictor for obstructive sleep apnea [373]. Mansfield et al. (2003) reported that central sleep apnea persist despite normalization of heart function and sympathetic nerve activity [371] and Javaheri et al (2004) found additionally that quality of life was significantly worse in heart transplant recipients with obstructive sleep apnoea [372].

To sum up, poor sleep quality and fatigue are highly prevalent after **liver transplantation**, when poor sleep quality is associated with higher body mass index and more anxious mood, and fatigue is a significant predictor of daily functioning and health related quality of life [375]. Sleep quality, anxiety, depression [375], use of sleep medications in the past month, and higher mood disturbance [374] are associated with fatigue severity [375]. In pre-transplant recipients, higher body mass index, sleep medication use and increased mood disturbance are all associated with poor sleep quality [374]. However, pre-transplantation fatigue is also associated with female gender, a higher body mass index, higher mood disturbance and poor sleep quality [374].

### **1.8.7. Sleep treatment in solid organ transplant recipients**

#### **1.8.7.1. Pharmacological sleep treatment**

While sleep drugs provide safe, effective treatment for many acute sleep disorders, transplant recipients require special consideration. Particularly sleep drugs acting on the cytochrome P450 and cytochrome 3A4 enzymes (see section 1.7.1.) have the potential to inhibit, induce, or compete for available sites in both systems, potentially altering the efficacy of immunosuppressives [260]. Sleep drugs might have an additive effect when adverse effect profiles are shared with other medications, but the effects vary widely between users. Therefore, each new drug has to be evaluated for the individual recipient as to whether its benefit outweighs its potential damage to the kidney or liver. A gap remains in the literature regarding recommendations for the use of sleep aids in solid organ transplant recipients. Regarding non-prescription cough suppressants, Gabardi et al.



(2011) have performed a review and provided recommendations for solid organ transplant recipients [387]. The main issues addressed involve interaction with calcineurin inhibitors (e.g., diphenhydramine).

Melatonin supplementation might be indicated for solid organ transplant recipients when treated with bisoprolol, which suppresses melatonin, and no option is available to change to nebivolol or carvedilol (which do not)[388]. (See section 1.6.4 for further details of melatonin and interactions).

#### **1.8.7.2. Non-pharmacological sleep treatment**

For the reasons outlined above, physicians are understandably reluctant to prescribe sleep drugs to solid organ transplant recipients. Possible alternatives include the implementation of sleep hygiene rules (see section 1.6.2 [152] and chronotherapeutics ((bright light or melatonin [389]), see 1.6.3.1 for details). At present, though, understanding is limited regarding the management of sleep disorders in transplant recipients. To our knowledge, only one pilot study has assessed the efficacy of mindfulness-based stress reduction in solid organ transplant recipients. The intervention consisted of a training program of eight weekly 2.5-hour classes; after its completion, the researchers reported reduction of distressing symptoms including anxiety, depression and poor sleep, along with improved quality of life [383]. To our knowledge no other intervention studies to improve sleep disturbances in this population have been published. Therefore, bright light intervention should be tested as an alternative to sleep drugs for sleep-wake disturbances in the renal transplant population.

### **1.9. Identified gaps in the state of science of sleep-wake disorders in solid organ transplant recipients**

In summary, the following gaps in the literature on “sleep-wake disturbances in solid organ transplant recipients” guided the proposal of this research project. Given the knowledge gaps remaining to be filled, the following rationales guided this research project regarding study design and sample selection.

Firstly, as described above (in sections 1.5.1 and 1.5.2 of the literature review), valid instruments are available to measure some aspects of sleep; however, these are extensive questionnaires. The time investment they demand entails a high risk of low response rates and missing data, making them impractical for the screening and long-term follow-up of sleep-wake disorders in clinical practice.

Although several instruments have been developed to measure sleep and related factors, a need remains for a short, easy screening tool for sleep quality and daytime sleepiness. Such a tool is already available for sleep quality [9]. For daytime sleepiness, however, content validity and validity in relation to other variables have yet to be established. Further, an assessment instrument validated for use in different organ transplant recipient groups will enable inter-group comparison.

Secondly, sleep disorders and sleep deprivation are causing an increasing public health burden (see sections 1.3.1 and 1.3.2). Sleep deprivation impairs the entire spectrum of mental abilities, ranging from simple psychomotor performance to executive mental functions [45], neurocognitive functions [46] and decision making [47]. The most obvious consequence of sleep deprivation is daytime sleepiness [36]. According to Naraine et al. (2009) [368], studies are needed to determine whether sleep is a risk factor and, if so, how it-or the lack of it-influences clinical outcomes [368]. As described in section 1.7.4, poor sleep quality is linked to immunosuppressive non-adherence, which directly impacts graft rejection rates [390].

As immunosuppressive non-adherence is a preventable factor of graft rejection, then, a daytime sleepiness component would be a valuable addition to the current battery of therapeutic tools. More precisely, it is necessary to establish the odds for taking and timing non-adherence in transplant recipients reporting daytime sleepiness. Based on this information, practice guidelines and an improved sleep assessment for transplant recipients can then be established in clinical practice to reduce the high prevalence of non-adherence. Also, Riegel et al. (2011) found that daytime sleepiness has proven associations with reduced medication adherence in patients with heart failure [51]. Renal transplant recipients have similarly high rates both of medication non-adherence and of daytime sleepiness, although no association has been established between these two variables.

Thirdly, in spite of a small number of sleep studies performed in solid organ transplant recipients, a strong need remains for studies that include sleep assessment interviews that go beyond a screening questionnaire. In particular, there is a need for studies focusing on the diagnosis of insomnia and circadian rhythm sleep disorders that cannot be assessed via one-night polysomnography (see Subchapter 1.5.1). According to Javaheri et al. (2003) [372] and to Eryilmaz et al (2005)[354], more sleep study variables should be chosen with a focus on improving health-related quality of life [354, 372]. Sleep is a vital parameter, impacting daily life in countless ways. In collaboration with patients, studies are therefore needed to explore ways of improving and reacting to related diagnoses.

This means that sleep assessment interview studies following the International Classification of Sleep Disorders will require a clear knowledge of the symptoms of poor sleep quality and daytime sleepiness identified in post-transplantation follow-up care. Renal transplant recipients have a high prevalence of sleep-wake disturbances [9, 391, 392] although it is not known to which sleep disturbance poor sleep quality and daytime sleepiness symptoms belong. Via a structured interview, it will be necessary to assess the prevalence of sleep disturbances in renal transplant recipients screened positive for poor sleep quality and / or daytime sleepiness.

Fourthly, according to Naraine et al. (2009) [368] and Eryilmaz et al (2005)[354], longitudinal studies including the assessment of the presence of sleep disturbance pre- and (up to several years) post-transplantation are needed to determine the effect of sleep diagnoses / interventions on clinical outcomes [368]. This will require researchers to ascertain whether and how sleep-related complaints persist after transplantation and how other relevant variables interact [354].

In addition, longitudinal studies such as the ongoing Swiss Transplant Cohort Study have to be improved by including not only a sleep quality item, but also a daytime variable such as daytime sleepiness. The sleep quality item has already been validated [9] and satisfactorily integrated into the Swiss Transplant Cohort Study's psychosocial questionnaire, which also assesses health related quality of life. For the first time, a single assessment tool will enable researchers to determine the impact of poor sleep quality on health related quality of life, and to examine prevalence data on the long-term pre- to post-transplantation development of sleep quality variables across all four solid organ transplant groups.

Fifthly, according to Rodrigue et al (2011), improving sleep disturbance interventions and testing their effectiveness in transplant recipients will require more research and development on both pharmacological and non-pharmacological interventions [357]. The testing component will require randomized controlled trials (Novak et al 2006) [358]. And Van de Beek et al. (2008) recommend longitudinal sleep studies with objective measurement tools [369]. As described in section 1.6.2 above, considerable knowledge has been established on chronotherapeutics and non-pharmacological interventions; however, none have been tested on solid organ transplant recipients.

In renal transplant recipients, whose daily medication regimens commonly balance twelve separate drugs, the high prevalence of sleep-wake disturbances makes them particularly vulnerable to accidental non-adherence. However, safe interventions, where no interaction occurs (especially with the immunosuppressive medications) are difficult to determine. As described in section 1.6.2, this makes physicians justifiably reluctant to

prescribe sleep drugs. Still, the comparative benefits of chronotherapeutics have never been assessed in transplant recipients. In particular, bright light therapy has yielded promising results against insomnia and circadian rhythm sleep disorders. A randomized controlled pilot trial is needed to establish the benefits of such therapy in renal transplant recipients diagnosed with post-transplantation sleep-wake disturbances, and to estimate the effect size for a full-powered study.

Thus far, the proposed dissertation and the included research program will contribute in multiple ways to the international scientific literature, as well as expanding the existing knowledge of sleep-wake disturbances in solid organ transplant recipients in Switzerland.

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# CHAPTER 2

## AIMS OF THIS RESEARCH PROGRAM

Given the identified gaps in the literature regarding a short validated item to measure daytime sleepiness and a safe intervention to treat sleep-wake disturbances, this research projects included the following aims:

- 1)
  - a) to evaluate the validity of a single item DS measure integrated in the Swiss Transplant Cohort Study (Chapter 3).
  - b) to describe the prevalence of immunosuppressive non-adherence in renal transplant patients (Chapter 4).
  - c) to assess the association between daytime sleepiness, depressive symptomatology and non-adherence to the immunosuppressive regimen (Chapter 4).
- 2) to categorize patients with sleep disorders following the International Classification of Sleep Diagnoses (ICSD-2 classification) (Chapter 5).
- 3)
  - a) to compare by type of organ transplant the prevalence and evolution of sleep quality from pre to post transplantation in kidney, liver, lung and heart recipients included in the Swiss Transplant Cohort study (a prospective nation-wide cohort study) from pre- to 2 years post-transplantation. (Chapter 6).
  - b) to assess the impact of sleep quality on perceived health status from pre- to 2 years post-transplantation (Chapter 6).
- 4) to assess the feasibility and effect size of bright light therapy in home dwelling renal transplant patients with sleep-wake disturbances (Chapter 7) on bedtime.



# CHAPTER 3

## VALIDATION OF A SINGLE ITEM TO ASSESS DAYTIME SLEEPINESS FOR THE SWISS TRANSPLANT COHORT STUDY



## Validation of a Single Item to Assess Daytime Sleepiness for the Swiss Transplant Cohort Study

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**Keywords:** transplantation, sleep quality, daytime sleepiness, validity

**Funding:** International Transplant Nurse Society and Swiss Renal Foundation: Alfred & Erika Bär-Spycher Foundation

### Reference

Burkhalter, H., Wirz-Justice, A., Cajochen, C., Weaver, T., Steiger, J., Fehr, T., Venzin, RM., De Geest, S. (2013). Validation of a single item to assess daytime sleepiness for the Swiss Transplant Cohort Study. *Prog Transplant*, 23(3), 220-228. doi: 10.7182/pit2013788

### 3.1. Abstract

**Context:** Daytime Sleepiness (DS) in renal transplant (RTx) recipients has emerged as a potential predictor of impaired adherence to the immunosuppressive medication regimen. Thus there is a need to assess DS in clinical practice and transplant registries.

**Objective:** To evaluate the validity of a single item DS measure integrated in the Swiss Transplant Cohort Study (STCS), using the American Educational Research Association (AERA) framework.

**Methods:** Using a cross-sectional design, we enrolled a convenience sample of 926 home-dwelling RTx patients [median age 59.69 years (Q25-Q75: 50.27-59.69), 63% men; median time since Tx 9.42 years (Q25-Q75: 4.93-15.85)] DS was assessed using a single item from the STCS and the 8 items of the validated Epworth Sleepiness Scale (ESS). ROC curve analysis was used to determine the cut-off for the STCS-DS item against the ESS score.

**Results:** Based on the ROC curve analysis, a score  $> 4$  on the STCS-DS is recommended to detect DS. Content validity was high as all expert reviews were unanimous. Concurrent validity was moderate (Spearman's rho,  $r_s$ : 0.531  $p < .001$ ) and convergent validity with depression and poor sleep quality although low, was significant ( $r_s$ : 0.235  $p < .001$  and  $r_s$ : 0.318  $p = .002$ , respectively). For the group difference validity: RTx recipients with moderate, severe and extremely severe depressive symptomatology scores showed 3.4, 4.3 and 5.9 higher odds of having DS, respectively, as compared with recipients without depressive symptoms.

**Conclusion:** The accumulated evidence provided evidence for the validity of this simple screening scale for DS: the STCS-DS.

## 3.2. Introduction

The Swiss Transplant Cohort Study is a nationwide prospective multicenter interdisciplinary cohort study including all patients receiving organ transplants in Switzerland in one of the 6 transplant centers (Lausanne, Geneva, Basel, Zürich, Bern, St. Gallen) [1, 2]. The STCS began patient enrollment and data collection on May 2<sup>nd</sup> 2008. In this study only one item assessing sleep quality was integrated. In view of the evidence described below we developed a daytime sleepiness item to be included, after validation, into the STCS and used for this same format as the 1-item sleep quality measure already included in this nation-wide cohort study

It is commonly recognized that lack of nocturnal sleep increases the tendency to fall asleep during the day. Daytime sleepiness (DS) is the subjective report of an increased desire to fall asleep and lack of energy during the day even after an adequate night's sleep.[3] DS is not a disorder in and of itself, yet it is an important symptom of many other sleep disorders. DS is associated with poor performance [4], cognitive slowing, attention failures, errors, [5] and accidents.[6] It is also a known predictor of increased morbidity and mortality in patients with cardiovascular disease [7, 8] and diabetes.[9]

So far, there is limited evidence for the presence and impact of DS in the renal transplant (RTx) literature. In a previous study, we found that 34.1% of RTx recipients suffered from poor daytime functioning, a measure similar to DS, although DS was not directly assessed as functioning was more related to performance.[10] The prevalence of DS in the general population ranges from 2.5% [11] to 25.7% [12] and in hemodialysis patients from 15% [13] to 27.3%. [14]

Because of its impact on clinical outcome, DS is emerging as a relevant parameter to assess in research and clinical practice. We therefore decided to integrate the assessment of DS in the Swiss Transplant Cohort Study (STCS) [2]. Many instruments exist to measure DS objectively such as the Multiple Sleep Latency Test [15], Maintenance of Wakefulness Test [16], and Psychomotor Vigilance Task,[17, 18] or subjectively, using self-report, such as the Epworth Sleepiness Scale (ESS).[19, 20] The commonality among these instruments is that they are time consuming and labor-intensive, and some are in a laboratory situation not reflecting daily life. Whereas the ESS is easy to administer, clinicians do not commonly use it outside the field of sleep medicine. This may be due to both a lack of awareness of the importance of DS problems or a reluctance to add 8 questions to an already lengthy medical assessment. Taking this into account, a simpler more direct question about DS might better serve as a screening tool. A single item

questionnaire has been previously published asking “Please measure your sleepiness on a typical day” (0 = none, 10 is highest; cutoff  $\geq 7$ ), however, this item is only validated in patients having a diagnosis of a sleep disorder and no specific recall period is used, making it unclear to patients which time frame to take into consideration when completing this item.[21]

DS, sleep quality and depression are interrelated and have been explored and explained in different models and approaches.[22-24] Poor sleep quality and DS are included in the criteria for the diagnosis of depression. The Diagnostic and Statistical Manual of Mental Disorders [25] define criteria for a Major Depressive Disorder: “Difficulty falling or staying asleep (insomnia), or sleeping more than usual (hypersomnia)” (criterion 1d) and feeling tired or having little energy (1e). For Dysthymic Disorder criterion 2 is set as “Sleeping too much or having difficulty sleeping” and criteria 3: “Low energy or fatigue”. Depression is common among RTx recipients; reported cumulative incidences were 5.05%, 7.29%, and 9.10% at 1, 2, and 3 years post-Tx.[26] The prevalence of poor sleep quality in RTx recipients ranges from 30% to 62%.[27-29]

Patients suspected to suffer from obstructive sleep apnea and a high score on the ESS also had a significantly higher score on the Center for Epidemiological Studies Depression Scale[30]. In a cross-sectional study with 3045 community-dwelling women aged 70 and older depression was associated with poorer sleep quality and DS.[31] Another cross-sectional study including 67 patients diagnosed with a depressive episode showed that DS measured with the ESS correlated highly with the Hamilton Depression Rating Scale ( $r = 0.69$ ,  $p < 0.001$ ).[32]

Given that transplant registries do not allow the use of lengthy measures because of subject burden, we developed a single item to measure DS prospectively as part of the STCS.[2] It needs to be determined, however, which cut-off with respect to other existing measures is appropriate to identify DS by a single item (i.e. cross-validation). Moreover, the validity of this single item STCS-DS instrument needs to be demonstrated before analyses on Tx outcomes can be performed.

### **Theoretical Background: Validity**

Assessing the validity of an instrument implies gathering as much evidence as possible to support validity related to test content, response processes, internal structure, relation to other variables, and consequences of testing, as outlined by the American Educational Research Association (AERA) framework.[33, 34] For the purpose of our study, we focused on evidence related to test content and relationships to other variables. In order to guide our validation process we developed four hypotheses based on empirical evidence

that outlines the relationships between DS, sleep quality, and depression to be tested as part of the validation process (Table 1) [33].

In absence of an established validated cut-off of the STCS-DS item, the first aim of this study was to identify the optimal cut-off point for classifying patients as having DS using the ESS as reference. However the main aim of this study was to assess the validity of the STCS-DS item using the American Education Research Association framework to assess evidence based on content and evidence based on relationship to other variables.

### 3.3. Methods

#### Design, Setting and Sample

This study used a cross-sectional multicenter correlational design. A convenience sample of 926 home dwelling RTx patients transplanted at 3 Swiss renal transplant centers participated in the study. Patients were included when they were at least 6 months post-transplant, had the ability to understand and read German, were 18 years of age or older, and provided written informed consent. Individuals were excluded if they were unable to complete the study questionnaire by themselves for any reason.

#### Variables and Measurements

Age (in years), gender, and time since transplantation (in years) were retrieved from the hospital charts. Daytime sleepiness was assessed by 2 measures, the Swiss Transplant Cohort Study Daytime Sleepiness (STCS-DS) item [2] and the Epworth Sleepiness Scale (ESS) [19]. The *STCS-DS* item asks subjects to rate their overall DS in the past four weeks on a scale of 0 (no sleepiness) to 10 (extreme sleepiness). This item is similar to a widely used but not validated item in sleep diaries carried out with actigraphy measurements.[21] The layout was made congruent with the STCS sleep quality item [10] derived from the Kidney Disease Quality of Life Short Form.[35] Receiver operating characteristic (ROC) curve analysis [36] has been utilized to establish an appropriate cutoff for the STCS-DS item.

The *ESS* is a validated questionnaire containing eight items that measure a subject's expectation of dozing in eight hypothetical situations. Dozing is defined as falling into a light sleep[37]. Dozing probability ratings range from 0 (no probability) to 3 (high probability). Scores on the eight items are summed, yielding a total dozing score between 0 and 24. An *ESS* sum score  $\geq 6$  indicates DS.[19] A score of  $\geq 10$  indicates that the subject is very sleepy and should seek medical advice.[19] Total *ESS* scores show high test-retest reliability ( $\rho = 0.82$ , ,  $p < 0.001$ )[38] and a high level of internal consistency (Cronbach's  $\alpha = 0.74-0.88$  in 4 different groups of chronically ill).[39] A single factor emerged when

performing factor analyses on ESS item scores of 150 patients and 104 students.[38] The ESS has been validated for application in German-speaking populations.[20]

### **Sleep quality**

Sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI), a self-rated questionnaire consisting of 19 items, assessing a wide variety of factors related to sleep quality over a 1 month time interval, including estimates of sleep duration and latency, and of the frequency and severity of specific sleep-related problems. These 19 items are grouped into seven component scores, each weighted equally on a 0-3 scale. The seven component scores are then summed to yield a global PSQI score, which has a range of 0-21; higher scores indicate worse sleep quality.

A cut-off of > 5 points is used to classify patients as having poor sleep quality.[40] A PSQI global score > 5 resulted in a sensitivity of 98.7 and specificity of 84.4 as a marker for sleep disturbances in insomnia patients versus healthy controls.[41] Backhaus et al. translated the PSQI into German using the back-translation method.[41] Item analysis confirmed internal consistency of the German version of the PSQI scale (Cronbach's alpha of 0.85).[41] The test-retest reliability for the short interval (2 days) was high for the global as well as for subscale scores (0.76 to 0.92). For the longer interval (45.6 ± 18 days), the test-retest reliability was low for the subscores "sleep quality" (r = 0.23) and "sleep disturbance" (r = 0.84) whereas it remained moderate to high for the global score (r = 0.86) and four of seven subscores, ranging from 0.59 to 0.83 [41]. Sleep diaries show a high correlation to the PSQI[41] indicating good validity based on relation to other relevant variables.[41]

### **Depression**

Depression was measured with the Depression, Anxiety, and Stress Scale (DASS 21): a 21-item self-report instrument, of which 7 items measure depressive symptoms (DASS-D) [42] on a ordinal 4 point Likert severity/frequency scale to rate the extent to which they have experienced each state over the past week: 0 = did not apply to me; 3 = applied to me very much over the last week. Scores are summed and multiplied by two resulting in a range of 0 to 42 for each subscale. The following cut-offs are used to evaluate severity of depressive symptomatology: 0-9 no depressive symptomatology, 10-13 mild, 14-20 moderate, 21-27 severe and 28+ extremely severe symptomatology.[43] Cronbach's alpha for the DASS-D scale is high (alpha= .88 (95% CI = .87-.89) and shows good concurrent validity with the Brief Symptom Inventory (r=0.70)[44], the Beck Depression inventory (r = 0.74) [42], the Personal Disturbance scale depression scale (r=.78) and the Hospital Anxiety and Depression Scale (r=.66) [45].

## Evidence based on content

### *Content validity*

Evidence supporting test content includes logical or empirical analyses of how adequately that content represents the domain of interest and can include the judgment of content experts.[33] Validity-related data analysis procedures were guided by research questions and hypotheses formulated to test item validity (see Table 1).

**Table 1:** Hypotheses and research questions guiding the validation process

<b>Evidence based on content</b>	Q 1	Does STCS-DS item reflect the concept of daytime sleepiness based on expert review?
<b>Evidence based on relation to other variables</b>	H 1	STCS-DS (low score means no DS) is positively correlated with ESS sum score (low score means no DS) [concurrent validity].
	H 2	There is a positive correlation between STCS-DS and the DASS depression score [convergent validity]
	H 3	There is a positive correlation between STCS-DS and sleep quality measured by the PSQI score [convergent validity].
	H 4	Higher levels of depressive symptomatology are associated with higher degree of daytime sleepiness. [group difference validity].

Legend: STCS-DS: Swiss Transplant Cohort Study - Daytime Sleepiness; DS= Daytime Sleepiness; DASS =Depression, Anxiety and Stress Scale; PSQI = Pittsburgh Sleep Quality Index

To test if the STCS-DS item indeed measures daytime sleepiness, we asked all members of the STCS Psychosocial Interest Group (transplant physicians, psychologists, nurses, physicians and epidemiologists) to evaluate whether the STCS-DS item captures DS, expressed as the percentage of agreement. First the item was evaluated and then voted at one of the in-person meetings of the STCS Psychosocial Interest Group.

### **Evidence based on relationships with other variables**

Evidence of relationships to other variables is commonly evaluated by assessing associations among variables. If the observed relationships match the hypothesized relationships, then the evidence supports the validity of the interpretation.[33]

### *Concurrent validity*

*Concurrent validity (or criterion related validity)* requires that both variables measuring the same concept are captured at one point in time. As the strength of the correlation increases, there is an increased probability that the variables measure the same concept.[46] DS is the subjective report of an increased desire to fall asleep and lack of energy during the day even after an adequate night's sleep.[3] Excessive DS is sleepiness in

a situation when an individual would be expected to be awake and alert.[47] Following these two definitions the ESS asks about 8 very concrete situations when an individual would be expected to be awake and alert. In contrast the STCS-DS asks for sleepiness over the past 4 weeks unrelated to a specific situation. The ESS is more precise in asking for these situations whereas the STCS-DS asks for a metacognitive process transforming the concept of DS into a daily life situation.

Therefore we expected a moderate to high correlation between the STCS-DS item and the ESS total score, given that STCS-DS asks for sleepiness in general in the past 4 weeks, and the ESS asks the same, but in specific circumstances[46].

#### *Convergent validity*

*Convergent validity* is when two measures of a construct that theoretically should be related to each other are, in fact, observed to be related to each other.[48] In order to provide evidence for convergent validity, we expect to observe [48] 1) a moderate to high correlation between the STSC-DS item and sleep quality, as measured by the PSQI; and 2) a low to moderate positive correlation between the STSC-DS item and depressive symptoms, measured by the DASS-D.

#### *Known group difference validity*

*Known group difference validity* is when data are collected from two groups that have expected differences on the measure of interest. If the measure is able to discriminate between the groups through statistically significant findings, this provides evidence for the validity of the measure.[49] The evidence states that depression is associated with poorer sleep quality and DS. [31] We hypothesize therefore that stratifying our sample on the DASS-D score will split the sample in a similar way for DS. If DASS-D scoring (normal, mild, moderate, severe, extremely severe) is able to discriminate between the groups through statistically significant findings, this provides evidence for the validity of the DS measure.[49]

#### **Data Collection**

Addresses of all patients who fulfilled the eligibility criteria were extracted from the centers' transplantation databases by the responsible physician and the head outpatient nurse. Each potential participant received a package containing an information letter, the informed consent documents, pre-stamped envelopes, and the questionnaires. Participants who consented to participate completed the study questionnaires and returned them to the researcher by mail. Patients not responding were contacted once by telephone and invited to participate again. If they agreed a new package was sent. The study was



approved by the ethics committee of Basel, Bern, and Zürich. Data were de-identified and stored in an electronic databank.

### **Statistical Analysis**

Data were entered once and randomly checked for discrepancies with original data (less than 1%). The Package IBM® SPSS® Statistics 19 (Version 19.0.0, IBM Corporation, Somers NY) was used for statistical analysis, setting 5% for all critical probability levels.

Descriptive statistics included mean, standard deviation (SD), median and interquartile ranges (IQR), and frequencies as appropriate based on measurement levels and distributions of variables. The Mann-Whitney-U test and Chi-squared was used to explore whether gender, age and years since transplantation differed between those who responded and those who did not send back the questionnaires.

#### *Establishing the best cut-off for the STCS-DS*

Receiver operating characteristic (ROC) curve analysis was utilized to establish an appropriate cutoff for the STCS-DS item. We plotted the true positive rate (sensitivity) as a function of the false positive rate (1-specificity) for different cutoff values for the STCS-DS item, relative to the ESS sum score (i.e. cut-off  $\geq 10$  - where a score of 10 or more indicates very sleepy and should seek medical advice and a cut-off  $\geq 6$  - whereas a score of 6-9 suggests DS [19]).

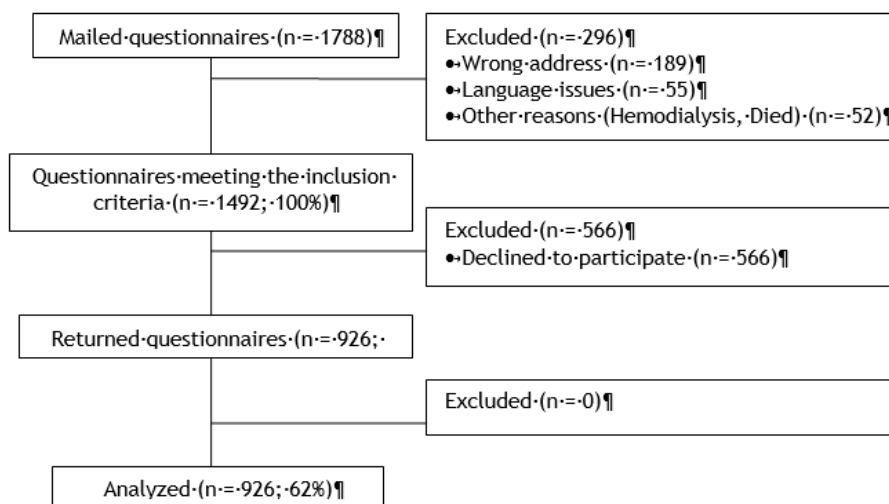
#### *Validity-related data analysis*

At an in-person meeting in January 2011, the DS concept was presented by the author in a 10 minute power-point presentation, showing different arguments and perspectives. After the presentation the members (N = 20) of the PSIG of the STCS were invited to comment and vote. The percentage of agreement was assessed by counting the participating members present at the meeting and dividing the number of members agreeing to the statement: “the STCS-DS item reflects the concept of daytime sleepiness” by that total. Spearman’s rank-order correlation was used to examine the association between the STCS-DS item and ESS sum score (H1), depressive symptomatology (H2) and poor sleep quality on the PSQI (H3). The group difference validity was done with a binary logistic regression with the DASS-D score (cut-off  $< 9$  normal; cutoff  $\geq 13$  mild depression; cut-off  $\geq 20$  moderate; cut-off  $\geq 27$  severe; cut-off  $\geq 28$  extremely severe) as a predictor of STCS-DS (H4).

### 3.4. Results

Out of 1788 renal transplant recipients, 1492 met the eligibility criteria and had a valid home address of which 926 returned a completed questionnaire (62% response rate) (See flow-diagram in Figure 1).

**Figure 1:** Flow diagram of sample



There were no differences between responders and non-responders apart from age: non responders ( $n = 509$ ) were significantly younger than responders ( $t = 2.51$ ,  $df = 1039$ ,  $p = .012$ ). The analyses were based on the 926 participants with complete data. The median age was 59.69 years (Q25-Q75: 50.27-59.69), 586 were men (63.3%) and the median time since transplantation was 9.42 years (Q25-Q75: 4.93-15.85) (Table 2).

**Table 2:** Description of the sample

	All	No Sleepiness (ESS<6)	DS (ESS>5)	No Sleepiness(ESS<10)	Excessive DS (ESS<9)
N	926	455	471	729	197
Males % (N)	63.3%(586)	60.9% (277)	65.6%(309)	62.6%(456)	66.0% (130)
Age in year					
Median/ Q25-Q75	59.69(50.27-59.69)	61.17(51.06-68.65)	58.68 (49.29-67.32)	60.61(50.85-68.23)	58.17(48.19-65.65)
Years since Tx					
Median/ Q25-Q75	9.42(4.93-15.85)	9.32(4.92-15.59)	9.58(4.96-16.15)	9.81 (5.01-16.29)	8.51 (4.85-14.99)
<i>Daytime sleepiness measured by the Epworth Sleepiness Scale</i>					
ESS Score					
Mean/SD	6 (3-9)	3 (2-4)	9 (7-11)	4 (3-7)	12 (11-14)
DS % (N)	50.9% (471)	0% (0)		37.6% (274)	
Excessive DS % (N)	21.3% (197)		41.8% (197)		100% (197)
<i>Daytime sleepiness measured by the Swiss Transplant Cohort Study Daytime Sleepiness Item</i>					
STCS-DS Score					
Median/ Q25-Q75	3 (1-5)	2 (1-3)	4 (2-6)	2 (1-4)	6 (3.5-7)
STCS-DS % (N)	32.4% (300)	16.5% (75)	47.8% (225)	31.4% (229)	75.1% (148)
<i>Sleep Quality measured with the Pittsburgh Sleep Quality Index</i>					
PSQI Score					
Median/ Q25-Q75	6 (4-10)	5 (3-8)	6 (4-10)	5 (3-8)	8 (5-11)
PSQI % (N)	49.5 % (456)	40.1% (181)	58.5% (275)	43.8% (317)	70.6% (139)
<i>Depressive Symptomatology measured with the Depression, Anxiety and Stress Scale</i>					
DASS Score					
Median/ Q25-Q75	3 (1-6)	2 (0-5)	3 (1-7)	2 (1-5)	5 (2-9)
DASS % (N)	33.9%(310)	26.3 %(118)	41.2% (192)	29.3% (211)	50.3% (99)

Legend: ESS= Epworth Sleepiness Scale; DS = Daytime Sleepiness cutoff  $\geq 6$ ; Excessive DS = Daytime Sleepiness cutoff  $\geq 10$ ; STCS = Swiss Transplant Cohort Study Daytime Sleepiness Item  $\geq 4$ ; PSQI =Pittsburgh Sleep Quality Index  $> 5$ ; DASS = Depression, Anxiety and Stress Scale  $> 9$

### Cut-off Values for the STCS-DS item

Based on ROC curve analyses, a cutoff value of 4.5 on the STCS-DS item yielded the highest levels of sensitivity and specificity in predicting the ESS cut-off  $\geq 10$  (= excessive DS) with a sensitivity of 67% and a specificity of 84%. A cut-off value of 3.5 for the STCS-DS item also had the highest sensitivity (57%) and specificity (77%) relative to the ESS cut-off  $\geq 6$  (= DS) (Table 3).

**Table 3:** Receiver operating characteristic (ROC) curve for the single DS item

Variable	N (Percent)	Property	STCS DS	STCS DS
Daytime Sleepiness <sup>£</sup>	469 (50.7%)	AUC (95% CI)	0.75 (0.71-0.78)	0.75 (0.71-0.78)
		Optimal cutoff	3.5	4.5
		Sensitivity	58%	48%
		Specificity	77%	84%
Excessive daytime Sleepiness <sup>§</sup>	197 (21.2%)	AUC (95% CI)	0.80 (0.77-0.83)	0.80 (0.77-0.83)
		Optimal cutoff	3.5	4.5
		Sensitivity	75%	67%
		Specificity	69%	87%

Legend: AUC = Area under the curve; £= DS on the Epworth Sleepiness Scale  $\geq 6$ ; §= DS on the Epworth Sleepiness Scale  $\geq 10$

Evidence based on content (Table 1, Q 1)

All experts (100%) agreed that the STCS-DS item reflects the concept of DS.

Evidence based on relations to other variables (Table 1, H 1-4)

The concurrent validity between STCS-DS item and the ESS Score [H1] showed a moderate but significant correlation (Spearman's rho,  $r_s$ : 0.531  $p < .001$ ). Convergent validity [H2] showed that the STCS-DS was correlated minimally but significantly with DASS-D score (Spearman's rho,  $r_s$ : 0.235  $p < .001$ ) and the [H3] STCS-DS  $\geq 4$  was correlated minimally but significantly with the PSQI score (Spearman's rho,  $r_s$ : 0.318  $p = .002$ ). Table 4 shows the group difference validity results. Higher levels of depressive symptomatology are associated with higher odds of DS. RTx recipients with moderate to extremely severe depressive symptomatology show 3.4, 4.3 and 5.9 higher odds to have DS, respectively as compared to those without depressive symptomatology.

Table 4: Predictors of STCS-DS in the simple logistic regression analysis

DASS-D	Odds( 95% CI)	p
Normal (reference)		
Mild	1.377 (0.91 - 2.09)	0.133
Moderate	3.411 (2.25 - 5.165)	P<.001
Severe	4.260 (2.29 - 7.93)	P<.001
Extremely severe	5.990 (2.86- 12.54)	P<.001

Legend: STCS-DS= Swiss Transplant Cohort Study- Daytime Sleepiness; DASS-D= Depressions Anxiety and Stress Scale- Depression

### 3.5. Discussion

This study examined the validity of using one item to measure DS as incorporated in the STCS. The STCS is a nationwide prospective cohort study that uniquely also assesses selected psychosocial and behavioral variables from pre-Tx to life-long post-Tx including sleep quality and DS.[2] As the STCS does not allow extensive assessment of each variable to limit subject burden, DS is assessed with 1 item derived from previous research. Testing the validity of the STCS-DS item was performed using a large dataset of renal transplant patients participating in a research program on sleep research in RTx recipients, a study separate from the STCS. Validity was tested in view of evidence related to test content and evidence related to relationships with other variables.[33]

#### Cut off score for STCS-DS item

As a cut-off for the STCS-DS item has not yet been established we used the ROC curve analysis to determine it. This analysis showed useable results based on 2 cut offs of the ESS, a validated and established instrument to assess DS. We did this analysis for both of the cut-offs of the EES thus allowing two suggested cut offs for our STCS-DS item. The ideal cut-off for DS is 3.5 and the ideal cut-off for excessive DS is 4.5. To avoid screening for a diagnosis of a sleep disorder where one does not exist, we recommend restrictive positive screening using values higher than or equal 4 in the STCS-DS item. These findings support its use for a general screening tool followed by in depth sleep disorder assessments.

#### Evidence based on test content

The agreement of our experts showed that the STCS-DS measures the DS concept. For further studies we suggest assessing the content validity index for the validity based on test content.[50]

### Evidence based on relationships with other variables

We provided first evidence for validity of STCS-DS item. H1 showed a significant moderate correlation, demonstrating the similarity of the concepts. We had hoped to find a higher correlation, however this was unrealistic considering the aim of replacing 8 items with one is very ambitious.

Depressive symptomatology (H2) and poor sleep quality (H3) were significantly correlated; this result may be, in part, due to the large sample. These results highlight the expected interaction of these variables with DS and demonstrate that they measure different things. The low correlation may indicate that other factors that we did not correct for and did not assess, affect the variability. For example we did not assess for past insomnia history; this factor is a predictor for future development of depression in older persons as well as young adults.[51] Further we had no polysomnography measurements to establish changes in sleep architecture. We will in future have actigraphy in a selected subgroup that may provide detailed information as to the nature of the diverse sleep disturbances in RTx. In addition, RTx recipients are subjected to other strong factors limiting the correlations and affecting sleep, for example the consequences of immunosuppressive drug therapy [52], impaired immune system [53] and high vulnerability for infections [54].

Group difference validity has been shown with the DASS-D scale. Higher levels of depressive symptomatology were significantly associated with a higher odds ratio of DS. These validities show that STCS-DS measures a similar concept to the ESS, that STCS-DS is related to but measures a different concept than depression and sleep quality; and that a positive score on the DASS-D scale is associated with an increased odds ratio for DS. This suggests that careful use of a simple screening is beneficial and - in case of a positive screening value - should be followed up by a thorough assessment for sleep disorder.

We suggest for a further validity study to test all sources of validity [34, 48], especially evidence based on response processes and evidence based on consequences of testing. Evidence based on internal structure is in this case irrelevant, as there is only one item. Validity based on response processes should be assessed with more assessments (interview techniques, verbal protocol methods, think-aloud techniques) at different time points.[33] Validity based on consequences of testing could be assessed by assessing the alertness and performance (the impact of DS score results) of the RTx recipients and the consequences on the nurses in charge in view of higher services. For example a study could measure the difference in immunosuppressive medication adherence between RTx recipients screened with DS receiving no intervention and RTx recipients screened with DS receiving light therapy to improve DS.

### **Limitations of the study**

This study has several limitations: The questionnaire responders were significantly older compared to non-responders, perhaps because they are retired [55] and thus have more time to answer the questionnaires. Next, the study aimed to include a broad sample with low selection criteria and low questionnaire and measurement burden. Therefore we had a big sample, only one time point measure and few items included in the questionnaire, limiting the analysis for testing other validity dimensions. A further limitation is that the questionnaire did not permit investigation of self-rated DS as related to specific sleep disorders. Lastly testing validity and reliability of a 1-item scale is limited [e.g: reliability (internal consistency) is only possible with more than 1 item] and study design (e.g: for test-retest validity and criterion validity a longitudinal study is needed).[46]

### **Conclusion**

The “Standards for Educational and Psychological Tests” proposed that validity is a unitary concept supported by theory and accumulating evidence provides a sound scientific basis for the proposed score interpretation. Our results support the importance of daytime sleepiness, sleep quality, and depressive symptomatology assessment in renal transplant patients. Our validity testing based on evidence “based on content” and “evidence based on relationship to other variables” provided supporting evidence for the validity of a single daytime sleepiness item in the STCS-DS.

### **Acknowledgement**

We gratefully acknowledge all the volunteers who helped with data collection and the ambulatory care teams for the excellent collaboration with information transfer.

This study was funded by research grants from the International Transplant Nurse Society and the Swiss Renal Foundation (Alfred and Erika Bär-Spycher Foundation).

### **Transparency declaration**

The authors have had no involvement, financial interests, arrangements, or relationships, direct or indirect, that might raise the question of bias in the work reported.

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# CHAPTER 4

## **DAYTIME SLEEPINESS IN RENAL TRANSPLANT RECIPIENTS IS ASSOCIATED WITH IMMUNOSUPPRESSIVE NON-ADHERENCE: A CROSS-SECTIONAL, MULTI-CENTER STUDY**

## Daytime Sleepiness in Renal Transplant Recipients is associated with Immunosuppressive Non-Adherence: A Cross-Sectional, Multi-Center Study

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**Keywords:** renal transplantation, daytime sleepiness, medication adherence

**Funding:** International Transplant Nurse Society and Swiss Renal Foundation: Alfred & Erika Bär-Spycher Foundation

Reference:

Burkhalter H., Wirz-Justice A., Cajochen C., Weaver T., Steiger J., Fehr T., Venzin, RM., De Geest, S. (2013). Daytime sleepiness is associated with immunosuppressive non-adherence in renal transplant recipients: a cross-sectional multi-center study. *Clinical Transplantation*, accepted.

## 4.1. Abstract

### Background

The aims of this study were to determine the prevalence of immunosuppressive non-adherence (NA) in renal transplant patients and describe whether the degree of daytime sleepiness (DS) and depressive symptomatology are associated with immunosuppressive NA.

### Methods

Using a cross-sectional design, 926 home-dwelling renal transplant recipients who were transplanted at one of three Swiss transplant centers provided data by self-report. The Basel Assessment of Adherence Scale for immunosuppressive was used to measure the taking, timing and overall NA to immunosuppressive medication. DS was assessed with the Epworth Sleepiness Scale (cutoff  $\geq 6$  for DS) and the Swiss Transplant Cohort Study DS item (cutoff  $\geq 4$  for DS), and depressive symptomatology was assessed with the Depression, Anxiety and Stress Scale (cutoff  $> 10$ ). An ordinal logistical regression model was applied for statistical analysis.

### Results

The prevalence of the Epworth Sleepiness Scale -DS was 51%. NA for taking timing and the median overall NA level assessed by 0 to 100% visual analogue scale was 16%, 42% and 0% respectively. Based on the multivariate analysis DS was significantly associated ( $p < 0.001$ ) with taking (1.08 [1.04-1.13]), timing (1.07 [1.03-1.10]) and overall NA (1.09 [1.05-1.13]). Very similar results were found for the Swiss Transplant Cohort Study DS item.

### Conclusion

DS is associated with immunosuppressive medication NA in renal transplant recipients. Admittedly the association's strength is limited.

## 4.2. Introduction

Medication non-adherence (NA) is defined as a deviation from the prescribed medication regimen sufficient to impair the regimen's intended effect [1]. Based on meta-analysis data, Butler et al. (2004) reported a median of 22% (IQR: 18%-26%) of immunosuppressive non-adherence in renal transplant recipients [2], and reported that non-adherence contributes substantially to graft loss; a median of 36% (interquartile range: 14%-65%) of graft losses were associated with prior non-adherence [2]. A preliminary analysis of an ongoing cohort study including kidney, liver, lung and heart Tx recipients showed a 28% prevalence of NA to immunosuppressive drugs in the past month pre-Tx, 8.2% at 6 months post-Tx, 11.6% at 1 year and 13.1% at 2 years, respectively [3].

Following transplantation, NA to immunosuppressive drug regimens is associated with an increased risk of graft loss [4] as well as negative economic outcomes [5]. Non-adherent patients have US \$12 840 higher medical costs over a period of 3 years compared to adherent patients [5]. Reported reasons for intentional NA include high medication costs and beliefs that the medication is harmful and causes side effects. The Swiss health system is regulated by the health insurance act that gives everyone living in Switzerland access to good medical care. This compulsory insurance covers the cost of medical treatment in case of illness or accident if the victim has no accident insurance. The insured person is free to select a health insurance provider. Immunosuppressive drugs are often paid for initially by the transplant recipient, who is then reimbursed 90% of the cost. Therefore, costs might be a factor influencing NA. Regarding self-reported behavior such as immunosuppressive NA, the key items to measure are taking the medication (ingestion), regular intake (timing adherence), drug holidays (not taking consecutive doses) and dose reduction [6].

Daytime sleepiness (DS) is a term used to describe difficulty maintaining a desired level of wakefulness, and refers to the feeling of drowsiness with a tendency to doze [7]. The clinical measurement in use reflects the implications that this level of sleepiness has for the individual's ability to perform a relevant tasks [8]. Thus, DS is not a disorder, but a symptom [9]. DS is measured by electroencephalographic correlates of sleepiness and markers of sleep with objective tests, such as the Multiple Sleep Latency Test or the Maintenance of Wakefulness Test. However, the rather high costs of these diagnostic tools restrict their overall usefulness in clinical practice [10]. Alternatives to the objective tests, are self-report questionnaires such as the Epworth Sleepiness Scale [11]. There is ample evidence for correlation between subjective and objective sleepiness [12].

Causes for DS vary: insufficient sleep duration, sleep apnea, narcolepsy, idiopathic hypersomnia, recurrent hypersomnia, circadian rhythm disorders, restless legs syndrome and periodic limb movement disorder, neurological conditions, somatic illness, psychiatric disorders and medication-induced somnolence [13]. It is known that DS diminishes cognitive and physical performance [14], with adverse impact on health [15], which include obesity and impaired glucose tolerance [16], cardiovascular disease and hypertension [17], mental distress, depressive symptoms, anxiety, and increased alcohol use [18]. DS is a public safety concern, particularly regarding the increased risk for workplace injuries and drowsy-driving accidents.

The rate of DS are between 1.4% [19] and 8% [20] in the general population and as high as 27.3% in hemodialysis patients [21]. The most common sleep disorders in hemodialysis patients are insomnia, restless legs syndrome, obstructive sleep apnea, and snoring [22]. In our RTx group, we found a 30.7% prevalence of poor sleep quality and a 34.1% prevalence of poor daytime functioning in the last 4 weeks [23]. RTx recipients commonly also suffer from other sleep disorders, such as chronic insomnia (8%), poor sleep quality (30% - 34%), obstructive sleep apnea (27%), restless legs syndrome (4.5%) [24], and periodic limb movement [25]. Sleep-wake disturbances in RTx recipients are multifactorial.

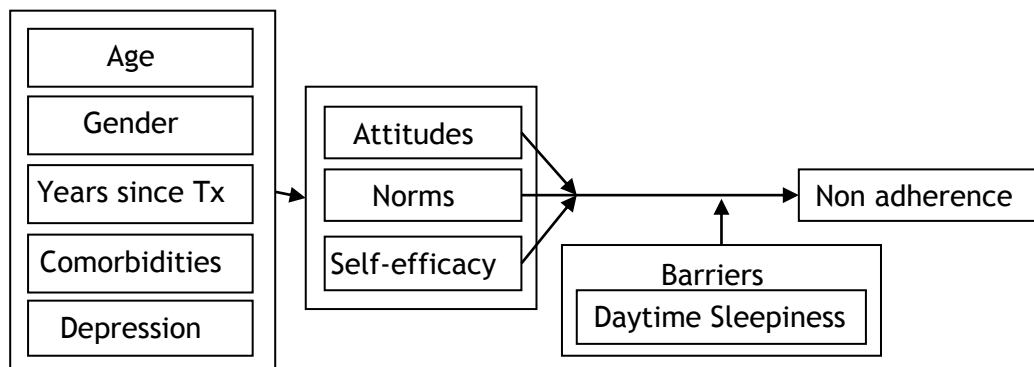
### **Theoretical Framework**

DS and NA have been positively associated in heart failure patients [26]. In these patients obstructive sleep apnea, disturbed sleep, impaired cognition and failure stage are the main determinants [27]. In RTx recipients the main determinates are unknown. RTx recipients follow a lifelong immunosuppressive treatment, to inhibit or prevent activity of the immune system. NA to immunosuppressive has very little forgiveness (NA >5% of doses not taken, resulted in a higher risk of acute rejection rate) [28], therefore factors (i.e.: DS) hindering adherence have to be quantified in RTx recipients as well as the impact on an important outcome variable: immunosuppressive non-adherence to plan targeted interventions.

To consider DS as a factor for medication NA [29] we used our adaptation of the Integrated Model of Behavioral Prediction (IMBP) [30], based on our previous work employing the IMBP to assess NA-associated variables in RTx groups [31]. Previous research has suggested that most NA in RTx is accidental (non-intentional) [32, 33]. As a non-intentional risk factor for NA, however, DS was not examined in these studies. The IMBP model posits that medication non-adherence results from intentional and unintentional cognitive factors and barriers [30]. In our adapted model, DS (a non-intentional tendency to fall asleep) is seen as a behavioral (unintentional) barrier to adherence (see Figure 1).



Figure 1: Theoretical model adapted from the Integrative Model of Behavioral Prediction - Schmid-Mohler et al.[31].



Using the IMBP, our aims were: (1) to describe the prevalence of NA, DS and depression in a cohort of RTx recipients, (2) to describe whether medication NA dimensions differed between RTx recipients with and without DS, and (3) to describe whether the degree of DS is associated with NA (controlling for age, gender, years since Tx, depression, and comorbidities).

### 4.3. Methods

#### Design, Setting and Sample

This study was a secondary data analysis using a cross-sectional multicenter design to gather data from a convenience sample of 926 home-dwelling RTx patients transplanted at three Swiss centers (parent study: Burkhalter et al.2013[34] ). For the parent study the ethic committee approved only the retrieval of the renal insufficiency cause, comorbid condition and immunosuppressive drugs. The inclusion criteria were: at least 6 months post-transplant with a functioning graft; ability to understand and read German; 18 years of age or older; and signed written informed consent. Individuals were excluded if: they were unable to complete the study questionnaires; participation was not approved based on a congruent evaluation (insufficient language proficiency, too ill to fill in a questionnaire or known cognitive impairments) by the responsible physician and the head nurse in charge of outpatient transplant follow-up care; or the patient was on dialysis.

#### Variables and Measurements

**Sample characteristics:** Age (in years), gender, years since transplantation and presence of comorbidities were retrieved from the participants' hospital charts. **Comorbidities** were assessed using the Charlson comorbidity index [35], which assigns weights to specific

diseases. The total score is calculated by adding the weights [35]. We examined every addressed patient's chart to determine whether any significant comorbidities were present.

### **Immunosuppressive non-adherence**

Medication adherence was assessed with three items of the Basel Assessment of Adherence Scale for Immunosuppressives (BAASIS), a self-report questionnaire assessing general medication adherence over the preceding month [36]. It assessed: taking NA (omission of single doses) and timing NA (timing deviations >2 h). These 2 items are rated on a 6-point ordinal scale: never (0), once per month (1), every second week (2), every week (3), more than once per week (4), and every day (5). Finally, a visual analogue scale (VAS) was used to assess patients' perception of their overall NA, ranging from 0% (never took medications as prescribed) to 100% (always took medications as prescribed). A prospective Italian study in liver Tx recipients (De Simone et al. University of Pisa, work in progress) supported the overall predictive validity of the BAASIS, while concurrent validity was demonstrated in Brazilian RTx recipients [37]. Dobbles et al (2010) compared the BAASIS with other adherence self-report instrument in Tx, showing positive results for this tool [36].

### **Daytime sleepiness**

Two measures were used to assess DS: the Swiss Transplant Cohort Study Daytime Sleepiness single-item scale (STCS-DS)[34] and the Epworth Sleepiness Scale (ESS)[11]. On the STCS-DS, study participants rated their DS over the past four weeks on a scale of 0 (no sleepiness) to 10 (extreme sleepiness). Its item response format was made congruent with the STCS sleep quality item [23]. Primary evidence supporting the validity of the STCS-DS has been developed by our research group [34]. Based on receiver operating characteristic analysis (using the ESS as gold standard), the recommended cutoff is  $\geq 4$  (details are described in Burkhalter et al. 2013 [34]).

The ESS is a validated eight-item questionnaire to measure a subject's expectation of dozing (falling into a light sleep) in eight hypothetical situations. Dozing probability ratings range from 0 (no probability) to 3 (high probability). An ESS total score  $\geq 6$  indicates DS [11]. A score  $\geq 10$  indicates that a person tends to become very sleepy and should seek medical advice [11]. Psychometric proprieties has been shown in English speaking populations: The ESS scores is reliable in a test-retest over a period of months ( $p < 0.001$ ); internal consistency is adequate Cronbach's  $\alpha = 0.88 - 0.74$  in 4 different groups of subjects and it has concurrent validity with self-rated problem sleepiness [38, 39]. In German-speaking populations [40] item analysis confirmed internal consistency of the scale (Cronbach's  $\alpha = 0.60$  in healthy adults, 0.83 in patients with various sleep disorders). The

item-to-total correlation ranged from 0.41 to 0.70. Test-retest reliability measured in a sample of 19 healthy subjects' obtained 5 months apart was acceptable with a mean difference in the total score of  $0.3 \pm 2.5$  (p: non-significant) [40].

### **Depression**

Depression was measured with the Depression, Anxiety and Stress Scale (DASS-21), a 21-item self-report instrument. Each component is measured with seven items [41] on a 4-point Likert-type severity/frequency scale rating the extent to which the patients have experienced each state over the past week (0 = did not apply to me; 3 = applied to me very much). Scores for depression, anxiety and stress are first summed, resulting in a range of 0 to 21 for each subscale. We evaluated results only for the DASS-depression (DASS-D) score (0-4 no depressive symptomatology; 5-6 mild, 7-10 moderate, 11-13 severe and 14 or more extremely severe symptomatology) [42]. The DASS-21 has strong construct validity, structure validity and concurrent validity [42]. To estimate a prevalence of depressive symptomatology we will adopt the cutoff  $>10$ .

### **Data Collection**

Addresses of all eligible patients were extracted from the transplant centers' databases. Each potential participant received a packet containing an information letter, consent form, pre-stamped, pre-addressed envelopes and the questionnaires. Participants returned the informed consent and the study questionnaires in separate envelopes to ensure anonymity.

Data were collected from the three centers sequentially, between December 2010 and September 2011 at the last center. Patients who had not responded within 2 months after their packets were sent, were called by a research associate to ask if they had received the materials and would still be willing to complete the questionnaire. Patients were called several times, after which they were categorized as not reachable. Packets that did not reach the patients, as they moved to another place, were sent to the new place if this was possible to track. If nobody knew where the patient moved to or if at this new place more than one had the same name, the packet was not sent. Ethics committees of the three transplant centers approved the study. Data were de-identified and stored in an electronic databank.

### **Statistical Analysis**

The categories of taking and timing NA were collapsed from 6 into 4 categories: never (0), once per month (1), every second week (2) and ranging from every week to every day (3) to have a meaningful sample size in each category. Descriptive statistics (means, standard

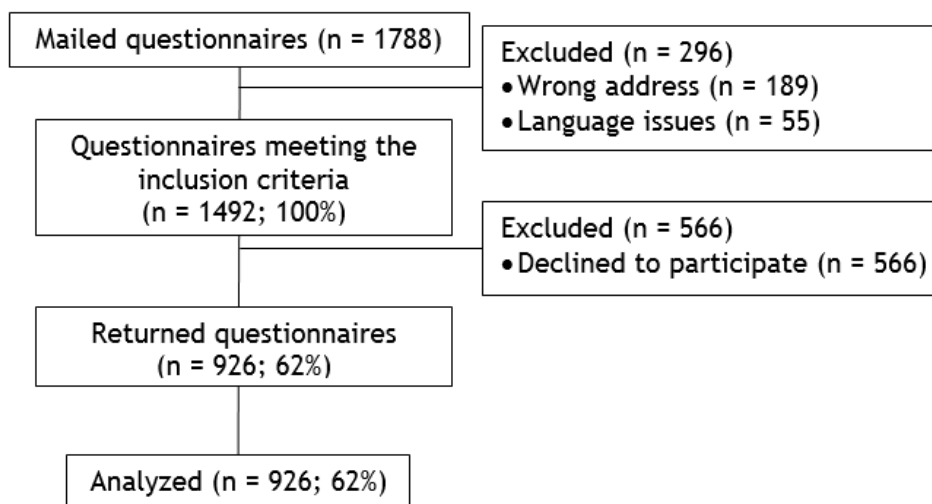
deviations (SD), medians, quartiles, frequencies) were used as appropriate for the measurement characteristics. The Mann-Whitney U and chi-squared tests (for nominal or dichotomous variables) were used to explore differences between participants and non-responders.

An ordinal logistic regression model was used to assess a possible association between DS and each of the 3 NA components (taking, timing and overall NA on the VAS), controlling for depression, comorbidities, gender, age and years since Tx. SPSS® Statistics software (Version 19.0.0, IBM Corporation, Somers NY) was used for statistical analysis, with all critical probability levels set to 5%.

#### 4.4. Results

Of the 1492 eligible patients, 926 returned completed questionnaires (response rate: 62%) (Figure 2). No significant differences on age, gender, year since transplantation and comorbidities were found between responders and non-responders. Analyses were based on 926 participants. Sample characteristics are displayed in Table 1.

Figure 2: Flow diagram of the sample



**Table 1:** Description of the sample

	Mean $\pm$ SD; Median (Q25-Q75); Percentage
<b>Characteristics (N = 926)</b>	
Males	63%
Age [Median (Q25-Q75)]	59.7 (50.26 - 67.77)
Years Tx <sup>£</sup> [Median (Q25-Q75)]	9.42 (4.93 - 15.85)
CCI >1*	52.9%
<b>Causes for renal insufficiency</b>	
Diabetic nephropathy	11.8%
Vascular nephropathy	9.4%
Chronic glomerulonephritis	24.0%
Interstitial nephropathy	12.1%
Cystic renal diseases	19.4%
System diseases	3.4%
Other causes	8.3%
<b>Most prevalent comorbid condition</b>	
Hypertention	85.6%
Acute myocardial infarction	4.8%
Congestive heart failure	33.2%
Peripheral vascular disease	9.5%
Liver disease	10.6%
Diabetes	17.9%
Diabetic complication	13.4%
Cancer	14.1%
<b>Immunosuppressive regimen</b>	
Cyclosporine	44.6%
Tacrolimus	40.5%
Sirolimus/Everolimus	8.8%
Mycophenolat mofetil	66.8 %
Azathioprine	15.8%
Corticosteroid	39.1%
<b>Daytime Sleepiness</b>	
ESS <sup>§</sup> $\geq$ 6	50.9%
ESS <sup>§</sup> $\geq$ 10	21.3%
STCS-DS <sup>+</sup>	40.7%
<b>Taking adherence</b>	
Never NA <sup>‡</sup>	84%
Once per month NA <sup>‡</sup>	10.5%
Every second week NA <sup>‡</sup>	3.5%
Every week to every day NA <sup>‡</sup>	1.9%
<b>Timing adherence</b>	
Never NA <sup>‡</sup>	57.9%
Once per month NA <sup>‡</sup>	14.4%
Every second week NA <sup>‡</sup>	20.4%
Every week to every day NA <sup>‡</sup>	7.3%
<b>Overall adherence</b>	
100% adherent	65%
90-99% adherent	26.5%
80-89% adherent	5.3%
70-79% adherent	1.6%
0-69% adherent	1.6%
<b>Depressive symptomatology<sup>⊗</sup></b>	33.7%

**Legend:** £= Years since the transplantation took place; \*= Charlson comorbidity index over 1 score point; §= Epworth Sleepiness Scale; += Swiss Transplant Cohort Study daytime sleepiness score; ‡ = Non-adherence; ⊗ = Depressive symptomatology based on the DASS-21 score

The prevalence of NA and ESS DS and STCS DS are displayed in Table 2. Both the ESS and the STCS-DS data indicated positive associations between DS and NA. Younger age was associated with timing and overall (VAS) NA and more years since transplantation was associated with higher NA and finally, the univariate analysis positively associated depression with timing NA (Table 2).

**Table 2:** Predictors of non-adherence in the univariate analysis

Univariate	Taking	p	Timing	p	VAS	p
	OR (CI 95%)		OR (CI 95%)		OR (CI 95%)	
Sex <sup>Δ</sup>	0.77 (0.53;1.11)	0.162	0.79 (0.61;1.03)	0.080	0.63 (0.47;0.84)	<0.001
Age/5 <sup>§</sup>	0.93 (0.87;1.00)	<b>0.047</b>	0.86 (0.82;0.91)	<0.001	0.86 (0.82;0.91)	<0.001
Years Tx/5 <sup>£</sup>	1.18 (1.08;1.29)	<0.001	1.14 (1.06;1.23)	<0.001	1.10 (1.02;1.19)	<b>0.010</b>
CCI <sup>*</sup>	0.97 (0.87;1.08)	0.625	0.94 (0.87;1.02)	0.129	1.02 (0.94;1.10)	0.628
ESS <sup>#</sup>	1.08 (1.04;1.13)	<0.001	1.08 (1.05;1.11)	<0.001	1.09 (1.05;1.12)	<0.001
STCS-DS <sup>+</sup>	1.13 (1.06;1.20)	<0.001	1.06 (1.01;1.11)	<b>0.027</b>	1.06 (1.01;1.11)	<b>0.030</b>
Depression <sup>&amp;</sup>	1.15 (1.00;1.33)	0.058	1.15 (1.03;1.28)	<b>0.010</b>	1.04 (0.93;1.17)	0.515

**Legend:** Δ= Reference category women =0; § = Age per 5 years; £ = Years since the transplantation took place per 5 years; \* = Charlson comorbidity index score; # = Epworth Sleepiness Scale score, + = Swiss Transplant Cohort Study daytime sleepiness score, & = Depressive symptomatology based on the DASS-21 score

In the multivariate model including the ESS score for DS (Table 3) controlling for age, gender, years since transplantation, comorbidities and depression, for each additional scale point on the ESS, the odds for taking NA increased by 8% (1.08 [1.04-1.13]), the odds for timing NA increased by 7% (1.07 [1.03-1.10]) and the odds for overall NA increased by 9% (1.09 [1.05-1.13]). For each additional five years since the Tx took place, the odds for taking NA increased by 20% (1.20 [1.09-1.31]), the odds for timing NA increased by 19% (1.19 [1.10-1.29]) and the odds for overall NA increased by 16% (1.07 [1.07-1.25]). Older age was associated with a 7% higher chance for taking NA (0.93 [0.86-1.00]) and a 14% higher chance for timing NA and overall (VAS) NA (0.86 [0.82-0.91]). Male sex was associated with a 62% higher chance for overall (VAS) NA (1.62 [1.19-2.21]).

**Table 3:** Predictors (including DS measured with the ESS) of non-adherence in the multivariate analysis

Multivariate	Taking OR (CI 95%)	p	Timing OR (CI 95%)	p	VAS OR (CI 95%)	p
Sex <sup>Δ</sup>	1.23 (0.82;1.83)	0.313	1.25 (0.94;1.65)	0.129	1.62 (1.19;2.21)	<b>0.002</b>
Age/5 <sup>§</sup>	0.93 (0.86;1.00)	<b>0.044</b>	0.86 (0.82;0.91)	<b>&lt;0.001</b>	0.86 (0.81;0.91)	<b>&lt;0.001</b>
Years Tx/5 <sup>£</sup>	1.20 (1.09;1.31)	<b>&lt;0.001</b>	1.19 (1.10;1.29)	<b>&lt;0.001</b>	1.16 (1.07;1.25)	<b>&lt;0.001</b>
CCI*	0.97 (0.87;1.08)	0.580	0.92 (0.85;1.00)	0.053	1.03 (0.95;1.12)	0.494
ESS <sup>#</sup>	1.08 (1.04;1.13)	<b>&lt;0.001</b>	1.07 (1.03;1.10)	<b>&lt;0.001</b>	1.09 (1.05;1.13)	<b>&lt;0.001</b>
Depression <sup>&amp;</sup>	1.07 (0.91;1.25)	0.440	1.09 (0.96;1.23)	0.176	0.95 (0.83;1.08)	0.439

**Legend:** Δ= Reference category women =0; § = Age per 5 years; £ = Years since the transplantation took place per 5 years; \* = Charlson comorbidity index score; # = Epworth Sleepiness Scale score, & = Depressive symptomatology based on the DASS-21 score

In the multivariate model including the STCS-DS item for DS (Table 4) controlling for age, gender, years since transplantation, comorbidities and depression, for each additional scale point on the STCS-DS scale, the odds for taking NA increased by 13% (1.13 [1.05-1.21]), the odds for timing NA increased by 5% (1.05 [0.99-1.10]) and the odds for overall (VAS) NA increased by 7% (1.07 [1.02-1.14]). For each additional five years since the Tx took place, the odds for taking NA increased by 18% (1.18 [1.08-1.30]) the odds for timing NA increased by 18% (1.18 [1.09-1.27]) and the odds for overall NA increased by 14% (1.14 [1.06-1.23]). Older age was associated with a 14% higher chance for timing NA and 14% higher chance for overall (VAS) NA (0.86 [0.81-0.91]). A 1-point increase in the depression score was associated with a 13% higher chance of timing NA (1.13 [1.00-1.27]). Male sex was associated with a 68% higher chance for overall (VAS) NA (1.68 [1.23-2.28]).

**Table 4:** Predictors (including DS measured with the STCS-DS) of non-adherence in the multivariate analysis

Multivariate	Taking OR (CI 95%)	p	Timing OR (CI 95%)	p	VAS OR (CI 95%)	p
Sex <sup>Δ</sup>	1.30 (0.88;1.94)	0.191	1.30 (0.98;1.73)	0.065	1.68 (1.23;2.28)	<b>&lt;0.001</b>
Age/5 <sup>§</sup>	0.93 (0.86;1.00)	<b>0.045</b>	0.86 (0.82;0.91)	<b>&lt;0.001</b>	0.86 (0.81;0.91)	<b>&lt;0.001</b>
Years Tx/5 <sup>£</sup>	1.18 (1.08;1.30)	<b>&lt;0.001</b>	1.18 (1.09;1.27)	<b>&lt;0.001</b>	1.14 (1.06;1.23)	<b>&lt;0.001</b>
CCI*	0.96 (0.86;1.08)	0.497	0.92 (0.85;1.00)	0.052	1.03 (0.94;1.11)	0.557
STCS-DS <sup>+</sup>	1.13 (1.05;1.21)	<b>&lt;0.001</b>	1.05 (0.99;1.10)	0.102	1.07 (1.02;1.14)	<b>0.013</b>
Depression <sup>&amp;</sup>	1.08 (0.93;1.27)	0.315	1.13 (1.00;1.27)	0.052	0.99 (0.87;1.13)	0.871

**Legend:** Δ= Reference category women =0; § = Age per 5 years; £ = Years since the transplantation took place per 5 years; \* = Charlson comorbidity index score; + = Swiss Transplant Cohort Study daytime sleepiness score, & = Depressive symptomatology based on the DASS-21 score

## 4.5. Discussion

The major finding of this study was that DS was significantly positively associated with taking, timing, and overall NA. With 926 patients from a multicenter setting, this is, to our knowledge, the largest sample in which DS in RTx recipients has ever been studied.

The prevalence of NA (Table 2) is comparable with data from other studies [30] confirming that the magnitude of NA is substantial (Table 1) in RTx recipients [31]. An estimate of 20% of late acute rejections and 16% of graft losses are associated with NA [28]. The current study's DS prevalence, as assessed with the ESS, was 50.8% using a cut-off of  $\geq 6$  and 21.3% with a cut-off of  $\geq 10$ . This prevalence is higher than in the general population, which ranges from 1.4% [19] to 8% [20], yet lower than those reported (ESS cut-off  $\geq 10$ ) in other chronically ill populations, e.g., hemodialysis (27%) [21], heart failure (23.6%) [43], gastroesophageal reflux disease (48.8%) [44] and primary biliary cirrhosis (51%) [9]. Our multivariate model showed that higher DS scores were associated with more immunosuppressive NA. Based on our theoretical model [30] (Figure 2), these findings support the premise that DS is a non-intentional barrier to adherence.

Table 4 showed 13% greater odds of being non-adherent in the drug taking, the statistical significance seems very small, though the clinical significance appears to be more impressive. A patient reporting a score of 4 on the STCS-DS (no daytime sleepiness), compared to a patient with a score of 8 has a 52% greater odds of being non-adherent (4 times 13%).

The time investment of screening a patient with a scale from 0 to 10 for DS is worth compared to the costs related to the consequences of NA [28]. The current literature highlights the importance of adherence to avoid graft rejection [2], therefore minimizing the risk for NA, will reduce the risk for acute rejection [45].

In the multivariate analysis, depressive symptomatology was associated with timing NA, showing independent predictability. In our data the prevalence for depressive symptomatology were higher (not significant) in the group of patients having DS. One criterion for major depressive disorder is "insomnia or hypersomnia nearly every day" [46]. Hypersomnia, a condition of DS, may appear before the patient meets the full diagnostic criteria for depression [47]. When it is a symptom of depression, DS creates distress and disrupts social functionality [48]. This is highlighted by an epidemiological study where sleep durations of less than 6 hours or more than 8 hours were associated with depression [49].



Length post transplantation in years, was positively associated with taking, timing and overall NA, confirming published findings [50-52].

### **Limitations**

The primary limitation of this study was the cross-sectional design, which allows the identification of associations but does not infer causality. As cross sectional studies cannot differentiate cause and effects from simple associations, we base the interpretation of the results using the theoretical framework that guided our study as a basis. Further, it was a secondary data analysis not allowing including some relevant factors. There is a need for NA research including prospective longitudinal studies to assess the evolution of NA over time and causality among factors as well as research specifically developed to assess risk factors of NA thus including a comprehensive set of variables or combination of variables in the model to predict NA. Longitudinal prospective cohort studies especially would allow to study changes and trends of DS over time controlling for different characteristics.

Additionally, this study was a secondary data analysis limiting the number and kind of variables we could include in our analysis such as medical conditions leading to fatigue, medication contributing to sleepiness, forgetfulness, symptoms and sleep diagnoses.

A further limitation is the use of self-reported data on immunosuppressive medication non-adherence and DS. NA self-reports may be underestimated [53], DS may be overestimated, [54] and a social desirability bias is possible; however, self-reports are easy to complete, inexpensive, and feasible for large samples [36] .

Thirty eight percent were non-responders, this prevalence is considerably higher than the previous study on poor sleep quality done in one center [23]. Participation seemed to be influenced by familiarity with the investigator as patients that had to be called were irritated if they did not know the physician responsible for the study. To conclude, this study was useful in identifying associations that can be more rigorously studied using a cohort or a controlled study.

### **Conclusion**

While DS, as the main factor in our analysis, showed associations with taking, timing and overall NA, it is a symptom for which treatment is available if its underlying cause is known. The high prevalence of DS in RTx recipients suggests a need to assess and treat DS as a means for reducing the likelihood of NA [55].

Very specific treatments are available for DS, and may consist of antidepressants, a diet to reduce weight and sleep apnea symptoms, short daytime naps to counteract drowsiness, or sunlight exposure (respectively light therapy) to increase alertness and

synchronize the subject's internal clock with the external day-night cycle [56]. Above all, the patient must be addressed as an individual, considering his predispositions and risk factors, to tailor an effective intervention. This means for the ambulatory follow-up care to inquire about sleep (i.e: using the STCS-DS screening tool) on a regular basis to detect sleep-wake problems. Interventions to prevent NA, focusing on DS as a non-intentional behavior, include implementing reminder systems, increasing social support, encouraging self-monitoring, and, if possible, simplifying the medication regimen's complexity [57].

### **Acknowledgement**

We gratefully acknowledge all the volunteers who helped with data collection, and the ambulatory care teams of the University Hospitals of Basel, Bern and Zürich for their excellent collaboration regarding information transfer. Further, we would also like to cordially thank C. Schultis for medical editing.

### **Transparency declaration**

The results presented in this paper have not been published previously in whole or part, except in abstract format: Burkhalter H., et al. *Daytime Sleepiness Associated with Immunosuppressive Non-Adherence in Renal Transplant Recipients: A Cross-Sectional Multi-Center Study*. in *44th Annual meeting of the Swiss Society of Nephrology 2012*. Kongresshaus Zürich, Switzerland: Swiss Medical Weekly.

This study was funded by a research grant from the Swiss Renal Foundation (Alfred and Erika Bär-Spycher Foundation) and an International Transplant Nurse Society research grant award. There are no conflicts of interest.

### **Authors' contributions**

H.Burkhalter, A.Wirz-Justice and S.De Geest designed the study, analyzed the data and wrote the paper. All other co-authors reviewed and gave input. C.Cajochen and T.Weaver contributed to daytime sleepiness background knowledge. H.Burkhalter, J.Steiger, T.Fehr and RM Venzin collected the data in the three centers

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# CHAPTER 5

## SELF-REPORTED SLEEP DISTURBANCES IN RENAL TRANSPLANT RECIPIENTS



## Self-reported Sleep Disturbances in Renal Transplant Recipients

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Reference:

Burkhalter, H., Brunner, D.P., Wirz-Justice, A., Cajochen, C., Weaver, T., Steiger, J., Fehr, T., Venzin, RM., De Geest, S. (2013). Self-reported Sleep Disturbances in Renal Transplant Recipients *BMC Nephrology*, 14(220), 1-12.

## 5.1. Abstract

### Background

Poor sleep quality (SQ) and daytime sleepiness (DS) are common in renal transplant (RTx) recipients; however, related data are rare. This study describes the prevalence and frequency of self-reported sleep disturbances in RTx recipients.

### Methods

This cross-sectional study included 249 RTx recipients transplanted at three Swiss transplant centers. All had reported poor SQ and / or DS in a previous study. With the Survey of Sleep (SOS) self-report questionnaire, we screened for sleep and health habits, sleep history, main sleep problems and sleep-related disturbances. To determine a basis for preliminary sleep diagnoses according to the International Classification of Sleep Disorders (ICSD), 164 subjects were interviewed (48 in person, 116 via telephone and 85 refused). Descriptive statistics were used to analyze the data and to determine the frequencies and prevalences of specific sleep disorders.

### Results

The sample had a mean age of 59.1 +/- 11.6 years (60.2% male); mean time since Tx was 11.1 +/- 7.0 years. The most frequent sleep problem was difficulty staying asleep (49.4%), followed by problems falling asleep (32.1%). The most prevalent sleep disturbance was the need to urinate (62.9%), and 27% reported reduced daytime functionality. Interview data showed that most suffered from the first ICSD category: insomnias.

### Conclusion

Though often disregarded in RTx recipients, sleep is an essential factor of wellbeing. Our findings show high prevalences and incidences of insomnias, with negative impacts on daytime functionality. This indicates a need for further research on the clinical consequences of sleep disturbances and the benefits of insomnia treatment in RTx recipients.

**Keywords:** renal transplantation, sleep disturbances, sleep quality, daytime sleepiness

## 5.2. Background

Poor sleep quality is common among renal transplant (RTx) recipients, with a prevalence ranging from 30% to 62% [1-4] as measured using the Pittsburgh Sleep Quality Index (PSQI). Subjective sleep quality (SQ) is an evaluation of sleep by the affected individual [5], covering elements such as total sleep time, sleep onset latency, total waking time, sleep efficiency and disruptive events. Daytime sleepiness (DS) involves difficulty maintaining a desired level of wakefulness, i.e., the feeling of drowsiness with a tendency to doze [6].

One cross-sectional study using the PSQI in a Swiss transplant center reported a poor SQ prevalence of 47.4% [7]. As measured using the Epworth Sleepiness Scale (ESS), [8] data from three Swiss transplant centers showed a prevalence of 52% for poor SQ [8] and 50.9% for daytime sleepiness (DS). Most cross-sectional studies suggest that poor SQ is higher pre-RTx (49%-78% [3, 9, 10]) than post-RTx (30%-52% [1, 11]). Similarly, insomnia (difficulty falling asleep, staying asleep, waking up before the desired time and being left tired during the day) in RTx candidates [12] has a prevalence of 15% in patients on maintenance dialysis, compared to 8% post-RTx [13]. Post-RTx SQ remains constant [14]. Supporting these findings, Sabbatini et al. (2005) showed that sleep significantly improved from pre- (PSQI mean:  $8.52 \pm 3.81$ ,  $P < 0.001$ ) to post-RTx (PSQI mean:  $6.46 \pm 3.71$ ,  $P < 0.001$ ), although it remained higher than in control subjects ( $3.54 \pm 1.61$ ,  $P < 0.0001$ ) [3]. Finally, poor SQ has been linked to pre-RTx impaired health status [14, 15], with post-RTx health status improving alongside SQ [13, 16].

The most frequent sleep disorders among hemodialysis patients are conditioned insomnia (unconscious association of bedtime with negative feelings), obstructive or central sleep apnea (repeated cessation of breathing during sleep), restless leg syndrome (an irresistible urge to move the legs) and periodic limb movement disorder (involuntarily limb movements) [17]. In patients with end-stage renal disease, several uremic and non-uremic factors are thought to contribute to the pathogenesis of sleep disorders [17]. Sleep apnea appears to be related to displacement of fluids which destabilize the control of breathing and narrow the upper airway [18]. Restless leg syndrome and periodic limb movement disorders are correlated with anemia, iron deficiency, and peripheral and central nervous system abnormalities. Therefore, most such disorders improve post-RTx [18]. Excessive daytime sleepiness occurs in approximately 50% of patients with end-stage renal disease [19], the etiology of which appears related to both uremia and sleep fragmentation [19].

Self-report screening questionnaires to assess sleep problems are an efficient preliminary step in a sleep diagnostic process before the first assessment interview. However,

screening survey data analyses cannot do more than generally categorize sleep complaints. A detailed diagnosis of a sleep disorder requires sleep experts and specific diagnostic tools. In sleep medicine, diagnosis follows the International Classification of Sleep Disorders (ICSD), which groups disorders into eight categories: (1) Insomnias; (2) Sleep Related Breathing Disorders; (3) Hypersomnias (excessive daytime sleepiness); (4) Circadian Rhythm Sleep Disorders; (5) Parasomnias (strange movements, behaviors, emotions, perceptions, and dreams during sleep); (6) Sleep Related Movement Disorders; (7) Isolated Symptoms, Apparent Normal Variants and Unresolved Issues; and (8) Other Sleep Disorders [20]. ICSD diagnosis guidelines require a clinical assessment interview and may specify diagnostic tools (e.g., polysomnography [21] or biophysiological measurement [22]) to differentiate sleep disorders from others with similar symptoms.

In summary, sleep quality normally improves after RTx; [3] however, a high proportion of the current study's RTx recipients were still suffering from sleep disorders several years post-Tx[8]. Prior to this study, no self-reported data existed on sleep disturbances among (post-Tx) RTx recipients. Therefore, the aims of this study were:

1. to describe the frequency of self-reported sleep disturbances in RTx recipients screened with the Survey of Sleep (SOS); and
2. based on structured sleep assessment interviews, to measure the prevalence of sleep disorders in RTx recipients.

### 5.3. Methods

#### Design, Setting and Sample

This study used a sequential cross-sectional multicenter design with a sample of 249 adult home-dwelling RTx patients, all of whom were participating in a larger study on sleep and daytime sleepiness. The inclusion criteria were: (1) RTx took place at one of the three participating Swiss transplant centers, (2) a functioning renal graft at least 6 months post-Tx, (3) the ability to understand and read German, (4) 18 years of age or older, and (5) participation in the preceding study with poor SQ (PSQI >5 [23]) and / or DS (ESS > 6 for increased DS [24]) scores. Candidates were excluded if they were undergoing dialysis or had not signed the written informed consent form.

The stage sampling approach used was based on candidates' PSQI and ESS scores, both of which were assessed as a part of the larger study [8]. The PSQI is a self-rated questionnaire consisting of 19 items, assessing a wide variety of factors related to sleep quality over a 1 month period, including estimates of sleep duration and latency, and of the frequency and

severity of specific sleep-related problems. These 19 items are grouped into seven component scores, each weighted equally on a 0-3 scale. The seven component scores are then summed to yield a global PSQI score, which has a range of 0-21; higher scores indicate worse sleep quality. A cut-off of > 5 points is used to classify patients as having poor sleep quality [23]. The *ESS* is a validated eight-item questionnaire to measure a subject's expectation of dozing (falling into a light sleep) in eight hypothetical situations. Dozing probability ratings range from 0 (no probability) to 3 (high probability). An *ESS* total score  $\geq 6$  indicates DS [25]. A score  $\geq 10$  indicates that a person tends to become very sleepy and should seek medical advice [25]. All 249 provided self-reported Survey of Sleep (SOS) data; a sub-sample (n=164) additionally participated in a sleep assessment interview (83 declined participation).

### Variables and Measurements

**Age** (in years), **gender**, **years since transplantation**, **body mass index** ( $\text{kg}/\text{m}^2$ ), **creatinine** ( $\mu\text{mol}/\text{l}$ ), **hemoglobin** ( $\text{g}/\text{l}$ ) and **drugs** (including sleep drugs) were retrieved from the participants' hospital medical charts. **Comorbidity** data were also extracted from patients' charts and categorized using the Charlson comorbidity index [26], which assigns various weights to specific conditions. Each of the 19 noted conditions was assigned a score of 1, 2, 3, or 6, depending on the associated mortality risk. For each patient the scores were summed to provide his or her overall comorbidity score [26]. Sleep quality and daytime sleepiness was extracted from the preceding study and categorized in three groups: 1)  $\text{PSQI} \leq 5$  (good SQ) &  $\text{ESS} \geq 6$  (DS); 2)  $\text{PSQI} > 5$  (poor SQ) &  $\text{ESS} < 6$  (no DS); 3)  $\text{PSQI} > 5$  (poor SQ) &  $\text{ESS} \geq 6$  (DS).

### Survey of Sleep (SOS)

The self-reported **Survey of Sleep (SOS)** questionnaire was developed at the University of Pittsburgh and translated into German by the second author. It is often used to report sleep symptoms in insomnia patients, [22] and studies often employ it as a preparatory step before carrying out sleep assessment interviews [27, 28]. The questionnaire consists of 7 sections: (1) **sleep overview** (existence of problem(s) (yes/no), general sleep problem (main complaint); duration (less/more than 1 year), course (getting worse, same, better, irregular), and frequency of the sleep problem (once/month, several times/week, nightly)); (2) **sleep habits** (including bedtime, get-up time and sleep latency in hours and minutes, whether the subject sleeps better in another location (yes/no), regularity of bedtimes (yes/no); (3) **sleep disturbances** (sleep-related symptoms and a list of 45 potential disturbances); (4) **daytime function** (typical feelings on getting up (energetic, optimistic, refreshed, low energy, irritable, depressed, confused, anxious); nap behavior

(intentional or unintentional naps, dreaming during the naps (yes/no), feeling more alert after the nap (yes/no), daytime function (sleepiness (not at all, slightly, moderately, extremely), accidents because of sleepiness (yes/no), fatigue (not at all, slightly, moderate, extremely), having to close eyes during the day to relax (yes/no), impaired daytime function (yes/no), most functional period of the day (early or late morning, afternoon or evening; night; no particular time), (5) **health habits** (use of sleeping drugs (Yes /No), caffeine (amount in cups), nicotine (number of cigarettes per day), alcohol use (glass unit per day), (6) **sleep history** (select the main complaint); and (7) **medical history** (diagnoses, drugs) [29].

The estimated time necessary to complete the SOS is 30 minutes. There is no sum scoring of the items and as of the time of writing no validity or reliability measures are available for it, as it was developed as a guide for an sleep assessment interview and not as a diagnostic tool [22]. The complete Survey of Sleep (SOS) questionnaire is available on request from the second author.

### **Sleep assessment interview**

Data from the SOS were used to prepare and structure the sleep assessment interview. All responses indicating possible sleep disturbances were addressed and elaborated on in the interview, which was structured to follow the 7 SOS sections, and lasted approximately one hour. The information generated by the interview helped to exclude some sleep disorders; however, as no follow-up visits took place and no further sleep diagnostic measurements or tools were used, the given diagnoses according to the ICSD criteria [20] should be regarded as preliminary.

The interviewer (first author) was trained to perform sleep assessment interviews by a certified sleep specialist and somnologist at the Hirslanden Sleep Disorders Center in Zollikon, Switzerland. This training included an overview of sleep disorders and of the techniques used to diagnose them. The second author checked a random sample of the completed interview transcripts and evaluated the comprehensive justification (to provide inter-rater reliability) of the preliminary sleep diagnoses. He also provided back-up assistance in view of resolving difficulties in assessment or categorization of sleep disorders.

### **Data Collection**

Patients were informed at the start of the research project [8] that they might be invited for a further screening and assessment if their initial data indicated poor SQ and/or DS (see flowchart, figure 1). Each such patient received a package containing an information

letter, informed consent documents, a pre-stamped return envelope and the Survey of Sleep questionnaire (SOS). Candidates were included in the study if they signed the informed consent form, completed the SOS and returned the documents.

Data collection started in June 2011 at the first transplant center and ended in June 2012 at the third. Patients who had not responded within 2 months of the document mailings were contacted by phone to ask whether they had received the material and would still be willing to complete the questionnaire. Each eligible patient (N= 249) was contacted to set up a sleep assessment meeting, which could be conducted either in person or via telephone. Only 48 agreed to in-person interviews; 116 agreed to a phone interview. After 10 unsuccessful call attempts, the patients were categorized as unreachable or it was noted that they had declined to participate (n=85). According to each participant's wishes, the first author either met him/her at a predetermined place or called at the predetermined time.

The study was approved by the ethics committees of all three transplant centers (Ethikkommission beider Basel; Kantonale Ethikkommission Bern; Kantonale Ethikkommission Zürich). Data were anonymized following the interview and stored in an electronic databank. Participants given preliminary diagnoses were encouraged to consult their nephrologists regarding their sleep problems. Any patient who wished also received a list of certified sleep disorder centers in Switzerland for further examination and treatment.

### **Statistical Analysis**

Descriptive statistics (means, standard deviations (SD), medians, quartiles, and frequencies) were used as appropriate, based on measurement levels and variable distributions. Likewise, comparisons between respondents and non-respondents were performed via t-test, Goodman and Kruskal's gamma test, or Mann-Whitney U test. Missing values were left blank and analysis was performed on the values given. SPSS® Statistics software (Version 19.0.0, IBM Corporation, Somers NY) was used for statistical analysis, with all critical probability levels set to 5%.

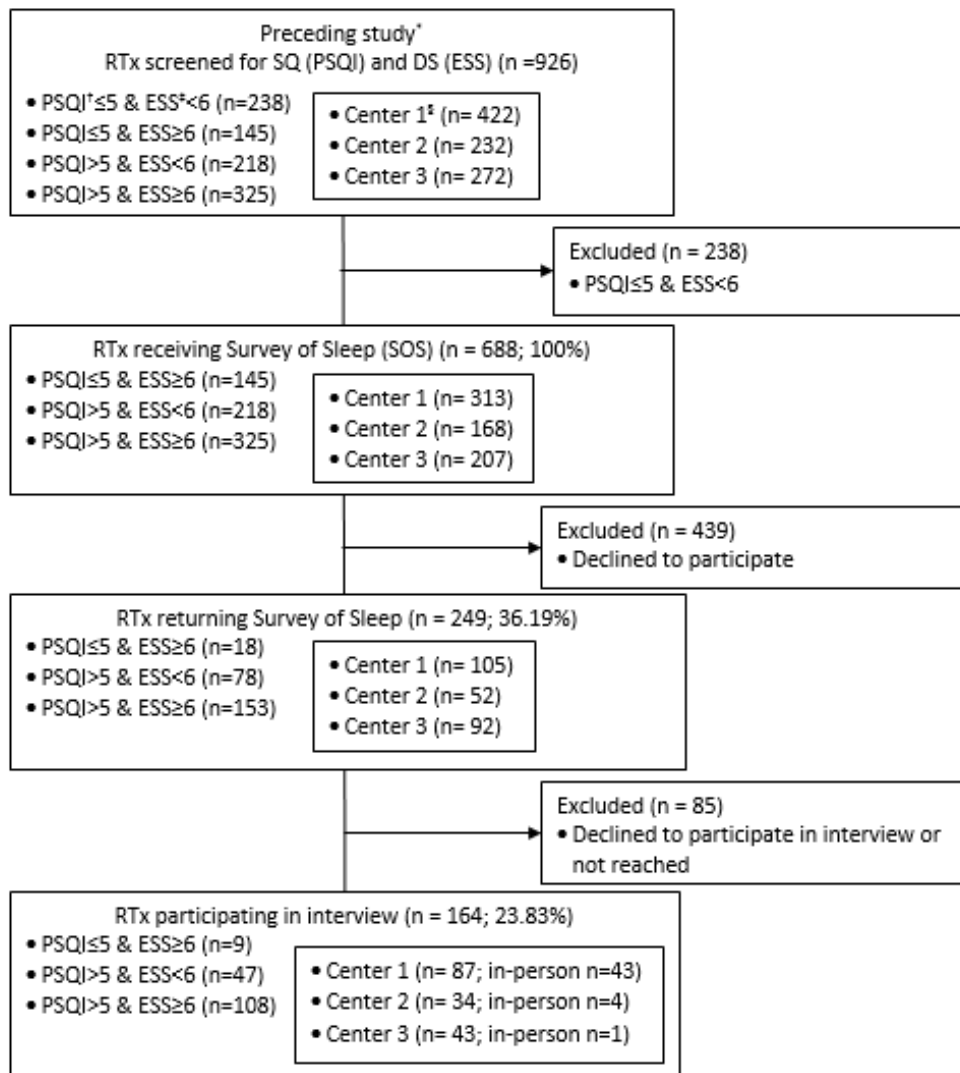
## **5.4. Results**

Of 688 RTx recipients invited to participate in this study, 249 (36.2%) agreed. Of 145 RTx with  $PSQI \leq 5$  (good SQ) &  $ESS \geq 6$  (excessive DS), 18 (12.41%) participated; of 218 with  $PSQI > 5$  &  $ESS < 6$ , 78 (35.78%) participated; and of 325 with  $PSQI > 5$  &  $ESS \geq 6$ , 153 (47.08%) participated (Figure 1). Participants did not differ significantly from non-participants regarding age, gender, years since transplantation, comorbidities or daytime sleepiness.

However, poor SQ (PSQI score  $>5$ ) was significantly more prevalent among participants (Gamma: 479, df: 48;  $p= 0.0001$ ). Of the 249 participants who filled in the SOS questionnaire, 164 (65.8%) participated in the subsequent sleep interview (Figure 1). The patients with PSQI $>5$  (poor SQ) & ESS  $\geq 6$  (excessive DS) scores also had the highest participation rate in the assessment interview (65.8%). Most in-person sleep assessment interviews ( $n=43$ ) were performed with patients from center 1 in connection with a nephrology follow-up visit, where the first author has a clinical position. Participation in the sleep interview was much lower for patients in centers 2 and 3, as each interview required 1-4 hours of travel either for the patient or for the interviewer, and no possibilities existed to connect the interviews with nephrology follow-ups.



Figure 1: Flowchart of the sample



**Legend:** † = Pittsburgh Sleep Quality Index (cutoff for poor SQ >5); ‡ = Epworth Sleepiness Scale (cutoff for increased DS ≥6); § = Center 1,2,3 = Numbering of the three participating swiss transplant centers; \* = Burkhalter H., et al., *Validity of a single item to assess daytime sleepiness for the Swiss Transplant Cohort Studys*, Prog Transplant, 2012. in press.

The participants had a mean age of 59.1±11.6y; 60.2% were male and the mean time since RTx was 11.1±7.0 years (Table 1). Immunosuppressive therapy, sleep drugs and co-medications, health habits and sleep history data are listed in table 1. Sleep drug frequency, as noted in the nephrology charts, was 1.6% for benzodiazepines and 2.0 % for other sleep drugs. The prevalence of self-reported sleep medication in the SOS was 32.9%.

**Table 1:** Characteristics of the sample [chart review and SOS part 5 (health habits), 6 (past sleep history) & 7 (medical history)]

<b>All (N=249)</b>	<i>Frequency</i>	<i>Percentage</i>
Male	151	60.2
	<i>Mean</i>	<i>Std</i>
Age in years	59.6	12.1
Years since RTx	11.1	7.0
Body Mass Index (kg/m <sup>2</sup> )	25.9	5.2
Creatinine (µmol/l)	125.0	81.6
Haemoglobin (g/l)	127.6	16.5
	<i>Median</i>	<i>(25Q-75Q)</i>
Charlson Comorbidities Index	1	0-2
<b>Immunosuppressive drugs</b>	<i>Frequency</i>	<i>Percentage</i>
Cyclosporin	103	41.4
Tacrolimus	93	37.3
Sirolimus, Everolimus	23	9.2
Mycophenolat	152	61.0
Azathioprine	38	15.3
Corticosteroids	78	31.3
<b>Co-medication chart review</b>		
Statin	97	39.0
ACE inhibitor	61	24.5
Angiotensin receptor blocker	68	27.3
Calcium channel blocker	43	17.3
Beta blocker	92	36.9
Anticoagulants	58	23.3
Antidepressants	14	5.6
Diuretics	42	16.9
Sleep drugs	9	3.6
<b>Self-reported sleep drug use</b>	82	32.9
<b>Caffeine use (&gt;2cups/d)</b>	132	62.3
<b>Nicotine use</b>	31	12.4
<b>Alcohol use (&gt;1 glass/day)</b>	64	25.8
<b>Past sleep history</b>		
Insomnia	24	9.6
Sleepwalking	16	6.4
Bed-wetting	24	9.6
Talking in your sleep	29	11.6
Nightmares	21	8.4
Night terrors (screaming in the middle of the night and being difficult to awaken)	6	2.4
Head-banging or body rocking	8	3.2
Seizures during sleep, while falling asleep, or while waking up	5	2.0
Daytime sleepiness	12	4.8
Snoring	12	4.8
Breathing difficulties	5	2.0

*Frequencies and percentage of sleep problems and sleep habits [SOS part 1 & 2]*

The most frequent sleep problem was difficulty staying asleep (49.4%), followed by difficulty falling asleep (32.1%) (Table 2). Most RTx recipients (61.4%) had experienced their sleep problems longer than 2 years without change (45%) and for 43.8% the problems occurred every night.

**Table 2:** General description of the sleep problem [SOS part 1 (overview) & 2 (sleep habits)]

General sleep problem	<i>Frequency</i>	<i>Percentage</i>
Having an actual problem with sleep or wakefulness	179	69.1
<b>Main sleep problem</b>		
Difficulty falling asleep	83	32.1
Difficulty staying asleep	128	49.4
Awakening early and being unable to fall back asleep	76	29.3
Excessive long sleep at night	21	8.1
Unusual behavior or experiences during sleep (e.g., nightmares, sleepwalking)	30	11.6
Excessive sleepiness during waking hours	66	25.5
Other problems	34	13.1
<b>Judgment of the sleep problem</b>		
Intense severity of the sleep problem (or problems)	67	26.9
Intense amount of interference with ability to function at home, at work, and with other people	48	19.3
Fairly intense sleepiness before bedtime	127	51.0
Better sleep outside compared to the sleep at home	11	4.4
Having regular sleep times	192	74.1
<b>Times related to sleep</b>		
	<i>Mean</i>	<i>Std</i>
Bedtime during the week	22.6	0.9
Bedtime at weekends	23.2	1.3
Time of lights off during the week	22.9	1.1
Sleep latency	28.1	32.1
Frequencies of sleep interruptions	2.8	1.8
Sleep latency after interruptions	21.9	27.3
Wakeup time during the week	6.5	1.2
Sleep duration	6.4	1.5
Get up time during the week	6.9	1.1
Get up time at weekends	8.0	1.1
	<i>Frequency</i>	<i>Percentage</i>
<b>How long having sleep problem</b>		
Between 6 months and 2 years	74	29.7
Between 2 and 5 years	60	24.1
>5years	93	37.3
<b>Course of the problem</b>		
Becoming worse	15	6.0
Same	112	45.0
Improving	17	6.8
Irregular	79	31.7
Recurring regularly	8	3.2
<b>Frequency</b>		
Every day/night	109	43.8
Sometimes in a week	24	9.6
Sometimes in a month	31	12.4

*Frequencies and percentage of sleep symptoms [SOS part 3]*

Of 45 sleep-related symptoms, the most prevalent were the need to urinate (62.9%), leg cramps during sleep (37.8%), frequent tossing and turning in bed (37.1%), feeling too hot or too cold (33.2%) and awakening for no particular reason (29.7%) (Table 3).

**Table 3:** The 32 most prevalent sleep disturbances out of 45 [SOS part 3 (sleep disturbances)]

Sleep Disturbance of N=249	Frequency	Percentage
Need to urinate	163	62.9
Leg cramps during sleep	98	37.8
Frequent tossing and turning	96	37.1
Feeling too hot or too cold	86	33.2
Awaken for no particular reason (spontaneous awakenings)	77	29.7
Feeling anxious or emotionally tense, or worrying about things at bedtime	72	27.8
Physical nervousness and agitation in the evening or at night	68	26.2
Restless, uncomfortable, or "crawling" sensation in your legs during the evening or at night	62	23.9
Awakened by dreams (not nightmares)	56	21.6
Snoring	54	20.8
Feeling physically tense at bedtime	42	16.2
Awakening because of noise or light	38	14.7
Jerking or twitching in feet, legs, or arms during sleep	34	13.1
Large body jerks as you are falling asleep	33	12.7
Awakened by noises	32	12.4
Awakened by recurring dreams	31	12.0
Other pain during sleep	31	12.0
Muscle aches during or after sleep	30	11.6
Grinding teeth	26	10.0
Nightmares	26	10.0
Heartburns or other burning in chest, stomach	24	9.3
Headaches beginning during sleep	24	9.3
Palpitations, heart racing, or irregular heart beat	23	8.9
Other sleep disturbances	22	8.5
Talking in your sleep	19	7.3
Hallucinations as you are falling asleep or waking up, i.e., seeing or hearing things which turn out not to actually be real	15	5.8
Frequent cough	15	5.8
Episodes of confusion during sleep or upon awakening	14	5.4
Awakening choking, smothering, or gasping for air	13	5.0
Periods of not breathing during sleep	13	5.0
Difficulty breathing (including wheezing)	11	4.3
Difficulty swallowing	11	4.2

*Frequencies and percentage of daytime function [SOS part 4]*

At wake-up time in the morning, 68 participants (26.2%) felt low energy, while an equal number felt optimistic. Only 16.9% napped unintentionally during the day; 47.2% napped intentionally. Half (49.8%) of all nappers felt more alert after a nap. During the day, 16.1% felt extreme sleepy, 16.9% intensely fatigued and 27.8% impaired in their daytime functions (Table 4).

**Table 4:** Description of daytime function [SOS part 4 (daytime function)]

	<i>Frequency</i>	<i>Percentage</i>
<b>Typical feelings at awakening in the morning</b>		
Optimistic	68	26.2
Low energy	68	26.2
Energetic	44	17.0
Refreshed	28	10.8
Irritable	18	6.9
Other	17	6.6
Depressed	16	6.2
Anxious	14	5.4
Confused	4	1.5
<b>Nap behavior</b>		
Intentional napping	118	47.4
Unintentional napping	42	16.9
Falling 1-2 times a day asleep or nap during the day	62	24.9
Often dreaming when falling asleep or nap during the day	10	3.9
Feeling more alert and awake after falling asleep or nap	124	49.8
<b>Daytime function</b>		
Extreme amount of sleepiness during daytime	40	16.1
Had an accident because of sleepiness or falling asleep	11	4.4
Intense amount of fatigue during the day	42	16.9
Have to close eyes during the day to relax	78	31.3
Impaired daytime functioning because of nighttime sleep disturbances, daytime sleepiness or fatigue	72	27.8
<b>Best function during the day</b>		
Early morning	102	39.4
Late morning	83	32.0
Early afternoon	38	14.7
Late afternoon	41	15.8
Early evening	34	13.1
Late evening	18	6.9
During the night	4	1.5
No specific time	35	13.5

*Frequencies and percentage of preliminary sleep diagnoses according to the ICSD*

The most prevalent preliminary sleep diagnosis was chronic insomnia (42.5%), followed by circadian sleep-wake disturbances. Table 5 presents the preliminary sleep diagnoses based on a single assessment interview.

**Table 5:** Frequency of preliminary sleep diagnosis based on the interview grouped into the international classification of sleep disorders categories.

N= 164	<i>Frequency</i>	<i>Percentage</i>
<b>Insomnias</b>		
Psychophysiological insomnia or paradoxical insomnia	53	32.3
Adjustment insomnia	3	1.8
Inadequate sleep hygiene	5	3.0
Insomnia due to medical condition	9	5.5
<b>Sleep Related Breathing Disorders</b>		
Obstructive Sleep Apnea, Adult	8	4.9
Other Sleep Related Breathing Disorders	5	3.0
<b>Hypersomnias of Central Origin Not Due to a Circadian Rhythm Sleep Disorder, Sleep Related Breathing Disorder or Other Cause of Disturbed Nocturnal Sleep</b>		
Behaviorally induced insufficient sleep syndrome	11	6.7
Idiopathic hypersomnia with long sleep time	7	4.3
Hypersomnia due to drug or substance use	1	0.6
<b>Circadian Rhythm Sleep Disorders (CRSD)</b>		
CRSD delayed sleep phase type	22	13.4
CRSD advanced sleep phase type	3	1.8
CRSD irregular Sleep-Wake Type	8	4.9
<b>Parasomnias</b>		
Nightmare Disorder	4	2.4
Parasomnia due to drug or substances	4	2.4
Confusional Arousals	4	2.4
Parasomnia due to med conditions	2	1.2
<b>Sleep Related Movement Disorders</b>		
Isolated Symptoms, Apparent Normal Variants, and Unresolved Issues	1	0.6
<b>No presumed diagnosis</b>		
	0	0.0
Other Sleep Disorders	14	8.5

## 5.5. Discussion

To our knowledge, this is the first study to focus on sleep problems in RTx recipients by using a detailed sleep questionnaire (SOS) and subsequent sleep assessment interview. This study describes the frequency of self-reported sleep disturbances in RTx recipients screened with the Survey of Sleep questionnaire (SOS) and the frequency of presumed sleep diagnoses based on the sleep interview.

As shown in table 1, of the 688 patients invited to participate, roughly 50% (n=325) registered poor SQ and DS. Figure 1 shows an increasing proportion of participants in the “poor SQ (PSQI>5) & and DS (ESS≥6)” group. Of these 325, 153 (47.1%) filled in the SOS and 108 (70.6%) participated in the assessment interview. In addition, poor SQ was significantly more prevalent in participants compared to non-participants. This would support a

hypothesis that, even where no therapeutic benefit can be hoped for, patients are more likely to participate in studies directly relevant to their personal experience.

### **Prevalence and percentages of sleep problems and sleep habits [SOS part 1]**

The most prevalent sleep problem was difficulty staying asleep, followed by problems falling asleep. Both are characteristic of insomnia [20]. Other characteristics of insomnia common in this group were the extended duration of the sleep problem (61.4% reported durations greater than 2 years), the severity of the sleep problem (26.9% called their problems severe), the high prevalence of nightly sleeping pill use (32.9%), sleep latency of  $28 \pm 19.3$  minutes, a high number of awakenings ( $2.8 \pm 1.8$ ) per night, long sleep latency after awakening ( $21.9 \pm 16.4$  minutes), and high ratios of time in bed to hours of sleep ( $8.3 \pm 1.3$  hours) to hours of sleep  $6.4 \pm 1.5$ . These results corroborate those of Moul et al. (2002), [30] who reported that 68% of insomnia patients exhibited long-term sleep problems (more than 1 year), severe sleep problems (81%), high nightly use of sleeping pills (89%), long sleep latency ( $53.3 \pm 51.8$  minutes), high numbers of awakenings ( $2.7 \pm 1.7$ ) per night, long sleep latency after awakening ( $56.0 \pm 64.7$  minutes), and high ratios of time in bed to hours of sleep ( $8.2 \pm 1.9$  hours in bed:  $5 \pm 1.7$  hours of sleep). The average sleep duration of  $6.4 \pm 1.5$  is very low, as studies have shown that chronic restriction of sleep to 6 h or less per night produces cognitive performance deficits equivalent to up to 2 nights of total sleep deprivation [31]. Sleep deficits seriously impair waking neurobehavioral functions (lapses in behavioral alertness) in healthy adults [31].

### **Prevalence and percentages of sleep habits [SOS part 2]**

One third of participants ( $n = 82$ ) reported using sleeping pills; however, the medical chart data showed that very few ( $n = 9$ ) had informed their nephrologists regarding their sleep problems or use of sleep medication. During their post-transplant hospitalization, all RTx recipients receive education regarding over-the-counter medication and medication prescriptions from other physicians, during which they are advised always to consult their nephrologist about possible interactions with their immunosuppressive drugs [32]. This discrepancy may indicate that patients are reluctant to bring up sleep problems, that they do not see sleep disorders as a topic that nephrologists can deal with, or that the nephrologists themselves simply consider sleep disorders a normal side effect of RTx immunosuppressive regimens. Compared to the general population, our prevalence of 32.9% self-reported sleep medication use is very plausible: sleep medications are used regularly by 3.2% of subjects 44 or younger, 13.3% of subjects between 45 and 64, 22% of those between 65 and 74 and 32% of individuals 75 or older [33].

### Prevalence and percentage of sleep symptoms [SOS part 3]

The most prevalent night-time symptom was nocturia. The frequency of its occurrence is key to further diagnosis. Nocturnal polyuria (nocturnal urine overproduction) and diminished nocturnal bladder capacity [34] require further testing to exclude urinary tract infections and prostate hyperplasia [35]. Also very prevalent were leg cramps and frequent turning in bed, indicating muscle fatigue, nerve dysfunction or electrolytic imbalances [36]. However, these symptoms could also be indices of restless leg syndrome, periodic limb movements, myositis, or peripheral neuropathy [36]. Similarly, turning or rocking in bed could indicate parasomnia (undesirable physical or behavioral phenomena occurring during the sleep period) [37]. For the diagnosis of parasomnias a careful physical examination is crucial and often a polysomnogram, including an expanded electroencephalographic montage, is necessary to distinguish between parasomnias (non-REM or REM) and nocturnal seizures [37].

Leg cramps during sleep were the second most prevalent sleep symptom (37.8%), followed by frequent tossing and turning in bed (37.1%). These two symptoms could be related to restless leg syndrome and/or periodic limb movements. The prevalence of restless leg syndrome in RTx recipients overall is 4.5% [38]. For periodic limb movements the overall prevalence is unknown, although there is an improvement from pre- to post-Tx [39]. Nocturnal leg cramps are often associated with vascular disease, lumbar canal stenosis, cirrhosis and hemodialysis [36], however no prevalence is known for RTx recipients. The sensorimotor symptoms of restless leg syndrome and/or periodic limb movements can be treated with dopamine agonists, gabapentin and its derivatives, and opioids [40]. To summarize, in-depth assessment of all these listed symptoms is crucial for the right treatment choice.

### Prevalence and percentage of daytime function [SOS part 4]

Table 4 shows the high prevalence of daytime sleepiness, tiredness and impaired daytime functioning, highlighting the importance for affected patients to use reminders (e.g., pillbox alarms, SMS reminder functions, or other cues) to ensure punctual intake of their immunosuppressive drugs. An earlier study showed correlations between DS and impaired immunosuppressive medication adherence [41]. However, it is possible that compensating behaviors such as increased use of mild stimulants (e.g., caffeine, nicotine) (table 1) account for the lower prevalence of non-adherence (16%) than of DS (52%)[42].

Napping behavior and sleep duration depends on cultural, environmental, occupational and health factors [43]. In this study, 47.4% of participants reported intentional napping, a behavior shown to be protective against mortality [43]. However, a nap lasting several



hours [44] might interfere with nighttime sleep—a point which would have to be borne in mind while counseling patients regarding sleep hygiene. The ideal nap duration for adults is about 10-20 minutes and the timing depends on the quality of sleep duration the preceding night, amount of prior wakefulness and morningness-eveningness tendencies [45].

### **Prevalence and percentages of preliminary sleep diagnoses**

This study's most prevalent sleep diagnosis was chronic insomnia, followed by circadian rhythm sleep disorders. The prevalence of insomnia in the general population is 15 -20% [46] and prevalence of circadian rhythm sleep disorders ranges from 3.1% in adults aged 40-64 to 16% in adolescents [47]. Our prevalence of 42.6% insomnia and 20.1% CRSD is only partially comparable based on our group's pre-selection criteria (RTx recipients having poor SQ and /or DS). Various publications suggest RTx recipients' sleep disorders are related to medications (e.g.,  $\beta$ -blockers [48], nonsteroidal anti-inflammatory drugs [49], corticosteroids [50] and mycophenolic acid [51]) and other clinical conditions [52, 53]. Molnar et al. [54] list numerous potential causes of sleep disorders in this group, including pre-existing sleep disorders, transplant surgery, hospitalization, anxiety and uncertainty, fear of organ rejection, immunosuppressive medication, deteriorating kidney function and co-morbid medical conditions, psychosocial problems, psychiatric and neurological disturbances, lifestyle, diet, environmental factors and aging. With so many possible contributing factors, the most appropriate course of action might be a referral to a sleep expert, who could counsel the patient on the full range of behavioral and medical interventions available, and help them to choose those best suited to their needs [55]. Sleep interventions for RTx recipients are the same as for the general population, apart from the risk of interaction with immunosuppressive therapy and the need to consider the long-term side effects of their therapy (e.g., osteoporosis, new onset of diabetes, pain).

### **Limitation of this Study**

Since only 249 RTx recipients filled in the questionnaire, of which only 164 (65.9%) gave interviews, the generalizability of this study's findings are limited. In addition, the high prevalence of RTx recipients in the “poor SQ (PSQI>5) & excessive DS (ESS $\geq$ 6)” group showing an increasing proportion along the study steps, limits the significance and comparability of the presumed sleep diagnoses.

### **Suggested further research**

Further research will be necessary to develop safe interventions for RTx recipients with sleep-wake disturbances, taking into account their impaired renal function (limited organ

survival), high risk of skin cancer (a side-effect of immunosuppressive treatment) and need to adhere to their medication regimens (high risk of acute graft rejection). These interventions should include education [56] regarding sleep disorders and their negative health impacts. Apart from established cognitive and behavioral interventions for insomnia, new chronotherapeutics treatments, particularly bright light therapy and melatonin supplementation [57] should be investigated. For RTx recipients, who already have a high number of medications to ingest daily, light therapy might be a realistic intervention to stabilize sleep-wake rhythms compared to melatonin supplementation (one more drug to ingest).

### **Conclusion**

Our findings show high prevalence of insomnia and of impaired daytime functionality. This indicates a need for further research on the clinical consequences of sleep-wake disturbances and the benefits of insomnia treatment in RTx recipients.

### **Authors' contributions**

HB conceived the study with SDG, DB, AW, JS, TF, RMV and TW. HB coordinated the data collection with the three centers, HB collected the data with the physician of the center JS, TF and RMV. HB performed the sleep assessments with the expertise of DB. HB and DB drafted the article and all authors read and approved the final manuscript.

### **Transparency declaration**

The results presented in this paper have not been published previously. This study was funded by a research grant from the Swiss Renal Foundation (Alfred and Erika Bär-Spycher Foundation). The results presented in this paper have not been published previously.

This study was funded by a research grant from the Swiss Renal Foundation (the Alfred and Erika Bär-Spycher Foundation). There are no conflicts of interest.

### **Acknowledgement**

We gratefully acknowledge all of the volunteers and the ambulatory care teams of the University Hospitals of Basel, Bern and Zürich for their excellent collaboration. Further, we would also like to cordially thank C. Shultis for medical editing.

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# CHAPTER 6

## **SLEEP QUALITY IMPROVES AND PREDICTS HEALTH STATUS FROM PRE TO POST SOLID ORGAN TRANSPLANTATION: A PROSPECTIVE COHORT STUDY**

## Sleep Quality improves and predicts health status from Pre to Post Solid Organ Transplantation: A Prospective Cohort Study

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<sup>5</sup> This study has been conducted in the framework of the Swiss Transplant Cohort Study, supported by the Swiss National Science Foundation and the Swiss University Hospitals (G15) and transplant centers. Responsible for the Swiss Transplant Cohort Study: I. Binet (SNSF Board), HC Bucher (Epidemiology), L. Buhler (SNSF Board), C. van Delden (Executive office, SNSF Board), T. Fehr (SNSF Board), P Mohasci (SNSF Board), NJ Mueller (Chairman of the Scientific Committee, SNSF Board), M. Pascual (Executive office, SNSF Board), J. Passweg (SNSF Board), J Steiger (Executive office, SNSF Board).

**Funding source:** The Swiss Transplant Cohort Study is funded by a grant from the Swiss National Research Foundation (Grant number 3347CO-108795). This work is further supported by unrestricted research grants of Astellas (CH & Europe), Roche (CH) and Novartis (CH)

**Keywords:** Cohort study, Sleep quality, Solid organ transplantation

**Abbreviations:** SQ, Sleep Quality; Tx, Transplant; STCS, Swiss Transplant Cohort Study

## 6.1. Abstract

### Background:

Poor sleep quality (SQ) is a risk factor for poor clinical outcomes in solid organ transplant (Tx) recipients. The aim of this study was to describe the prevalence and variability of SQ from pre to post Tx simultaneously in kidney, liver, lung and heart recipients included in the Swiss Transplant Cohort study (a prospective nation-wide cohort study), and to test the predictability on health status.

### Methods:

SQ was assessed at pre-Tx, 6, 12 and 24 months post-Tx using a single question ranging from 0 (very poor) to 10 (very good), where the cut-off for poor SQ was  $< 6$ . Health status was assessed with the visual analogue scale from 100 (best) to 0 (worst). Random intercept regression analysis was used to identify statistically significant associations.

### Results:

1076 patients (age:  $52.4 \pm 13.1$  years; 65% males; 639 kidney, 215 liver, 126 lung, 96 heart) were included. Poor SQ decreased from pre-Tx (39.41%) to 12 months post Tx (24.75%) for all. Liver and heart recipients had the highest prevalence of poor SQ pre-Tx while all organs decreased to prevalence between 22-30% at 12 months and remained constant at 24 months except for lung recipients (42%). SQ significantly predicted patient's health status ( $p < .0001$ ).

### Conclusion:

SQ improved from pre-to post-Tx and SQ predicted health status.

## 6.2. Background

Sleep in the general population is a critical determinant of health and poor sleep has been associated with a wide range of health consequences [58] such as higher risk for cardiovascular disease [59], diabetes [60], and an increased mortality [61-63]. Short sleep (<5 hours) is associated with coronary artery calcification [64], an increased risk of overall cardiovascular events and myocardial infarction [65]. In hemodialysis patients poor sleep quality was a significant independent predictor for poor quality of life [66] and the relative risk of mortality was 16% higher for hemodialysis patients with poor sleep quality [9]. In solid organ transplant recipients only little is known.

Sleep quality (SQ) is defined as the excellence in sleep evaluated by the individual [5], covering a number of elements such as total sleep time, sleep onset latency, total wake time, sleep efficiency and disruptive events. In the general population between 7% to 40% reported poor SQ [67]. In renal transplant (RTx) recipients the prevalence of poor SQ ranges from 30% - 62% [1-4, 11, 14, 68] and from 51% to 77% in liver Tx (LiTx) recipients [69, 70]. For lung (LuTx) recipients only prevalence on sleep disordered breathing are available (36% [71] and 63% [72]) and for heart transplant (HTx) recipients only prevalence on obstructive sleep apnea (36% [73, 74] and 58% [75]) and prevalence on periodic limb movements (33% [73]) are available.

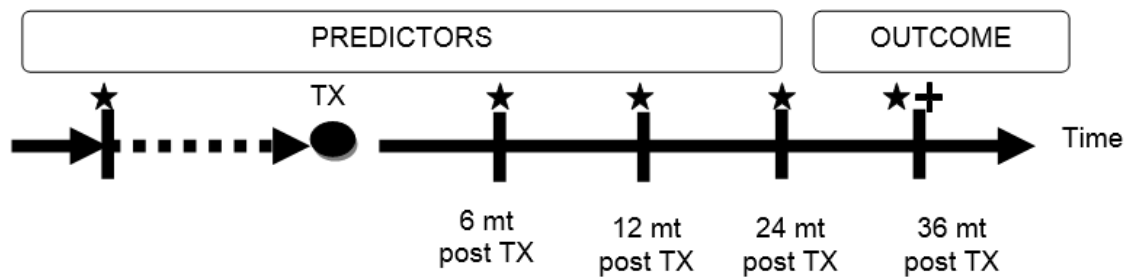
Further it is known that insomnia improves from pre to post RTx (15%-8%) [13] and fatigue decreases significantly from  $8.99 \pm 5.5$  pre to  $6.81 \pm 5.5$  post RTx [11]. There is a similar study in LiTx reporting an improvement of fatigue from 86 to 76% [70], however another prospective study reported a worsening from 60 to 62% [69]. Finally sleep disorder breathing in LuTx improved from 44% to 36% at post Tx [71]. Similarly, health status improved from pre to post renal [13, 14, 16] and liver [76] Tx. Health status is a generic measure of subjective perceived health [77]. For H-LuTx and LuTx recipients only post Tx numbers are available, indicating that health status is similar to the general population [52]. There is only one study that assessed SQ and health related quality of life at 6 and 12 months post RTx, revealing that SQ worsened from 36.7% to 38.3% and that health related quality of life decreased especially in the vitality and role emotional domains [14]. In addition when they compared good and poor they found that the poor sleepers had lower health related quality of life scores [14].

### Theoretical model

The theoretical framework guiding our study (Figure 1) indicates that different factors influence clinical Tx outcomes. This study focused on SQ as potential predictor of Tx

outcome (i.e: health status), based on previous research that already found this relation in hemodialysis patients [66]. In addition selected socio-demographic (age, gender, time since Tx) and psychosocial factors (depression) were included as potential confounders while exploring the relations between SQ and health status.

Figure 1: Theoretical model and design of the cohort study showing the evolution of sleep quality and depression as predictors for the outcome perceive health status.



Legend: ★=psychosocial questionnaire assessing sleep and depression; + psychosocial questionnaire assessing perceived health status

Depression needs to be controlled for in SQ analysis, as poor SQ is a symptom belonging to the diagnosis of depression [20]. There is evidence of high prevalence of depression after Tx [9% at 3 years post RTx [78], 30% 2 years post LuTx [79] and 26% 2 years post HTx [79], 29% 1-2 years post LiTx [80]] and higher depression levels were associated with a 3 to 4-fold increased risk of graft failure and mortality 18-months post-RTx [81].

Yet, sleep quality, health status and depression in all these cited studies were measured in a different way and with other measurement tools making comparisons across studies difficult. Prevalence data from all solid organ Tx group at pre and post Tx, as well as evolution data of SQ at different time point after Tx would strengthen enormously the evidence base in view of SQ as a predictor for health status in solid organ Tx recipients. The gap in the literature is that there are no studies assessing sleep longitudinally and in all solid organs populations simultaneously using the same methodology. The data of the Swiss Transplant Cohort Study provide a unique possibility to fill this gap in the literature.

### Study Aims

The aims of the study are therefore:

- (1) to describe the prevalence and evolution of SQ from pre Tx until 24 months post Tx in kidney, liver, lung and heart Tx recipients
- (2) to investigate differences in prevalence and evolution of SQ in kidney, liver, lung and heart Tx recipients groups within and across assessment times (pre Tx, 6, 12

and 24 months post Tx) controlling for age, gender, depressive symptomatology and the number of months between the pre Tx measurement and the Tx date, and

- (3) to determine if poor SQ is predictive with regard to health status across Tx groups and assessment times (pre Tx, 6, 12 and 24 months post Tx) controlling for age, gender, depressive symptomatology and the number of months between the pre Tx measurement and the Tx date.

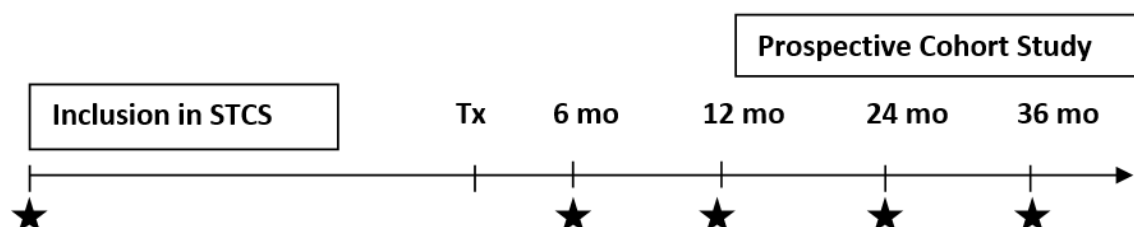
### 6.3. Material and methods

This study used the data from the Swiss Transplant Cohort Study (STCS). The STCS is a prospective open cohort study including all patients transplanted in Switzerland in one of the 6 Tx centers (Lausanne, Geneva, Basel, Zürich, Bern, St. Gallen). The STCS started patient enrollment and data collection on May 2<sup>nd</sup> 2008. Because all subjects receiving an organ qualify for enrollment in the STCS, no patient selection process is involved in the design [82, 83]. The STCS is unique as it includes not only a comprehensive set of biomedical and genetic data yet also includes a psychosocial data collection from pre to lifelong post Tx. SQ, health status and depressive symptomatology are parameters assessed in this regard. We used therefore data already collected by the STCS.

#### *Sample and Setting*

For this analysis we included all single first kidney, liver, lung, and heart Tx recipients till a re-transplantation, death, graft loss or drop-out, aged 18 years or older; German, French, English or Italian speaking; able to self-complete the STCS Psychosocial Questionnaire. For the analysis, we included only the patients who had complete data on SQ for at least two of five measurement times (pre Tx, 6, 12, 24 and 36 months post Tx) (Figure 2).

**Figure 2:** Design of Swiss Transplant Cohort Study in view of sleep quality



Legend: ★ =psychosocial questionnaire assessing for example sleep and depression

## Variables and Measurements

As mentioned, the STCS collects biomedical and psychosocial variables [83]. The psychosocial questionnaire data collection points are: pre Tx at time of listing (or inclusion in STCS for patients already on the waiting list on May 2<sup>nd</sup> 2008); at 6 months post Tx, 1 year post Tx and yearly thereafter.

### *Socio-demographic variables*

Demographic characteristics as *age* (in years) and *gender* and clinical variables (*transplanted organ type*) were abstracted from the STCS database. Other socio-demographic factors were assessed by the psychosocial questionnaire including educational level and living situation.

### *Sleep quality*

*Sleep quality* (SQ) was assessed with one item derived from the ‘Kidney Disease Quality of Life-Short Form’ initially developed for patients with end stage renal disease [84]. Patients were asked, “On a scale of 0 to 10, how would you rate your sleep quality overall?”, where 0 represents ‘very bad’ and 10 represents ‘very good’. Values lower than 6 were used in this study to define poor SQ. This SQ item has been validated in view of evidence based on content and evidence in view of relationships to other variables [85]. Content validity was assessed using the content validity index (CVI: .81); concurrent validity by comparing the scale to the Pittsburgh Sleep Quality Index ( $r_s$ :  $-.737$   $p < .01$ ) and discriminate validity by examining associations with depression and quality of life [85]. Predictive validity with regard to mortality in hemodialysis patients has been demonstrated with the Dialysis Outcome and Practice Pattern Study data assessing SQ at 4 months intervals [9, 84].

### *Health Status*

*Health status* is assessed with the visual analogue scale (VAS) [77]. This scale is part of the standardized measure of health related quality of life developed by the EuroQol Group [86], in order to provide a simple, generic measure of health status for clinical and economic appraisal. This item records the respondents self-rated health on a vertical drawn scale, whereby the endpoints are labeled ‘Best imaginable health state’ (value = 100) and ‘Worst imaginable health state’ (value = 0). This item has shown validity for the measurement of health status in RTx patients [87].

### *Depressive symptomatology*

*Depressive symptomatology* was measured with the 7-item subscale of the Hospital Anxiety and Depression Scale (HADS), a self-reported non-diagnostic screening instrument



and developed to assess cognitive symptoms of anxiety and depression in medically ill patients. The HADS is widely used and well validated as a screening instrument for depression in the general medical population, and, to some extent, in the context of RTx [88]. Each item has 4 choice possibilities (i.e.: not at all, not often, sometimes, most of the times) that are transformed into values from 0 to 3. Total score is calculated by summarizing the items in a score ranging from 0 to 21. A score of 8 or more indicates presence of depressive symptomatology based on sensitivity and specificity [89]. It has been shown in clinical group comparisons and in studies with several aspects of disease and quality of life that the HADS gives clinically meaningful results as a psychological screening tool. It is sensitive to change both during the course of disease and in response to medical and psychological interventions [90].

### ***Data collection***

Data collection follows the description of Koller et al [82] and De Geest et al [83]. Organ Tx candidates are invited to be part of the STCS, upon providing written informed consent [83]. Psychosocial questionnaire data collection started in May 2008. Data collection at follow-up, occur either at a scheduled appointment or at home after mailing patients the PSQ which they return in a pre-addressed, pre-stamped envelope. Completeness of the PSQ is checked by the local STCS data managers in the local Swiss Tx centers, where data are entered into a centrally managed database. Further details on data collection in the STCS have been published elsewhere [82, 83]. The STCS was approved by the ethical committees of the 6 participating Tx centers.

### ***Statistical analysis***

Descriptive analysis on sample characteristics included frequencies, proportions, measures of central tendency (mean, median) and of dispersion (standard deviation, interquartile range) as appropriate, based on measurement level and distribution.

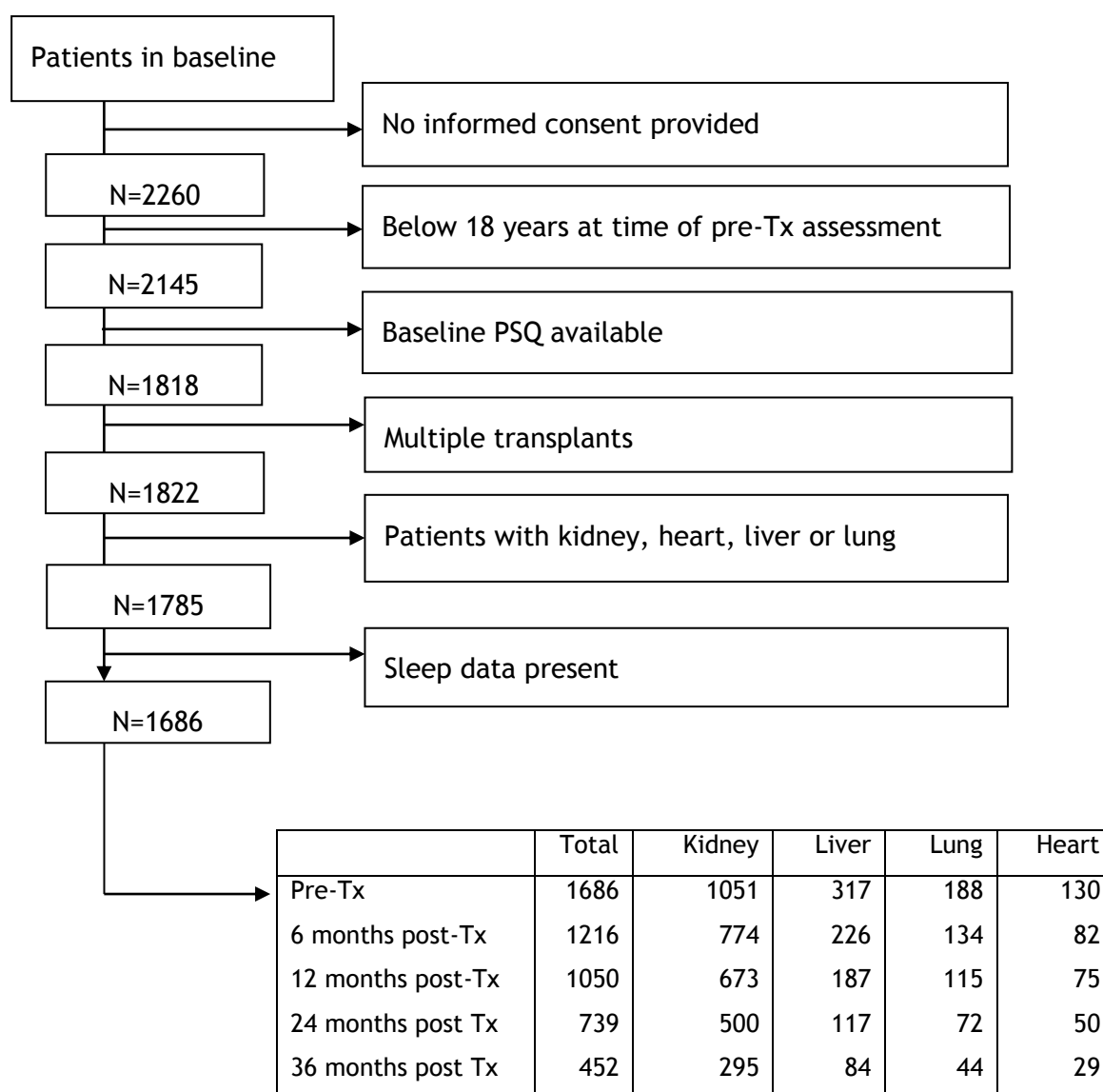
Modeling of SQ and health status across time and organs was performed using generalized linear mixed modeling. In both instances, 'patient' was added as random variable. Next to entering transplanted organ and time into the equation, we controlled for the following confounding variables: age, gender, depression and the number of months between the pre-Tx measurement and the Tx date. Changes over time were plotted for the different organs. We only included an interaction term between time and organ if observation of the data indicates that different organs showed different trajectories with regard to the outcome variable over time, in which case we used contrast statements to answer specific hypotheses e.g. differences between specific organs. Analyses were performed in SAS 9.1.3 (SAS Institute Inc., Cary, NC, USA). The alpha level was set at 5%.

## 6.4. Results

### Sample characteristics

A total of 2260 patients were included in the STCS by December 31<sup>st</sup> 2011 of which 1686 patients were eligible for this study based on the inclusion criteria. At the pre-Tx assessment 1051 patients were waiting for a kidney, 317 for a liver, 188 for a lung and 130 for a heart Tx. Over the course of the follow up period, the sample size decreased progressively as this is an open progressive cohort study which is enrolling new patients on a continuous basis (Figure 3) and has not yet reached steady state. A description of the sample can be found in Table 1. At enrollment, the mean age was  $52.66 \pm 13.00$  years and 64.53% were male.

**Figure 3:** Flowchart showing the sample as selected from the STCS overall sample



**Table 1:** Sample characteristics at time of pre-transplantation and of six months post transplantation for all organs

Variable		Pre-Tx
Age	Mean (std) in years	52.66 ±13.00
Gender	Male - N (%)	1088 (64.53)
Marital status	Single - N (%)	287 (17.02)
	Married/living together - N (%)	1120 (66.43)
	Widow/widower - N (%)	50 (2.97)
	Divorced - N (%)	171 (10.14)
	Separated - N (%)	42 (2.49)
	Answer refused - N (%)	16 (0.95)
	Highest completed educational degree	No completed school or professional education - N (%)
Mandatory school (9 years in Switzerland) - N (%)		394 (23.37)
Finished apprenticeship - N (%)		647 (38.37)
Higher professional education - N (%)		95 (5.63)
Higher technical or commercial school - N (%)		50 (4.69)
Bachelor - N (%)		149 (8.84)
University - N (%)		155 (9.19)
Other - N (%)		81 (4.80)
Health-related Quality of Life	Mean (std)	56.17 (22.42)
Depressive symptomatology	Mean (std)	8.76 (1.79)
	Depressive symptomatology N (%)	1322 (79.35)
Organ type	Kidney - N (%)	1051 (62.69)
	Liver - N (%)	317 (18.81)
	Lung - N (%)	188 (10.06)
	Heart - N (%)	130 (7.71)
Time between inclusion in STCS and Tx	Median (25 <sup>th</sup> & 75 <sup>th</sup> Percentile) in mo	4.23 (0.2-12.4)

Legend: Tx= transplantation; STCS (Swiss Transplant Cohort Study)

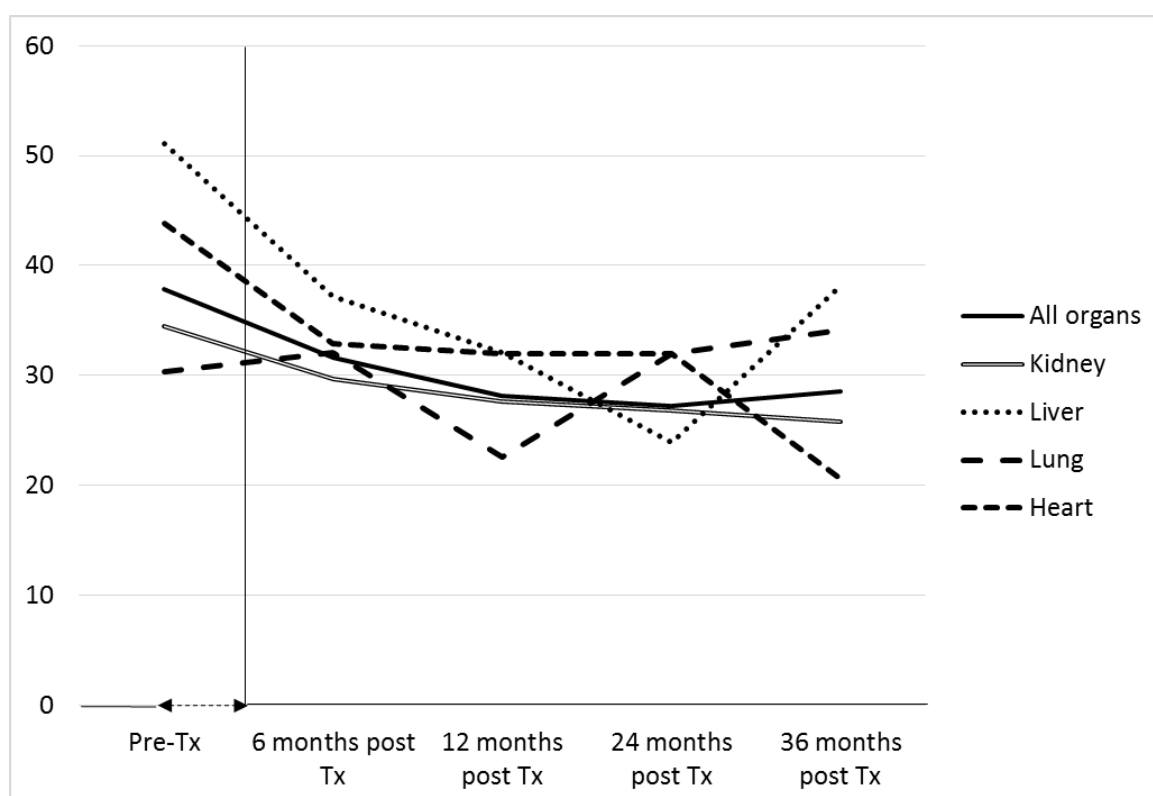
### *Sleep quality*

Prevalence of overall poor SQ was 37.84% at pre Tx, 31.58% at 6 months post Tx, 28.19% at 12 months, 27.20% at 24 months post Tx and 28.54% at 36 months post Tx (Table 2).

The slopes per organ are extremely different: LiTx recipients seems to profit most from transplantation until 2 years post Tx, however at the 3 year assessment poor SQ (38%) increases to the 6 months post Tx level (37%). Similar is the slope for HTx. An improvement after Tx followed by a steady state and a mayor improvement at 3 year. LuTx recipients are the only group that shows a slight increase of the poor SQ prevalence at 6 months post

Tx. At 1 year post Tx the prevalence decreases, followed by an impressive increase in recipients with poor SQ, with higher prevalence compared to pre and 6 months post Tx. RTx recipients showed a steady decreasing prevalence over time (Table 3). The improvement seen in Figure 4 until one year and subsequent leveling off is confirmed by the fact that the drop in occurrence of poor SQ pre Tx to 12 months is significant ( $p < .0001$ ), whereas the differences month 12, 24 and 36 are not.

**Figure 3:** Percentage of poor sleep quality at time of listing till 3 years post-Tx (overall & per Tx group)



**Table 2:** Descriptive statistics of poor sleep quality over time by organ

		All organs	Kidney	Liver	Lung	Heart
At pre-Tx	N total	1686	1051	317	188	130
	N poor SQ	638	362	162	57	57
	% poor SQ	37.84	34.44	51.1	30.32	43.85
At 6 months post Tx	N total	1216	774	226	134	82
	N poor SQ	384	230	84	43	27
	% poor SQ	31.58	29.72	37.17	32.09	32.93
At 12 months post Tx	N total	1050	673	187	115	75
	N poor SQ	296	186	60	26	24
	% poor SQ	28.19	27.64	32.09	22.61	32

	N total	739	500	117	72	50
At 24 months post Tx	N poor SQ	201	134	28	23	16
	% poor SQ	27.2	26.8	23.93	31.94	32
	N total	452	295	84	44	29
At 36 months post Tx	N poor SQ	129	76	32	15	6
	% poor SQ	28.54	25.76	38.1	34.09	20.69

Legend: SQ = Sleep quality; Poor SQ = Poor SQ (cut-off<6)

**Table 3: Modeling poor SQ: differences in SQ between measurement points and organs**

Parameters	Contrast	Odds ratio (95% confidence interval)	Chi <sup>2</sup> value	p-value
Intercept		-2.44 (-3.04;-1.84)	64.19	<.0001
Age		0.99 (0.99-1.00)	0.06	0.8011
Gender		<b>1.31 (1.00-1.57)</b>	<b>9.01</b>	<b>0.0027</b>
Depressive symptoms		<b>1.16 (1.11-1.22)</b>	<b>47.16</b>	<b>&lt;.0001</b>
Number of months pre-transplant		1.00 (0.99-1.00)	0.07	0.79
Organ	Kidney vs Liver	<b>0.66 (0.53-0.81)</b>	<b>14.90</b>	<b>0.0001</b>
	Lung vs Liver	<b>0.64 (0.46-0.89)</b>	<b>7.06</b>	<b>0.0079</b>
	Heart vs Liver	0.91 (0.62-1.33)	0.23	0.6319
	Lung vs Kidney	0.98 (0.73-1.30)	0.01	0.9278
	Heart vs Kidney	1.38 (0.97-1.96)	3.25	0.0714
	Heart vs Lung	1.41 (0.92-2.18)	2.48	0.1154
Measurement point	6 months post Tx vs pre-Tx	<b>1.30 (1.13-1.49)</b>	<b>14.19</b>	<b>0.0002</b>
	12 months post Tx vs 6 months post Tx	<b>0.83 (0.71-0.96)</b>	<b>6.06</b>	<b>0.0138</b>
	24 months post Tx vs 6 months post Tx	<b>0.79 (0.66-0.94)</b>	<b>6.65</b>	<b>0.0099</b>
	24 months post Tx vs 12 months post Tx	0.96 (0.80-1.14)	0.22	0.6370
	36 months post Tx vs 6 months post Tx	0.84 (0.67-1.04)	2.40	0.1210
	36 months post Tx vs 12 months post Tx	1.02 (0.82-1.26)	0.02	0.8795
	36 months post Tx vs 24 months post Tx	1.06 (0.86-1.30)	0.32	0.5709

### Health-status

SQ significantly predicted patient's health status ( $p < .0001$ ). Those with poor SQ scored on average 10 points lower on the 100-points VAS scale measuring health status (Table 4).

**Table 4:** Modeling Health-Related Quality of Life: prediction by sleep quality

Parameters	Contrast	Estimate	Standard Error	DF	t value	p
Intercept		64.67	2.72	1663	23.82	<.0001
Sleep	Optimal vs suboptimal	11.21	0.56	3283	19.89	<.0001
Age		-0.03	0.03	3283	-1.1	0.2715
Gender		-0.06	0.75	3283	-0.08	0.9393
Depressive symptoms		-0.47	0.15	3283	-3.09	0.002
Number of months pre-transplant		-0.07	0.03	3283	-2	0.0454
Measurement point	0	-15.55	0.83	3283	-18.75	<.0001
	6	-0.49	0.85	3283	-0.57	0.5657
	12	1.87	0.86	3283	2.17	0.0303
	24	1.48	0.90	3283	1.64	0.101
	36	0.00	.	.	.	.
Organ	Heart	1.00	1.68	3283	0.59	0.5529
	Kidney	8.50	1.15	3283	7.38	<.0001
	Liver	5.54	1.35	3283	4.12	<.0001
	Lung	0.00	.	.	.	.

## 6.5. Discussion

This study provided relevant clinical insights in view of prevalence and evolution of poor SQ in the different solid organ Tx recipients. This study also provided insights that SQ has an impact on health status being the first step in the exploration of the clinical importance of health status in solid organ Tx. This paper reports to our knowledge the largest study sample of self-reported SQ in solid organ Tx recipients simultaneously studied with the same methods.

Poor SQ is prevalent from pre to post Tx, showing variability among organ groups. SQ improved significantly from pre to post Tx over all organs, confirming sleep studies in solid organ Tx recipients. Our prevalence for pre RTx is around 15% lower than the prevalence reported in the Dialysis Outcomes and Practice Patterns Study (49%) [9]. The prevalence at 6 months is 7% lower and at 1 year 11% lower than the study of Silva et al. (2012) (36.7% respectively 38.3%) including only a small sample of 60 RTx[14]. Compared to the recent study of Reilly-Spong et al. [91] (41.6%) we had a 15% lower prevalence. Overall SQ

improved after RTx, remaining on 27% to 27% to 26% plateau level at 1, 2 and 3 year post Tx, suggesting a chronification of sleep disturbances.

In LiTx patients we found as well lower prevalence compared to other reports. Compared to the study of Rodrigue et al (2010) (73% respectively 77%) we had 22% lower prevalence at pre LiTx and 40% lower at post LiTx [70]. We assume that these two small studies might be biased as patients having a poor SQ were more inclined to fill in a survey about sleep. Compared to 25 LiTx transplanted in the mean  $4.5 \pm 4.9$  years ago (48% poor SQ) we had a 11% lower prevalence [91].

For HTx and LuTx recipients there is only one study that measured sleep quality in a sample of 13 HTx and 12 LuTx [91] recipients. The prevalence was 38.5% of poor HTx sleepers assessed in the mean  $9.5 \pm 6.1$  year after Tx and 27.3% at  $3.4 \pm 3.5$  year after LuTx [91]. Our prevalence at 3 years are 17% lower for HTx and 6% higher for LuTx. We hope that the small sample biased the results and that Reilly-Spong et al. overestimated the prevalence for HTx and that we overestimated the prevalence for LTx.

The prevalence data found in our study are lower than other study reports however higher as population based prevalence (4% of poor SQ in a face to face interview study including a sample of 2559 [92]). Poor SQ was highest pre LiTx (51%) and lowest in LuTx (30%) patients. A reason for this huge difference might be that for liver patients the Tx priority is determined by the MELD (model for end-stage liver disease) score [93], implying that pre-Tx patients have a very low health status [94]. Two years post LiTx the prevalence is 24% (a 27% drop) this is in line with the quality of life improvement after LiTx [95].

We were surprised by the low prevalence of poor SQ in pre LuTx patients, as another studies reported a high prevalence of sleep apnea (44%) [71]. However sleep apnea and insufficient breath with hypercarbia might have hindered the awareness of the real seriousness of poor SQ [96]. This prevalence is contrasting with the low prevalence at 1 year post LuTx (22%) and the high prevalence (34%) three years post LuTx. This worsening result might be looming a beginning condition of infection or broncholithiasis obliterans: according to the most recent data of International Society for Heart and Lung Transplantation (ISHLT), actual survival is 79%, 63%, 52% and 29% at 1, 3, 5 and 10 years respectively, with a current overall survival half-life of 5.3 years, and more than 7 years for those who survived 1 year or more [97]. However, survival depends on different parameters such as underlying disease, data relative to the donor, the recipient and/or the Tx procedure [98]. The most frequent causes of death between 1 and 3 years post-lung Tx are broncholithiasis (25.4%), infection (22.9%) and graft failure (19.3%) [99]. Another hypothesis for the worsening is the increase in prevalence of obstructive sleep apnea,

resulting from an increase in body weight and blood pressure [71, 72]. In addition this aggravation must be considered carefully as the sample size is very small (N=44). SQ improves significantly from pre (44%) to post Tx (21%) for HTx recipients. HTx recipients undergo very stringent selection criteria and some live with mechanically assisted circulatory support before Tx; that may be reflected in the positive trend for good SQ in these patients [100]. A further reason might be that heart failure patients require numerous medications that can affect sleep, such as beta blockers or antihypertensive drugs [101]. HTx recipients benefit most from Tx compared to the other solid organ transplant recipients, [102], in spite of high rate of graft failure (23%) [99]. According to the registry of the ISHLT, HTx recipients experience a major improvement in quality of life in the first year after Tx [103, 104], as can be seen from our results on SQ. Finally our analysis showed that pre Tx poor SQ is somewhat indicative for post Tx poor SQ. This fact highlights the importance of behavioral changes going along with the transplantation. As soon as the surgery is over new sleep-wake pattern and lifestyles have to be established.

SQ significantly predicted patient's health status, this is in line with the study of Silva et al. (2012) that reported that poor sleepers had lower scores in health related quality of life [14]. An area of future study might be to see if poor SQ could be a predictor of acute rejection and graft loss. Of high interest and relevance will be in a near future the analysis of the predictive value of SQ in view of mortality in the STCS. These data could then be compared to the Dialysis and Outcome Practice Pattern Study that is using the same measurement tool for SQ [9]. The regular assessment of psychosocial variables belonging to a chronically ill follow up program is becoming of increasing importance as short-term outcomes after Tx are good and long term outcomes need improvement. Psychosocial outcomes themselves influence long-term post Tx morbidity and mortality rates [105, 106]. For clinical practice the regular screening for poor SQ and health status and the following assessment in case of a positive screening might be preventive for chronic sleep disorders, subtle infections or health status deterioration. Interventions to counteract this high prevalence of poor SQ must be evaluated from pre to post Tx including comorbid conditions bearing the risk of aggravating the already poor SQ or to trigger a new condition.

### *Limitation of Study*

This study was a secondary data analysis using data from the STCS. The psychosocial questionnaire including SQ, depressive symptomatology and health status had an item restriction to keep the participant's burden low, in addition these items are unspecific and therefore not comparable to full assessment questionnaires, yet they showed validity (see



method section). Further, we included only the most frequent Tx organ groups (heart, liver, lung, and kidney) to have large sub samples and enough statistical power for the inferential analysis. This prospective cohort study that did not reach yet steady state has decreasing sample sizes per organ group over time. As the cohort study started in 2008, we did not have data on 24 months follow up on patients included in 2010. However, the STCS will allow us to follow up SQ of patients for the next years. Furthermore, a reassessment for patients on the waiting list is planned to have more precise assessments pre-Tx.

### **Conclusion**

Poor SQ affects around a third of Tx recipients. In addition, SQ improves following Tx, however, variability among organ Tx groups exists. As we reported that sleep predict health status, we have a further argument to increase the awareness for sleep disorders in solid organ Tx recipients. However, further analyses on our data registry are necessary to evaluate the predictive validity of this cut-off value for negative patient outcomes, such as graft loss and mortality.

### **Acknowledgment**

We would like to extend our appreciation to the STCS core team, the Psychosocial Interest Group of the STCS and to the 6 Swiss Tx centers for supporting this work. We would also like to thank Chis Schultis for editing and proof reading the manuscript. The authors do not have any conflicts of interest or disclosures with regards to the data presented in this manuscript.

### **Transparency declaration**

The results presented in this paper have not been published previously in whole or part, except in abstract format:

Burkhalter H., Denhaerynck K., De Geest S., (June 2<sup>nd</sup>-6<sup>th</sup> 2012). *Sleep quality improves from time of listening to 2 years post- transplant in solid organ transplant recipients: a prospective cohort study*, poster presentation (Poster session Disparities to Outcome and Access 729) at the American Transplant Congress, Boston, MA

### **Authorship roles**

Hanna Burkhalter and Sabina De Geest designed the study. Hanna Burkhalter and Kris Denhaerynck analysed the data. Hanna Burkhalter and Sabina De Geest wrote the paper and all members of the PSIG were invited to review and give inputs.

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# CHAPTER 7

## A PILOT RANDOMIZED CONTROLLED STUDY OF LIGHT THERAPY FOR SLEEP-WAKE DISTURBANCES IN RENAL TRANSPLANT RECIPIENTS

## A Pilot Randomized Controlled Study of Light Therapy for Sleep-Wake Disturbances in Renal Transplant Recipients

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**ClinicalTrials.gov Identifier:** NCT01256983

**Keywords:** renal transplantation, light therapy

**Funding:** International Transplant Nurse Society and Swiss Renal Foundation: Alfred & Erika Bär-Spycher Foundation

### Transparency declaration

The results presented in this paper have not been published previously in whole or in part. This study was funded by a research grant from the Swiss Renal Foundation (Alfred and Erika Bär-Spycher Foundation).

There are no conflicts of interest.

### Authors' contributions

H. Burkhalter, A. Wirz-Justice and S. De Geest designed the study. H. Burkhalter and K. Denhaerynck (statistician) analysed the data. H. Burkhalter, S. De Geest and K. Denhaerynck wrote the paper. All other co-authors reviewed and gave input. A. Wirz-Justice, C. Cajochen and T. Weaver contributed to chronotherapy and actigraphy/sleep methods and analyses knowledge. H. Burkhalter, J. Steiger, T. Fehr and R.M. Venzin were involved in the data collection process in the three centres and contributed to nephrology background knowledge.

## 7.1. Abstract

### Background

The aim of this study was to evaluate the feasibility and the outcomes of morning light therapy in renal transplant (RTx) recipients with diagnosed sleep-wake disturbances (primary outcome: bedtime; secondary outcome: circadian and sleep parameters, depressive symptomatology, subjective feelings and cognitive executive function).

### Methods

A randomized controlled wait-listed pilot trial was conducted. Thirty home-dwelling RTx recipients (aged  $59.6 \pm 12.6$  y) were assigned 1:1 to the intervention group (3 times 3 weeks: baseline, intervention, follow-up) or wait listed group (intervention after 9 weeks usual care). Morning light (10'000 lux) was individually scheduled for 30 min daily over a 3-week period. Subjects' rest-activity cycles were monitored with wrist actimeters (sleep and circadian data). Data were analysed using a random-intercept regression model to test group\*time interaction. A secondary analysis included full wait listed design (pre-post analysis) intervention data.

### Results

Light therapy was feasible and induced a phase advance in bedtime (20 min) and get-up time (25 min). The pre-post analysis showed a phase advance only in get-up time only. Light therapy improved mood in the whole group without affecting cognitive executive function.

### Conclusion

This is the first evidence for a beneficial effect of light therapy on sleep and mood in RTx recipients with sleep-wake disturbances.



## 7.2. Introduction

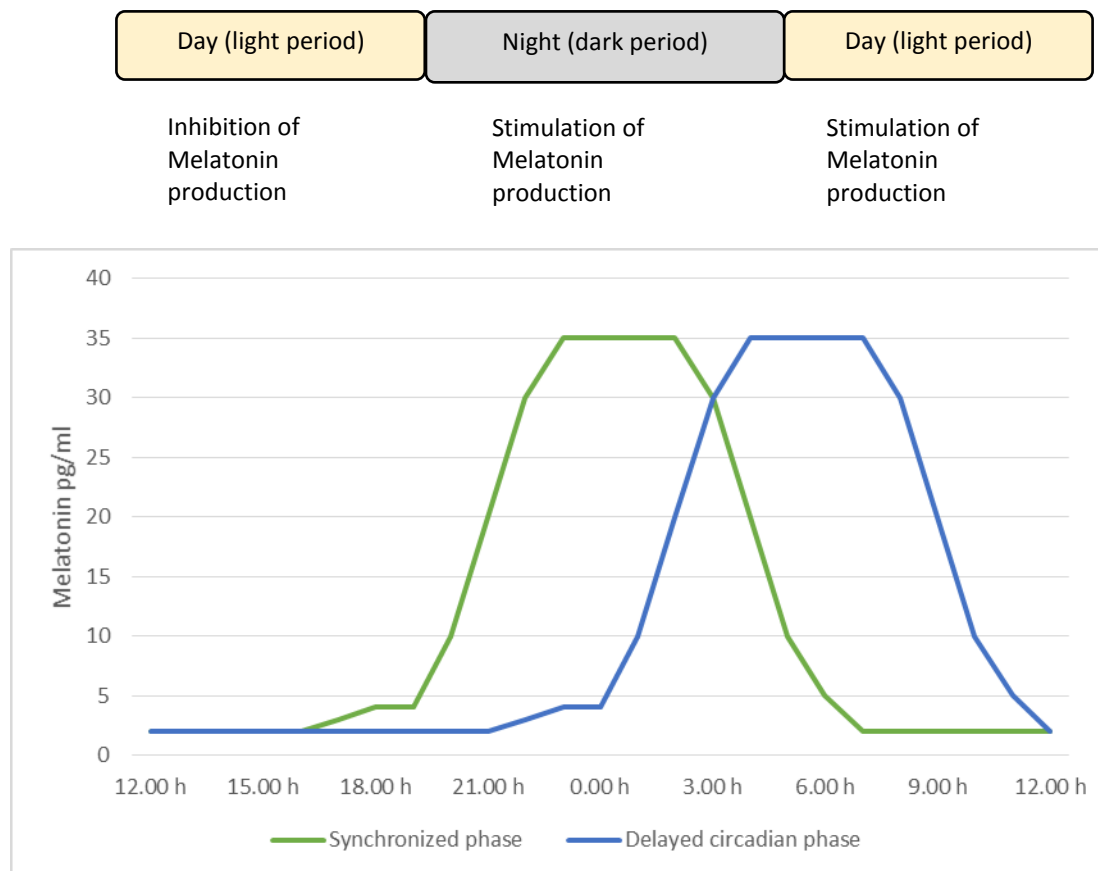
About half (49%) of RTx recipients report poor sleep quality [1, 2] and/or poor daytime functioning (34.1%)[1] and 51% say they suffer from daytime sleepiness[2]. The prevalence is 8% for insomnia[3] (inability to fall asleep or to stay asleep as long as desired), 4.5% for restless legs syndrome[4] and 27% for obstructive sleep apnea[5]. In the previous study, belonging to this project we found that insomnia and sleep-wake disturbances are common among renal transplant (RTx) recipients[6]; nearly 30% of RTx recipients reported that they suffer impaired daytime functioning because of night-time sleep disturbances, daytime sleepiness or fatigue[6]. In addition the mean chronotype score of the previous study ranging from 16 to 86 [ $58.61 \pm 9.94$ , mean age  $57.73 \pm 13.11$  (unpublished data of Burkhalter et al.2013)] was lower (more evening chronotypes)[1] compared to a similar age group in the general population [7, 8]. Evening chronotypes manifest a delayed sleep phase characterized by inability to fall asleep or wake up at the desired time and excessive daytime sleepiness[9].

Pharmacological treatment for sleep-wake disturbances in general population is very common[10]; however in RTx recipients only efficacious, reliable and safe drugs should be added to the lifelong immunosuppressive regimen. Interventions to reduce sleep-wake disturbances after transplantation are needed, and non-pharmacological strategies may be preferred due to the complexity of transplant medication regimens[11].

### Bright Light Therapy

Light therapy via the eye is a low-risk non-pharmacological option for treating sleep-wake disturbances directly via the biological clock[12]. Neurones in the suprachiasmatic nuclei in the anterior hypothalamus generates the circadian rhythms and daily light impinging the retina resets their phase, determining the timing of sleep and wake[13]. Proper circadian entrainment (i.e. optimal synchronization of the endogenous circadian clock with the external 24-h light-dark cycle) is essential for good sleep and healthy functioning in general[14] and light is the most powerful agent to do this. Morning light can advance circadian rhythm phase (inhibiting the melatonin production), including the sleep-wake cycle (Figure 1). This has been applied to effectively treat delayed sleep phase syndrome with timed morning light[15, 16]. Light therapy has many applications with little risk of adverse side effects: side effects may include agitation, headache, or nausea - but they are all rapidly reversible by reducing light intensity or duration[17].

**Figure 1:** The influence of light and darkness on the circadian rhythm of nocturnal melatonin secretion driven by the suprachiasmatic nuclei



### Bright light therapy and sleep-wake rhythm consolidation

Light therapy is used to synchronize abnormal sleep-wake cycles with the external environment[18]. This consolidation is hypothesized to improve mood[19], depressive symptomatology[20], sleep disturbances[21], and performance (e.g.: reaction time)[22]. In addition, light triggers the brain's production of serotonin (a major neurotransmitter involved in mood regulation)[23]. Two meta-analysis have published effect sizes for light therapy in non-seasonal depression (ES: 0.84 (95% CI, 0.60-1.08)[24] and (ES: 0.53; 95% CI, 0.18-0.89)[25] and in seasonal depression (ES: 0.73; 95% CI, 0.37-1.08)[24]. Persons with Alzheimer's disease or related dementia have often a pronounced circadian disruption[12] and many studies showed improvements in nighttime sleep and increased daytime wakefulness as well as mood and cognition with light therapy. In particular a randomized double blind placebo controlled long term intervention showed significant attenuation on cognitive deterioration, ameliorated depressive symptoms and improved activities of daily living[26] and a further randomized controlled trial with seniors in long term care showed significant improvement in cognition[27]. In internal medicine, a pilot study has applied

light therapy to sleep-wake disturbances in cirrhosis patients[28]. To our knowledge, there are no studies that evaluated a light therapy treatment in RTx recipients.

To address sleep-wake disturbances in RTx recipients we conducted a randomized controlled pilot trial to test the feasibility and the effect of morning bright light therapy and its effect on a number of selected functional categories: directly sleep-related (bedtime, get-up time, sleep latency and sleep efficiency) and circadian-related (characteristics of the sleep-wake cycle such as interdaily stability [IS], intradaily variability [IV], relative amplitude [RA][29]) - both evaluated from actimetry; timing of nocturnal secretion of the pineal hormone melatonin, the major circadian marker that can be measured in saliva (defined as Dim Light Melatonin Onset (DLMO); mood [depressive symptomatology[30] and subjective feeling scales]; and cognitive executive function [Stroop task[31]].

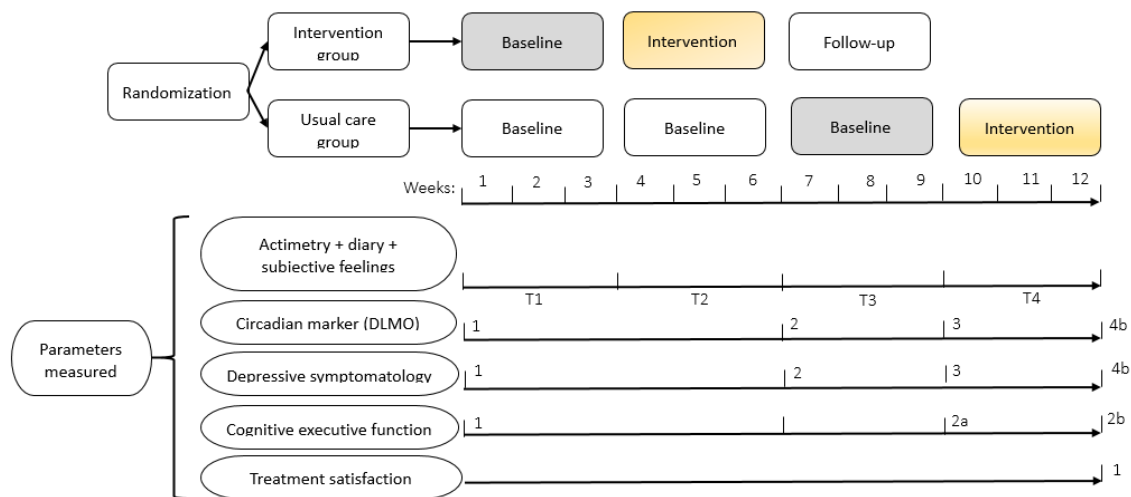
The aim of this pilot study was to evaluate the feasibility and outcomes of morning light therapy on phase advancing bedtime (primary outcome), circadian and sleep parameters, depressive symptomatology, subjective feeling and cognitive executive function (secondary outcomes) in RTx recipients diagnosed with sleep-wake disturbances.

### 7.3. Material & Methods

#### Design

We used a randomized controlled pilot wait-listed design with a 1:1 randomisation sequence. The intervention group received morning light therapy early (after 3 weeks), while the control group received usual care and bright light therapy following completion of the RCT (after 9 weeks) (figure 2). The group the participant was randomized to, was concealed from the research team until each RTx recipient opened the envelope containing their group information.

Figure 2: Randomized controlled wait-listed design including the pre-post design for the analysis of the early and late intervention



Legend: T= Time period; DASS 21= Depression, anxiety and stress scale; Stroop task = Colour-word interference task to measure cognitive process; grey = analysis of the early and late intervention; a= Measurement only for the early group; b= Measurement only for late group.

### Participants, eligibility criteria, and setting

Participants were recruited at the University Hospitals of Basel, Bern and Zurich from a prior study assessing sleep disturbances in adult, home-dwelling RTx recipients[6]. Patients previously diagnosed with sleep-wake disturbances were asked to participate in the current study. The inclusion criteria were: adult RTx recipients more than 1 year post-transplant; German speaking; on stable immunosuppressive drugs; no signs of acute organ rejection; normal ocular function (by self-report and by chart review) and diagnosed with sleep-wake disturbances in the prior study. Exclusion criteria were: acute illness or hospitalization.

### Bright Light Therapy Intervention

Bright light therapy was realized by a bright light box (Philips: bright light Energy HF 3304) that each participant received at home. The primary investigator (HB) instructed participants on its use. To provide the appropriate intensity (10'000 lux), patients were instructed to sit 30-50 cm from the lamp at eye level for 30 minutes every day at the time determined by their individual chronotype[6]. We allowed for a 1.5 h deviation from the theoretical optimum starting time.

## Measures

### Bedtime (Primary outcome)

Bedtime was measured with actimetry (movements of the non-dominant wrist) which collects motor activity at 1 min intervals to provide a 24-hour pattern of rest and activity, and indirectly, characteristics of sleep. Actimetry has been established as a reliable and objective method for the naturalistic study of sleep and wakefulness[32]. Over the entire study period, the participants were instructed to continuously wear a wrist-worn combination actimeter/light monitor (Daqtometer® by Daqtix GbR, Oetzen Germany)[33]. We were unable to use the light exposure data gathered, since several of the participants' wrist-worn light monitors were covered by their sleeves a lot of the time. This data would have allowed monitoring both adherence to the intervention and overall individual light exposure.

The participants were also 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 time(s) they got up during the night, the time(s) they awoke, and the time period the actimeter was off their wrist[34]. Activity data gaps during the daytime, reflecting actimeter removal (e.g., to shower) reported in the diary, were replaced with the average activity counts for that 24-h period. If no data were recorded for more than 3 hours in 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, UK).

### Secondary outcomes

#### Sleep and circadian parameters from the rest-activity cycle

Actimetry data were edited with the self-reported diary of the participant following standardized criteria[32]. The actimetry software generates one value for each day. Three sleep parameters were assessed via actimetry data: (1) get-up time, (2) sleep latency, and (3) sleep efficiency. For circadian parameters of the sleep-wake cycle, non-parametric circadian rhythm analysis were used over the 3 week periods: interdaily stability (IS), intradaily variability (IV), and relative amplitude (RA) [29]. IS indicates the strength of the association between the rest-activity rhythm and the day-night cycle (the consistency of activity patterns across the individual days)[29]. The IV index indicates the degree to which the subject's sleep rhythm is fragmented (comparing days over a week). Each day's RA was calculated from the ratio of the most active 10-h period to the least active 5-h period across the averaged 24-h profile[35]. The RA's are the oscillation amplitude divided by the overall mean.

### **Circadian marker (DLMO)**

Dim Light Melatonin Onset (DLMO) is the most reliable marker for human circadian phase position, and it can be assayed in sequential evening blood or saliva sampling[36]. To determine participants' DLMOs, saliva samples were self-collected using Salivettes® (Sarstedt AG, Switzerland) over 3 evening periods. For each 24-hour collection period, each participant collected up to 11 samples and stored them in his refrigerator: at 1-h intervals starting 5 h before and ending at bedtime, at wake-up, on getting up, 1 and 2 h after rising, midday and 3pm. The sleep diary included reminders of patients' sampling days and times, a checklist for the sampling times and six pictures showing the sample collection procedure.

Melatonin was measured via direct double-antibody radioimmunoassay with an analytical sensitivity of 0.2 pg/ml and a functional minimum detectable dose of 0.65 pg/ml (Bühlmann Laboratories AG, Allschwil / Switzerland)[37]. DLMO was calculated using the Hockey-stick method developed by Danilenko et al.[38] based on the five melatonin values collected before bedtime. Saliva melatonin shows normally values during the day below 3 pg/ml and before bedtime levels up to 10 pg/ml[39] with large individual variability in the amount of melatonin secreted with peak values ranging from 2 to 84 pg/ml[40]

### **Depressive symptomatology**

Depressive symptomatology was assessed via the Depression, Anxiety and Stress Scale (DASS 21), a 21-item self-report instrument (see figure 2 for assessment times). The DASS 21 measures depressive symptomatology via seven items utilizing a 4-point Likert-type severity / frequency scale, on which patients rate the extent to which they experienced each state over the past week (0 = did not apply to me; 3 = applied to me very much). Only the DASS-depression score (0-4 no depressive symptomatology; 5-6 mild, 7-10 moderate, 11-13 severe and  $\geq 14$  extremely severe) is reported here[30]. The DASS-21 has strong construct[41] and concurrent validity[42] in depressed patients and primary care patients[41].

### **Subjective feelings**

Subjective feelings (relaxed; physical well-being; alertness, feel sated; mood) were assessed daily via diary before bedtime and at get up time on a visual analogue scale from 0 to 10.

### **Cognitive executive function**

Attention, cognitive flexibility and reaction time (executive function) were measured via the Stroop color-word interference task [31]. This task has three parts: (1) reading 74

colour words printed in black on a white background, (2) reading 74 coloured ink printed rectangles and (3) naming 74 colour words printed in non-matching colours. Each part is associated with a large decrease in colour naming speed, i.e., “the colour-word interference effect”. The task was administered by a member of the research team 2 respectively 3 times (days 1, 63, and 84). Following the task manual, the time measures for each task were analysed for the mean of the interference t-score[43].

### **Treatment satisfaction**

At the end of the diary, as a proxy measure for satisfaction, subjects were asked whether they would recommend light therapy to a friend (yes/ no), and whether they felt light therapy was efficacious (yes/no).

### **Feasibility**

Feasibility was measured with the proportion of participants that stayed in the study until the end, number of adverse events or side effects and number of extra calls and visits due to problems with the study equipment.

### **Clinical characteristics**

Clinical characteristics (age in years, gender, years since transplantation, BMI ( $\text{kg}/\text{m}^2$ ), creatinine level ( $\mu\text{mol}/\text{l}$ ), haemoglobin level ( $\text{g}/\text{l}$ ) and medications used (including sleep drugs)) were retrieved from the participants’ hospital medical charts. Comorbidity data were also extracted from patients’ charts and categorized using the Charlson comorbidity index[44]. Sleep quality (measured with the Pittsburgh Sleep quality Index), daytime sleepiness (measured with the Epworth Sleepiness Scale), and chronotype (measured with the Morningness-Eveningness questionnaire) were extracted from the preceding study[6] (Table 1).

### **Data collection**

The current study was approved by the ethics commissions of Basel, Bern and Zürich. Data collection was from December 2010 until September 2012. After providing written informed consent, participants were contacted by telephone to arrange a home visit during which the researcher explained the study details and answer any questions. At the first home visit, the participant opened a randomly allocated opaque envelope containing the message early light therapy or the message late light therapy. The actimeter was then activated and the respective sleep diary containing information for the early or late light therapy was explained. The researcher gave the light box and saliva melatonin kit with written and oral information on light box use and saliva melatonin collection to participants of both groups during the initial visit. Salivette® samples were to be stored in

the participant's home freezer until collected at the end of the study by the first author. Participants were provided with the researcher's telephone in case they had questions or needed assistance. Follow up calls were planned individually, as the respective diary told the participant each day what to do. At least once, specifically on day 63, the researcher called each RTx recipient to administer the Stroop task. At study's end, subjects received 160 Euro as a token of appreciation for their cooperation.

### **Statistical analysis**

Descriptive statistics were used as appropriate for the level of measurement and distribution. The primary and secondary outcome measures were summarized using appropriate descriptive statistics. Hypothesis testing for the RCT was performed via linear mixed regression modelling, to which we added 'patient' as a random effect and 'group assignment', 'time point' (baseline, intervention, post-intervention) and their interaction term as fixed effects, using an unstructured working correlation matrix. We also analysed the late intervention data of the control group by pooling them with the data of the early intervention group and performing a pre-post analysis using the three weeks' data preceding the intervention as baseline data (for the outcome variables of bedtime, get-up time, sleep efficiency and sleep latency). Effect sizes were calculated as the standardized estimate of the interaction coefficient (RCT) and the time variable (late intervention data). For the post-hoc analysis, we controlled for the presence of beta-blockers (BB) and (acetylsalicylic acid) ASA. Analyses were performed with the mixed procedure in SAS 9.1.3 (SAS Institute Inc., Cary, NC, USA).

## **7.4. Results**

Of 30 subjects who began the randomized controlled pilot wait-listed study, 14 received the early intervention and 14 the usual care. One subject in each group perceived the study too burdensome. Twenty-six completed the study (figure 3). Table 1 shows both groups' baseline demographics. There were no significant participant differences between groups and no meaningful clinical differences.



Figure 2: Flow diagram of sample

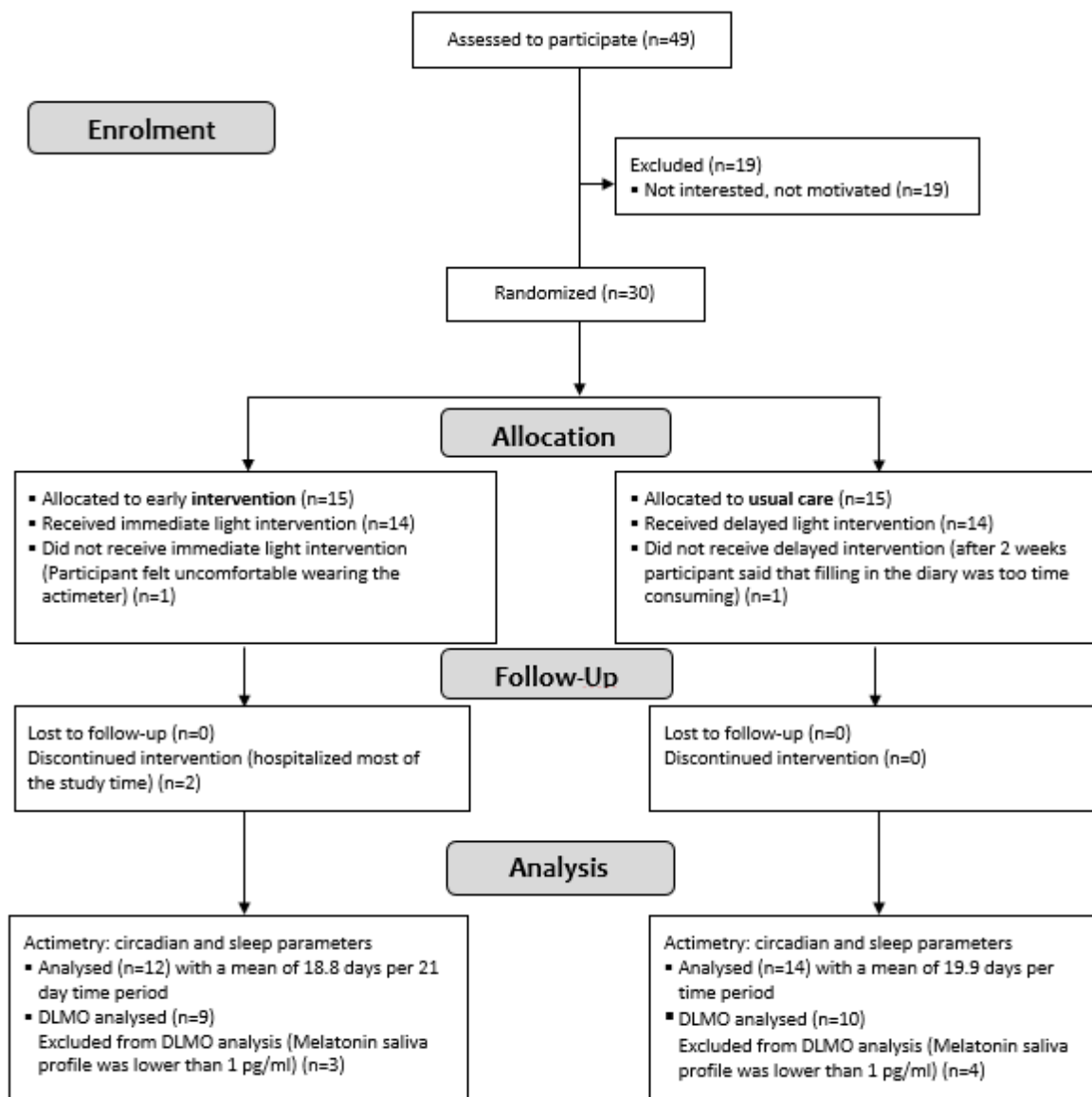


Table 1: Descriptive characteristics of the sample

	All (N=30)		Early intervention (N=15)		Usual care /Late intervention (N=15)	
	N	Percentage	N	Percentage	N	Percentage
Centre 1	13	43.33	6	20	7	23.33
Centre 2	4	13.33	2	6.67	2	6.67
Centre 3	13	43.33	7	23.33	6	20
Males	15	50	8	26.67	7	23.33
	Mean	SD	Mean	SD	Mean	SD
Age	59.63	12.65	60.72	10.33	58.54	14.91
Years since Tx	12.65	6.6	10.33	6.83	14.91	6.6
Chronotype (MEQ)	62.03	10.3	63	10.29	61.06	10.58
Comorbidity Index (CCI)	1.47	1.63	1.8	1.79	1.13	1.46
BMI kg/m <sup>2</sup>	25.12	5.51	24.44	3.69	25.8	6.95
Crea $\mu$ mol/L	144.88	50.94	145.92	60.92	143.85	41.14
Hb g/l	123.42	11.73	122.86	14.47	124.2	7.92
Sleep quality (PSQI)	12.3	3.41	13.27	2.84	11.33	3.75
Daytime sleepiness (ESS)	7.9	3.65	7.93	4.01	7.87	3.4
	N	Percentage	N	Percentage	N	Percentage
Cyclosporin	14	46.67	5	33.33	9	60
Tacrolimus	12	40	7	46.67	5	33.33
Sirolimus/Everolimus	2	6.67	2	13.33	0	0
Mycophenolate mofetil	18	60	9	60	9	60
Azathioprine	7	23.33	3	20	4	26.67
Corticosteroids	10	33.33	5	33.33	5	33.33
Statin	15	50	9	60	6	40
ACE	5	16.67	2	13.33	3	20
ARB	14	46.67	7	46.67	7	46.67
CCB	2	6.67	1	6.67	1	6.67
B-blocker	11	36.67	6	40	5	33.33
Diuretika	5	16.67	3	20	2	13.33
Anticoagulants	9	30	4	26.67	5	33.33
Acetylsalicine	10	33.33	5	33.33	5	33.33
Oral antidiabetica	1	3.33	0	0	1	6.67
Antidepressiva	5	16.67	2	13.33	3	20
Anxiolytika	1	3.33	1	6.67	0	0
Antiepileptica	3	10	3	20	0	0
Benzodiazepine	1	3.33	0	0	1	6.67

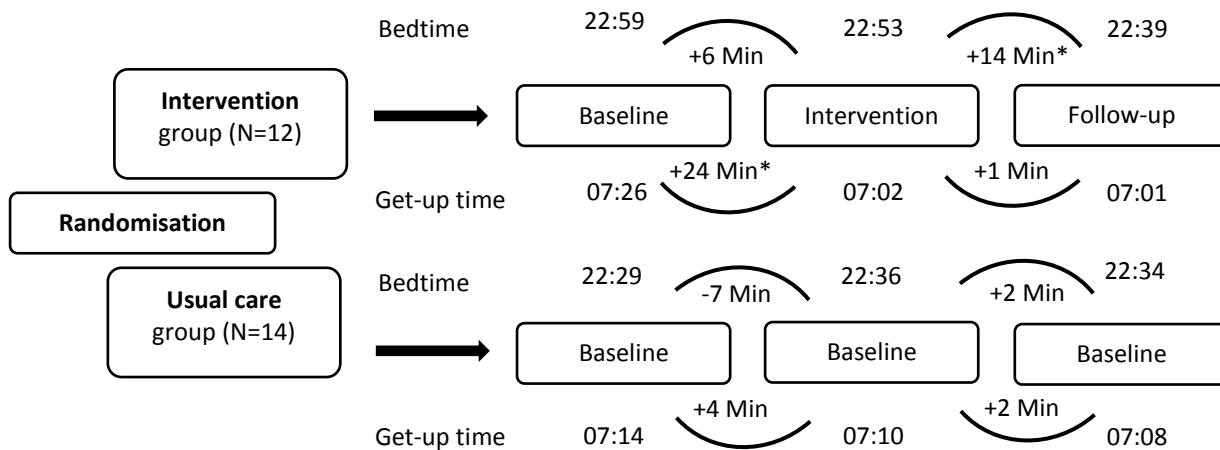
Legend: SD = Standard deviation; MEQ = Morning Eveningness Questionnaire [16-52 evening type; 53-64 normal type; 65-86 morning type]; CCI = Charlson Comorbidity Index; PSQI = Pittsburgh Sleep Quality Index [Score >5 means poor sleep quality]; ESS = Epworth Sleepiness Scale [Score >10 means daytime sleepiness]; BMI = Body Mass Index; Crea = Creatinine; Hb = Haemoglobin; ACE = angiotensin-converting-enzyme inhibitor; ARB = angiotensin receptor blocker; CCB = Calcium-channel blockers;

## Randomized Trial Results

## Primary outcome

Morning light therapy showed a significant phase advance for get-up time from baseline to intervention (+24 min) and a small (+14 min) but significant phase advance for bedtime from intervention to follow-up (Table 2 and Figure 4). A phase advance was specified with a plus sign and a delay with a minus.

Figure 4: Bedtime and get up time for the three measurement periods



Legend: \* = significant outcome; + = Phase advance; - = Phase delay

## Secondary outcomes

Night time sleep latency decreased slightly (-7 min) during therapy and increased again at follow-up. The circadian parameters showed no differences. The circadian hormonal marker (DLMO) was not significantly changed for the early intervention group (baseline to intervention: -13 min and intervention to follow-up: +5 min); however, the usual care group, which was expected to remain stable, experienced an overall phase advance (baseline 1 to baseline 2: +1hour and 44 min). Figure 5 shows the very low melatonin values in our sample, that could have biased the DLMO analysis. Light therapy improved (not statistically significant) subjective feelings in the morning (well-being [+3 points on a scale from 0-10], alertness [+1] and mood [+3]) and depressive symptomatology in the intervention group (baseline-intervention: 5.92-5.75 and intervention to follow-up: 5.75-4.08 [score >5 means depressive symptomatology]). Cognitive executive function was not modified.

## Results of the analysis of the combined early and late intervention datasets

For this pre-post design, we performed a post hoc analysis, adding baseline of the intervention group to baseline 3 of the usual care group and intervention of the early intervention group to intervention of the late intervention group (N=26). Morning light therapy showed a significant phase advance (+17 min) for get-up time from baseline to intervention (Table 2). Other measurements showed no significant effects.

Table 2: Comparison of outcome variables with time

		Usual care Group			Early intervention Group			Analysis of the early & late intervention		
		N	Mean	SD	N	Mean	SD	SE (95% CI)	SE (95% CI)	
Bed time	T1	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	284	22.6	1.49	211	22.89	2.02	T2-T3	<b>-0.25 (-0.41; -0.09)</b>	
	T3	280	22.56	1.28	217	22.66	1.83	T1-T3	-0.13 (-0.29; 0.03)	
Get-up time	T1	276	7.24	1.39	248	7.44	1.69	T1-T2	<b>-0.23 (-0.42; -0.03)</b>	<b>-0.21 (-0.32; -0.11)</b>
	T2	284	7.17	1.37	211	7.03	1.79	T2-T3	<b>-0.22 (-0.42; -0.03)</b>	
	T3	280	7.13	1.16	217	7.01	1.42	T1-T3	0.00 (-0.19; 0.20)	
Sleep efficiency	T1	276	73	17.61	247	77.16	12.44	T1-T2	0.00 (-0.16; 0.17)	0.07 (-0.02; -0.15)
	T2	284	72.1	17.16	211	75.67	12.76	T2-T3	-0.05 (-0.21; 0.12)	
	T3	280	71.82	17.47	217	74.72	12.4	T1-T3	-0.05 (-0.21; 0.11)	
Sleep latency	T1	276	33.21	0.80	277	45.35	0.81	T1-T2	-0.18 (-0.40; 0.04)	-0.07(-0.18;-0.04)
	T2	284	33.55	0.81	211	38.38	0.16	T2-T3	0.08 (-0.14; 0.30)	
	T3	280	34.61	0.86	217	49.15	0.76	T1-T3	0.26 (0.04; 0.48)	
Interdaily stability	T1	14	0.59	0.11	12	0.59	0.09	T1-T2	0.18 (-0.42; 0.78)	-0.11(-0.42;-0.19)
	T2	14	0.57	0.09	12	0.57	0.12	T2-T3	0.25 (-0.36; 0.86)	
	T3	14	0.58	0.1	11	0.62	0.11	T1-T3	0.07 (-0.54; 0.68)	
Intradaily variability	T1	14	0.74	0.14	12	0.72	0.13	T1-T2	0.00 (-0.04; 0.04)	0.02 (-0.01;-0.05)
	T2	14	0.76	0.18	12	0.74	0.15	T2-T3	0.00 (-0.04; 0.05)	
	T3	14	0.76	0.18	11	0.73	0.13	T1-T3	0.01 (-0.04; 0.05)	
Relative amplitude	T1	14	0.8	0.1	12	0.84	0.05	T1-T2	0.09 (-0.41; 0.59)	-0.14 (-0.39;-0.10)
	T2	14	0.78	0.13	12	0.81	0.1	T2-T3	-0.17 (-0.68; 0.33)	
	T3	14	0.81	0.11	11	0.84	0.09	T1-T3	-0.26 (-0.77; 0.24)	
Dim Light Melatonin Onset	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	T1	10	49.2	5.77	12	49.17	10.08			0.10 (-0.21;-0.41)
	T2	8	50.38	14.73	11	48.45	6.52			
	T3									

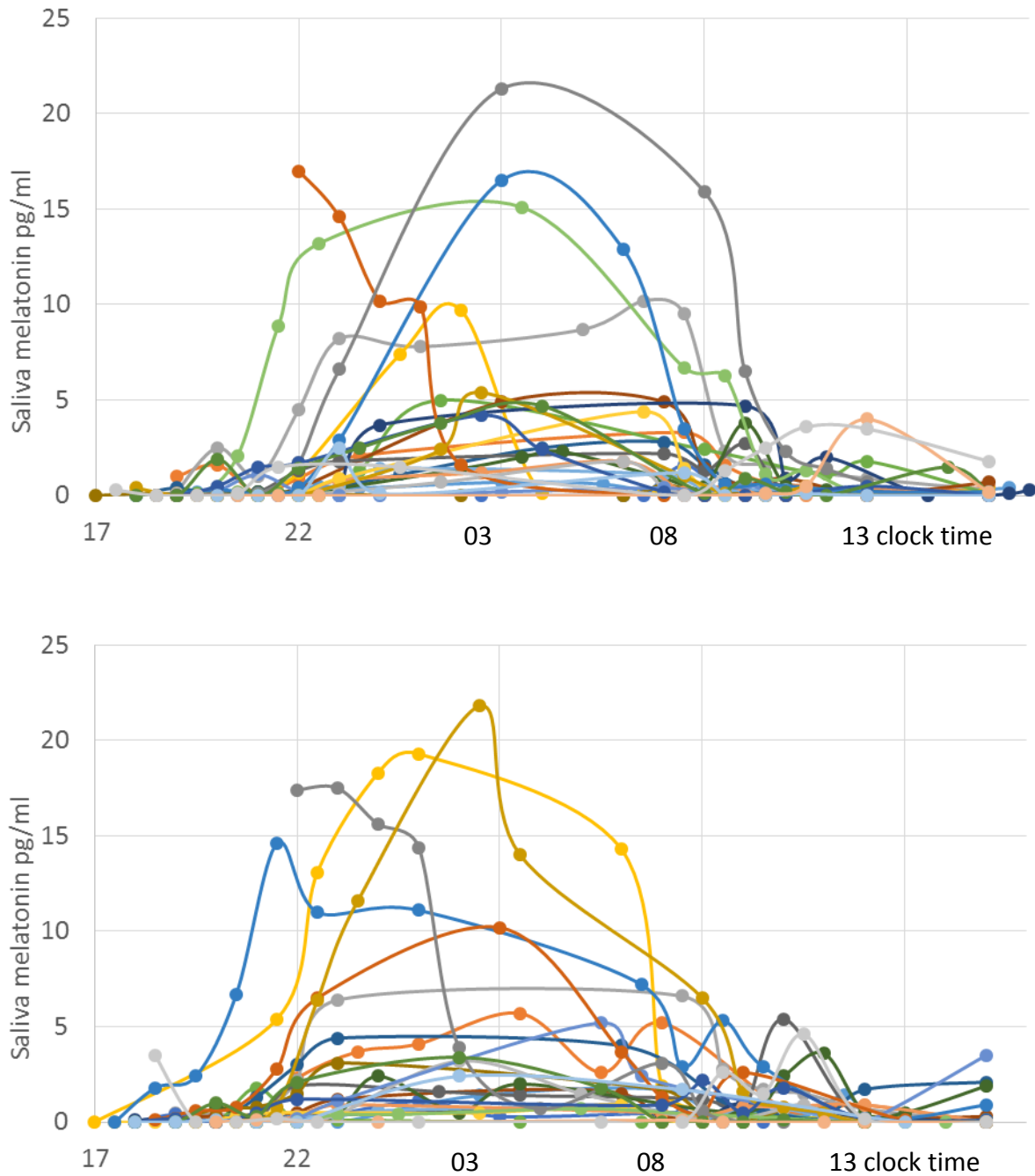
Legend: SD = Standard deviation; T= time; SE = Standardized Estimates; 95% CI = 95% confidence interval

## Post-hoc subgroup analysis of the combined early and late intervention datasets

Intriguing was the high incidence of low melatonin secretion in many patients (figure 5). Beta-blockers (BB) and acetylsalicylic acid (ASA) are known to suppress melatonin[45], however it is unclear whether ASA inhibits melatonin secretion via prostaglandin synthesis as is known for non-steroidal anti-inflammatory drugs[46]. Therefore we postulated the following post-hoc hypotheses: RTx recipients taking BB and /or ASA will not show a light effect on phase advancing bedtime and get up time, and sleep efficiency and sleep latency will not improve. The Post-hoc subgroup analysis of the combined early and late intervention datasets showed that in total, 17 patients were taking BB and/or ASA, known to possibly block melatonin secretion. Compared to these 17, those using neither BB nor ASA showed a non-significant phase advance 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, i.e., with a power of 80%, would require much larger samples (N=260,182 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.

Figure 5: Saliva melatonin (pg/ml) profiles at baseline and after light therapy (N=26)



Legend: Each color sequence represent one participant

### Treatment satisfaction and adverse reaction

Twenty of 25 subjects who answered the question wrote that they would recommend light therapy to a friend. However, only 13 reported that they considered it helpful. No adverse reactions or symptom complaints were registered. Only 2 participants stopped the study because it was “too burdensome” and there were no extra calls and visits due to problems with the study equipment.

## 7.5. Discussion

This is the first study testing the feasibility and the effect size of morning light therapy on improving sleep problems in a sample of chronically ill RTx recipients, measuring circadian and sleep parameters over several weeks. Morning light therapy phase advanced bedtime and get-up time, but circadian parameters, including the onset of nocturnal melatonin secretion, showed no earlier shift. Depressive symptomatology, mood and well-being improved, as did alertness, confirming this treatment's previously described benefits[47]. Light therapy had no effect on cognitive executive function, which was not impaired at baseline when compared with healthy similar age cohorts[48].

Analysis of the combined early and late intervention data showed only a small phase advance after bright light therapy for get-up time, possibly indicating that participants adhered to the timing of the intervention resulting in a sleep restriction (because of the intervention participants had to get up). However, no direct impact of bright light therapy on bedtime was seen for the entire group.

This relatively small improvement in sleep-wake function indicated that perhaps the treatment timing or dosing was inadequate or, that RTx recipients have more complex clinical problems that short-term light therapy cannot influence. This is suggested by the large inter-individual differences in response. Intriguing was the high incidence of low melatonin secretion in many of these patients. Most RTx recipients' medication regimens include co-treatment for cardiovascular prophylaxis[49], including BB and ASA[50]. The post-hoc analyses indicated a possible connection with BB and /or ASA use inhibiting melatonin secretion and thus indirectly affecting sleep. This suggests that BB treatment in these patients should preferably be with drugs not suppressing melatonin (nebivolol or carvedilol[51]), rather than bisoprolol, which may prevent development of sleep-wake disorders. Supplementation with melatonin should be considered, however with caution, as melatonin might interact with other drugs[52] and might cause sleepiness and dysphoria[53]. No studies have been published on melatonin supplementation in RTx

recipients, although it has shown short-term benefits in haemodialysis patients[54] regarding sleep efficiency, sleep duration and sleep fragmentation[55].

Another reason for the low saliva melatonin profiles could be the calcification of the pineal gland and the melatonin pathways[56, 57]. Most RTx recipients have a more or less pronounced renal failure that might result in disturbances of bone formation and degradation, biochemical blood changes increasing soft-tissue and blood vessel calcification. Depending on the therapy adherence for hyperphosphatemia and supplementation of active vitamin D, the calcification of the pineal gland and melatonin pathways may be more or less pronounced.

The phase advance of +14 minutes for bedtime was statistically significant. The internal clock of humans has an endogenous circadian period of 24.18h [58]-roughly 12 minutes longer than the external 24-h day-night cycle-requiring daily phase-advancing synchronisation by zeitgebers, primarily light [58]. Thus, a phase advance of a quarter-hour is also biologically meaningful.

There are studies suggesting that increasing the duration of light therapy is more effective than increasing light intensity[59, 60]. Thus, our 30 minute light treatment may have been too brief, and longer expositions may be required - both per day and in number of weeks. An analogy is found in major depression - although patients with seasonal affective disorder generally improve with the 30 min regimen within two weeks[61], non-seasonal depressives require at least an hour of this intensity light for at least five weeks[62]. Using a lamp but prescribing additional regular time spent outdoors (where light intensity is much greater) may be an effective practicable combination. Another possible reason for the lack of a large effect could have been that we did not control the exposure to light in the evening, which may have cancelled out the morning light induced phase advance[22]. Here, the use of blue-blocking glasses in the evening, which prevent the strong phase delaying effect of blue wavelengths, may be helpful[63].

### **Strengths and Limitations**

Compared to other RCT or pre-post studies using actimetry and measuring melatonin profiles, this was a large study[24]. However, as this was a pilot study, estimation of uncertainty in generalizability of relationships found was only of secondary interest; therefore no p-values are displayed and no alpha correction has been performed. Future studies could limit baseline to two weeks with a two-week follow-up (to reduce study burden), although we recommend 5 weeks of light therapy rather than three[47].

### **Conclusion**

This pilot study on the effect of morning light therapy on RTx patients' sleep disorders showed a phase advance in bedtime and get-up time and improved depressive mood. A number of hypothesis-generating analyses suggest that melatonin production inhibitors interfere with the optimal response to light therapy in this population.

### **Acknowledgement**

We gratefully acknowledge R. Roth and A. Trevisan for their help in the data collection. Further, we acknowledge T. Kepper and J. Tai for their assistance in meticulously editing actimetry data. Special thanks are also due to Dr. V. Bromnudt and Dr. D. Taibi for sharing actimetry experiences, C. Renz for instruction regarding melatonin centrifugation and freezer organization, as well as to Prof. C. Müller & I. Klimmek, Prof. J. Steiger & D. Biemann for their assistance with long-term melatonin sample freezer storage. Finally, we cordially thank C. Shultis for his medical editing.



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# CHAPTER 8

**GENERAL DISCUSSION OF THE DISSERTATION  
TITLED: “BRIGHT LIGHT THERAPY IN RENAL  
TRANSPLANT RECIPIENTS WITH SLEEP-WAKE  
DISTURBANCE”**



sleep-wake disturbances in solid organ recipients following the diagnostic criteria used in sleep medicine.

Using data from the Swiss Transplant Cohort Study (a prospective nation-wide cohort study), we conducted a secondary data analysis (N=1076) to describe the prevalence and variability of sleep quality from pre- to two years post-transplantation in kidney, liver, lung and heart recipients and to examine the association between impaired sleep quality and perceived health status. Our analyses revealed that sleep quality improved from pre- to post-transplantation, and that sleep quality predicted health status. The analysis of the sleep quality screening item at pre- and yearly post-solid organ transplantation showed that, of the four major organ transplantation groups, liver transplant recipients had the highest prevalence of poor sleep quality pre-transplantation. At six months post-transplantation, all organ groups showed improved sleep quality, with prevalence of poor sleep quality stabilizing at 22-30%.

Those individuals diagnosed with sleep-wake disturbances during the sleep assessment interview were invited to participate in a pilot randomized controlled bright light intervention study. The primary aim was to examine the impact of the intervention on bedtime (assessing whether light phase advanced their rhythm). As secondary outcomes, the impacts on circadian and sleep parameters, depressive symptomatology, mood and selective attention were also analysed. All members of the group (N=30) were treated with morning light therapy. They were randomized into two equal groups, with fifteen assigned to the intervention group (light therapy after a 3 week baseline assessment) and fifteen to the control group (light therapy after a 9 week baseline assessment, wait-listed).

Compared to the control group, the intervention group showed significant phase advances in both bedtime and get-up time, i.e., 19 min and 22 min respectively. (The internal clock of humans has an endogenous circadian period of 24.18h [2]-roughly 12 minutes longer than the external 24-h day-night cycle-requiring daily phase-advancing synchronisation by zeitgebers, primarily light.[2] Thus, a phase advance of a quarter-hour is biologically meaningful. A second analysis, using full wait-listed design (pre-post analysis) intervention data, showed a phase advance only in get-up time (17 min). As saliva melatonin profiles were extremely low, changes were difficult to detect. No significant phase advance could be determined in the intervention group. However, post-hoc analysis revealed that light therapy significantly increased sleep efficiency (4.9%) and decreased sleep latency (6 min) in renal transplant recipients taking neither beta-blockers nor acetylsalicylic acid (substances with known potentials to inhibit melatonin secretion). Light therapy also improved depression and mood in the entire group without affecting selective attention.



## 8.2. Discussion and implication for practice

The results of this research program emphasize the principle that sleep is a central function that needs to be incorporated into long-term follow-up after solid organ transplantation [3]. In the introduction to section 1.7.2, we reviewed studies showing short-term outcomes following solid organ transplantation [4-10]. These studies show that solid organ transplantation has become a routine procedure, allowing expansion of the criteria for transplantation [11]. Still, while there have been major improvements in short-term sleep-related outcomes following transplantation, the same improvements have not been observed in long-term outcomes [12]. This short-term improvement is basically a reduction in acute rejection rates, leaving a strong need to understand and control the side effects and long-term consequences of immunosuppressive treatment [11, 13]. Improving long-term outcomes in view of sleep, health-related quality of life, morbidity and mortality requires a holistic follow-up program rooted in the chronic illness framework [14, 15]. In the Chronic Care Model, Wagner et al. (2001) defined essential elements of a system to increase care quality beyond the capacity of the acute care model. Cross-linked (community, health system, self-management support, delivery system design, decision support and clinical information systems) evidence-based concepts foster productive interactions between informed patients who take an active part in their care and providers with resources and expertise [16]. Recapitulating, the chronic illness management approach combines four basic components: (1) ensuring access to and continuity of care; (2) increasing opportunities for patients to participate in their care process; (3) coordinating care between care settings; and (4) providing continuous self-management support.

### 8.2.1. Sleep tracking in the chronic illness management

Psychosocial outcomes have their own influence on long-term post-transplant morbidity and mortality rates [17, 18]. Quality of life improves from pre- to post-transplantation, however there is no consistently positive change in psychological health [19]. The longitudinal study of Silva et al (2012) shows excellent evidence that sleep improves from pre- to post-renal transplantation; however, in long-term follow-up, sleep remains poor and poor sleep remains associated with poorer perceived health status [12]. In other chronically ill patients, sleep disturbances are among the factors shown to negatively impact long-term outcomes, and are associated with higher risks of cardiovascular disease [20], metabolic derangements [21-25], diabetes [26], chronic inflammation [27, 28] and accelerated mortality [29-33] in the general population. Likewise, short sleep times (<5

hours) are associated with coronary artery calcification [34], with increased risks of overall cardiovascular events and myocardial infarction [35]. Finally, sleep duration of less than 6 hours or more than 8 hours has been associated with depression [36]. The best survival rate was found among those who slept 7 hours per night [37].

Considering these results, our research supports the importance of addressing sleep-related issues in the follow-up care of transplant recipients. Using a single validated item (Chapter 3) to measure daytime sleepiness, we demonstrated the high prevalence of this sleep-related disturbance in renal transplant recipients. Just over half of the 935 renal transplant recipients surveyed reported daytime sleepiness. An extensive review of the literature on sleep disorders in transplant recipients revealed only one study that had previously measured daytime sleepiness, but which, unfortunately, did not report its prevalence. In this same sample (Chapter 4) we found a significant association between daytime sleepiness and medication non-adherence—another behavior shown to negatively impact long-term transplantation outcomes [38]. We were the first investigators to report the prevalence of daytime sleepiness following transplantation and to examine its relationship to medication non-adherence in renal transplant recipients. Our association confirms the findings of Riegel et al. (2011) [39], who reported that the odds of non-adherence increased by 11% for each unit increase in the daytime sleepiness score (adjusted OR: 1.11; 95% confidence interval: 1.05-1.19;  $p = .001$ ). Indeed, we found a 9% increase for each unit increase in the daytime sleepiness score (adjusted OR: 1.09; 95% confidence interval 1.04-1.14;  $p = .001$ ) [40].

The findings of both these studies have important implications for clinical practice and research. Both emphasize the importance of screening for daytime sleepiness during transplant recipients' follow-up care. When patients report daytime sleepiness, it is emphasized that clinicians should assess medication adherence and implement interventions, such as reminders and/or cueing systems. Since daytime sleepiness has such a high prevalence in renal transplant recipients, it is advisable to examine its prevalence in other transplant populations as well, along with its impact on other transplant-related outcomes. In addition, future studies should identify effective interventions (interventions to target the patient, health care provider, health care organization or health care system) against this sleep-related problem to minimize its impact on medication non-adherence.

### **8.2.2. Sleep screening in prospective studies**

In the study described in Chapter 6, we examined changes in the prevalence of impaired sleep quality from pre- to post-transplant in heart, lung, liver and kidney transplant recipients. While we found that reports of poor sleep quality decreased from

pre- to 6 months post-transplantation, 32 to 39% of the 1076 patients surveyed continued to report impaired sleep quality. Measurements were conducted via the sleep quality item validated in our previous research [41, 42], which was subsequently incorporated in the ongoing assessment of subjects in the Swiss Transplant Cohort Study.

In the same cohort of subjects (Chapter 6), we found a positive association between sleep quality and perceived health status, i.e., analysis revealed that sleep quality was a significant predictor of patients' health status ( $p < .0001$ ). Those with poor sleep quality scored on average 10 points lower on the 100-point VAS self-reported health status scale [43]. This supports the findings of Silva et al. (2012), who reported that renal transplant recipients with poor sleep quality also had lower scores in health related quality of life [12]. Conversely, and also consistent with our findings, an epidemiological study using personal interviews of 1139 healthy adults reported that good sleep quality was related to better physical health ( $r = 0.26$ ;  $p < .001$ ) [44]. Further, a study analyzing the electroencephalographic sleep parameters of 185 healthy older adults found that, controlling for age, gender, and baseline medical burden, individuals with baseline sleep latencies greater than 30 minutes were at 2.14 times greater risk of mortality ( $p = .005$ , 95% CI: 1.25;3.66) within the range of 4.1-19.5 years follow-up time. Those with sleep efficiency less than 80% were at 1.93 times greater risk ( $p = .014$ , CI: 1.14;3.25). All of these points highlight the importance of assessing sleep to improve perceived health status, health related quality of life and even mortality rates.

Plans to examine the predictive value of sleep quality regarding mortality in the Swiss Transplant Cohort Study are also both interesting and relevant. The results could then be compared to those of the Dialysis and Outcome Practice Pattern Study, which used the same sleep quality measurement tool and showed that the relative risk of mortality was 16% higher for hemodialysis patients with poor sleep quality [45] within the range of 0-5.2 years follow-up time. Elder et al. (2008) reported that serum phosphorus (uremia related factor) and poor health-related quality of life accounted for the main associations with poor sleep quality.

Our findings in relation to both sleep quality and daytime sleepiness support the importance of screening all transplant recipients for these important characteristics. Integrating sleep parameters in prospective longitudinal studies is a sign of the paradigm change towards a chronic care model, i.e., one focusing on tracking long-term outcomes. The two sleep items we validated as part of this research and a previous study [42] provide a simple and valid means of screening for sleep disorders in both clinical practice, where the time allotted for clinical encounters is often limited, and in research, where subject burden needs to be considered during measure selection. Short valid items with predictive

value regarding long-term outcomes and mortality rates will have the highest chance of integrated into prospective longitudinal cohort studies. In fact, the issue of patient burden may soon become decisive for studies' approval. As departments of health and ethics commissions are tightening regulations on participants' health and well-being, updated guidelines limit the lengths of information documents and questionnaires [46]. By developing and testing a short item measuring daytime sleepiness in renal transplant recipients, the research presented here contributed to this process by reducing the participants' burden (Chapter 3) [1].

### **8.2.3. Importance of in-depth sleep assessments**

While screening is the first step in identifying patients with sleep disorders, screening questions alone are insufficient to diagnose specific sleep disorders. Poor sleep quality and daytime sleepiness can be symptoms of insomnia, circadian rhythm sleep disorders, sleep related breathing disorders or sleep related movement disorders. Values higher than 4 on the daytime sleepiness item [1] or lower than 6 on the sleep quality item [42] should trigger a more detailed assessment by health care professionals. A positive screening result could indicate an acute or chronic sleep problem. Therefore, assessment questionnaires, such as the “Survey of Sleep” used in our research program (chapter 5), are useful in identifying the type of sleep disorder the patient is experiencing as well as identifying those patients who should be referred to a sleep specialist.

While the most effective intervention will vary with the type of sleep disorder the patient is experiencing, the sleep hygiene rules (see section 1.6.2) are safe first-line interventions for most patients with sleep disorders. All healthcare professional should be familiar with these simple and safe interventions, which can be recommended while the more detailed assessment is being conducted. The findings on this assessment questionnaire, including comments of one or more family members, screen patients for chronic sleep disturbances. The questionnaire responses can be evaluated by a certified sleep expert, who can then prescribe any further diagnostic measures and eventually recommend evidence based interventions. Ideally this should be integrated in a chronic illness management approach.

At this point the follow-up care team needs to be involved to ensure that the selected treatment does not compromise immunosuppression or otherwise endanger the transplanted organ. According to Buysse (2013), given insomnia's interactions with comorbid conditions and medications, primary care physicians or other health care professionals (e.g., advanced practice nurses) should have competencies to tailor and

deliver the appropriate treatment [47]. A thorough evaluation and treatment by a sleep specialist are appropriate when the patient has symptoms or clinical features of another sleep disorder, such as excessive daytime sleepiness, narcolepsy, sleep-related breathing disorders (apnea, loud snoring or witnessed apneas), circadian rhythm sleep disorders (pronounced alteration of sleep timing), or parasomnia (unusual sleep behaviors, including somnambulism, that can endanger the patient) [47]. Buysse recommends that transplant physicians or advanced practice nurses should be trained in the interpretation of the major sleep diagnosis questionnaires (e.g., Survey of Sleep). This implies integration of sleep assessment and knowledge into school curricula and routine clinical assessment procedures.

In our study examining the prevalence of specific sleep disorders in renal transplant recipients, the prevalence was 42.5% for insomnia, 20.1% for circadian rhythm sleep disorders, 4.9% for obstructive sleep apnea and 0.6% for sleep related movement disorders [48]. Compared to those reported in previous studies of renal transplant recipients, the prevalence of insomnia was higher (8%[49, 50] - 16%[51]), while the rates of obstructive sleep apnea (25% [51, 52]), periodic limb movements (16% [53] - 27% [51]) and restless legs syndrome (4% to 5% [49, 50, 53-55]) were lower. One possible explanation for these discrepancies is that we used a preselected sample, i.e., included only renal transplant recipients screened for poor sleep quality and / or daytime sleepiness. Further, we assumed that most patients who participated had further “hidden” sleep disorders. Very often snoring, sleep apnea and movement disorders are perceived by a patient's spouse reported and treated. However, the reliability of spouses' observations is unknown, and our medical reports include no sleep reports indicating the prevalence of obstructive sleep apnea, periodic limb movements or restless legs syndrome in renal transplant recipients. If the assumption is false, i.e., if spouses are actually very poor reporters of such symptoms, this could explain the apparently low prevalence in our sample of obstructive sleep apnea, periodic limb movements and restless legs syndrome.

Further, these studies used different methodologies and assessment systems. Earlier researchers assessed insomnia with the Athens Insomnia Scale (an 8-item questionnaire) [49-51] and no assessment interview. In addition, while the studies assessing obstructive sleep apnea, periodic limb movements and restless legs syndrome used polysomnography [51, 53] or the restless legs questionnaire [49, 50, 54, 55], we used a general assessment interview. These inconsistencies in the reported prevalence of specific sleep disorders support the need for additional research to characterize both the sleep disorders experienced by renal transplant recipients and the risk factors attached to those disorders.

#### 8.2.4. Bright light therapy for sleep-wake disturbances

While the most appropriate treatment for sleep disorders will vary with the type of disorder, in our final research study (Chapter 7), we evaluated the impact of a self-managed intervention -bright light therapy- in renal transplant recipients with sleep-wake disturbances (insomnia and circadian rhythm sleep disorders). We chose this therapy as it is safe (no increased risk of skin cancer, no interaction with pharmacological treatment or eye damage as ultraviolet rays are filtered [56]), and has been used effectively to correctively shift, synchronize, and stabilize circadian rhythms in non-transplant populations [57-62].

Bright light therapy is effective in the early morning to phase advance the circadian rhythm [57, 58] and in the early evening to phase delay it [59]. Further, Yoon et al. (2002) showed that light therapy aids night shift workers' adaptation to their changed schedules. [60] Crowley et al. (2004) added that bright light improved performance, alertness, and mood during night-shift work [61]. Eastman et al. (2005) in a lab study to develop a practical pre-eastward flight treatment found that morning light therapy combined with evening light restriction has significant benefits against eastward flight jet-lag [62], while evening light therapy and morning light restriction is useful for westward flights [63]. Light therapy was first developed for treating seasonal affective disorder [64]. In Switzerland, bright light therapy is the first choice treatment for this disorder and is covered by standard health insurance. Furthermore, light therapy has been used efficaciously as an adjunct therapy to improve mood [65], sleep [66], major depression [67, 68], antepartum depression [69], eating disorders [70], attention deficit hyperactivity disorder [71], borderline personality disorder [72], Parkinson's disease [73] and Alzheimer's disease [74]. Of two studies using light therapy after surgery, one showed reduced delirium scores [75], while, in the other, fewer arrhythmias were recorded [76] in patients following surgery for oesophageal cancer.

Our decision to use bright light therapy was based on the observation that most of the patients we assessed had late chronotypes, with complaints including difficulty falling asleep and staying asleep at night, and daytime sleepiness [48]. Evening chronotypes manifest a delayed sleep phase, characterized by inability to fall asleep or wake up at the desired time, followed by excessive daytime sleepiness [77]. Bright light capacity to shift the biological clock forward or backward, depending on time of administration, gives it particular therapeutic value for circadian rhythm sleep disorders, and for adjusting to shift work or jet lag [57]. Light therapy improves the robustness of the circadian rhythm [78-80]. Circadian rhythm phase shifts can be indirectly measured via the timing of bedtime

and wake-up time, core body temperature [81], but most precisely by the onset of nocturnal melatonin secretion [82].

In our randomized controlled pilot study, we measured significant phase advances both for bedtime (14 minutes between the light intervention period and follow-up), and for get-up time (24 minutes from baseline to intervention completion). The overall phase advance is not surprising, as early morning bright light therapy is commonly used to phase advance delayed sleep syndrome [57]. However, it is interesting that more than 3 weeks (the intervention period) were necessary to phase advance bedtime. This confirms studies suggesting that increasing the duration of light therapy is more effective than increasing light intensity [83, 84]. Regarding get-up time, the phase advance was related to the light treatment time scheduled according to the chronotype; therefore, this result only reflects subjects' adherence to the early morning light therapy.

Our findings in relation to the onset of melatonin secretion lack a conclusive explanation. In the usual care group, whose melatonin levels were expected to remain stable, we measured a considerable overall phase advance (baseline 1 to baseline 2: +1h:44min). We presume that this phase advance was related to a rise of melatonin in the early evening, which might have been an artefact of the low salivary melatonin profiles we had originally recorded, compared to those of other studies sampling salivary melatonin [72, 79, 85, 86]. Previously reported reasons for lack of melatonin response include hormone cycle dysfunction, damaged melatonin receptors or disease-precipitated night-day rhythm reversal (Smith-Magenis Syndrome, a developmental disorder) [87].

Reasons for low profiles include: 1) personal characteristics (e.g., individual variation, gender [88, 89], age [90] and body size [91, 92]); 2) comorbidities (e.g., glaucoma, cataracts, retinal detachment, retinopathy hindering the light to act on the pineal gland); 3) medication side-effects (e.g., non-steroidal anti-inflammatory drugs (which suppress melatonin)[93]; treatment with calcium channel blockers (which reduce melatonin output [94]), oral contraceptives [95], anti-coagulants (warfarin [96]), diabetes medications [97], and beta blockers such as bisoprolol (which suppresses melatonin [98])); and 4) calcification of the pineal gland (location of melatonin secretion) [99]. Regarding the condition of the pineal gland, urinary measurement of melatonin (levels of 6-sulfatoxymelatonin) positively correlate with the volume of uncalcified pineal tissue [100]. Calcification is a cellular degeneration process which increases with age [101, 102].

Most renal transplant recipients were treated with hemodialysis pre-transplantation; therefore, they commonly suffer from decreased calcitriol production, which leads to a mineral-bone metabolic disorder. This disorder is expressed in abnormal

serum calcium, phosphorus and parathyroid hormone levels [103]. Consequently, hemodialysed patients have a higher prevalence of aortic calcification compared to the general population (79% vs. 37.5%) [104]. It follows that the probability that hemodialysis recipients also have calcified pineal glands is very high. This hypothesis should be explored further.

For these reasons the low level of melatonin profiles could be a remnant of end stage renal disease. Except beta blockers and acetylsalicylic acid levels, none of the described factors were assessed, leaving considerable uncertainty as to which factor was the most relevant in our patient group. We assume that beta blockers and acetylsalicylic acid were a major factor in our pilot study, as controlling for these medications resulted in a significant improvement in sleep efficiency (+4.9%) [Standardized estimates: 0.42; 95%CI 0.20; 0.65] and sleep latency (-6 min) [Standardized estimates: -0.28; 95%CI -0.45; -0.10]. Finally, measures of wellbeing, alertness, mood and depressive symptomatology improved (though non-significantly) following light therapy. We presume that this lack of significance results from not having included subjects with clinical depression (the baseline score of depressive symptomatology was not pathological; bright light therapy known to be beneficial in the treatment of patients with depression [105]). Also, in chronic illness patients, longer treatment times and/or higher dosages of light may be necessary. In summary, our results do not support prescribing bright light therapy for all renal transplant recipients with sleep-wake disturbances. Future bright light intervention studies should address dosage and duration issues, and be fully powered to allow a stratification of many of these factors that might compromise its effects.

Should future studies support the benefits of light therapy in treating sleep disorders in transplant recipients, alternatives to light applied with a special lamp are to take a daily walk lasting at least an hour outside (light intensity for a cloudy day 5000 lux), [106], or reduce the exposure to light in the evening [57]. One technique for this is the use of amber (blue-blocking) glasses in the evening [107]. Since evening light, especially blue light, suppresses melatonin production [108]), amber lenses support the melatonin rise in the evening, thereby advancing sleep timing [107].

Another alternative to light therapy is melatonin supplementation in the evening to phase advance or stabilize the circadian rhythm. Melatonin has to be prescribed carefully in low dosage: it produces soporific effects which are helpful for falling asleep rapidly in the evening, but can result in residual morning sleepiness. Compared to other drugs used for insomnia, melatonin supplementation has a benign side-effect profile, low cost and limited evidence of habituation or tolerance [109]. A recent meta-analysis demonstrated that melatonin decreases sleep onset latency, increases total sleep time and improves



overall sleep quality [109]. Melatonin supplementation has the strongest effect when taken in the late afternoon, 2-4 h before the normal dim light melatonin onset (9-11 h before sleep midpoint) [110]. For solid organ transplant recipients no contraindications are known; however, all of the aspects mentioned above (section 1.7.4) have to be considered before supplementation.

### 8.3. Implications for future research

Implications for future research that can be derived from this thesis include: (a) the need for sleep diagnosis prevalence studies in heart, lung and liver transplant recipients; (b) the need for prospective studies examining the impact of sleep disorders and their effect on long-term outcomes following transplantation, and (c) the need for a full-powered study (allowing for the control of potential confounders) to test the beneficial effect of bright light therapy.

To advance the current knowledge regarding sleep prevalence data in kidney, heart, lung and liver transplant recipients, larger cohort studies are needed. Future studies should collect regular sleep follow-up screening data, as well as including information of the assessment, the diagnosis, and treatment of any sleep disorders identified. The sleep and daytime sleepiness screening data collected in the Swiss Transplant Cohort Study over the coming years should be analyzed in view of acute and chronic rejection and mortality. These data could be compared with the Dialysis Outcome and Practice Pattern Study, which showed the predictive validity of poor sleep quality in view of mortality in hemodialysis patients [45].

Our pilot randomized controlled trial revealed a relatively small improvement in sleep-wake function, suggesting that renal transplant recipients may have more complex clinical problems than short-term light therapy can influence. However, the phase advance and the small improvement for depressive symptomatology and subjective feelings in an underpowered study might have occluded the effect. From this perspective a fully powered study using light therapy as an intervention to synchronize sleep-wake disturbances is clearly necessary. Such a study would allow adjustment for beta blockers, non-steroidal anti-inflammatory drugs and calcification processes in the pineal gland. A longer course of treatment with longer daily light sessions may be useful [83, 84] to ensure the minimal exposure of 30 minutes, [111] which we hoped to achieve in our randomized controlled pilot study.

Finally, improving long-term transplantation outcomes will require the integration of chronic illness based follow-up programs [112], including screening for sleep, standardized

operational procedures for positive screeners and a choice of safe sleep interventions for solid organ transplant recipients. Wagner et al. (2001) promoted the concept of the informed and active patient [16]. Models that adopt this explicitly patient-oriented approach, i.e., “complex intervention research”, are likely to have the greatest effects on patient outcomes (Zwar et al., 2006)[113]. The model and its process are complex, as the experimental and control interventions include several interacting components, and the main focus is effectiveness in everyday practice [114]. Another framework for intricate interventions is the intervention mapping approach [115, 116]-a protocol for complex guidance and a tool for the planning and development of health promotion interventions [115]. The planning process is iterative rather than linear, and the program planners move back and forth between tasks and steps. The process is cumulative, i.e., each step is based on the results of previous steps, so inattention at one stage may lead to later mistakes and inadequate decisions [116].

#### 8.4. Conclusion

The multicenter sleep survey described here provided interesting prevalence data for daytime sleepiness (prevalence 51%; mean age:  $58.0 \pm 12.3$  y.; mean years since transplantation:  $10.6 \pm 7.6$ ) in renal transplant recipients. Furthermore, validation of the single item measuring daytime sleepiness was achieved, allowing quick, easy measurements of daytime sleepiness in longitudinal cohort studies with item restrictions. Using data from the Swiss Transplant Cohort Study, we found that sleep quality is predictive of perceived health status ( $p < .0001$ ). Analysis of the multicenter sleep survey data also confirmed the hypothesized theoretical association between non-adherence and daytime sleepiness. Based on multivariate logistic regression analysis, daytime sleepiness was a significant predictor ( $p < 0.001$ ) for taking (1.09 [1.04-1.14]), timing (1.06 [1.03-1.10]) and overall non-adherence (1.09 [1.05-1.13]) in a sample with a mean age of  $58.0 \pm 12.3$  y and a mean of  $10.6 \pm 7.6$  y years since renal transplantation. The sleep assessment interview study revealed a high prevalence of sleep-wake disturbances in renal transplant recipients. Most (49.4%) reported difficulty staying asleep, followed by problems falling asleep (32.1%). The assessment interview showed that most suffered from insomnia. In the pilot RCT, bright light therapy showed a beneficial effect in a subgroup of patients (renal transplant recipients taking neither beta-blockers nor acetylsalicylic acid, both of which are known to inhibit melatonin secretion), which provided valuable data on how to improve the intervention study, possibly with longer daily doses of light and/or a longer duration of treatment, and to plan a larger randomized controlled trial.

## References Chapter 8

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# CURRICULUM VITAE & PUBLICATIONS

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# CURRICULUM VITAE

## Education

### Graduate

- 2010-present: PhD student (ongoing) University Basel, Switzerland  
 2007-2009: MASTER'S DEGREE IN NURSING SCIENCE University Basel, Switzerland

### Undergraduate

- 2006-2007: BACHELOR'S DEGREE IN NURSING SCIENCE University Basel, Switzerland  
 2002-2004: Specialization in Intensive Care Nursing Department of Intensive Care University Hospital of Basel, CH  
 1995-1999: Basic Nursing Degree: Diplommiveau 2; Berufsschule für Gesundheit und Krankheit Chur, CH  
 1991-1995: Matura Typ Economics; Gymnasium: Liceo Cantonale di Locarno, CH

## Appointments and Positions

### Non-academic / clinical appointments

- 04.2011- present: Research assistant 25%; SNF Project Swiss Transplant Cohort Study; Institute of Nursing Science, University of Basel, CH  
 10.2009 - present: Research assistant 15%, Institute of Nursing Science (40% until 1.4.2011); Institute of Nursing Science, University of Basel, CH  
 02.2009 - present: Clinical Nurse Specialist 20%; Outpatient Clinic of the Department of transplantation immunology and nephrology University Hospital Basel, CH  
 09.2008 - 09.2009: Student Research assistant 40%, Institute of Nursing Science, University of Basel, CH  
 10.2009 - 04.2009: Staff nurse, Intensive care Unit, University Hospital Basel, CH  
 09.1999- 09.2002: Staff Nurse, Internal Medicine/ Oncology; Hospital Thuisis, CH

### Licensure and Certification

- 2004: Swiss Red Cross - Intensive care nursing License (Nr.7267)  
 1999: Swiss Red Cross - Nursing License (Nr. DNII-CH-1999-38)

### Membership in Professional and Scientific Societies

- Society for Light Treatment and Biological Rhythms  
 2012-present: Member

- Leuven Basel Adherence Research Group (LBARG)  
2009-present: Member
- Swiss Transplant Cohort Study - Psychosocial Interest group  
2008-present: Member of the Psychosocial Variables interest Group.
- International Transplant Nurse Association (ITNS)  
2008-present: Member
- Swiss intensive care Association (IGIP)  
2002-2009: Member
- Swiss Nursing Association (SBK-ASI)  
2002-present: Professional association of all the nurses working in Switzerland

## Research Grants

**Burkhalter, H., Sereika, S. M., Engberg, S., Wirz-Justice, A., Steiger, J., De Geest, S.** Validity of two sleep quality items for the Swiss Transplant Cohort Study in renal transplant recipients. Swiss Foundation of Nephrology, Alfred- and Erika-Baer-Spycher-Foundation. Switzerland 2008. Direct costs: 30000.- Swiss Francs. Role: Investigator. Time period 2008-2009. Role: Principle Investigator.

**Burkhalter, H., Wirz-Justice A., Weaver T., Steiger, J., De Geest, S.** The prevalence and characteristics associated with sleep - wake regulation. International Transplant Nurse Society. Pittsburgh 2010. Direct costs: 2500.- US Dollars. Time period 2010-2011. Role: Principles Investigator.

**Burkhalter, H., Wirz-Justice, A., Steiger, J., De Geest, S.** Daily Light for Renal Transplant Recipients having a Sleep-wake Dysregulation. Swiss Foundation of Nephrology, Alfred- and Erika-Baer-Spycher-Foundation. Switzerland 2010. Direct costs: 30000.- Swiss Francs. Role: Investigator. Time period 2010-2011. Role: Principles Investigator.

## Travel Award

**Burkhalter, H., Wirz-Justice A., Cajochen, C., Steiger J., Fehr, T. Venzin, R., De Geest, S.** (2011). Timing non-adherence is associated with chronotype in renal transplant recipients. Sleep and Biological Rhythms (9): 318. Worldsleep2011, October 16<sup>th</sup> -20<sup>th</sup> 2011, Kyoto International Conference center (ICC Kyoto), Japan. Travel Award: 50,000 JPY. Role: Oral and Poster presenter

**Burkhalter, H.,** Denhaerynck K., Wirz-Justice A., Cajochen, C., Steiger J., Fehr, T.Venzin, R., De Geest, S. (2013). A pilot randomized controlled Study of Light Therapy for sleep-wake disturbances in Renal Transplant Recipients. Society for Light Treatment and Biological Rhythms Abstract (25): 53. Society for Light Treatment and Biological Rhythms 2013, June 21<sup>st</sup> -23<sup>rd</sup> 2013, Starling Hotel and convenience Center, Geneva, Switzerland. Travel Award: 500 US\$. Role: Oral presenter

### **Best of abstracts nominee**

**Burkhalter, H.,** Wirz-Justice, A., Cajochen, C., Weaver, T., Steiger, J., De Geest, S. Daytime Sleepiness is Associated with Taking and Timing Non-adherence in Renal Transplant Recipients. September 17<sup>th</sup> 2011, International Transplant Nurse Society, 20th Annual Symposium and General Assembly "Transplant Nursing: Pride, Passion and Possibilities", Göteborg, Sweden. Best of abstract nominee in the category "psychosocial outcomes".

### **Abstract/Poster of Distinction**

**Hanna Burkhalter,** Anna Wirz-Justice, Jürg Steiger, Thomas Fehr, Reto Venzin, Christian Cajochen, Terry Weaver, Sabina De Geest. Poor Sleep Quality and Daytime Sleepiness Are Associated with Worse Biochemical Parameters, Psychological & Behavioural Functioning in Renal Transplant Recipients. June 2<sup>nd</sup>-6<sup>th</sup> 2012, American Transplant Congress, Boston, MA. Poster of distinction in the category "Outcomes and Miscellaneous".

# PUBLICATIONS

## Peer reviewed Publications

De Geest, S., Burkhalter, H., De Bleser, L., Berben, L., Duerinckx, N., De Bondt, K., Dobbels, F. *Non-adherence to immunosuppressive drugs in transplantation: What can clinicians do?* Journal of Renal Nursing, 2010, 2: 59-63.

Burkhalter H, Sereika SM, Engberg S, Wirz-Justice A, Steiger J, De Geest S. *Structure validity of the Pittsburgh Sleep Quality Index in renal transplant recipients: A confirmatory factor analysis.* Journal of Sleep and Biological Rhythms, 2010, 8: 274-281.

Burkhalter H, Sereika SM, Engberg S, Wirz-Justice A, Steiger J, De Geest S. *Validity of 2 sleep quality items to be used in a large cohort study of kidney transplant recipients.* Progress in Transplantation, 2011, 21: 27-35

Burkhalter H, Wirz-Justice A, Cajochen C, Weaver T, Steiger J, Fehr T, Venzin R, De Geest S. *Validation of a Single Item to Assess Daytime Sleepiness for the Swiss Transplant Cohort Study.* Progress in Transplantation, submitted, accepted for publication December 2012

Burkhalter, H., Wirz-Justice, A., Cajochen, C., Weaver, T., Steiger, J., Fehr, T., Venzin, R.M., De Geest, S., *Daytime sleepiness is associated with immunosuppressive non-adherence in renal transplant recipients: a cross-sectional multi-center study,* Clinical Transplantation, 2013, accepted.

Burkhalter, H., Brunner, D.P., Wirz-Justice, A., Cajochen, C., Weaver, T., Steiger, J., Fehr, T., Venzin, R.M., De Geest, S., *Self-reported Sleep Disturbances in Renal Transplant Recipients,* BMC Nephrology, 2013, 14(220): 1-12

## Other Publications

Burkhalter, H., *[A helmet with many advantages].* Krankenpflege. Soins Infirmiers, 2005. 98(2): 10-3.

Burkhalter, H., *[Light modifies convalescence].* Krankenpflege. Soins Infirmiers, 2009. 102(6): 32-3.



Burkhalter, H., [*Sleep as source of joyful life*]. *Krankenpflege. Soins Infirmiers*, 2010. 103(12): 34-5.

## Edited Books

\*De Geest S. for the **Leuven Basel Adherence Research Group**. *Patient's adherence in transplantation: Where we are, where are we going?* In Filipponi F, De Geest S, Russell CL, De Simone P (editors): *Transplant nursing: current practice, future challenges*. PLUS-Pisa University Press, ISBN 978 88 8492 699 9, 2010, 83

Burkhalter H, Sereika SM, Engberg S, Wirz-Justice A, Steiger J, De Geest S. *Sleep quality description based on the Pittsburgh Sleep Quality Index in Renal Transplant Recipients* In: Weimar W, Bos MA, Busschbach JJ, eds. *Organ Transplantation: Ethical, Legal and Psychosocial Aspects*, Vol. II . Lengerich / Germany: PABST Science Publishers ISBN 978-3-89967-639-6, 2011, 337-346

## Thesis

DISSERTATION:

*University of Basel, Institute of Nursing Science 2013*

Bright Light Therapy in Renal Transplant Recipients with Sleep-Wake disturbances.

MASTER'S THESIS:

*University of Basel, Institute of Nursing Science 2009*

Validity of two sleep quality items for the Swiss Transplant Cohort Study in renal transplant recipients.

## Published Abstracts

Burkhalter, H., Sereika, SM., Engberg, S., Wirz-Justice, A., Steiger, J., De Geest., S. (2009, August 30 - September 2). *Validity of two sleep quality items for the Swiss Transplant Cohort Study in renal transplant recipients*. Abstracts for the 14th Congress of the European Society for Organ Transplantation, Paris, France, in *Transplant International*, 2009; 22 (S2), 178.

Burkhalter H, Sereika SM, Engberg S, Wirz-Justice A, Steiger J, De Geest S. (March 25-26th, 2009). *Sleep quality in renal transplant recipients*, Annual conference of SSSSC &

SSBP. Sleepless mind. Mindless sleep? Abstract for the Swiss Society of Sleep Research, Sleep Medicine and Chronobiology (SSSSC) and the Swiss Society of Biological Psychiatry (SSBP): Bern, UPD Waldau Switzerland, in *Neuropsychobiology* 2009; 59 (4), 265-266

**Burkhalter H**, Sereika SM, Engberg S, Wirz-Justice A, Steiger J, De Geest S.; (December 2nd- 4th 2009), *Validity of two sleep quality items for the Swiss Transplant Cohort Study in renal transplant recipients*. Abstract for the 41st Annual Meeting Swiss Society of Nephrology, Schweizerische Gesellschaft für Nephrologie (SGN): Kursaal Interlaken Switzerland, in *Swiss Medical Weekly* 2009; 139 (225), 45-46

**Burkhalter H**, Wirz-Justice A, Cajochen C, Weaver T, Steiger J, De Geest S.; (September 4<sup>th</sup> - September 7<sup>th</sup> 2011), *Daytime sleepiness is associated with taking and timing non-adherence in renal transplant recipients*. Abstracts for the 14th Congress of the European Society for Organ Transplantation, Glasgow United Kingdom, in *Transplant International* 2011; 24 (S2), O-060, 16.

**Burkhalter, H.**, Wirz-Justice A., Cajochen, C., Steiger J., Fehr, T., Venzin, R., De Geest, S., (October 16<sup>th</sup> -20<sup>th</sup> 2011). *Timing non-adherence is associated with chronotype in renal transplant recipients*. Abstract for Worldsleee2011, Kyoto International Conference center (ICC Kyoto), Japan, in *Sleep and Biological Rhythms* (9): AS-5-3 and PO-1-195, 318.

**Burkhalter H.**, Denhaerynck K., De Geest S., (June 2<sup>nd</sup>-6<sup>th</sup> 2012). *Sleep quality improves from time of listing to 2 years post-transplant in solid organ transplant recipients: A Prospective Cohort Study*. American Transplant Congress, Boston, MA. *American Journal of Transplantation*, 2012; 12 (6) 244

**Burkhalter H.**, Wirz-Justice A., Steiger J., Fehr T., Venzin R., Cajochen C., Weaver T., De Geest S., (June 2<sup>nd</sup>-6<sup>th</sup> 2012), *Poor sleep quality and daytime sleepiness are associated with worse biochemical parameters, psychological & behavioural functioning in renal transplant recipients*. American Transplant Congress, Boston, MA. *American Journal of Transplantation*, 2012; 12 (6) 250

De Geest S., **Burkhalter H.**, Bogert L., Berben L., Glass T., Denhaerynck K., (June 2<sup>nd</sup>-6<sup>th</sup> 2012), *Medication non-adherence pre-transplant predicts post-transplant non-adherence with immunosuppressive drugs in liver, renal, lung and heart transplant recipients*. June 2<sup>nd</sup>-6<sup>th</sup> 2012, American Transplant Congress, Boston, MA. *American Journal of Transplantation*, 2012; 12 (6) 47

**Burkhalter H.**, Wirz-Justice A., Cajochen, T. Weaver, C., Steiger J., Fehr, T. Venzin, R., De Geest, S., (December 5<sup>th</sup> - 7<sup>th</sup>, 2012), *Daytime sleepiness is associated with immunosuppressive non-adherence in renal transplant recipients: a cross-sectional multi-center study*. 44<sup>th</sup> Annual meeting of the Swiss Society of Nephrology, Kongresshaus Zürich. Swiss Medical Weekly, 2012; 142 (Suppl 196), OC18

## Oral Presentations

### International

**Burkhalter H**, Sereika SM, Engberg S, Wirz-Justice A, Steiger J, De Geest S.; (September 24-26<sup>th</sup>, 2009), *Prevalence of poor sleep quality in renal transplant recipients*. Oral presentation at the Annual ITNS Symposium and General Assembly, International Transplant Nurses Society: Montréal, Quebec Canada.

**Burkhalter H**, Sereika SM, Engberg S, Wirz-Justice A, Steiger J, De Geest S.; (September 24-26<sup>th</sup>, 2009), *Validity of the three factor model of the Pittsburgh Sleep Quality Index in renal transplant recipients: a confirmatory factor analysis*. Oral presentation at the Annual ITNS Symposium and General Assembly, International Transplant Nurses Society: Montréal, Quebec Canada.

**Burkhalter H**; (October 28<sup>th</sup> - 30<sup>th</sup>, 2010), *Sleep quality in renal transplant recipients*. Oral presentation at the ITNS 19<sup>th</sup> Annual Symposium and General Assembly "Transplant Nursing: Reflections on Caring", International Transplant Nurses Society: Minneapolis, Minnesota USA

**Burkhalter H**, Wirz-Justice A, Cajochen C, Weaver T, Steiger J, De Geest S.; (September 4<sup>th</sup> - September 7<sup>th</sup> 2011), *Daytime sleepiness is associated with taking and timing non-adherence in renal transplant recipients*. Oral presentation at the 15<sup>th</sup> Congress of the European Society for Organ Transplantation, Glasgow, United Kingdom.

**Burkhalter H**, Wirz-Justice A, Cajochen C, Weaver T, Steiger J, De Geest S.; (September 17<sup>th</sup> 2011), *Daytime sleepiness is associated with taking and timing non-adherence in renal transplant recipients*. Oral presentation at the International Transplant Nurse Society, 20<sup>th</sup> Annual Symposium and General Assembly "Transplant Nursing: Pride, Passion and Possibilities", Göteborg, Sweden.

**Burkhalter H.**, (September 15<sup>th</sup> 2011), *Daily light intervention in renal transplant recipients having a sleep-wake dysregulation*. ITNS Research Grant Awards and oral presentation at the International Transplant Nurse Society, 20th Annual Symposium and General Assembly "Transplant Nursing: Pride, Passion and Possibilities", Göteborg, Sweden.

**Burkhalter, H.**, Wirz-Justice A., Cajochen, C., Steiger J., Fehr, T.Venzin, R., De Geest, S., (October 16<sup>th</sup> -20<sup>th</sup> 2011), *Timing non-adherence is associated with chronotype in renal transplant recipients*. Oral presentation (AS-5-3) at the Worldsleee2011, Kyoto International Conference center (ICC Kyoto), Japan

**Burkhalter H.**, De Geest S.; (December 2<sup>nd</sup> 2011), *Organizzazione per la ricerca ed attività di ricerca. Impatto delle malattie croniche sullo stato di salute dei pazienti e delle loro famiglie*. Invited presentation at the Convegno nazionale, La ricerca delle professioni sanitarie. Reggio Emilia, Italy

**Burkhalter H.**, Wirz-Justice A., Cajochen, T. Weaver, C., Steiger J., Fehr, T.Venzin, R., De Geest, S., (October 25<sup>th</sup> - 27<sup>th</sup> 2012), *Daytime sleepiness associated with immunosuppressive non-adherence in renal transplant recipients: A cross-sectional multi-center study*. Selected oral presentation at the 15<sup>th</sup> Annual Meeting European Society for Patient Adherence, COMpliance, and Persistence (ESPACOMP). Monasterium PoortAckere Gent, Belgium.

**Burkhalter H.**, Wirz-Justice A., (February 5<sup>th</sup>-6<sup>th</sup> 2013), *Techniques and experience with chronotherapy (for nurses)*, Invited presentation at the chronotherapeutics course in Prague for the integration of chronotherapeutics into official guidelines and clinical practice in the Czech Republic, Czech-Swiss collaboration in chronotherapy.

**Burkhalter, H.**, Denhaerynck K., Wirz-Justice A., Cajochen, C., Steiger J., Fehr, T.Venzin, R., De Geest, S. (2013). *A pilot randomized controlled Study of Light Therapy for sleep-wake disturbances in Renal Transplant Recipients*. Selected oral presentation at the 25<sup>th</sup> Annual Meeting of the Society for Light Treatment and Biological Rhythms 2013, June 21<sup>st</sup> - 23<sup>rd</sup> 2013, Starling Hotel and convenience Center, Geneva, Switzerland.

## National

**Burkhalter H.**, (September 17<sup>th</sup> 2010), *Die Last der chronischen Krankheiten, Lösungsansätze durch neue Organisationsformen und Versorgungsmodelle*. Invited presentation at the Unternemerforum Physioswiss, Physioswiss:Bern, Switzerland

**Burkhalter H.**, (September 24<sup>th</sup>, 2012), *Sleep quality, sleepiness and sleep disorders in renal transplant recipients: Time to wake up!* Invited presentation at the TNT Seminar - Hot Topic in Transplantation, University Hospital Zürich, Switzerland

**Burkhalter H.**, Wirz-Justice A., Cajochen, T. Weaver, C., Steiger J., Fehr, T. Venzin, R., De Geest, S., (December 5<sup>th</sup> 2012), *Daytime sleepiness is associated with immunosuppressive non-adherence in renal transplant recipients: a cross-sectional multi-center study.* Selected oral presentation at the 44<sup>th</sup> Annual meeting of the Swiss Society of Nephrology, Kongresshaus Zürich, December 5<sup>th</sup> -7<sup>th</sup>, 2012.

**Burkhalter H.**, (December 5<sup>th</sup> 2012), *Schlafstörungen bei Dialysepatienten und nach der Transplantation.* Invited workshop presentation at the 44<sup>th</sup> Annual meeting of the Swiss Society of Nephrology, Kongresshaus Zürich, December 5<sup>th</sup> -7<sup>th</sup>, 2012.

**Burkhalter H.**, Jehle A., Fischer M., De Geest S., (October 22<sup>nd</sup>, 2013) *Das Problem der Therapie-Adhärenz bei haemodialyse Patienten.* Invited presentation at the 40th Seminal for Dialysis, Hörsaal des Luzerner Kantonsspitals, October 21<sup>nd</sup> -23<sup>rd</sup>, 2013.

**Burkhalter H.**, Jehle A., Fischer M., De Geest S., (December 4<sup>th</sup>, 2013) *Adhärenz bei Dialyse Patienten.* Invited presentation at the 45<sup>th</sup> Annual Meeting Swiss Society of Nephrology, Kursaal Interlaken, December 4<sup>th</sup> -6<sup>th</sup>, 2013.

## Poster Presentations

**Burkhalter H**, Sereika SM, Engberg S, Wirz-Justice A, Steiger J, De Geest S.; (March 25-26th, 2009), *Sleep quality in renal transplant recipients.* Poster presentation at the Annual conference of SSSSC & SSBP. Sleepless mind. Mindless sleep? Swiss Society of Sleep Research, Sleep Medicine and Chronobiology (SSSSC) and the Swiss Society of Biological Psychiatry (SSBP): Bern, UPD Waldau Switzerland

**Burkhalter H**, Sereika SM, Engberg S, Wirz-Justice A, Steiger J, De Geest S., (August 30th-September 2nd 2009), *Validity of two sleep quality items for the Swiss Transplant Cohort Study in renal transplant recipients.* Poster presentation at the Annual Congress of the European Society for Organ Transplantation, Paris France

**Burkhalter H**, Sereika SM, Engberg S, Wirz-Justice A, Steiger J, De Geest S.; (December 2nd- 4th 2009), *Validity of two sleep quality items for the Swiss Transplant Cohort Study in*

*renal transplant recipients*. Poster Presentation at the 41st Annual Meeting Swiss Society of Nephrology, Schweizerische Gesellschaft für Nephrologie (SGN): Interlaken, Kursaal Interlaken

**Burkhalter H**, Sereika SM, Engberg S, Wirz-Justice A, Steiger J, De Geest S.; (April 17<sup>th</sup> - 20<sup>th</sup> 2010), *Nighttime toileting as major reason for sleep disturbance in renal transplant recipients*. Poster presentation at the 2nd ELPAT Congress - Organ Transplantation: Ethical, Legal and Psychosocial Aspects - Expanding the European Platform: World Trade Center, Rotterdam, Netherlands

**Burkhalter H**, Sereika SM, Engberg S, Wirz-Justice A, Steiger J, De Geest S.; (April 17<sup>th</sup> - 20<sup>th</sup> 2010), *Nighttime toileting as major reason for sleep disturbance in renal transplant recipients*. Poster presentation at the ITNS European Conference: "Transplantation: Improving Patient Outcomes": Langenbeck Virchow Haus, Berlin, Germany

**Burkhalter, H.**, Wirz-Justice A., Cajochen, C., Steiger J., Fehr, T., Venzin, R., De Geest, S., (October 16<sup>th</sup> -20<sup>th</sup> 2011). *Timing non-adherence is associated with chronotype in renal transplant recipients*. Poster presentation (1-195) at the Worldsleep2011, Kyoto International Conference center (ICC Kyoto), Japan

**Burkhalter H.**, Denhaerynck K., De Geest S., (June 2<sup>nd</sup>-6<sup>th</sup> 2012). *Sleep quality improves from time of listing to 2 years post- transplant in solid organ transplant recipients: a prospective cohort study*. Poster presentation (Poster session Disparities to Outcome and Access 729) at the American Transplant Congress, Boston, MA

**Burkhalter H.**, Wirz-Justice A., Steiger J., Fehr T., Venzin R., Cajochen C., Weaver T., De Geest S., (June 2<sup>nd</sup>-6<sup>th</sup> 2012). *Poor Sleep Quality and Daytime Sleepiness Are Associated with Worse Biochemical Parameters, Psychological & Behavioural Functioning in Renal Transplant Recipients*. Poster presentation (Poster session Outcome and Miscellaneous 748) at the American Transplant Congress, Boston, MA

**Burkhalter H**, Wirz-Justice A., Cajochen C, Weaver T, Steiger J., Fehr T., Venzin R., De Geest S. (June 24<sup>nd</sup>-27<sup>th</sup> 2012), *Bright light intervention in renal transplant recipients having poor sleep quality and daytime sleepiness*. Poster presentation at the 24th Annual Meeting of the Society of Light Treatment and Biological Rhythms, Geneva, Switzerland. Society for Light Treatment and Biol Rhythms Abst 2012; 24:27.

S. De Geest, H. Burkhalter , L. Bogert , L. Berben , T. Glass , K. Denhaerynck for the Swiss Transplant Cohort Study (STCS) and the STCS' Psychosocial Interest Group (October 25<sup>th</sup> - 27<sup>th</sup> 2012), *Medication non-adherence pre-transplant predicts post-transplant non-adherence to immunosuppressive drugs in kidney, liver, lung and heart transplant recipients*. Poster presentation at the 15<sup>th</sup> Annual Meeting European Society for Patient Adherence, **COM**pliance, and **P**ersistence (ESPACOMP). Monasterium PoortAckere Gent, Belgium.

**END**

“If the LORD doesn’t build a house, the work of its builders is useless. If the LORD doesn’t watch over a city, it’s useless for those on guard duty to stand watch over it. It’s useless for you to work from early morning until late at night just to get food to eat. God provides for those he loves even while they sleep”. Psalm 127:1-2, New International Reader's Version (NIRV) 2012.