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Daytime sleepiness in renal transplant recipients is associated with immunosuppressive non-adherence: a cross-sectional, multi-center study

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

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 following: taking, timing, and overall NA to immunosuppressive medication. DS was assessed with the Epworth Sleepiness Scale (ESS) (cut-off ≥6 for DS) and the Swiss Transplant Cohort Study DS item (cut-off ≥4 for DS), and depressive symptomatology was assessed with the Depression, Anxiety, and Stress Scale (cut-off>10). An ordinal logistical regression model was applied for statistical analysis.
Results: The prevalence of the ESS-DS was 51%. NA for taking, timing, and the median overall NA level assessed by 0–100% visual analog scale (VAS) 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.

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Key words: daytime sleepiness – medication adherence – renal transplantation

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Medication non-adherence (NA) is defined as a deviation from the prescribed medication regimen sufficient to impair the regimen's intended effect (1). On the basis of meta-analysis data, Butler et al. (2) reported a median of 22% (IQR: 18–26%) of immunosuppressive NA in renal transplant recipients, and reported that NA contributes substantially to graft loss; a median of 36% (interquartile range: 14–65%) of graft losses was associated with prior NA (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 six months post-Tx, 11.6% at one yr, and 13.1% at two yr, 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 three yr compared with 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 (ESS) (11). There is ample evidence for correlation between subjective and objective sleepiness (12).

Causes for DS vary and it is given in the following: 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 four wk (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), and 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 NA 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 NA 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 Fig. 1).

Using the IMBP, our aims were given in the following: (i) to describe the prevalence of NA, DS, and depression in a cohort of RTx recipients, (ii) to describe whether medication NA dimensions differed between RTx recipients with and without DS, and (iii) to describe whether the degree of DS is associated with NA (control-

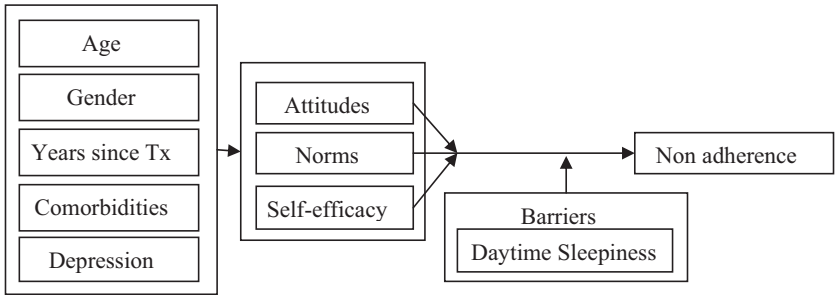

Fig. 1. Theoretical model adapted from the Integrative Model of Behavioral Prediction - Schmid-Mohler et al. (31).

ling for age, gender, years since Tx, depression, and comorbidities).

Methods

Design, setting, and sample

This study was a secondary data analysis using a cross-sectional multi-center design to gather data from a convenience sample of 926 home-dwelling RTx patients transplanted at three Swiss centers (parent study: Burkhalter et al. [34]). For the parent study, the ethics committee approved only the retrieval of the renal insufficiency cause, comorbid condition, and immunosuppressive drugs. The inclusion criteria were as follows: at least six-month post-transplant with a functioning graft; ability to understand and read German; 18 yr 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 the following: taking NA (omission of single doses) and timing NA (timing deviations >2 h). These two items are rated on a six-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 analog 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. (36) compared the BAASIS with other adherence self-report instrument in Tx, showing positive results for this tool.

Daytime sleepiness. Two measures were used to assess DS: the Swiss Transplant Cohort Study Daytime Sleepiness single-item scale (STCS-DS) (34) and the ESS (11). On the STCS-DS, study participants rated their DS over the past four wk 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 cut-off is ≥4 (details are described in Burkhalter et al. [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 ≥6 indicates DS (11). A score ≥10 indicates that a person tends to become very sleepy and should seek medical advice (11). Psychometric properties have been shown in English speaking populations: The ESS scores are 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 four

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 five months apart was acceptable with a mean difference in the total score of 0.3 ± 2.5 (p: non-significant) (40).

Depression. Depression was measured using the Depression, Anxiety, and Stress Scale (DASS–21), a 21-item self-report instrument. Each component is measured with seven items (41) on a four-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 0–21 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 cut-off >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 two 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 six into four 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*-test and chi-square 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 three 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, USA) was used for statistical analysis, with all critical probability levels set to 5%.

Results

Of the 1492 eligible patients, 926 returned completed questionnaires (response rate: 62%) (Fig. 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.

The prevalence of NA and ESS DS and STCS DS is displayed in Table 1. Both the ESS and the STCS–DS data indicated positive associations between DS and NA. Younger age and more years since transplantation were associated with higher NA and the univariate analysis positively associated depression with timing NA (Table 2).

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 yr 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

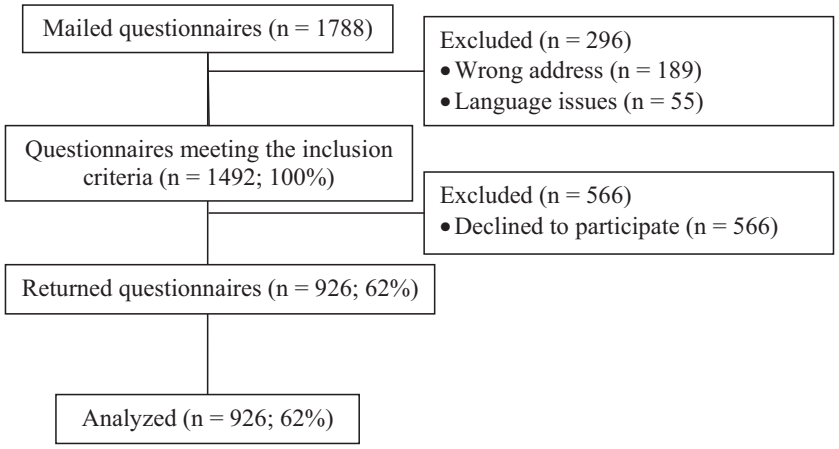

Fig. 2. Flow diagram of the sample.

for overall NA increased by 16% (1.16 [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]).

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 yr 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 one-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]).

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 multi-center 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 ≥6 and 21.3% with a cut-off of ≥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 ≥10) in other chronically ill populations, for example, hemodialysis (27%) (21), heart failure (23.6%) (43), gastro-esophageal 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) (Fig. 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 four on the STCS-DS (no DS), compared to a patient with a score of eight has a 52% greater odds of being non-adherent (four 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 was 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

Table 1. Description of the sample

	Mean ± SD; Median (Q25-Q75); (%)
Characteristics (N = 926)	
Males	63
Age [Median (Q25-Q75)]	59.7 (50.26 – 67.77)
Years Tx[a] [Median (Q25-Q75)]	9.42 (4.93 – 15.85)
CCI > 1[b]	52.9
Causes for renal insufficiency	
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
Most prevalent comorbid condition	
Hypertension	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
Immunosuppressive regimen	
Cyclosporine	44.6
Tacrolimus	40.5
Sirolimus/Everolimus	8.8
Mycophenolat mofetil	66.8
Azathioprine	15.8
Corticosteroid	39.1
Daytime sleepiness	
ESS ≥ 6	50.9
ESS ≥ 10	21.3
STCS-DS	40.7
Taking adherence	
Never NA	84
Once per month NA	10.5
Every second week NA	3.5
Every week to every day NA	1.9
Timing adherence	
Never NA	57.9
Once per month NA	14.4
Every second week NA	20.4
Every week to every day NA	7.3
Overall adherence	
100% adherent	65
90–99% adherent	26.5
80–89% adherent	5.3
70–79% adherent	1.6
0–69% adherent	1.6
Depressive symptomatology[c]	33.7

ESS, Epworth Sleepiness Scale; STCS-DS, Swiss Transplant Cohort Study daytime sleepiness score; NA, non-adherence.
[a]Years since the transplantation took place.
[b]Charlson Comorbidity Index over one score point.
[c]Depressive symptomatology based on the Depression, Anxiety, and Stress Scale (DASS-21) score.

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 six h or more than eight h 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. Furthermore, 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. In addition, 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 NA 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 (55).

Thirty-eight percent were non-responders, and 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 nurse responsible for the study. To conclude, this study was useful in identifying associations that can be more rigorously studies 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

Table 2. Predictors of non-adherence in the univariate analysis

Univariate	Taking OR (CI 95%)	p	Timing OR (CI 95%)	p	VAS OR (CI 95%)	p
Sex[a]	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[b]	0.93 (0.87;1.00)	0.047	0.86 (0.82;0.91)	<0.001	0.86 (0.82;0.91)	<0.001
Years Tx/5[c]	1.18 (1.08;1.29)	<0.001	1.14 (1.06;1.23)	<0.001	1.10 (1.02;1.19)	0.010
CCI	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	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	1.13 (1.06;1.20)	<0.001	1.06 (1.01;1.11)	0.027	1.06 (1.01;1.11)	0.030
Depression[d]	1.15 (1.00;1.33)	0.058	1.15 (1.03;1.28)	0.010	1.04 (0.93;1.17)	0.515

CCI, Charlson Comorbidity Index score; ESS, Epworth Sleepiness Scale score, STCS-DS, Swiss Transplant Cohort Study daytime sleepiness score; VAS, visual analog scale.
[a]Reference category women = 0.
[b]Age per five yr.
[c]Years since the transplantation took place per five yr.
[d]Depressive symptomatology based on the Depression, Anxiety, and Stress Scale (DASS-21) score.

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[a]	1.23 (0.82;1.83)	0.313	1.25 (0.94;1.65)	0.129	1.62 (1.19;2.21)	0.002
Age/5[b]	0.93 (0.86;1.00)	0.044	0.86 (0.82;0.91)	<0.001	0.86 (0.81;0.91)	<0.001
Years Tx/5[c]	1.20 (1.09;1.31)	<0.001	1.19 (1.10;1.29)	<0.001	1.16 (1.07;1.25)	<0.001
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	1.08 (1.04;1.13)	<0.001	1.07 (1.03;1.10)	<0.001	1.09 (1.05;1.13)	<0.001
Depression[d]	1.07 (0.91;1.25)	0.440	1.09 (0.96;1.23)	0.176	0.95 (0.83;1.08)	0.439

CCI, Charlson Comorbidity Index score; ESS, Epworth Sleepiness Scale score; DS, daytime sleepiness; VAS, visual analog scale.
[a]Reference category women = 0.
[b]Age per five yr.
[c]Years since the transplantation took place per five yr.
[d]Depressive symptomatology based on the Depression, Anxiety, and Stress Scale (DASS-21) score.

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

	Taking OR (CI 95%)	p	Timing OR (CI 95%)	p	VAS OR (CI 95%)	p
Univariate						
Sex[a]	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[b]	0.93 (0.87;1.00)	0.047	0.86 (0.82;0.91)	<0.001	0.86 (0.82;0.91)	<0.001
Years Tx/5[c]	1.18 (1.08;1.29)	<0.001	1.14 (1.06;1.23)	<0.001	1.10 (1.02;1.19)	0.010
CCI	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	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	1.13 (1.06;1.20)	<0.001	1.06 (1.01;1.11)	0.027	1.06 (1.01;1.11)	0.030
Depression[d]	1.15 (1.00;1.33)	0.058	1.15 (1.03;1.28)	0.010	1.04 (0.93;1.17)	0.515
Multivariate						
Sex[a]	1.30 (0.88;1.94)	0.191	1.30 (0.98;1.73)	0.065	1.68 (1.23;2.28)	<0.001
Age/5[b]	0.93 (0.86;1.00)	0.045	0.86 (0.82;0.91)	<0.001	0.86 (0.81;0.91)	<0.001
Years Tx/5[c]	1.18 (1.08;1.30)	<0.001	1.18 (1.09;1.27)	<0.001	1.14 (1.06;1.23)	<0.001
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	1.13 (1.05;1.21)	<0.001	1.05 (0.99;1.10)	0.102	1.07 (1.02;1.14)	0.013
Depression[d]	1.08 (0.93;1.27)	0.315	1.13 (1.00;1.27)	0.052	0.99 (0.87;1.13)	0.871

CCI, Charlson Comorbidity Index score; STCS-DS, Swiss Transplant Cohort Study daytime sleepiness score; DS, daytime sleepiness; ESS, Epworth Sleepiness Scale; VAS, visual analog scale.
[a]Reference category women = 0.
[b]Age per five yr.
[c]Years since the transplantation took place per five yr.
[d]Depressive symptomatology based on the Depression, Anxiety, and Stress Scale (DASS-21) score.

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 sun-

light 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).

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Transparency declaration

The results presented in this study have not been published previously in whole or part, except in abstract format: Burkhalter H, et al. DS Associated with Immunosuppressive NA 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.

Authors' contributions

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

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