Patient Preference and Adherence

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Optimization of Electronically Monitored Non-Adherence in Highly Adherent Renal Transplant Recipients by Reducing the Dosing Frequency – A Prospective Single-Center Observational Study

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Patient Preference and Adherence

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Background: Non-adherence (NA) after renal transplantation poses a major risk for allograft rejection, graft loss, and patient mortality. Yet, there is still ambiguity about its etiology and its possible relationships with patient-related factors. In order to prevent poor outcomes after transplantation, it is crucial to gain a more refined understanding of potential determinants, to identify patients at risk, and to intervene accordingly. The objective of this study was to assess potential risk factors of NA by prospectively applying electronic monitoring.

Materials and Methods: This was a single-center prospective observational study. Prior to study initiation, sociodemographic, biomedical, and psychosocial variables (depression, health-related quality of life, self-efficacy, social support, attachment, experiences and attitudes towards immunosuppressive medication, emotional responses after organ transplantation, satisfaction with information about immunosuppressive medication, and perceptions and beliefs about medications) were assessed. Thereafter, immunosuppressive adherence behavior was measured prospectively via electronic monitoring (EM, VAICA©) during a 3-month period to receive the percentage frequency of Taking and Timing Adherence (±2h, ±30min) for each patient. Focus of this study was the phase of medication implementation.

Results: A total of 78 patients participated in our study (mean age 55.28, 56% male). We found rates of 99.39% for Taking Adherence, 98.34% for Timing Adherence ±2h, and 93.34% for Timing Adherence ±30min, respectively. Multiple regression analyses revealed that the type of medication could significantly predict Taking Adherence. Patients receiving Advagraf© (once daily) depicted better Taking Adherence than patients receiving Prograf© (twice daily) (p=0.04). No associations were found for Timing Adherence (±2h, ±30min). Sociodemographic, biomedical, or psychosocial variables were not found to be associated with adherence behavior.

Discussion: In highly adherent populations, only a few factors can be altered to improve adherence. Changing the immunosuppressive regimen from twice-daily to once-daily could be an option for optimizing adherence. However, risk factors for NA could be different in a less adherent population.

Keywords: adherence, patient-related factors, psychosocial variables, electronic monitoring, immunosuppressive medication

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Background

Vrijens et al[1] define adherence as "the process by which patients take their medications as prescribed". Despite its hazardous impact on allograft rejection,

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graft loss, and patient mortality,[2–4] non-adherence (NA) to immunosuppressive medication is a common phenomenon in renal transplant recipients. Even minor deviations are considered to have harmful effects on organ survival,[5] yet mean prevalence rates vary around 35.6% of patients per year.[6] In order to prevent NA in the first place, it is crucial to examine its reasons and risk factors that can be targeted during professional interventions. So far, recent research suggests beneficial effects of interventions on adherence behavior in renal transplant recipients.[7–10] Overall, multidimensional interventions are considered more effective than single-component ones in improving medication adherence.[10,11] Especially individualized interventions that comprise a combination of behavioral, educational, and emotional components seem promising.[10] However, there is still insufficient knowledge about which components are most effective and what specific patient-related factors must be targeted to optimize adherence.[11] Since medication adherence is a complex phenomenon characterized by an interplay of a variety of factors,[11] a more comprehensive understanding of potential determinants is necessary to identify patients at risk and to develop more refined interventions that are tailored to the specific needs of each patient.

When developing interventions, there is a particular need for identifying modifiable patient-related factors. A sound theoretical model that comprises factors on the individual-level and is often cited in the context of adherence is the Health Behavior Model. Health belief theory postulates that health behavior results from individual cost-benefit evaluations of adverse health outcomes and the specific actions that are necessary to prevent these outcomes.[12] In this context, factors such as negative beliefs and attitudes towards medication or treatment,[13–16] as well as adherence barriers[14,16,17] were previously examined and found to be significantly associated with adherence behavior. However, various other patient-related factors have been linked to medication NA in renal transplant recipients as well, such as depression,[13,15,18-20] anxiety,[13,18] sex,[21–23] education,[20,21] marital status,[13,24] lower self-efficacy,[22,25,26] avoidant attachment,[27] lower social support,[18,21,28,29] lower quality of life,[14,28] non-white ethnicity,[4,20] higher frequency of medication intake,[30–34] type of renal graft,[20,35] longer time since transplantation,[20,23,36] and younger age.[2,4,20,24,28,36]

Still, there are many contradictory findings in the current research, due to different measurement methods of NA.[28] A bandwidth of direct and indirect measurement methods for NA has emerged lately: Direct measures include direct observation, measurement of immunosuppressive (IS) levels or biomarkers in the blood, whilst indirect measures comprise pill counts, self-reports, physicians' reports, pharmacy records, or electronic monitoring (EM).[37,38] Although EM is viewed as expensive and labor-intensive,[37,38] a growing body of research has pursued the implementation of this method.[8,22,39,40] Functional errors, induced intervention effects, and problems with utilization might constitute reasons for measurement inaccuracy.[41–45] Although highly debated, some research considers EM the best measure of adherence currently available.[4,11,46] To our knowledge, most studies rely on self-reports, physician's estimates, or IS levels in the blood when examining possible determinants for NA,[13,15,17,18,21,23,25-28,36] whilst only a few have examined this association by applying EM.[22,24,30,31,35]

Therefore, the aim of this study was to investigate the associations between electronically monitored adherence and patient-related factors in order to unravel the etiology of adherence as well as to optimize future adherence interventions.

Materials and Methods

Design, Sample and Setting

This was a prospective, single-center observational study and is part of the APT (Adherence and Psychological Health after Transplantation) research project of the Department of Psychosomatic Medicine and Psychotherapy. The study was conducted in cooperation with the Department of Nephrology and Hypertension at the University Hospital in Erlangen. Recruitment took place at the nephrologic outpatient clinic from March 2018 to April 2019. Potential participants were informed about the study prior to their regular follow-up appointment. Questionnaires and the electronic pillbox were handed out to interested patients during their appointment. For the following 3 months, EM took place at the patients' homes. Feedback on the individual adherence behavior was optional for each participant at the end of the study. The study procedure can be viewed in Figure 1. A more extensive study design was previously published in Lieb et al[47]

Inclusion criteria were renal transplant recipients who were at least 18 years of age, received tacrolimus (Advagraf© or Prograf©) as their main immunosuppressive medication, and were at least 6 months post-transplant. Excluded were patients with insufficient German language skills, severe mental disorders, and/or

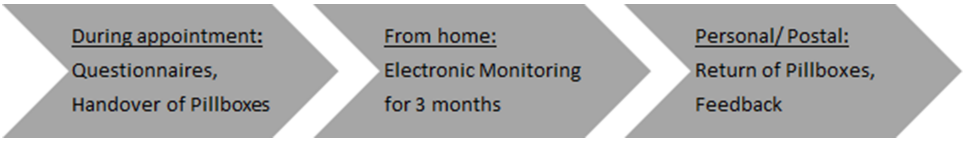

Figure 1 Study procedure.

cognitive impairments. Adherence behavior was no eligibility criterion. Research focus was medication implementation, whilst cases of initiation were excluded.[1,48] Before study participation, written informed consent was given by all participants. Institutional ethics board approval was obtained from the Clinical Ethics Committee of the University Hospital Erlangen (Friedrich-Alexander-University, Erlangen-Nürnberg, FAU).

Data Collection and Measurement Methods

Questionnaires

For the assessment of psychosocial variables, the questionnaires depicted in Table 1 were applied. The choice of instruments was theory-guided and is based on the Health Belief Model. In addition, we conducted a short adherence interview with each patient comprising the following questions following the Life-Routine Model by Russell et al:[40] a) Are you being supported by someone when taking your immunosuppression? b) Are you using reminders for the regular intake of your immunosuppressive medication? c) Have you linked your medication intake with certain daily routines? d) Are there obstacles in your daily life that could prevent you from taking your immunosuppression regularly and/or punctually (travel, appointments, irregular working times, going out)?

Electronic Monitoring

For the electronic assessment of immunosuppressive NA, each patient received an electronic pillbox (VAICA SimpleMed©, Tel Aviv, Israel) for home use over the period of 3 months. Each pillbox allows the storage of medication up to 7 days and four doses a day in a total of 28 cells. The individual medication plan including the specific intake times for the main immunosuppressant (Advagraf© or Prograf©) was entered on the corresponding web portal for each patient. During the study course, each opening of the pillbox cells was automatically registered. The respective pill extraction times were instantly transferred to the corresponding web-based pillbox record via cellular reception. This way, the pillbox allows a real-time surveillance of medication adherence. We only monitored the main immunosuppressive medication, to reach comparability between all patients. We monitored three adherence parameters for the course of 3 months: 1) Taking Adherence: Percentage of prescribed doses taken, 2) Timing Adherence ±2h: Percentage of prescribed doses taken within a 2-hour interval (according to the time interval defined by BAASIS©[46]), 3) Timing Adherence ±30min: Percentage of prescribed doses taken within a 30-minute interval (according to the time interval recommended in our hospital). If extraction did not coincide with pill intake (eg pill is taken later) or if the medication was taken from another source, patients were asked to keep diaries in order to improve validity.[22,64] We used the percentage of (on-time) taken immunosuppressants, in order to treat the two different dosing regimens (once-daily vs twice-daily) equally. The percentage of (on time) taken immunosuppressants was calculated for the whole study course (3 months), reaching values between 0% and 100%.

Data Management and Statistical Analysis

Deficient electronic data were completed by using notes from the patients' diaries. If inconsistency of diary use was stated (ratings ≤5 from a scale of 0–10), repeated technical failure, incorrect pillbox use, or multiple incidents of bad reception were evident during the monitoring period, the respective patients were excluded from the analysis.[42,44] If patients did not use the pillbox for a certain period (eg, travel, hospitalization, weekend, etc.), we extended the individual study period for the respective time, if it was feasible. EM-Imputations were used to replace single missing values in the questionnaires. Missing values for EM and whole psychometric scales were not replaced. We indicated the number of patients that were included in the respective analyses.

For descriptive statistics, we depicted mean values, standard deviations, and ranges. Electronically monitored adherence is depicted in percentages (%). Timing Adherence ±30min includes all cases of Timing Adherence ±2h while Timing Adherence ±2h includes all cases of Taking

Table 1 Measurement Methods of Psychosocial Variables

Psychosocial Construct	Questionnaire	Information
Depression	PHQ-9[49,50]	Self-report screening instrument of depression, 9 Items, 4-point scale
Perceived Social Support	FSozU-7[51]	Self-report instrument on social support (practical support, emotional support, social integration), Short form of F-SozU, 7 items, 5-point scale
Perceived Health Related Quality of Life	WHOQoL-BREF[52]	Self-report instrument on perceived health related quality of life (physical health, psychological health, social relationships, environment), short from of WHOQoL-100, 26 items, 5-point scale
Self-Efficacy	SWE[53,54]	Self-report questionnaire, 10 Items, 4-point scale
Attachment	RSQ[55,56]	Self-report questionnaire, 30 Items, 5-point scale
Subjective Experiences and Attitudes Towards Immunosuppressive Medication	MESI[57]	Self-report questionnaire, 7 Items, 5-point scale
Emotional Responses After Organ Transplantation	TxEQ[58,59]	Self-report questionnaire on emotional responses after Tx (guilt, worry, disclosure, adherence, responsibility), 23 Items, 5-point scale
Satisfaction with Information About Immunosuppressive Medication	SIMS-D[60,61]	Self-report questionnaire, 17 Items, 5-point scale
Perceptions of and Beliefs About Medications	BMQ[62,63]	Self-report questionnaire, 18 items, 5-point scale

Adherence. For correlations, we used the Pearson coefficient r, for group comparisons we applied Chi^2-Tests. In the case of highly skewed distributions, we used Mann–Whitney-U-Tests for group comparisons and Kendall's tau for correlations. Three multiple regression analyses were conducted with Taking Adherence, Timing Adherence ±2h, and Timing Adherence ±30min as outcome variables, respectively. We used Bootstrap Confidence Intervals with 10,000 iterations in case of severe deviations from the normal distribution. Data were processed and analyzed using the software SPSS 21 for Microsoft Windows©.

Results

Of 184 contacted patients, 78 participated in our study (42.39% Response-rate). Sickness, lack of time, and impracticability of the pillbox were reasons for non-participation. No differences were found between Responders and Non-Responders concerning age, year of transplantation, and sex ($p > 0.05$, see also Lieb et al[47]).

Of the 78 participants, only two patients dropped out before study completion (2.56%). Due to improper pillbox use and/or poor reception, which leads to an untenable amount of missing data, we had to discard the data of 11 patients (14.47%). For a total of 65 patients, we were able to collect a complete electronic data set over the duration of the 3-month course. Figure 2 outlines patient eligibility, drop-outs and data loss.

Sociodemographic, biomedical, and psychosocial data are depicted in Table 2.

As shown in Table 3, we conducted several Mann–Whitney-U-Tests and Kendall's τ correlations. Neither sociodemographic variables nor biomedical data, such as type of renal graft, total number of medications, or time since last transplantation, showed any significant correlation with Taking or Timing Adherence (±2h, ±30min). However, we found a significant difference in Taking Adherence depending on the immunosuppressive medication ($U=346.50$, $p=0.01$). Patients receiving Advagraf© as immunosuppressant (once-daily regimen) had better Taking Adherence than patients receiving Prograf© (twice-daily regimen). No difference was found concerning Timing Adherence (±2h, ±30min). Except for self-assessed adherence, no emotional responses after transplantation were associated with electronically monitored adherence behavior. Equally, psychosocial functioning such as depression, health-related quality of life, social support, self-efficacy, attachment, and subjective experiences and attitudes towards medication did not show any association with adherence. We further found no association between adherence and receiving support for medication intake, using reminders, linking medication intake to daily

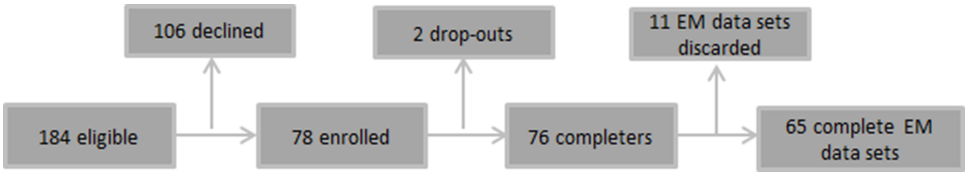

Figure 2 Flow chart for eligibility, drop-outs and data loss.

routine, and obstacles. However, the degree to which patients considered their immunosuppressant necessary for their health and survival was significantly correlated to Taking Adherence (τ=0.22, p=0.04), but not Timing Adherence (±2h, ±30min). Instead, general beliefs concerning physicians' overuse and possible harmful effects of medication showed a significant association with Timing Adherence ±2h (τ=−.19, p=0.04), but not Taking Adherence or Timing Adherence ±30min. How well the patients felt informed about their medication in case of action and usage was significantly correlated with Timing Adherence ±2h (τ=0.20, p=0.05).

In our sample, 11% exhibited clinically relevant depressive symptoms (PHQ ≥10). Self-efficacy, social support, attachment, and perceived health-related quality of life were comparable to an average healthy population.

Due to statistical preconditions of limited predictor count in multiple regressions, we extracted variables with sound scientific support that have repeatedly been related to NA in previous research. We consequently narrowed the variables down to the following: age, sex, time since last transplantation, immunosuppressive medication, depression, and perceived social support.[65] For Taking Adherence we added the predictor Specific—Necessities and for Timing Adherence ±2h SIMS – Action and Usage since it correlated significantly with the respective outcome in our sample (Table 3). The regression model revealed immunosuppressive medication as a significant predictor for Taking Adherence (Table 4). The belief in the necessity of the respective immunosuppressant did no longer show a significant influence on Taking Adherence. For Timing Adherence (±2h, ±30min), none of the variables were significant.

Discussion

This study prospectively investigated the association between a variety of potential risk factors and electronically monitored NA in renal transplant recipients. Over the study period of 3 months, adherence was relatively high with adherence rates of 99.39%, 98.34%, and 93.34% for Taking Adherence, Timing Adherence ±2h, and Timing Adherence ±30min, respectively. Despite these high prevalences, similar rates could be found in previous studies applying EM.[22,66]

We only found immunosuppressive medication to be associated with Taking Adherence. Patients receiving Advagraf© (once-daily) depicted better Taking Adherence than patients receiving Prograf© (twice-daily). This is in line with previous research which indicates that patients with a once-daily dosage of immunosuppressive medication display higher adherence than patients with a more frequent dosing regimen.[30–34] This finding also corresponds to literature investigating this phenomenon in other transplant populations.[67,68] Although most research confirms our findings, in clinical practice still many patients receive immunosuppressants with a higher dosing frequency. In our sample, 38.5% still had a twice-daily dosing regimen of their immunosuppressant. The switch to a once-daily extended release of tacrolimus was found to be medically safe and more convenient for renal transplant recipients.[32–34,69] In liver transplant recipients the conversion was even found to improve medical outcomes.[70] Thus, efforts should be made to reduce the dosing schedule in the future. Still, it must be noted that dose omission cannot be prevented. Although it is less likely to miss a dose when on a once-daily dosing schedule, missing a once-daily dose can lead to a 24-hour interval without dose at all.[30] Even though pharmacological effects of different dosing errors have not been investigated thoroughly, potential changes in clinical outcomes cannot be excluded.[30] Subsequently, the effects of dosing errors and the specific needs of each patient must be considered carefully when changing the dosing frequency.[30]

Our data further revealed that Timing Adherence was not affected by dosing frequency, which means that a second dose is either taken on time or not at all. Except for dosing frequency, our study revealed no further associations of potential determinants with electronically monitored adherence when combining the relevant factors in a regression model. These findings are somewhat contradictory to current research. Although

Table 2 Sociodemographic, Biomedical and Psychosocial Variables

Sociodemographic and Psychosocial Variables		Total sample (N=78)
Age		55.28 (±11.52), 30–78
Sex	Males Females	56 (71.8) 22 (28.2)
Marital Status	Married/in a relationship Single/Widowed/Divorced	60 (76.9) 18 (23.1)
Employment Status	Employed (full or part-time) Unemployed/retired No information/Other	30 (38.5) 41 (52.6) 7 (8.9)
Education	Intermediate school or less (< 12years) High School or higher (>12 years) No information	61 (78.2) 16 (20.5) 1 (1.3)
Migration Background[a]	Yes No (German) No information	5 (6.4) 72 (92.3) 1 (1.3)
Immunosuppressive Medication	Advagraf© (once daily) Prograf© (twice daily)	48 (61.5) 30 (38.5)
Total Number of Medications		10.85 (±4.17), 3–22
Type of Renal Graft	Living Postmortem	31 (39.7) 47 (60.3)
Total Number of Tx	1 2 3	70 (89.7) 6 (7.7) 2 (2.6)
Types of Organs Transplanted	Single Kidney Transplantation Dual Kidney Transplantation Pancreas-Kidney Transplantation	70 (89.7) 1 (1.3) 7 (9.0)
Time Since Last Transplantation (In Years) Primary Disease	 Glomerulonephritis Systemic disease Metabolic/hypertensive Genetic Other Unknown	5.64 (±4.23), <1 −17[e] 27 (34.6) 7 (9.0) 19 (24.4) 10 (12.8) 12 (15.4) 3 (3.8)
Frequent Comorbid Conditions[b]	Diabetes Heart condition Hypertension Hyperuricemia Hyperparathyroidism Hyperlipidemia Obesity Anemia	18 (23.1) 25 (32.1) 62 (79.5) 15 (19.2) 7 (9) 20 (25.6) 5 (6.4) 5 (6.4)
Total Number of Comorbid Conditions		3.32 (1.75), 1–8
Pathological Events During Study Course	None Rejection reactions Acute graft failure	75 (96.2) 2 (2.6) 1 (1.3)

(*Continued*)

Table 2 (Continued).

Sociodemographic and Psychosocial Variables		Total sample (N=78)
Hospitalizations During Study Course	0 1 2	67 (85.9) 8 (10.3) 3 (3.8)
Depression		4.74 (±4.12), 0–17 (0–27)
Depression Dichotomous (≥10)	Low High	68 (88.31) 9 (11.69)
Perceived Social Support		4.33 (±0.85), 1.29–5.0 (1–5)
Perceived Health-Related Quality of Life	Physical Health Psychological Health Social relationships Environment	73.38 (±16.99), 36–100 (0–100) 74.30 (±17.28), 8–100 (0–100) 68.10 (±21.60), 0–100 (0–100) 81.53 (±14.35), 38–100 (0–100)
Self-Efficacy		29.78 (±5.11), 17–40 (10–40)
Attachment[c]	Fear of separation Fear of closeness Lack of trust Desire for independence	2.48 (±0.62), 1.40–4.80 (1–5) 2.11 (±0.68), 1.00–4.00 (1–5) 1.92 (±0.72), 1.00–4.86 (1–5) 3.70 (±0.78), 1.00–5.00 (1–5)
Subjective Experiences and Attitudes Towards Immunosuppressive Medication		13.56 (±5.50), 4–23 (4–33)
Emotional Responses After Organ Transplantation[d]	Guilt Worry Disclosure Adherence Responsibility	2.56 (±0.41), 1.67–3.5 (1–5) 2.77 (±0.85), 1.0–4.6 (1–5) 4.48 (±0.82), 1.67–5.0 (1–5) 4.52 (±0.62), 2.0–5.0 (1–5) 3.42 (±0.97), 1.0–5.0 (1–5)
Satisfaction with Information About Immunosuppressive Medication	Total Action and usage Potential problems of medication	12.96 (±3.84), 3–17 (0–17) 7.70 (±1.69), 2–9 (0–9) 5.26 (±2.74), 0–8 (0–8)
Perceptions of and Beliefs About Medications	General – Total General – Overuse General – Harm Specific – Total Specific – Necessities Specific - Concerns	17.19 (±5.67), 8–29 (8–40) 7.49 (±2.90), 3–15 (3–15) 9.71 (±3.41), 5–18 (5–25) 33.10 (±3.79), 25–43 (10–50) 23.05 (±2.60), 15–25 (5–25) 10.04 (±3.80), 5–20 (5–25)
Support When Taking Medication	Yes No No information	8 (10.3) 69 (88.5) 1 (1.3)
Use of Reminders	Yes No No information	27 (34.6) 50 (64.1) 1 (1.3)
Intake is Linked to Daily Routine	Yes No No information	20 (25.6) 57 (73.1) 1 (1.3)

(*Continued*)

Table 2 (Continued).

Sociodemographic and Psychosocial Variables		Total sample (N=78)
Obstacles	Yes No No information	23 (29.5) 54 (69.2) 1 (1.3)
Taking Adherence*		99.39 (±1.75), 86.92–100
Timing Adherence ±2h*		98.34 (±3.16), 77.57–100
Timing Adherence ±30min*		93.34 (±11.37), 21.5–100

Notes: Except as indicated, categorical data are presented as count (percentage), continuous data are presented as mean (±standard deviation), range (total range possible). [a]Migration background is defined as either immigrated personally or having at least one parent who has immigrated, [b]Several conditions per patient possible [c]German factorization,[55] [d]German interpretation of TxEQ,[58] [e]<1 includes patients >6 months to <1 year. *n = 65.

we could not find an association between depression and NA, intentionality of NA must be taken into account. Griva et al[15] found that depression was only related to intentional NA, but not to non-intentional NA like forgetfulness. Whilst we did not examine the reasons for omitted intakes, it is likely that patients did not act deliberately. The absence of an association between depression and NA can also be seen in other studies.[17,24]

The lack of further associations between NA and other patient-related factors in our sample could be explained by our highly adherent population. Influential factors on adherence behavior could subsequently be different for less adherent patients. A possible reason could also be the low prevalence of depression in our cohort (11.69%), compared to other study populations depicting prevalence rates between 13.2% and 60%.[15,18,28,71] At the same time, protective factors such as self-efficacy, social support, and quality of life, as well as satisfaction with information were average to high and comparable to an average healthy population.

In sum, this field of research still displays a high ambiguity in results since associations between adherence and possible influential factors are not straightforward.[28,72] Whilst most research was able to link NA to lower social support, some could not.[65,73] The same heterogeneity applies to age,[23] sex,[4,18] time since transplantation,[28] and a variety of other psychosocial factors.[65] Further research is necessary in order to gain more consistent results. Especially, a standardization of measurement methods should be pursued in order to attain a better comparability across studies.

Limitations

One limitation of your study is our uniformly adherent sample with little variation in electronically monitored data, which makes inferences challenging. In this context, a possible responder bias towards more adherent patients cannot be excluded.

Also, this study was restricted to patient-related factors, whereas health system and health care provider factors might also play a key role in the development of adherent behavior.[2,11,74] This could also explain why our statistical model on taking adherence only explained a variance of 16%, which limits generalizability. Especially due to our limited sample size, results should be interpreted with caution.

A further constraint of this study is that potential electronic measurement errors might have occurred.[41–45] Especially, a possible intervention effect caused by the use of electronics could subsequently bias the interpretation of our results.[42,44,47]

It is also possible that patients' diaries were incomplete and thus electronic data were biased. Especially since a more thorough diary keeping could be associated with higher adherence[64] and thus increasing the gap between adherent and less adherent patients.

Conclusion

In highly adherent populations, only a few factors can be altered to improve adherence. However, changing the immunosuppressive regimen from twice-daily to once-daily could be an option for optimizing Taking Adherence. Risk factors for NA could be different for less adherent patients; therefore, our results should be replicated in a less adherent and bigger population of renal transplant recipients. Future studies should also include factors from the meso- and macro-level, such as health care system and health care provider factors[2,11,74,75] in order to gain a more thorough picture of NA. Subsequent projects should also

Table 3 Associations Between Psychosocial Variables and Electronically Monitored Adherence

Sociodemographic and Psychosocial Construct		Taking Adherence Total (n=65)	Timing Adherence ±2h (n=65)	Timing Adherence ±30min (n=65)
Age		τ = −0.05, p = 0.61	τ = −0.02, p = 0.85	τ = −0.02, p = 0.81
Sex		U = 432.00, p = 0.93	U = 385.50, p = 0.43	U = 381.00, p = 0.42
Marital Status	Single In a relationship	U = 363.00, p = 0.82	U = 303.500, p = 0.24	U = 362.50, p = 0.85
Employment Status	Employed (full or part-time) Unemployed/retired	U = 358.50, p = 0.45	U = 383.00, p = 0.83	U = 390.00, p = 0.92
Education	Intermediate school or less (< 12years) High School or higher (>12 years)	U = 233.50, p = 0.09	U = 300.00, p = 0.83	U = 261.50, p = 0.38
Migration Background	Yes No (German)	Not computable	Not computable	Not computable
Immunosuppressive Medication	Advagraf© (once daily) Prograf© (twice daily)	**U = 346.50*, p = 0.01**	U = 380.00, p = 0.09	U = 381.50, p = 0.12
Total Number of Medications		τ = 0.17, p = 0.08	τ =0.10, p = 0.28	τ = 0.05, p = 0.60
Type of Renal Graft	Living Postmortem	U = 462.50, p = 0.73	U = 388.00, p = 0.17	U = 358.00, p = 0.09
Time Since Last Transplantation		τ = −0.07, p = 0.51	τ = −.03, p = 77	τ = −.06, p = 0.50
Depression		τ = 0.05, p = 0.60	τ = 0.02, p = 0.83	τ = 0.12, p = 0.19
Depression Dichotomous (≥10)		U = 161.50, p = 0.73	U = 161.00, p = 0.73	U = 149.00, p = 0.54
Perceived Social Support		τ = −0.16, p = 0.12	τ = 0.01, p = 0.94	τ = 0.03, p = 0.74
Perceived Health-Related Quality of Life	Physical Health Psychological Health Social relationships Environment	τ = −0.03, p = 0.75 τ = 0.01, p = 0.95 τ = −0.10, p = 0.34 τ = 0.12, p = 0.29	τ = −0.07, p = 0.44 τ = 0.07, p = 0.48 τ = 0.04, p = 0.70 τ = 0.08, p = 0.39	τ = −0.14, p = 0.11 τ = 0.01, p = 0.94 τ = −0.03, p = 0.73 τ = −0.06, p = 0.54
Self-Efficacy		τ = −0.09, p = 0.38	τ = −0.02, p = 0.82	τ = 0.02, p = 0.84
Attachment	Fear of separation Fear of closeness Lack of trust Desire for independence	τ = 0.04, p = 0.67 τ = −0.08, p = 0.30 τ = 0.10, p = 0.30 τ = −0.09, p = 0.39	τ = 0.09, p = 0.36 τ = −0.14, p = 0.14 τ = −0.00, p = 0.99 τ = −0.12, p = 0.26	τ = 0.13, p = 0.14 τ = −0.14, p = 0.11 τ = −0.06, p = 0.48 τ = −0.09, p = 0.34
Subjective Experiences and Attitudes Towards Immunosuppressive Medication		τ = 0.10, p = 0.32	τ = 0.13, p = 0.16	τ = 0.11, p = 0.23
Emotional Responses After Organ Transplantation	Guilt Worry Disclosure Adherence Responsibility	τ = −0.09, p = 0.39 τ = −0.01, p = 0.93 τ = 0.10, p = 0.37 **τ = 0.30**, p < 0.01** τ = 0.06, p = 0.53	τ = −.015, p = 0.12 τ = −0.01, p = 0.89 τ = 0.01, p = 0.95 **τ = 0.36**, p < 0.01** τ = 0.00, p = 0.99	τ = −0.10, p = 0.28 τ = −0.06, p = 0.49 τ = 0.01, p = 0.95 **τ = 0.39**, p < 0.01** τ =−0.06, p = 0.52

(*Continued*)

Table 3 (Continued).

Sociodemographic and Psychosocial Construct		Taking Adherence Total (n=65)	Timing Adherence ±2h (n=65)	Timing Adherence ±30min (n=65)
Satisfaction with Information About Immunosuppressive Medication	Total Action and usage Potential problems of medication	τ = 0.08, p = 0.44 τ = 0.12, p = 0.27 τ = 0.04, p = 0.68	τ = 0.15, p = 0.12 **τ = 0.20*, p = 0.05** τ = 0.11, p = 0.25	τ = 0.08, p = 0.36 τ = 0.10, p = 0.30 τ = 0.07, p = 0.47
Perceptions of and Beliefs About Medications	General – Total General – Overuse General – Harm Specific – Total Specific –Necessities Specific - Concerns	τ = −0.12, p = 0.22 τ = −0.13, p = 0.19 τ = −0.07, p = 0.51 τ = 0.12, p = 0.21 **τ = 0.22*, p = 0.04** τ = 0.02, p = 0.88	**τ = −0.19*, p = 0.04** τ = −0.17, p = 0.07 τ = −0.17, p = 0.08 τ = −0.03, p = 0.76 τ = 0.04, p = 0.68 τ = −0.04, p = 0.67	τ = −0.14, p = 0.12 τ = −0.15, p = 0.11 τ = −0.10, p = 0.29 τ = −0.05, p = 0.58 τ = 0.08, p = 0.40 τ = −0.10, p = 0.24
Support When Taking Medication		Not computable	Not computable	Not computable
Use of Reminders		U = 418.00, p = 0.69	U = 421.00, p = 0.77	U = 403.50, p = 0.60
Intake is Linked to Daily Routine		U = 383.00, p = 0.985	U = 344.00, p = 0.52	U = 380.00, p = 0.95
Obstacles		U = 282.00, p = 0.09	U = 258.00, p = 0.07	U = 293.00, p = 0.24

Notes: For correlations, we depicted Kendall's tau; for dichotomous variables, we used Mann–Whitney *U*-Tests. Significant results are depicted in bold: **p ≤ 0.01, *p ≤ 0.05.

Table 4 Multiple Regression Analyses

Dependent Variable	Parameter	B	95% CI	p	R2
Taking Adherence	Constant	100.84	97.68, 103.28	**<0.01***	0.16
	Age	-0.01	–03, 0.01	0.34	
	Sex	0.17	-0.24, 0.63	0.46	
	Immunosuppressive Medication	-0.49	-0.87, 0.001	**0.04***	
	Perceived social support	-0.18	-0.57, 0.25	0.44	
	Depression	0.00	-0.08, 0.10	0.99	
	Last transplantation	-0.00	-0.08, 0.10	0.86	
	Specific - Necessities	0.01	-0.05, 0.08	0.74	
Timing Adherence ±2h	Constant	98.28	90.17, 103.82	**<0.01***	0.14
	Age	-0.01	-0.06, 0.04	0.67	
	Sex	-0.11	–1.23, 1.13	0.86	
	Immunosuppressive Medication	-0.21	–1.06, 0.81	0.65	
	Perceived social support	0.02	-0.92, 1.19	0.98	
	Depression	0.07	-0.14, 0.31	0.55	
	Last transplantation	-0.02	-0.15, 0.10	0.78	
	General – Total	-0.07	-0.17, 0.63	0.16	
	SIMS – Action and Usage	0.24	-0.04, 0.63	0.14	
Timing Adherence ±30min	Constant	89.27	69.06, 104.36	**<01***	0.09
	Age	-0.07	-0.27, 0.09	0.40	
	Sex	1.75	–2.36, 6.30	0.40	
	Immunosuppressive Medication	–1.16	–4.64, 2.92	0.52	
	Perceived social support	1.43	–1.70, 5.24	0.42	
	Depression	0.59	-0.04, 1.36	0.11	
	Last transplantation	-0.04	-0.45, 0.41	0.83	

Notes: Advagraf = 0, Prograf = 1; estimates are based on 10,000 Bootstrap-samples. Significant results are depicted in bold: *p < 0.05.

investigate the characteristics of this sample more profoundly in order to identify possible reasons for this highly adherent behavior.

Abbreviations

NA, non-adherence; EM, electronic monitoring; IS levels, immunosuppressive levels.

Data Sharing Statement

The data supporting our findings can be requested from Dipl.-Psych. Marietta Lieb (marietta.lieb@uk-erlangen.de) and Prof. Yesim Erim (yesim.erim@uk-erlangen.de).

Ethics Approval and Informed Consent

Before study participation, written informed consent was given by all participants. Institutional ethics board approval was obtained from the Clinical Ethics Committee of the University Hospital Erlangen (Friedrich-Alexander-University, Erlangen-Nürnberg, FAU). All organs were donated voluntarily with written informed consent. Organ transplantation was conducted in accordance with the Declaration of Istanbul.

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Author Contributions

ML designed and performed the study, collected and analyzed the data, and drafted the manuscript. MS enabled and supported the conduction of the study. YE supervised the conceptualization of the study and conduction of the study. All authors (ML, MS, YE) contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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