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Medication Non-adherence among Liver Transplant Recipients

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Abstract

Purpose of Review We provide an overview of the recent evidence on the prevalence, risk factors, and consequences of medication non-adherence (NA) in liver transplant (LT) recipients.

Recent Findings NA in LT is associated with socio-demographic and medication-related factors, low social support, and poor health literacy. Patient-reported adherence is one of the most common methods to measure NA using validated assessments; immunosuppression (IS) drug levels and electronic monitoring may also be used. Simplification of IS regimens such as the conversion from twice daily to once daily has been shown to be safe, effective, and improves adherence. Relatively few studies have prospectively investigated NA predictors or interventions to reduce NA in LT.

Summary Medication non-adherence is a multi-faceted issue that is common among LT recipients and associated with adverse outcomes. NA in LT recipients warrants further study as only a few interventions have been published focused on reducing NA in LT.

Keywords Immunosuppression; outcomes · Electronic monitoring · Compliance · Self-care · Rejection · Tacrolimus standard deviation

Introduction

Over the last few decades, long-term outcomes in liver transplantation (LT) have continued to improve with advances in surgical techniques, immunosuppression (IS) management, and careful candidate selection. Given these trends, medication non-adherence (NA) post-transplant is a leading cause of graft rejection, graft failure, and poor long-term outcomes [1–3]. Adherence is generally defined as the extent to which patient behavior matches agreed-upon provider recommendations. In the LT population, NA to IS medication is common (15–40%) though slightly lower than in the general population where NA is about 50%. Etiologies of NA are multi-factorial and may be related to patient factors (e.g., forgetfulness) as well as medical regimen complexity, frequently changing drug doses, possible side effects, and financial barriers. Additionally, pre-transplant psychiatric comorbidities and lack of social support play important roles in post-transplant adherence [4, 5]. Although precise estimates are not widely available, NA is associated with about 25% increased risk for graft loss and increased post-transplant hospitalizations [6]. The recognition of NA by clinicians is challenging as patients may not generally volunteer that they may be experiencing medication issues. Unintentional NA due to cognitive impairment, confusion regarding frequency, spacing, or dosing may further complicate post-transplant management [6]. Furthermore, adherence is not uniformly assessed as part of routine clinical practice in transplantation and is only recognized after an adverse event such as an infection or graft rejection. In this manuscript, we provide an overview of the most current evidence on the prevalence, risk factors, and consequences of medication NA in LT recipients. To date, a handful of high-quality studies to improve medication adherence have been conducted among LT recipients.

Defining Medication Non-adherence

The definition of medication NA is variable [7]. Fine et al. summarized the proceedings of a national conference of 66

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medical and allied health transplant and non-transplant experts who defined medication NA as the "deviation from the prescribed medication regimen sufficient to influence adversely the regimen's intended effect" [8]. Drug NA can be expanded beyond this standard definition by factors such as missed doses of medication, taking extra doses, drug holidays, variable timing of intake, and poor medication understanding [5–7].

Risk Factors for Medication Non-adherence

Retrospective studies have evaluated rates and risk factors for NA after LT. A meta-analysis by Dew et al. analyzed 147 studies assessing global adherence behaviors in solid organ transplantation, 30 of which were conducted among LT recipients [9]. Most studies were cross-sectional or retrospective, and about one quarter were primarily focused on medication NA (see Fig. 1). The overall rate of IS NA was 22.6 per 100 persons per year and was significantly lower among LT recipients at 6.7 per 100 persons per year; by contrast IS NA was 35.6 per 100 persons per year among kidney recipients. North American studies found higher rates of NA than European, possibly due to healthcare financing issues. Pooled multi-organ estimates showed that IS NA was associated with non-white ethnicity, poorer social support, and worse self-perceived health. Interestingly, self-reported NA rates were higher than those obtained through electronic monitoring [9].

Post-transplant return to alcohol use has also been investigated; however, the relationship to NA has not been consistently established. A recent study by Deutsch-Link et al. found that alcohol relapse was associated with allograft rejection (HR 2.33, 95% CI 1.11–4.91, $p = 0.03$) [10].

Unintentional NA and poor medication understanding as risk factors were examined by Serper et al. Limited health literacy was associated with lower medication knowledge scores as well as higher risk of NA as measured by tacrolimus levels (OR 3.8, $p = 0.05$) [6]. Serper et al. additionally examined financial barriers to transplant medication adherence by asking patients to report medication trade-offs, e.g., choosing between food and essential medications [11•]. A total of 17% of LT recipients reporting having medication trade-offs either reporting difficulty affording medications, spacing out medications, or making choices between buying medications and buying food. Patients with limited literacy, higher number of comorbid conditions, and Medicare insurance (potentially due to lack of supplementary prescription coverage) were more likely to report tradeoffs. Trade-offs were associated with lower mean self-reported medication adherence, 77% adherence with trade-offs compared with 89% without trade-offs ($p < 0.001$).

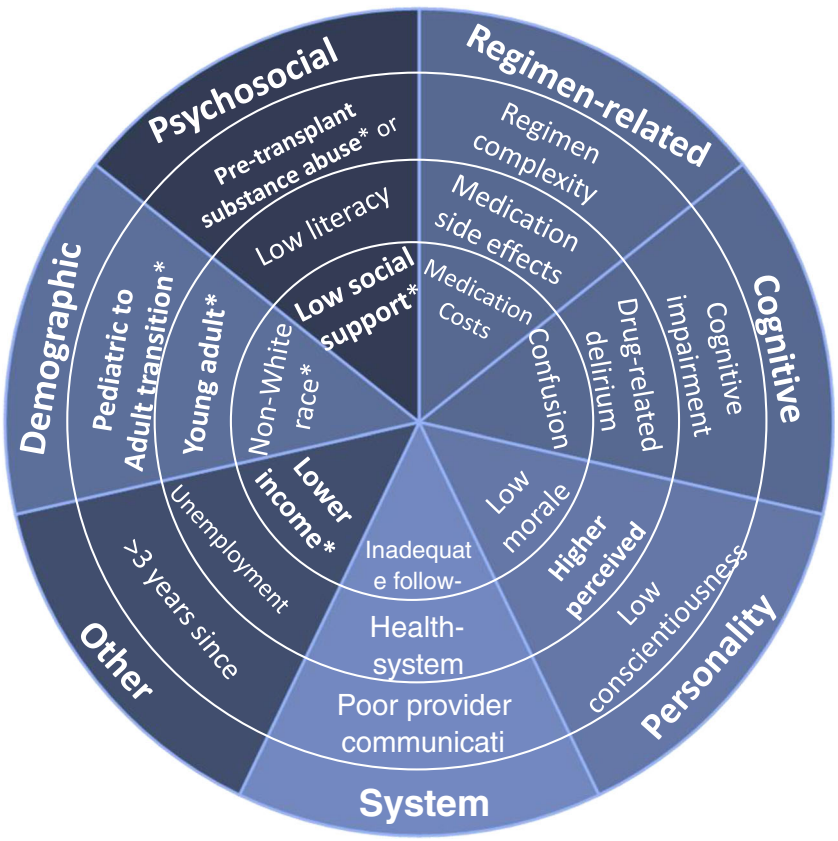

Fig. 1 Factors associated with medication non-adherence after liver transplant
*Factors found to be predictive across multiple studies.
Liver Transplantation - LT.

De Geest et al. conducted a multi-organ study, which included 274 LT recipients evaluating pre-transplant correlates of post-transplant medication NA [12]. Overall, self-reported NA decreased from pre-transplant at 26.6% to post-transplant with a nadir of 7.6% at 6 months post-LT and increasing to 17.4% at 3 years post-LT. In addition to longer time from transplant, factors associated with post-transplant NA included receipt of liver compared to kidney graft, lower educational attainment, and living alone.

Although studies evaluating medication NA risk factors are heterogeneous, certain domains have been identified that place patients at high risk [8]. Factors identified in the psychosocial domain include poor social support, ongoing psychiatric illness, active substance abuse, low income, low literacy, and lower educational attainment. Medication-related factors include costs, medication side effects, regimen complexity, and lack of medication knowledge.

Measurement of Medication NA

Measurement of medication adherence can be done directly through direct observation, blood metabolite analysis, electronic monitoring (EM), or in an indirect manner by reviewing a patient's electronic health record (EHR), pharmacy refill data, or self-report data [13]. Both methods have their strengths and weaknesses, and some have yet to be validated for widespread clinical application [1].

Immunosuppression Levels

Direct measures of adherence in post-liver transplantation populations are often achieved through serologic analysis of IS drug levels. Since tacrolimus (TAC) is the most common IS drug in LT, direct measures of adherence are done though evaluating TAC trough levels in the outpatient setting. Stable TAC troughs are indicative of appropriate medication dosing, compliance, and a lower risk of rejection [14]. Higher variability in TAC as measured by the standard deviation (SD) or the Medication Level Variability Index (MLVI) is associated with poorer post-transplant outcomes and a greater risk for graft failure [1, 2, 15]. In general, it is recommended that TAC SD values should be calculated from blood drawn at least 3–6 months post-transplant to avoid inaccurate calculations early post-transplant when IS dosing is more variable [1, 2, 16]. Blood draws used for TAC troughs and calculating SD are typically done in the outpatient setting during routine clinic visits [1, 16, 17]. The MLVI is typically calculated by computing the SD from least 3 consecutive outpatient TAC levels, with NA and generally defined by a value of >2.5; however, thresholds ranging from 1.8–3.0 can also be used (higher threshold values are more specific, but less sensitive with the converse being true of lower thresholds) [2, 16].

Supelana et al. retrospectively evaluated the MLVI among 150 adult LT recipients and noted that the MLVI was significantly higher among LT recipients with biopsy-proven rejection episodes compared with those without rejection (3.8 versus 2.6, $p < 0.01$) [2]. The authors reported that a threshold MLVI of 2.0 yielded 77% sensitivity and 60% specificity in predicting rejection and a threshold of 1.8 resulted in a sensitivity of 92% and a specificity of 48%. Leven et al. also employed the MLVI in a retrospective study of 248 patients to evaluate medication adherence and allograft rejection among recipients 65 or older compared with those younger than 65 [16]. TAC values were measured starting at 1-year post-LT, and a minimum of 3 values was used to calculate MLVI. Based upon the percentage of above-MLVI threshold scores, patients ≥ 65 were more adherent than younger patients (65% versus 42%, $p = 0.02$); however, MLVI was not associated with graft rejection.

Lieber et al. more recently conducted a retrospective review investigating whether pre-LT psychosocial risk factors predict NA and graft rejection in 248 adult LT recipients at least 1 year post LT [18]. Using MLVI as a biomarker of adherence, they found that 50% of patients had a MLVI of >2.5, a surrogate for NA. Black recipients and White recipients had higher MLVI values than Hispanic and Asian LT recipients. Of the 50% of patients with MLVI >2.5, 17% of these patients had biopsy-proven rejection.

Shemesh et al. conducted a prospective multi-centered study to investigate whether MLVI could predict LT outcomes [19•]. They found that the MLVI predicted late acute rejection in the pediatric population. The authors reported that in a sample of 379 pediatric liver transplant recipients, 53% of the adolescents with MLVI >2 in the first year post-transplant had LAR by the end of the second year post-LT. Additionally, a higher MLVI was associated with secondary outcomes such as elevated liver enzymes.

Electronic Monitoring

In addition to self-report, electronic monitoring (EM) is commonly used to measure medication NA. EM allows one to measure the taking, timing, and frequency of doses through implementation monitoring systems that use sensors to record activity. As compared with self-report, electronic monitoring consistently reports higher levels of NA [20]. Commonly, pill bottles are fitted with electronic caps that record opening and closing of the bottle are used to calculate dosing compliance. Specifically, the Medication Event Monitoring System (MEMS, Aardex Ltd., Switzerland) has been used in a number of the studies [21–23]. Other forms of electronic monitoring include electronic pill boxes, mobile phone applications, text messaging, and online patient diaries [24]. Stilley et al. utilized an electronic monitoring system to track medication adherence in a population of 152 adult LT recipients for the first

6 months after transplant [20]. The authors found that 72.9% of patients took less than all of the prescribed doses, 13% took more than the prescribed doses, and 44.6% took the correct dose less than 90% of the days EM was used. In a study of 108 LT recipients using EM, with a median of four years post-LT, taking compliance ranged from 60 to 105%, dosing compliance was between 58 and 100% (median 99%), and the range of timing compliance was between 42 and 100% [25]. Evidence of a drug holiday of more than 48 h was found in 55% of patients.

Self-Report Questionnaires

Because of ease of implementation and potential for retrospective application, a majority of studies utilize indirect measures of NA to evaluate post-transplantation populations [5, 13]. Of the publications reviewed, patient self-report of NA through responses to short questionnaires was most commonly used. Examples of validated transplant-specific questionnaires in the literature include the Immunosuppressive Adherence Scale (ITAS), the Basel Assessment of Adherence with Immunosuppressive Medication Scale (BAASIS), the 59-Item Modified Transplant Symptom Occurrence and Symptom Distress Scale (MTSOSD-59R), and the Medication Experience Scale for Immunosuppressants (MESI) [21, 26]. With the exception of the MTSOSD-59R (which is lengthier), the questionnaires are brief with 4–10 questions that ask participants about taking and timing of medication, forgetfulness, and reduction of medication doses (see Table 1).

In 2010, Dobbels et al. conducted a systematic review to determine which self-report measurement tool is the most appropriate for use in clinical practice with transplant populations [27••]. Of 20 self-report tools reviewed, they reported only three that met specific criteria that included short length, assessment of taking and timing of medication intake, and established reliability and validity. These included BAASIS, the Brief Antiretroviral Adherence Index (AACTG) questionnaire, and the Medication Adherence Self-Report Inventory (MASRI). These tools were favored since they assessed both medication taking and timing, were simple to use and score, and had good psychometric properties.

Non-transplant specific questionnaires were also used to assess self-report of medication adherence. A number of studies utilized general medication adherence scales or questionnaires that asked about medication ingestion habits, frequency of pill-taking, symptom control, and medication adherence recall [1, 28–32]. These questionnaires aim to comprehensively assess how patients feel about their medications and elucidate that patterns and behaviors associated with NA. The Treatment Satisfaction Questionnaire for Medication (TSQM) was used by Albekairy et al. to investigate if patient satisfaction and medication adherence were related [29]. Of the 154 post-LT recipients surveyed, 60% were adherent and reported significantly higher satisfaction scores than in the non-adherent cohort ($p < 0.05$). Of the studies that used self-report, it was common for more than one questionnaire to be used to get a more comprehensive understanding of how patient behavior is related to medication adherence. Self-reported NA among LT recipients has wide variability ranging from 15 to 40%, but up to 60% in some studies based on the definition. Patients experiencing higher overall symptoms burden had lower medication adherence scores [25, 26].

A study by Dharancy et al., which compared self-reported with clinician-reported adherence among 135 LT recipients, found discordant results [33]. Physicians utilized a visual analogic scale (VAS) measure patient medication adherence, which consisted of the following prompt: "Do you consider this patient to be compliant with treatment?" with a score from 0 (non-compliant) to 10 (perfectly compliant). Adequate adherence was defined as greater than the median score. Patient self-report was completed using a compliance evaluation test (CET), which uses 6 yes/no questions to evaluate taking and timing as well as knowledge of the drug regimen. According to the VAS scale, 49% of LT patients showed adequate adherence, compared with 40% by CET scores. There was a significant discrepancy between patient self-report/CET and physician review/VAS ($\kappa = 0.13$).

Combination Approach

Several studies reviewed employed combined methods to evaluate medication NA. A multifaceted approach has been suggested to provide the most accurate assessment [1, 13, 25]. A third of the studies reviewed utilized combination methods such as electronic monitoring and self-report, or electronic monitoring, chart review and TAC SD.

Summary

Multiple methods to measure medication adherence post-LT have been developed and employed. Apart from direct observation, which is not feasible in clinical practice, all methods have advantages and disadvantages, and as such, no "gold standard" method exists. In general, self-report, transplant-specific instruments such as the BAASIS perform well even if they may under-report NA. TAC SD (MLVI) levels above a threshold of 2.5 have been associated with graft rejection; however, the data on their use in prospectively monitoring adherence are still emerging. Electronic monitoring is accurate, however, is costly, and therefore, should probably be deployed for at-risk patients given limited resources. Although expert consensus is that triangulation among several methods of adherence measurement is the best way to

Table 1 Validated questionnaires to measure non-adherence by self-report

Scale	Abbreviation	Items/measures	Scoring
Basel Assessment of Adherence Immunosuppression Scale[1]	BAASIS	4-item 6-Likert scale; assesses taking, timing, and dosing over previous 1-month period	Each response is measured on 6 point scale: 0, never; 1, once/month; 2, every other week; 3, every week; 4 more than once/week; 5, everyday; If patients answer 'Never' on ≥ 1 question, the patient is non-adherent
Medication Adherence Report Scale[6]	MARS	10-item questionnaire of Yes/No questions; Assesses taking and value of medication during previous week	Responses are given a score of 0 or 1; 0 is indicative of non-compliance, and 1 is indicative of a compliant attitude; depending on the questions, Yes or No will be scored 0 or 1 - Compliant equals 'No' response for q1–6, 9–10, 'Yes' response for q7,8
Medication Adherence Self-Report Inventory[5]	MASRI	12-item questionnaire; Addresses the amount the timing of medication intake, 2 parts: Likert scales and VAS_{DOSE}	Part 1:5 Likert scale items – questions 1–5; Part 2: VAS_{DOSE} items - 0 to 100% in 10% intervals, with 100% every dose of medicine is taken
Beliefs about Medicine Questionnaire[2]	BMQ	18-item questionnaire; Assesses medication necessity for taking and concern of side effects	Total scores for both the Necessity and Concern scales ranged from 5 to 25; higher scores indicate strong necessity and concern belief
Immunosuppressive Therapy Adherence Instrument[3]	ITAS	4-item questionnaire; Assesses taking of medication, barriers to adherence (forgetfulness)	Reponses scored 0–3 points each (3 none, 0 very frequent); 0–12 numerical score, 0 is NA, 12 is optimal adherence
59-item Modified Transplant Symptom Occurrence and Symptom Distress Scale[4]	MTSOSD-59R	59-item questionnaire (can be modified to have less); Measures symptom experience of IS side-effects	Symptom occurrence assessed via 5-point scale: 0 (never occurring) to 4 (always occurring); symptom distress on a 5-point scale ranging from 0 (not at all distressing) to 4 (extremely distressing); scores range from 0 to 236, with higher scores indicating greater symptom burden
Girerd Questionnaire[8]	Girerd	6-item questionnaire; Measures adherence to timing, taking, and attitude towards medication	Responses are scored 0 or 1, with 0 for 1, 1 for yes; Scores greater than 3 indicate nonadherence

1 - Leuven-Basel Adherence Research Group, Sabina De Geest, University of Basel 2005

2 - Horne R, Weinman J, Hankins M. The Beliefs about Medicines Questionnaire: the development and evaluation of a new method for assessing the cognitive representation of medication. Psychol Health. 1999;14:1–24

3 - Chisholm MA, Lance CE, Williamson GM, et al. Development and validation of an immunosuppressant therapy adherence barrier instrument. Nephrol Dial Transplant 2005; 20: 181

4 - Dobbels F, Moons P, Abraham I, Larsen CP, Dupont L, De Geest S. Measuring symptom experience of side-effects of immunosuppressive drugs: the Modified Transplant Symptom Occurrence and Distress Scale. Transpl Int. 2008;21(8):764–773

*The Katholieke Universiteit Leuven, Belgium holds the copyright of the MTSOSD-59R

5 – Walsh, John C.; Mandalia, Sundhiya; Gazzard, Brian G. Reponses to a 1-month self-report on adherence to antiretroviral therapy are consistent with electronic data and virological treatment outcome. AIDS. 16(2):269–277, January 25, 2002

6 – Thompson K, Kulkarni J, Sergejew AA. Reliability and validity of a new Medication Adherence Rating Scale (MARS) for the psychoses. Schizophr Res. 2000;42:241–247

8 - Mulazzi I, Cambou JP, Girerd X, et al. Six-item self-administered questionnaires in the waiting room: an aid to explain uncontrolled hypertension in high-risk patients seen in general practice. J Am Soc Hypertens. 2009;3:221–227

IS – immunosuppressive drugs; q – Question; VAS – Visual Analog Scale

accurately assess NA in LT recipients, optimal ways to deploy these strategies in clinical practice have yet to be developed [1, 7, 8, 13, 27].

Tacrolimus Conversion Trials

The complexity of the prescribed immunosuppressant regimen has been consistently shown to influence medication adherence [14, 34, 35]. As such, dosing simplification has been a targeted area of research in LT recipient populations. Specifically, multiple studies have examined the conversion from twice-daily tacrolimus (TAC-BID or TAC-TD) to once-daily tacrolimus (TAC-OD) [17, 21, 33–40]. Compared with TAC-BID, TAC-OD is in a modified release form that is released more slowly over time [33]. Most of the studies implemented a dose conversion ratio of 1:1 and TAC trough levels were serially evaluated over the study period. Generally, investigation and study outcomes were focused on the safety and efficacy of TAC-OD as well as the effects on clinical outcomes, medication adherence, and patient preferences. In

general, conversion studies were effective and showed improved adherence to immunosuppression as measured by self-report [17, 34–40].

Interventions to Improve Medication Adherence

Data on prospective interventions to improve medication adherence in LT recipients are emerging (see Table 2). In 2009, De Bleser et al. published a systematic review of such interventions among solid organ transplant recipients (SOTs) [7]. Of the 12 studies identified, there were three liver studies, two of which were pediatric, and one that pertained to adult LT recipients. The single intervention aimed at adults implemented a pharmaceutical care program, which improved medication adherence measured by IS drug levels (91 vs. 78% in target) [22]. Since that time, several studies have been published leveraging electronic monitoring, mobile health (mHealth) applications, and enhanced pharmaceutical management programs.

Klein et al. described a prospective randomized-controlled trial of the effect of a 12-month pharmaceutical care program among 50 LT recipients in Germany [22]. Patients randomized to the intervention ($n = 26$) received additional pharmacist counseling prior to hospital discharge and had quarterly meetings with pharmacists in the first post-transplant year. Medication adherence with IS was assessed with medication event monitoring systems (MEMS, Aardex Ltd., Zug, Switzerland), IS drug levels, and self-report questionnaires. Patients in the intervention arm had significantly higher dosing compliance 90.2% ± 6.2% (77.3–100.0%) compared with 80.8% ± 12.4% (57.3–99.1%) in the control group ($p = 0.015$). By immunosuppression level-assessed adherence, 78% of drugs levels in the intervention group and 51% in the control group were classified as "target" ($p < 0.001$). There were no differences in rejection episodes.

Asavakarn et al. reported on a prospective, uncontrolled study of a pharmaceutical program among 50 LT recipients in Thailand [41]. Pre- to post-educational program scores increased from 3.5 to 13.3 out of a possible 20 points ($p < 0.001$). Reported drug events and NA were less than 10%; however, these were not described in detail and the measurements of NA were not provided.

Dobbels et al. reported on a prospective, randomized, controlled, and multi-faceted, multi-organ (heart, lung, liver) intervention, Medication Adherence Enhancing Strategies in Solid Organ Transplantation (MAESTRO-Tx) trial to improve electronically monitored adherence via the Helping Hand™ tool (B&O Medicom, microchip system that measures blister pack removal and taking/timing of medication), and 5-year event-free survival [42••]. The study recruited 205 solid organ recipients, which included 53 LT recipients. Patients were recruited at greater than 1s-year post-transplant as clinical visits are less frequent at that time. Patients in the intervention group received 5 study visits every 3 months and a tailored, multi-component intervention which included education, problem solving, and employed motivational interviewing techniques. Visits included discussion and feedback based on electronically measured adherence for the previous 3 months. EM adherence was significantly 16–20% in the intervention group, whereas self-reported adherence was similar across groups. Survival was 10% higher in the intervention group; however, this did not reach statistical significance.

Zanetti-Yabur reported on a 6-month, prospective US pilot among 74 kidney and liver recipients to assess their use of the Transplant Hero™ (available for Apple iOS) mobile application, which allows for medication organization and provides electronic reminders [30]. Among the recruited patients, only 7 were LT recipients. No differences in self-reported adherence, serum creatinine, or IS drug levels were noted between mobile app users and non-users; however, the sample size was small.

Shellmer et al. conducted a study to test the development and use of a *m*Health application called Teen Pocket Path® (TPP) [43]. A purposive sample of 7 adolescent SOT recipients, of which 4 were LT recipients, and their primary caregivers ($n = 9$) were enrolled in usability sessions and a 6-week field test of TPP. The adolescents used TTP to track medications and their doses and the application delivered reminders and warnings related to medication timing and taking. A total of 90% of the adolescents found the visuals of missed doses useful.

To date, a handful of high-quality studies to improve medication adherence have been conducted among adult LT recipients. Early results suggest that high intensity, tailored, and multi-faceted interventions with electronic monitoring, real-time adherence measurement and feedback, enhanced pharmaceutical care services, and targeted counseling are more likely to effective, more studies are clearly needed in this population. Future studies should further evaluate how technology-enable solutions be harnessed to promote adherence after LT.

Medication Non-adherence among Special Populations

Psychiatric Illness

Psychiatric illness is often cited as a potential risk factor for medication NA, but there are few studies that have shown that it significantly influences post-transplant outcomes. Price el al. described the risks associated with history of mental disorders prior to organ transplantation and subsequent transplant outcomes [44]. While the review found evidence that social isolation, lack of social support, pre-transplant NA, and pre-

Table 2 Intervention studies to reduced medication non-adherence in liver transplantation

Author	Study design	Patient population	Adherence measure(s)	Intervention	Outcome(s)	Effect size
Asavakarn et al. (2016)	Prospective, cross-sectional	Adults LT recipients ($n = 50$)	Survey/questionnaire	Systematic pharmaceutical educational program	Medication literacy; post-intervention test score	Mean post-test score significantly increased ($p < 0.001$)
Dobbels et al. (2017)	Prospective, RCT	Adult heart, liver, and lung Tx recipients > 1 year post-Tx ($n = 205$, 53 LT)	Electric monitoring; self-report (BAASIS)	Staged multicomponent tailored behavioral intervention; motivational interviewing; electronic monitoring	Medication Adherence; 5-year clinical event-free survival	Post-intervention dosing adherence higher in IG (95.1% IG, 79.1% CG; $p < 0.001$), IG odds of adherence 5 times higher than CG (odds ratio 5.17, 95% CI 2.86–9.38); IG effect sustained during 6-month follow-up (IG 97.8% vs CG 78.6%; OR 12.36, 95% CI 6.96–21.97; $p < 0.0001$)
Shellmer et al. (2016)	Prospective, purposive sample	Adolescent solid organ Tx recipients ($n = 7$) + Primary Caregivers ($n = 9$)	Electronic monitoring	Teen Pocket PATH® mHealth Application	Feasibility, Usability	90% of adolescents endorsed the visuals of missed/late medication dosing as useful. 100% endorsed the remaining features (e.g., medication list, dose time reminders/warnings) as useful
Klein et al. (2009)	Prospective, RCT	Adult LT recipients (n = 50)	Medication event monitoring systems (MEMS)*; pill counts; blood TAC SD; questionnaire; self-report	Pharmaceutical care program	Medication compliance	Mean DC of the intervention group was 90% ± 6% compared with 81% ± 12% in the control group ($p = 0.015$); 98/125 (78%) serum concentrations in the IG and 62/121 (51%) serum concentrations were on-target ($p < 0.001$)
Zanetti-Yabur et al. (2017)	Prospective, interventional	Adult LT or KT recipients ($n = 74$, 7 LT)	Self-report via survey (BMQ, IAT); TAC SD, Creatinine, BPAR	Transplant Hero™ mobile phone application	Medication adherence	No significant differences were found between app users and non-users

Abbreviations: Biopsy-proven Acute Rejection; CG – Control Group; CI – Confidence Interval; DC – Dosing Compliance; Immunosuppression Assessment Test (IAT); IG – Intervention Group; KT – Kidney Transplant; LT – Liver Transplantation; m-Health – mobile Health; OR – Odds Ration; RCT – Randomized Clinical Trial; TAC SD – Tacrolimus Standard Deviation; Tx – Transplant

*MEMS, Aardex Ltd., Zug, Switzerland

transplant substance abuse were associated with NA, there was an identified lack of evidence to support that psychiatric illness per-se resulted in poorer post-transplant outcomes and medication NA. Of the 16 publications reviewed, 11 were case reports that did not show differences in adherence between psychiatric patients and those without mental illness. One study that compared post-transplant outcomes between patients with and without psychiatric comorbidities showed no differences in survival, rejection, and infection rates. The review did cite one large cohort study that correlated graft loss due to medication NA to psychiatric illness, but the psychiatric illness was not a pre-existing condition, but rather drug-induced delirium and/or diagnosed depression post-transplantation. More comprehensive research needs to be conducted to further evaluate the risk that a pre-existing psychiatric illness poses to survival and thriving after solid organ transplantation.

Adolescent to Adult Transition

Medication NA among adolescent LT recipients is cited to be up to four times higher than among adults [45, 46]. As adolescents age and transition to adult care, they are at higher risk for increased medication NA and graft loss. According to developmental theory, many of the characteristics associated with adolescence, such as increased autonomy and interactions with peers, are at odds with behaviors one must sustain to stay adherent to medications. As such, adolescents and young adults are at particularly high risk for NA and graft loss. Recommendations to support a successful transition include clearly outlined healthcare instructions, promoting the patient's understanding of impact of being a transplant recipient on daily functioning and its relationship to medication adherence, potential side effects, and family planning concerns if applicable. In addition, potential socio-economic barriers such as insurance coverage and affordability of drug copays should be addressed prior to the transition. Several interventions to promote medication adherence among adolescents transitioning to adulthood have investigated the role of a transition coordinator (providing additional support, teaching towards independent self-care, and a transition checklist) and text message reminders [47, 48]. Both having a transition coordinator and text message reminders successfully improved medication adherence as measured by tacrolimus SD levels.

Mitchell et al. conducted a retrospective chart to investigate outcomes in a population of 18 pediatric LT recipients that transitioned to adult care [49]. Adherence was measured through serum drug levels and clinic attendance. Tacrolimus adherence was assessed in 7 of the patients and was the same before and after transition (57%). Of the 18 patients, 11 (61.1%) had a clinic attendance rate of greater than 80%. Of the 7 patients that were non-compliant with clinical attendance, 5 had a documented psychological history compared with 2 patients in the compliant group.

Conclusions

Medication NA is common among LT recipients and is associated with adverse outcomes such as allograft rejection and increased hospitalizations. Common risk factors for NA include low social support, pre-transplant substance misuse, and depression and demographic factors such as younger age (particularly the adolescent to adult transition), financial barriers, medication-related factors such as side effects, regimen complexity, as well as poor understanding and low literacy. Although no gold standard for medication adherence measurement exists, several brief, validated self-report assessments have been developed to measure NA in clinical settings. Electronic monitoring and IS drug levels are additional ways to accurately measure and address NA. Though optimal ways to improve medication NA among LT recipients are in need of further study, promising interventions include automated (text message or smartphone reminders), pharmacist counseling, and medical regimen organization to promote adherence behaviors. Multi-faceted approaches and those that are individualized and targeted towards specific adherence barriers for at-risk groups show the highest promise.

Compliance with Ethical Standards

Conflict of Interest Disclosures - Dr. Marina Serper received personal fees from BioVie, Inc. unrelated to the submitted work
- Student Doctor Lauren Jones has no conflicts of interest to disclose

Human and Animal Rights Disclosure All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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•• Of major importance

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