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Journal
Digestive Diseases and Sciences, 62(2)

ISSN
0163-2116

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Publication Date
2017-02-01

DOI
10.1007/s10620-016-4391-z

Peer reviewed

Published in final edited form as:

Dig Dis Sci. 2017 February ; 62(2): 543–549. doi:10.1007/s10620-016-4391-z.

Factors associated with medication non-adherence in patients with end-stage liver disease

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Abstract

Background—Low medication adherence is known to contribute to worse health outcomes in the general population.

Aim—We aimed to evaluate the medication regimen and determine the adherence levels among patients with end-stage liver disease.

Methods—We measured adherence in patients awaiting liver transplantation at a single center using the 8-item Morisky Medication Adherence Scale (MMAS-8), with a score <8 classified as low-adherence. Medication regimen complexity was assessed using the Medication Complexity Regimen tool (MRCI). Factors associated with low-adherence were identified by logistic regression.

Results—Of 181 patients, 33% were female, median age was 62, and Model for end-stage liver disease (MELD) score was 13. The median (IQR) number of medications was 10 (7–13) and the MRCI was 19 (13–27). 54 (30%) were high adherers, and 127 (70%) were low-adherers. 42% reported sometimes forgetting to take their medication and 22% reported intermittent adherence within the past 2 weeks. The most common reasons for low-adherence were: forgetfulness (27%), and side effects (14%). Compared to high adherence, low-adherence was associated with higher number of medications, medication complexity, and diabetes, but lower rates of hepatocellular carcinoma and self-perceived health. In univariable logistic regression, total medication number (OR 1.08), MRCI (OR 1.04), diabetes (OR 2.38), HCC (OR 0.38) and lower self-perceived health (OR 1.37), were statistically significant factors associated with non-adherence. In multivariate analysis, only medication number without supplements (OR 1.14) remained significantly associated with medication non-adherence.

Conclusion—A majority of patients awaiting liver transplantation demonstrate low medication adherence. Total number of medications and regimen complexity were strong correlates of adherence. Our data underscore the need for chronic liver disease management programs to improve medication adherence in this vulnerable population.

Keywords

Medication adherence; liver transplantation; end-stage liver disease

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Conflicts of interest: None to disclose

INTRODUCTION

Poor adherence to medication regimens adversely impacts health outcomes in many chronic conditions. In the United States, up to 69% of all medication-related hospital admissions are due to medication non-adherence alone [1,2]. In the context of transplant, poor adherence to immunosuppressive therapy is considered one of the leading causes of preventable graft failure, it is estimated to be involved in 20% of late acute rejection episodes and 16% of graft losses [3]. Specifically, in liver transplant recipients, the mean self-reported non-adherence was 14%, whereas 32% were shown to be non-adherent to medications based on tacrolimus levels [4]. While the data on medication adherence in organ transplantation is mainly focused on the post-transplant period, there is a clear paucity of studies in the pre-transplant period [3–6].

Since poor adherence to medication can be modifiable, it is critical to understand the predictors and risk factors of non-adherence in the transplant setting – particularly given that pre-transplant non-adherence may impact post-transplant outcomes [7]. This is even more important to address in the pre-transplant setting given that the MRCI of transplant specific medications in liver transplant patients is 18 with an average of 8.5 medications [5]. Therefore, in this study, we aimed to assess medication adherence in patients with end-stage liver disease awaiting liver transplantation with the intent of identifying modifiable factors associated with medication non-adherence.

METHODS

Study population

Included were consecutive adult (≥18 years), English-speaking patients with end-stage liver disease listed for liver transplantation who presented for an outpatient clinic visit to the UCSF Liver Transplant Clinics between April 2015 through November 2015. Patients at any Child Pugh score and MELD score were eligible to enroll. Excluded were patients with severe hepatic encephalopathy, defined by the time to complete the Numbers Connection Test of >120 seconds, as we felt that severe hepatic encephalopathy would impair a patient's ability to complete the study procedures [8].

Study procedures and data collection

All patients in this study filled out the Morisky Medication Adherence Scale (MMAS), an instrument widely used to measure medication adherence for a variety of chronic diseases and was initially validated in patients with hypertension [9]. The MMAS contains 8 self-reported items with seven yes or no questions and one question answered on a 5-point Likert scale (α reliability = 0.83). Each "no" answer yields one point; any score <8 points is classified as "low-adherence", as there is no room for medication error with transplant patients on the waitlist.

Each patient's medication regimen was obtained by electronic health record review on the date of assessment. Medication reconciliation is a required part of every outpatient, and it is performed twice, first by the medical assistant and then by the clinician. Drugs were

categorized according to the Anatomical Therapeutic Chemical Classification System (ATC code) [10]. Medication complexity was assessed using the Medication Regimen Complexity Index (MRCI) tool [11]. The MRCI score incorporates the number of medications, dosage frequency, dosage forms, and administration instructions. There are no upper or lower limits for the MRCI scale. For reference, the MRCIs of patients with HIV, diabetes mellitus, and hypertension have scores of 22, 23, and 18, respectively [12]. Topicals, shampoos, and natural substances were not included in the analyses.

Patient demographics including medical co-morbidities, ascites, insurance status, marital status and laboratory studies within 3 months of the study visit were collected from the patient's electronic health record.

At the same visit, we asked patients the following question derived from the National Health Interview Study [13] to rate their general health status:

> "Would you say your health in general is excellent (0), very good (1), good (2), fair (3), poor (4), or very poor (5)?"

Statistical analysis

Patients were classified as highly adherent if they scored 8 on the MMAS-8, and low adherers if they scored <8. Differences in baseline characteristics by medication adherence status were analyzed using chi-square or Wilcoxon rank sum tests for categorical and continuous variables, respectively. Univariate logistic regression was performed to determine which factors were associated with low medication adherence. Multivariate logistic regression was performed with inclusion of all factors statistically associated with low medication adherence in univariate analysis. A cut-off p-value <0.05 was used to determine statistical significance.

STATA® v11 (College Station, Texas) was used for all statistical analyses.

RESULTS

Baseline demographics of the cohort

Baseline characteristics of the 181 patients with end-stage liver disease awaiting liver transplantation are presented in column A of Table 1. The median (IQR) age was 62 (56–65), 33% were female, 57% were non-Hispanic White, 48% had chronic HCV, 36% had HCC, and 21% had a caregiver that was not themselves. With respect to medical co-morbidities: 48% had hypertension, 28% had diabetes, and 6% had coronary artery disease. The median (IQR) MELD score was 13 (10–17), and the proportion with Child Pugh Score A, B, and C was 38%, 46%, and 16%, respectively.

Medication regimen of patients with end-stage liver disease

The median (IQR) number of total medications per patient (including supplements) was 10 (7–13). Not including supplements, the median number of medications per patient was 7 (5–10). The median MRCI of the total medications for each patient was 19 (13–27). For

reference, the MRCIs of patients diagnosed with HIV, diabetes mellitus, and hypertension, have mean MRCI scores of 22, 23, and 18, respectively [12].

The patient cohort had a total of 1,800 unique medications; 395 (22%) were over-the-counter supplements (Supplemental Table 1). The most commonly prescribed medications were related to the gastrointestinal tract and metabolism (30%) - primarily proton pump inhibitors (6%). Liver related medications were the second most commonly prescribed, which included loop diuretics (6%), osmotic laxatives (5%), followed by potassium-sparing diuretics (5%). Of the supplements, vitamins accounted for 12% of the total medications.

Assessment of medication adherence

Based on the MMAS-8 survey, 54 (30%) patients were classified as highly adherent and 127 (70%) patients as low-adherers. Overall, 42% of patients reported that they “sometimes forget to take their medication” and 28% of the patients reported that “there were times I did not take my medications in the past two weeks” (Table 2).

Baseline characteristic differences associated with medication non-adherence

Median MELD scores and Child Pugh scores were similar between patients with low versus high medication adherence, but rates of HCC were lower in patients with low adherence (29% vs. 52%; p=0.004) (Table 1). Patients with low versus high adherence had higher rates of diabetes (32% vs. 17%; p=0.03) despite similar medication complexity by MRCI score (18 vs. 20; p=0.09).

The low adherence group had a median of 10 medications per patient (IQR 7–13) compared to the high adherence group, which had 8 medications (6–12; p=0.01). Both groups had a median of 2 supplements. After adjusting for supplements, there was still a statistically significant difference in medication number in the low adherence group compared to the high adherence group (8 vs. 6.5; p=0.008). Compared to patients reporting high medication adherence, patients with low adherence had a higher medication complexity by MRCI score (20 vs. 17, p=0.02). Patients with low adherence also reported significantly lower self-reported health (58% vs. 28% reported “good” and 13% vs. 35% reported “fair”; p=0.001). There was no association between the percent of patients on medications of different classes.

Patient reported reasons for non-adherence

Of the 181 patients, there were 211 total responses when asked the reason for not taking medication. The most commonly stated reason was “I forget to take my medication” (27%). The second most common reason was “side effects” (14%) (Table 3). There were 109 total responses for the medications least likely to take, and the most common response was lactulose (27%), followed by diuretics (16%), nighttime medications (8%), and all other medications were <6% of the responses.

Factors associated with medication non-adherence

In univariable logistic regression, MRCI (OR 1.04 95%CI 1.00–1.08; p=0.03), total medication number (OR 1.09 95%CI 1.00–1.07; p=0.04), medication number without supplements (OR 1.14 95%CI 1.03–1.25; p=0.009), diabetes (OR 2.38 95%CI 1.06–5.34;

p=0.04), and HCC (OR 0.38 95%CI 0.20–0.74; p=0.004), and lower self-assessment of health status (OR 1.39 95%CI 0.98–1.98; p=0.07) were significantly associated with non-adherence. In multivariable logistic regression, after allowing for all factors associated with medication non-adherence in univariable analysis, only medication number without supplements (OR 1.14 95%CI 1.03–1.25; p=0.009) remained significantly associated with medication non-adherence.

DISCUSSION

Patients with end-stage liver disease suffer from complications such as ascites, hepatic encephalopathy, and variceal bleeding, on top of their underlying chronic liver disease (e.g., chronic hepatitis B, autoimmune hepatitis). In addition, as the population ages, they are increasingly presenting with multiple co-morbidities such as hypertension and diabetes that can be independent of their liver disease but also contribute directly to their liver dysfunction. Management of all of these conditions involves pharmacotherapy, but as these conditions add up, the medication burden for the patient can become seemingly overwhelming.

In this paper, we describe this burden and its consequential effects of medication adherence in patients with end-stage liver disease. We assigned everyone who was not perfectly adherent as “low-adherers”, because in the transplant setting, there is no room for medication error as patients can quickly develop liver rejection or opportunistic infections. We observed a high rate of medication non-adherence (70%). This is all the more alarming given that our study population consists of a select subgroup of patients who have been listed for liver transplantation for which the perceived ability to adhere to medications *after* transplant is a pre-requisite. On average, a patient in our cohort only waits one year for transplantation, which further highlights the urgency of the situation, as many of these patients were likely non-adherent to their medications close to their transplant date. Even though the MRCI scores of this patient cohort were on par with other chronic diseases, our data demonstrate that a higher medication burden is an associated factor of non-adherence. Each unit increase in number of medications was associated with a 14% increase in odds of being non-adherent to medications. Interestingly, liver disease severity, as measured by MELD or Child Pugh score, was not significantly associated with medication non-adherence in multivariable analysis. Having diabetes was associated with medication non-adherence despite there being no difference in MRCI scores, indicating that there is a separate component to having diabetes that puts patients at risk for non-adherence. Not surprisingly, patients with hepatocellular carcinoma had lower overall MRCIs, which likely explains why patients with HCC have better medication adherence. Lower self-assessments of a patient’s general health was also a correlate of non-adherence. A lack of insight into one’s own illness has been recognized as a barrier to drug adherence, and it is possible that the patients who report a lower self-perceived health status have a more negative outlook and belief about their disease state. However, it is also possible that patients feel worse due to a lack of control of their symptoms from their poor adherence. Regardless, the patient’s self-assessment can serve as a quick identifier of patients at risk for non-adherence.

Our study also provides a detailed evaluation of the medication regimens of patients with end-stage liver disease. This population of patients has medication regimens that span a wide range of categories, with a degree of complexity (e.g., frequency, route of administration) that is comparable to other chronic diseases such as HIV and diabetes patients [12]. As with other chronic diseases, end-stage liver disease is hardly a “singular” condition; it is associated with multiple co-morbidities (e.g., hyperlipidemia, hypertension, diabetes) and leads to multiple complications (e.g., ascites, hepatic encephalopathy, and osteoporosis) – all of which involve at least one if not multiple medications for optimal management. It has been shown that many cirrhotics lack the knowledge required to manage their own disease, but simple educational interventions have proven effective, which could potentially translate into better medication adherence [14]. In addition, studies in the liver transplant recipients have shown that higher scores in treatment knowledge and demonstrated regimen use were associated with reductions in post-transplant rehospitalizations [4]. In the kidney transplant setting, limited literacy was associated with non-adherence [6]. Systematic reviews on interventions for chronic conditions have shown that dosage simplification and repeated assessment of medication use with feedback were by far the most effective interventions [15]. The behavioral intervention of 3 telephone calls to assess adherence, provide feedback and give recommendations in patients with dyslipidemia, provided the largest effect size [16]. It is imperative that novel strategies that combine dosage simplification, such as development of single pill combinations, and educational interventions tailored to patients with end-stage liver disease are designed and tested in this more acutely sick patient population.

We acknowledge several limitations to our study. The MMAS-8 tool has not previously been tested in a population of patients with end-stage liver disease, but this tool has been validated in several other chronic conditions, including hypertension, diabetes, and epilepsy [9,17,18]. It relies on self-report to assess adherence, rather than pharmacy records; however, on prior study has shown strong correlation with MMAS-8 scores and pharmacy refill adherence for anti-hypertensive medications in patients with hypertension [19]. Given our relatively small sample size, effects that were not statistically significant may still be important factors of non-adherence. Furthermore, the sample size limited our ability to correlate non-adherence to clinical outcomes, which will be critical to assess in future studies. We only collected overall adherence to the medication regimen as a whole, and were unable to assess adherence levels to specific medications or medication categories. Though our limited sample size could have resulted in underpowering, it is the largest study to date that investigates adherence in patients awaiting transplant. Patients with severe hepatic encephalopathy were excluded from the study, but they only account for 2% of the patient cohort, which is unlikely to have a large effect on the data analysis. Patients in this cohort were from a single center and only patients proficient or fluent in English were included in the study, which may limit generalizability to non-English speaking patients. Both medication regimens and medication adherence levels are independently dynamic throughout a patient’s life, and we only assessed medication adherence at a single time-point. Despite this, our study still identified alarmingly high rates of low-adherence, and our data collection of potential factors was done at the same time-point that the MMAS-8 tool was administered.

In conclusion, patients with end-stage liver disease awaiting liver transplantation display low medication adherence predominantly related to the total burden of medication regimens. Given that medication adherence *prior to* transplant is strongly associated with medication adherence *after* transplant [7], we advocate for the development and implementation of pre-transplant chronic disease management programs that include structured medication support. Future research should also focus on clinical outcomes, such as hospitalizations or decompensations, which may directly result from medication non-adherence. Our work serves as strong justification for future research to develop novel strategies to enhance medication adherence in this vulnerable patient population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Baseline Characteristics of 181 patients with cirrhosis awaiting liver transplantation

Characteristics	All n=181	High Adherence (8) n=54 (30%)	Non-Adherence (<8) n=127 (70%)	p-value
Age, years	62 (56–65)	62 (56–65)	61 (56–64)	0.59
% Female	33%	28%	35%	0.37
% White	57%	61%	55%	0.51
BMI	29.6 (25.9–32.4)	28.9 (25.2–32.7)	29.7 (25.9–32.4)	0.65
Etiology of liver disease				0.66
HCV	48%	48%	48%	
Alcohol	20%	24%	19%	
Other	31%	28%	33%	
HCC	36%	52%	29%	0.004
Medical co-morbidities				
Hypertension	48%	43%	50%	0.39
Diabetes	28%	17%	32%	0.03
Coronary artery disease	6%	0%	9%	0.03
Married	64%	61%	65%	0.58
Primary Care Giver that is not self	21%	15%	24%	0.18
Insurance				0.2
Medicare	18%	11%	21%	
Private Insurance	71%	80%	67%	
Medi-Cal	11%	9%	12%	
Self-assessment				0.001
Excellent/very good	24%	15%	21%	
Good	36%	58%	28%	
Fair	29%	13%	35%	
Poor/very poor	11%	7%	8%	
Laboratory MELD	13 (10–17)	13 (10–17)	14 (11–17)	0.41
Ascites	24%	19%	25%	0.38
Numbers connection Test, seconds	36 (28–48)	34 (25–49)	39 (28–48)	0.22
Child Pugh Score				
A	38%	41%	36%	0.78

Characteristics	All n=181	High Adherence (8) n=54 (30%)	Non-Adherence (<8) n=127 (70%)	p-value
B	46%	45%	47%	
C	16%	14%	17%	
Total number of medications	10 (7–13)	8 (6–12)	10 (7–13)	0.01
Number of medications	7 (5–10)	6.5 (4–9)	8 (5–10)	0.008
Number of supplements	2 (1–3)	2 (1–3)	2 (1–3)	0.9
MRCI	19 (13–27)	17 (9–24)	20 (14–28)	0.02
Anti-infectives	66%	61%	68%	0.4
Blood and blood forming organs	28%	15%	34%	0.009
Genitourinary	12%	13%	12%	0.8
Musculoskeletal	30%	24%	32%	0.3
Nervous System	36%	30%	39%	0.2
Respiratory System	30%	26%	32%	0.4
Cardiovascular System	31%	26%	34%	0.3
GI and Metabolism	90%	87%	91%	0.4
Systemic Hormones	15%	13%	17%	0.5
Liver Related Medications	90%	83%	92%	0.08

Table 2
The 8-item Morisky Adherence Questions

The MMAS-8 was used to determine levels of adherence for each patient. The total percentage of yes answers to each question is reported.

Questions	% of Yes
1. Do you sometimes forget to take your medicine?	42%
2. People sometimes miss taking their medicines for reasons other than forgetting. Thinking over the past two weeks, were there any days when you did not take your medicine?	28%
3. Have you ever cut back or stopped taking your medicine without telling your doctor because you felt worse when you took it?	15%
4. When you travel or leave home, do you sometimes forget to bring along your medicine?	17%
5. Were there any medications you did not take yesterday?	12%
6. When you feel like your symptoms are under control, do you sometimes stop taking your medicine?	11%
7. Taking medicine every day is a real inconvenience for some people. Do you ever feel hassled about sticking to your treatment plan?	23%
8. How often do you have difficulty remembering to take all your medicine? (1) Never/rarely (2) Once in a while (3) Sometimes (4) Usually (5) All the time	1 – 72% 2 – 22% 3 – 4% 4 – 1% 5 – 1%

Table 3

Reasons for not taking medications

Patient reported reasons for not taking their medication and the frequency of each answer. There were 211 responses, as some patients listed more than one reason, and some of the highly adherent patients did not have a response.

Reasons for Not Taking Medication:	Frequency
I feel like my symptoms are under control	6 (3%)
Side effects	30 (14%)
Cost of medication or other barriers to obtaining medication	2 (0.9%)
I do not think the medication is helping control my symptoms	2 (0.9%)
I forget to take my medication	57 (27%)
The reason I need to take my medication was not made clear to me	4 (2%)
Other Reason:	56 (27%)
- Timing or scheduling issue	29 (14%)
- Too busy with other activities/Travelling	3 (1%)
- Doesn’t like the taste or taking	8 (4%)
Not applicable, always takes medication	54 (26%)