Difference in Effectiveness of Medication Adherence Intervention by Health Literacy Level

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Perm J 2016 Summer;20(3):15-200

E-Pub: 06/29/2016

http://dx.doi.org/10.7812/TPP/15-200

ABSTRACT

Context: There is little research investigating whether health information technologies, such as interactive voice recognition, are effective ways to deliver information to individuals with lower health literacy.

Objective: Determine the extent to which the impact of an interactive voice recognition-based intervention to improve medication adherence appeared to vary by participants' health literacy level.

Design: Promoting Adherence to Improve Effectiveness of Cardiovascular Disease Therapies (PATIENT) was a randomized clinical trial designed to test the impact, compared with usual care, of 2 technology-based interventions that leveraged interactive voice recognition to promote medication adherence. A 14% subset of participants was sent a survey that included questions on health literacy. This exploratory analysis was limited to the 833 individuals who responded to the survey and provided data on health literacy.

Main Outcome Measures: Adherence to statins and/or angiotensin-converting enzyme inhibitors and/or angiotensin II receptor blockers.

Results: Although intervention effects did not differ significantly by level of health literacy, the data were suggestive of differential intervention effects by health literacy level.

Conclusions: The differences in intervention effects for high vs low health literacy in this exploratory analysis are consistent with the hypothesis that individuals with lower health literacy may derive greater benefit from this type of intervention compared with individuals with higher health literacy. Additional studies are needed to further explore this finding.

INTRODUCTION

Treatment nonadherence with cardiovascular disease (CVD) therapy has been well documented[1] and is a major contributor to increased cardiovascular risk and morbidity.[2] At the population level, low adherence is often the broken link between effective new therapies and improved health outcomes.[3] Nonadherence has also been identified as a key target for reducing unnecessary health care costs.[4,5]

The most effective adherence interventions include both educational and behavioral strategies[6]; however, these strategies are costly and require both staff time and specialized counseling skills, which can limit the likelihood for dissemination. Furthermore, most interventions evaluated thus far have enrolled highly select and small patient populations, thus limiting generalizability. More recently, research has focused on using health information technologies (HIT) to develop low-cost interventions that can be delivered to large populations to promote adherence for patients with chronic illness.[7-9] For example, one recent study described an intervention among 5216 adults who were newly prescribed a statin but had failed to fill the prescription.[10] The intervention group received automated telephone reminder calls followed by mailed letters. The intervention improved initial fill rates during the next 25 days by 16 percentage points. These and other studies suggest that HIT-based reminder interventions offer a promising, "light-touch" option for promoting adherence in large populations.[11-14]

Although HIT-based interventions may be more easily disseminated, reach a greater number of people, and be lower cost, they may exacerbate certain health disparities, because more educated and technologically advanced individuals will benefit disproportionately from such advances.[15,16] Patients with low health literacy—individuals who face challenges with respect to their capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions[17]—are likely to be particularly vulnerable in this regard.[18] Individuals with low health literacy, for example, are much less likely to use computers, mobile applications, and other consumer and patient medical devices.[19,20] Consequently, it has been argued that interactive voice recognition (IVR) is one type of HIT that may be particularly well suited for delivering interventions to low-literacy individuals because it 1) delivers information via speech instead of text and 2) uses the telephone so that computer access and computer literacy are not required.[19,21,22]

An Institute of Medicine report[23] in 2004 called for studies that establish effective approaches to reduce the negative

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effects of limited health literacy. However, there is still little research to date investigating whether IVR systems are, in fact, effective ways to deliver health information to lower health literacy individuals with chronic disease.

The purpose of the present exploratory analysis was to explore whether an IVR-based intervention to improve medication adherence among individuals with CVD or diabetes mellitus would yield differences in outcomes according to participants' health literacy level.

METHODS

Study Design

The Promoting Adherence to Improve Effectiveness of Cardiovascular Disease Therapies (PATIENT) study was a randomized pragmatic clinical trial in which 21,752 adults were randomly assigned to receive either usual care or 1 of 2 HIT-based interventions designed to increase adherence to statins, angiotensin-converting enzyme inhibitors (ACEIs), and angiotensin II receptor blockers (ARBs). Before randomization at baseline, a subgroup of potentially eligible individuals (n = 2965) were recruited to participate in an interviewer-administered survey via telephone in English, which was conducted centrally by a team of experienced interviewers. The baseline survey was administered from September through December 2011 and had a completion rate of 57% (n = 1678). Among those who completed the survey, 833 respondents ultimately were randomly assigned to participate in the intervention. Data for the present study were based on this subgroup of individuals.

Research Setting

Participants were members of 1 of 3 Regions of Kaiser Permanente (KP), a health maintenance organization providing comprehensive, prepaid health care to its members. The three Regions, Northwest (KPNW), Hawaii (KPHI), and Georgia (KPGA), collectively serve a population of about 944,000 individuals. The institutional review boards at all 3 study sites approved the study. An external data and safety monitoring board and local clinician advisory boards at each site approved the study protocol and monitored the study for safety and data quality.

The PATIENT Study

We have previously described the PATIENT study in detail.[24] Using each Region's electronic medical records (EMRs), we identified participants aged 40 years and older with diabetes mellitus and/or CVD, with suboptimal (< 90%) adherence to a statin or ACEI/ARB during the previous 12 months, and who were due or overdue for a refill. Individuals with medical conditions that might contraindicate the use of these medications (eg, allergic to the medication, liver failure, cirrhosis, rhabdomyolysis, end-stage renal disease, chronic kidney disease) and those on KP's "do not contact" list were excluded. In each Region, we randomly assigned a sample of eligible members to the 3 study arms (usual care and 2 intervention arms) in a 1:1:1 ratio at the study outset and repeated this process for newly eligible members for each of the following 5 months. Study enrollment began in December 2011 and continued through May 2012. Intervention and outcome assessment continued through November 2012.

In the first intervention arm, IVR, participants received automated phone calls when they were due or overdue for a refill of their ACE/ARB and/or statin. Patients were offered a transfer to KP's automated pharmacy refill line. In the second intervention arm, enhanced IVR, participants received the same calls as in the IVR arm but also received a personalized reminder letter if they were 60 to 90 days overdue and a live outreach call if they were 90 days or more overdue, as well as EMR-based feedback to their primary care clinicians. Participants in the enhanced IVR arm received additional written and graphic materials, including a personalized health report with their most recent blood pressure and cholesterol levels, a pill organizer, and bimonthly mailings to answer common questions. The IVR call scripts, letters, and other mailings were written at a sixth-grade reading level.

Study Measurements

Electronic Medical Record Data

We used a modified version of the Proportion of Days Covered for our primary measure of medication adherence.[25] Because we were measuring long-term medications that the patients were known to be taking at the time of randomization, we modified the Proportion of Days Covered to include the whole follow-up period as the denominator timeframe rather than time from first dispensing.[26] We also accounted for medication on hand at randomization and ignored any medication remaining at the end of follow-up. We computed the modified Proportion of Days Covered separately for statins and ACEI/ARBs. To simplify enrollment logistics, we defined study eligibility at baseline using the simpler Medication Possession Ratio, which we computed by dividing total days' dispensed supply by 365 and capping at 1.

We used the EMR to capture age, race, sex, physical and mental health comorbidities, smoking status, body mass index, number of medications dispensed, health care utilization, hospital and Emergency Department visits, and blood pressure and lipid levels. We defined baseline systolic and diastolic blood pressure levels as the mean of the 6 most recent measurements taken during the 12 months before randomization. Follow-up blood pressure was defined as the mean of the 6 most recent measurements taken before the end of the study period, which ranged from 6 to 12 months of follow-up depending on when randomization occurred. We defined blood pressure control as blood pressure below 140/90 mmHg and lipid control as a low-density-lipoprotein cholesterol level below 100 mg/dL.

Survey Data

Participants were asked three single-item health literacy questions (see Sidebar: Health Literacy Questions). The first question, used previously by Williams and colleagues,[27] aimed to assess participants' use of a surrogate reader: "How often do you need to have someone help you when you read instructions, pamphlets, or other written materials from your doctor or

Health Literacy Questions

1. How often do you need to have someone help you when you read instructions, pamphlets, or other written materials from your doctor or pharmacy?
2. How confident are you filling out medical forms by yourself?
3. How would you rate your ability to read?

Table 1. Characteristics of study population, total and by health literacy level

Characteristic	Total (N = 833)	Health literacy level		Significance[a]
		Low (n = 148)	High (n = 685)	
Age, years (mean ± SD)	65.2 ± 11.6	69.5 ± 13.2	64.3 ± 11.0	*t* = -5.01, p = < 0.001
Sex, %				
Women	51.0	51.3	50.9	χ^2 = 0.008, p = 0.93
Men	49.0	48.7	49.1	
Race/ethnicity, %				
Asian	12.9	19.1	11.6	χ^2 = 10.70, p = 0.03
Black/African American	17.0	12.9	17.9	
Native Hawaiian/Pacific Islander	6.1	5.4	6.2	
White	57.7	53.1	58.7	
Other	6.3	9.5	5.6	
Hispanic	2.7[b]	1.0[c]	3.06[d]	χ^2 = 1.31, p = 0.25
Highest level of education, %				
High school or less	34.3	60.8	28.5	χ^2 = 34.82, p = < 0.001
Some college/college degree	53.9	33.8	58.2	
Some graduate school/graduate degree	11.9	5.4	13.3	
Household income, %				
< $25,000	20.6	36.9	17.3	χ^2 = 39.21, p = < 0.001
$25,000-$49,000	35.5	43.4	33.8	
$50,000-$74,999	20.5	10.7	22.5	
≥ $75,000	23.4	9.0	26.4	
Marital status, %				
Single	13.3	10.8	13.9	χ^2 = 5.48, p = 0.07
Married/partnered	62.8	58.1	63.9	
Separated/divorced/widowed	23.8	31.1	22.2	
Health history				
Uncontrolled blood pressure,%	14.7	19.3	13.7	χ^2 = 3.03, p = 0.08
Uncontrolled LDL cholesterol, %	30.2	27.3	30.8	χ^2 = 0.59, p = 0.44
Baseline statin adherence among users, mean ± SD	0.59 ± 0.27	0.60 ± 0.25	0.59 ± 0.27	t = -0.11, p = 0.91
Baseline ACEI/ARB adherence among users, mean ± SD	0.65 ± 0.30	0.62 ± 0.32	0.66 ± 0.29	t = 1.11, p = 0.27
No. of medications dispensed, %				
1-5	39.1	41.9	38.5	χ^2 = 0.17, p = 0.68
6-12	39.1	32.4	40.6	
≥ 13	21.7	25.7	20.9	
ED visit in last 6 months, %	10.6	13.5	9.9	χ^2 = 1.66, p = 0.20
Hospitalization in last 6 months, %	4.2	3.4	4.4	χ^2 = 0.30, p = 0.58
Health care utilization in last 6 months, mean	6.5 ± 6.8	7.8 ± 8.3	6.2 ± 6.3	*t* = −2.64, p = 0.01
HUI2, mean ± SD	0.84 ± 0.17	0.79 ± 0.20	0.85 ± 0.17	*t* = 3.06, p = 0.00
HUI3, mean ± SD	0.77 ± 0.28	0.60 ± 0.35	0.80 ± 0.25	*t* = 7.43, p = < 0.001
Satisfied with care, %	93.0	92.6	93.1	χ^2 = 0.06, p = 0.81
Depression diagnosis, %	3.4	6.1	2.8	χ^2 = 4.10, p = 0.04
BMI,[e] %				
18.5-24.9	11.8	14.9	11.1	χ^2 = 3.30, p = 0.07
25.0-29.9	29.7	39.2	27.8	
30.0-39.9	47.2	35.1	49.7	
≥ 40	11.3	10.8	11.4	
Smoker, %	10.1	11.2	9.9	χ^2 = 0.23, p = 0.23

[a] Two-sided p values based on F test for continuous variables, Pearson χ^2 test for unordered categorical data, and Mantel-Haenszel χ^2 test for ordered categorical data;
[b] N = 589. [c] n = 1. [d] n = 15. [e] kg/m^2.

ACEI/ARB = angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker; BMI = body mass index; ED = Emergency Department; HUI = Health Utilities Index mark; LDL = low-density lipoprotein; SD = standard deviation.

pharmacy?" Participants responded using a five-item Likert scale ranging from "never" to "always." We considered participants who indicated that they "always" or "often" needed help as having low health literacy for this question. The second question, used by Chew and colleagues,[28,29] aimed to assess participants' confidence with medical forms: "How confident are you filling out medical forms by yourself?" Participants responded using a five-item Likert scale ranging from "not at all" to "extremely." We considered participants who indicated that they were "not at all" or "a little bit" confident as having low health literacy for this question. The third question, also used by Williams and colleagues,[27] aimed to assess participants' self-rated reading ability: "How would you rate your ability to read?" Participants responded using a six-item Likert scale ranging from "very poor" to "excellent." We considered participants who indicated that their reading ability was "very poor" or "poor" as having low health literacy for this question. For the purposes of this study, we assigned individuals to the low health literacy group if their responses met those criteria on any of the three questions.

Participants were asked about their current health status and health-related quality of life using the Health Utilities Index. Both the Mark 2 and Mark 3 Health Utilities Index instruments were used to provide a comprehensive health status classification based on the domains of health and levels of functional ability/disability in each domain. These domains included vision, hearing, speech, ambulation, dexterity, cognition, pain, self-care, and emotion.[30]

Participants were asked whether they were satisfied with the care they received from their clinicians and whether they could indicate that they were "very satisfied," "satisfied," "uncertain," "unsatisfied," or "very unsatisfied." Individuals were categorized as satisfied with their health care if they endorsed that they were either "very satisfied" or "satisfied" in response to this question.

Finally, participants were asked about their highest level of schooling completed, total household income, and marital status.

Statistical Analysis

Among those who participated in the baseline survey (N = 1678), complete health literacy and intervention outcome data were available for only 833 of these individuals. The other 845 individuals who completed the survey were not randomly assigned to participate in the intervention. Therefore, our analyses are restricted to this subset of 833 participants. For bivariate analyses, we used *t*-tests for comparisons of means of continuous variables, Pearson χ^2 tests for comparing unordered categorical data, and Mantel-Haenszel χ^2 tests for comparing ordered categorical data. Separate analyses were conducted for users of statins and users of ACEI/ARBs. We assessed whether intervention effects differed by health literacy level in general linear models with main effects for treatment arm, health literacy, and their interaction. Main effect estimates were adjusted for site and sex. We assessed follow-up from randomization until the end of the study or loss of Health Plan coverage, whichever came first.

Because the study was not designed to examine whether the intervention effects differed by health literacy level, these post hoc analyses are inevitably exploratory in nature, and we made no adjustment for multiple comparisons or to conduct retrospective power calculations. Statistical software (SAS v9.2, SAS Institute, Cary, NC) was used for statistical analyses.

RESULTS

The study population was approximately 65 years of age on average, equally men and women, predominantly white (approximately 58%), had some college or a college degree (approximately 54%), were middle income, and were currently married or with a partner (approximately 63%). Approximately 18% of participants had low health literacy (n = 148). Participants who had low health literacy were more likely to be older, have a lower level of education, report a lower total household income, use health care services more frequently, report poorer health status, and have a depression diagnosis compared with participants who had higher health literacy (Table 1).

Although both the IVR and enhanced IVR interventions increased adherence to statins and ACEIs/ARBs compared with usual care in the full trial analysis, in this much smaller sample we did not observe statistically significant differences between either IVR or enhanced IVR and usual care in subgroups defined by health literacy status (Table 2). Of more immediate relevance to the focus of this exploratory analysis, however, the data were suggestive of differential intervention effects for low and high health literacy. Among participants

Table 2. Analysis of adherence by health literacy level

Follow-up adherence by health literacy level	Enhanced interactive voice recognition	Interactive voice recognition	Usual care	Enhanced interactive voice recognition vs usual care		Interactive voice recognition vs usual care	
				Δ[a]	Significance[b]	Δ[a]	Significance[b]
Adherence to statins (interaction p = 0.202)							
Low	0.61 ± 0.034[c]	0.56 ± 0.36	0.52 ± 0.32	**0.105** (-0.035, 0.246)	0.143	**0.09** (-0.061, 0.241)	0.244
High	0.58 ± 0.34	0.58 ± 0.29	0.59 ± 0.32	**-0.026** (-0.094, 0.042)	0.460	**-0.032** (-0.101, 0.036)	0.359
Adherence to ACEI/ARBs (interaction p = 0.116)							
Low	0.70 ± 0.32	0.62 ± 0.37	0.52 ± 0.33	**0.146** (-0.023, 0.316)	0.091	**0.075** (-0.091, 0.241)	0.375
High	0.58 ± 0.37	0.62 ± 0.31	0.62 ± 0.31	**-0.053** (-0.133, 0.027)	0.196	**-0.011** (-0.089, 0.067)	0.780

[a] Net intervention effect, expressed as mean (and 95% confidence interval).

[b] Two-tailed significance level based on linear regression analysis adjusting for site and sex as fixed main effects. Health literacy subgroup analyses also include the corresponding treatment by subgroup interaction.

[c] Raw, unadjusted adherence, expressed as mean ± standard deviation.

ACEI/ARB = angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker.

with low health literacy, for example, the IVR and enhanced IVR interventions were associated with statin adherence that was 9% to 10.5% higher than for usual care. By contrast, among participants with high health literacy, statin adherence in the IVR and enhanced IVR groups was 2.6% to 3.2% *lower* than for usual care.

We observed a similar pattern for ACEI/ARB adherence. Participants with low health literacy in either IVR group (IVR or enhanced IVR) had ACEI/ARB adherence that was 7.5 percentage points to 14.6 percentage points higher than for usual care, whereas among participants with high health literacy the IVR and enhanced IVR interventions were associated with ACEI/ARB adherence that was 1.1 percentage points to 5.3 percentage points lower than for usual care. However, although consistent with an interaction effect, none of the tests of health literacy by treatment interactions was statistically significant.

DISCUSSION

Although not statistically significant, the differences in observed intervention effects for high vs low health literacy in the study sample are certainly consistent with the hypothesis that individuals with lower health literacy may derive greater benefit from this type of intervention compared with individuals with higher health literacy. In a review of promising HIT interventions for diabetes, Boren[21] identified telephone interventions for education, counseling, and reminding as an appropriate method for individuals with limited health literacy. Our results provide some preliminary support for this notion.

Approximately 18% of the study population in the present study had low health literacy; this estimate is generally consistent with prior studies. Depending on the study population and health literacy measure employed, the prevalence of low health literacy ranges from 11% to 44%.[31-35] Also consistent with the prior literature, we found that individuals with lower health literacy are more likely to be of lower socioeconomic status compared with higher health literacy individuals. For example, other studies have similarly reported that years of school completed[31-34,36-39] and income[32-34,38,39] are significantly associated with health literacy level.

… lower health literacy populations may be more responsive to this type of interactive voice recognition-based intervention compared with higher health literacy populations, a finding that may lead to even more efficient patient outreach.

Individuals with low health literacy in the present study were more likely to have poorer health-related quality of life and a depression diagnosis compared with those with high health literacy. Prior studies have consistently reported that lower health literacy populations frequently experience poorer health status as indicated by 1) specific biochemical and biometric health outcomes such as higher blood pressure[37,40] and poor control of Type 2 diabetes,[32,41,42] 2) disease prevalence and incidence such as higher rates of depression,[43-46] and 3) global health status.[31,33,38,47-49] In contrast to previous studies, individuals with low health literacy in this study were not more likely to have Emergency Department visits or hospitalizations in the previous six months compared with individuals with higher health literacy.[50-53] They were, however, more likely to use other health services such as regular office visits compared with individuals with higher health literacy.

Interestingly, individuals with low health literacy did not differ from individuals with high health literacy with respect to baseline statin or ACEI/ARB adherence. Although one study found a positive association between poor health literacy and low adherence to cardiovascular medications,[54] a recent systematic review examining this phenomenon concluded that the current evidence does not show a consistent relationship between health literacy and medication adherence in adults with CVD or diabetes.[55]

The present study has several limitations. First, the small intervention effect seen in the parent trial, combined with the much smaller sample size for this analysis, greatly limits our power to detect significant interactions. Second, although the survey completion rate was satisfactory (approximately 57%), individuals who decided to participate in the survey may differ from those who declined to participate. For example, previous studies suggest that certain subgroups may be less likely to participate in telephone surveys, including men, those with less education, and individuals in poorer health.[56-58] Third, because the survey was administered only in English, individuals for whom English was a second language and/or who were uncomfortable or unable to complete the survey in English were not included; therefore, our findings cannot be generalized to these populations. Fourth, although we used 3 well-validated, reliable, single-item measures for identifying poor health literacy,[59] our *summed* health literacy score based on these 3 items has not been compared against one of the gold standard instruments, such as the Rapid Estimate of Adult Literacy in Medicine[60] or the Test of Functional Health Literacy in Adults.[61]

However, Hardie and colleagues[51] similarly provided a summed health literacy score based on participants' responses to 3 single-item questions and reported that these questions correctly identified individuals with inadequate health literacy 90% to 95% of the time. Therefore, we feel confident that we have accurately categorized the individuals who have low health literacy in our population. Another benefit of using these 3 items includes a shorter time burden for patients, as they take only a few minutes to complete (in contrast to the Test of Functional Health Literacy in Adults, which can take up to 30 minutes). In addition, these questions pose less risk of embarrassment to patients in contrast to the Rapid Estimate of Adult Literacy in Medicine, which asks patients to read aloud medical terms such as *herpes, testicle,* and *hemorrhoids*.

CONCLUSIONS

Attractive features of health interventions include both effectiveness and cost savings. With use of HIT and automation of the delivery of such health education messaging, there are possible cost savings associated with reduced personnel time.[62] Furthermore, our findings suggest that lower health literacy populations may be more responsive to this type of IVR-based intervention compared with higher health literacy populations, a finding that

may lead to even more efficient patient outreach. By allowing the health system to better tailor intervention activities to specific patient characteristics, limited financial resources can be allocated where there is the potential for the greatest impact. Future studies are needed to explore the most effective and efficient methods for identifying and reaching individuals with lower health literacy. ❖

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

Acknowledgment

Kathleen Louden, ELS, of Louden Health Communications provided editorial assistance.

How to Cite this Article

Owen-Smith AA, Smith DH, Rand CS, et al. Difference in effectiveness of medication adherence intervention by health literacy level. Perm J 2016 Summer;20(3):15-200. DOI: http://dx.doi.org/10.7812/TPP/15-200.

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People Are Not Like This

Nowadays people are not like this [ie, temperate in eating and drinking]; they use wine as beverage and they adopt reckless behavior … . Their passions exhaust their vital forces; their cravings dissipate their true [essence]; they do not know how to find contentment within themselves; they are not skilled in the control of their spirits. They devote all their attention to the amusement of their minds, thus cutting themselves off from the joys of long [life]. Their rising and retiring is without regularity. For these reasons they reach only one half of the hundred years and then they degenerate.

— *The Yellow Emperor's Classic of Internal Medicine,* Huangdi, c 2704 BC - 2598 BC, known as the Yellow Emperor, a legendary Chinese sovereign and culture hero