Published in final edited form as:

Clin Gerontol. 2012 May 1; 35(3): . doi:10.1080/07317115.2012.657294.

Tailored Information and Automated Reminding to Improve Medication Adherence in Spanish- and English-Speaking Elders Treated for Memory Impairment

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Abstract

Medication adherence is recognized as an issue of critical importance within health care, as many patients do not take their medications as prescribed. This study evaluated two interventions targeted at improving adherence in elderly patients being treated for memory impairments. Twenty-seven participants were randomly assigned to control ($n = 11$), automated reminding ($n = 8$), or tailored information conditions ($n = 8$). Medication adherence was evaluated with an electronic pill bottle. Generalized estimating equation (GEE) models assessed the effects of the interventions on electronically monitored medication adherence after controlling for covariates. Results showed that individuals in both intervention groups had higher levels of medication adherence than those in the control group. The presence of a caregiver was associated with substantially higher levels of adherence. Verbal memory, but not general cognitive status, predicted better adherence. Mood, health literacy, and executive functions were not associated with adherence. Results thus suggest that both automated reminding and tailored information interventions may improve medication adherence in elders, even among those with memory impairments.

Keywords

adherence; Alzheimer's disease; cognition; memory disorders

Medication adherence has been increasingly recognized as a significant factor in health outcomes. A factor that may have been key in this increase are the related observations that many patients do not take their medication as prescribed (Benner et al., 2002; Chapman, Petrilla, Benner, Schwartz, & Tang, 2008) and that patients with better adherence have

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better health outcomes (Granger et al., 2005; Hays et al., 1994; Origasa, Yokoyama, Matsuzaki, Saito, & Matsuzawa, 2010) including reduced risk of mortality (Simpson et al., 2006). Several authors have argued that interventions to improve medication adherence deserve serious attention (Cutler & Everett, 2010; Murray et al., 2007; Osterberg & Blaschke, 2005; Simpson, 2006).

Adherence refers to the extent to which patients who are prescribed medications for a disorder in fact take them at the appropriate time in the correct amount and manner (e.g., with or without food) as recommended by a clinician (Insel, Morrow, Brewer, & Figueredo, 2006). Studies have shown that patients may be inconsistent or irregular in taking medications at levels that compromise the effectiveness of their treatment (Benner et al., 2002; Grosset et al., 2009; Jackevicius, Mamdani, & Tu, 2002). Adherence may also decline over time, a problem that can reduce the long-term effectiveness of medications prescribed for chronic problems such as hypertension or hyperlipidemias (Chapman et al., 2008). The reasons for declines in adherence over time are not clear, but may include an accumulation of factors such as problems in paying for medications, ongoing experience with side effects, and lack of evidence that medications have a positive effect (Chapman et al., 2008). Elderly patients may be especially at high risk for medication nonadherence, especially if they have memory impairments. The development of strategies to improve medication adherence is thus critical to successful patient care and disease management.

Two strategies that have shown promise in promoting medication adherence include (a) reminding techniques that prompt patients to take their medication at appropriate times, addressing a common reason patients report for not taking their medications (Fulmer et al., 1999; Osterberg & Blaschke, 2005) and (b) those that are designed to increase their internal motivation to take their medication regularly. Reminding interventions have included: directly observed therapy (in which a second person actually watches the person take their medication), special pill bottles, automated telephone calls, and text messaging (Hardy et al., 2011; Kirkland et al., 2002; Marquez et al., 2005; Pop-Eleches et al., 2011). Strategies to affect patients' motivation have focused on providing information about treatment, dealing with barriers to adherence such as side effects or complex dosing regimens, and training in adherence-related skills (Fisher et al., 2011).

A particularly effective strategy for communicating information with patients, in a way that is likely to increase their motivation for adherence, has been through the use of tailored information. While simple educational interventions improve patient adherence (Berrien, Salazar, Reynolds, & McKay, 2004; Grosset & Grosset, 2007), information that is individually tailored to a patients' personal characteristics, interests, or needs may have a significantly greater impact on their behavior. Information can, for example, be tailored to a person's gender, race, or ethnicity through related graphic elements such as pictures. Information can also be tailored to an individual's level of knowledge through the administration of a pretest, or to his or her interests by administering a questionnaire that assesses his or her interests in specific topics. Tailored information interventions have been effective in promoting behavior change with respect to healthcare behaviors (Kreuter & Wray, 2003).

Several reviews have documented the effectiveness of combinations of reminding and motivational interventions in improving medication adherence (Conn et al., 2009; Haynes, Ackloo, Sahota, McDonald, & Yao, 2008; van Eijken, Tsang, Wensing, de Smet, & Grol, 2003). Effective strategies to improve adherence, however, have often involved complex and multifactorial interventions that include multiple components each of which may have an impact (Lee, Grace, & Taylor, 2006). For example, the intervention used by Lee et al. (2006) included not only individualized patient education but also special medication blister

packs with medications grouped for each daily dose, and bi-monthly in-person follow-up visits with a clinical pharmacist. The relative contribution of each element (education, packaging, follow-up visits) is difficult to detect in this study. A clearer understanding of the mechanisms through which interventions for adherence result in a positive impact on outcomes requires some type of comparative effectiveness trial which compares distinct interventions with known efficacy.

Computer-based applications may be useful as a method for implementing both types of adherence-promoting interventions for patients by reducing costs associated with reminding or motivation-enhancing interventions. While it is difficult or expensive to employ clinicians in reminding patients to take medications or in providing tailored information, computers can be employed to reduce the amount of clinician time required to implement the intervention. An alternative to using clinicians to ensure that patients take their medications appropriately, for example, has been to use technology to provide them with indirect reminders. Reminders have been provided via special pill bottles, voice telephone calls, and text messaging (Conn et al., 2009). It has been shown, for example, that computer-based automation can be used to send daily medication reminders to patients (Friedman et al., 1996; Piette, Weinberger, & McPhee, 2000). A reminder message can be recorded and played back at a predetermined time by an automated system. Once programmed, a computer can dial the patient's phone number, provide the reminder message, and request a response in the form of a verbal response or a keypress on the telephone from whomever answers the telephone (recognizing that the patient may not always answer the telephone). The program can also redial a predetermined number of times if the telephone is not answered, and provide records of the number of times the message is delivered.

Tailored information interventions delivered by computers have also been shown to be effective in changing healthcare-related behaviors (Hawkins, Kreuter, Resnicow, Fishbein, & Dijkstra, 2008; Kreuter & Wray, 2003). In fact, Johnson and colleagues (2006) showed that a computer-based algorithm for information tailoring can improve medication adherence. A review of interventions for medication adherence has shown that computer-administered interventions were the most effective among various modes of delivery (Cutrona et al., 2010). As with automated reminding, computer-based programs can reduce the cost of tailored information interventions by automating the assessment and tailoring process (Ross, 2008).

Given the incidence of memory impairment in older individuals and the relation of increasing age to risk for Alzheimer's disease, medication adherence in older adults may be an especially important problem. Several studies have investigated medication adherence in patients with memory impairment or Alzheimer's disease. Memory problems are commonly treated with cholinesterase inhibitors and for these patients adherence to a prescribed regimen of therapy is essential to maintaining cognitive function. In spite of the importance of sustained adherence to therapy, research suggest that these patients do not take their medications regularly or persistently (Borah, Sacco, & Zarotsky, 2010; Gadzhanova, Roughead, & Mackson, 2010; Gardette et al., 2010). Although no readily identifiable study has investigated interventions to promote adherence in this population, one group has reported on an intervention to improve medication adherence in patients treated for Parkinson's disease (Grosset & Grosset, 2007). Although both the patients with and treatments for Alzheimer's and Parkinson's diseases are different in important ways, affected patients are often similar with respect to age and comorbidities. Patients with Parkinson's disease may have cognitive impairments as well, and this study showed that providing the patients information on the underlying neurochemistry of the disease and how its pathology can be addressed through medications helped to improve their medication adherence (Grosset & Grosset, 2007).

A number of factors have been associated with medication adherence. Depression has consistently been related to poorer medication adherence (Dimatteo, Lepper, & Croghan, 2000; Krousel-Wood et al., 2010) as have specific cognitive abilities (Hayes, Larimer, Adami, & Kaye, 2009) such as memory or executive functions (Insel et al., 2006). Level of health literacy has also been related to medication adherence (Gazmararian et al., 1999; Kalichman, Ramachandran, & Catz, 1999).

In summary, interventions have been shown to improve patients' medication adherence, but effective interventions have usually included multiple components. This strategy makes it difficult to determine which elements of the interventions are key contributors to their success. Both reminding and information interventions may be effective in promoting adherence, and computer-delivered interventions may be less costly than those that depend on individual interventions. However, the efficacy of these strategies has not been compared. Further, no readily identifiable study has investigated the impact of interventions targeted at improving medication adherence in elders with memory problems or Alzheimer's disease. The purpose of this study was thus to evaluate the effect of two distinct interventions on medication adherence in elders treated for memory problems while taking factors such as depression and cognitive status into account. We hypothesized that both approaches would significantly improve adherence but had no a priori hypothesis about either method's superiority.

METHOD

Participants were recruited from a university-affiliated memory disorders clinic in Miami Beach, Florida, and had previously been evaluated by a multidisciplinary team and judged to have clinically significant memory impairments. The clinic is one of several memory disorder clinics supported by the state of Florida and draws patients from all of Miami-Dade County. Approximately 50% of new patients are Spanish-speaking, and patients come from a range of socioeconomic backgrounds. Patients in this clinic are typically older than 50 years of age, and in an earlier study we showed that they often have been prescribed multiple medications for several problems as is typical of many older persons (Ownby, Hertzog, Crocco, & Duara, 2006).

Participants were included in the study if they had been clinically judged to have a memory problem and were being treated with one of the approved cholinesterase inhibitor medications (donepezil, rivastigmine, or galantamine) or memantine and judged to be able to give informed consent for their participation as described below. Some participants were usually accompanied to the clinic by a spouse or other caregiver such as an adult child, while others participated independently of other assistance. No participants were excluded due to an inability to provide informed consent.

This study was completed under a protocol approved by the University of Miami Office of Human Subjects Protection.

Treatment Conditions

Control—Participants assigned to the control condition participated in all study assessments and regular monthly visits, but did not receive any additional information about their condition, medication, or the importance of adherence.

Automated reminding—Participants in this condition participated in regular study visits and assessments, but also received automated daily phone calls consisting of a recorded message from the investigator reminding the participant to take their medication. The

message consisted of a recording of the first author stating that he was calling the patient to remind them to take their medication, either in Spanish or English.

The time of day that the message was programmed for delivery was determined at the time of the second study visit (at which baseline adherence data were collected and participants were randomized to one of the study conditions). The time was chosen based on patient preference and the time of day at which they indicated that they usually took their medication.

Tailored information—Participants in this condition at the second study visit received a 20-minute tailored information intervention that consisted of completing a questionnaire about information they wanted to receive about memory disorders and their treatment. Responses to the questionnaire, their preferred language, and their level of health literacy as assessed by the Test of Functional Health Literacy in Adults (Parker, Baker, Williams, & Nurss, 1995) were used as input to a computer program that then created a written response tailored to participants' language, level of health literacy, and requests for information. This program, written in Visual Basic by the first author, allowed the investigator, also the first author, to provide participants with individually-tailored information about memory problems and aging, dementing illnesses, and their treatment. A list of topics consisting of common issues that arise in clinical work with older individuals with memory problems was first created by the first author. It was then reviewed by the director of the memory disorders clinic, and a nurse with extensive experience in work with older adults.

During the study intervention, this list of topics was reviewed by the first author with the participant and his or her caregiver. The participant indicated which topics were of interest to them. These topics were then checked in the user interface of the computer program, which then created a personalized information handout that included the participant's name and the date. In a separate procedure, a digital photograph of the participant was taken and printed on a sheet that was inserted in a binder that also then included with the printout of the requested information. The individually tailored information was then reviewed with the participant and provided to him or her as a booklet for use at home. No other follow-up was provided to this group other than the same procedures that all other participants completed.

Procedure

Participants were recruited during routine clinical visits at the memory disorders clinic or from contact information available because they had participated in other research studies at the clinic and randomized to one of the three conditions after written informed consent was obtained. Participants were only included if they were judged to have the ability to provide informed consent based on their understanding of the nature of the study and its requirements. This determination was made by the first author during the informed consent process after consideration of the participant's understanding of key elements of informed consent, such as the fact that they would participate in a research study, that their participation was voluntary, and that declining to participate would not affect their future treatment at the clinic. In cases in which participants came to study sessions with a caregiver, the caregiver also was involved in the informed consent process.

At the initial study visit, participants completed a baseline battery of measures that included assessments of cognitive status, mood, health literacy, self-efficacy, and health-related quality of life. At this visit, they were also oriented to the use of the Medication Event Monitoring System (MEMS; Aaprex, Union City, CA), the method used as the primary measure of medication adherence. The system includes a pill bottle cap that records the date and time of each opening. Recordings can be read into a computer on which software allows the computation participants' adherence. It calculates several measures of adherence based

on when medications are taken in relation to the participants' prescribed regimen. The index used in this study is an index of the percentage of medication doses taken at appropriate intervals ($\pm 25\%$ of the interval), sometimes called "timing adherence" (Grosset & Grosset, 2007).

At this first visit, the battery of cognitive measures included the Alzheimer's Disease Assessment Scale, Cognitive subtest (ADAS-Cog; Rosen, Mohs, & Davis, 1984) in a form that included the supplemental delayed recall, maze, and checking tasks (Mohs et al., 1997). The battery also included the Hamilton Depression Rating Scale (Hamilton, 1960) and the Test of Functional Health Literacy in Adults (Parker et al., 1995). Following completion of the battery, participants were instructed in the use of the MEMS pill bottle, and their current anticholinesterase medication was transferred to the MEMS pill bottle. At the second visit one month later, participants' baseline medication adherence was recorded, and they were randomized to one of the three treatment conditions and followed at monthly intervals for the first 12 months and at 3-month intervals for a second year. At monthly visits, the MEMS cap was read into the computer, and participants were rated on the HAM-D. At quarterly study visits (every three months), participants' cognitive status was reassessed via readministration of the ADAS-Cog with supplementary tests.

All assessment and intervention materials were available in both Spanish and English. Spanish translations of assessment materials were already available. Tailored information materials, including the questionnaire and educational materials, were first composed by the first author in English and then translated by him into Spanish. Spanish translations were then reviewed and corrected by an experienced bilingual clinician with extensive background in memory disorders and general gerontology.

Data Analysis

Study hypotheses were evaluated using generalized estimating equation models. This strategy was chosen in order to allow for the use of all available data while allowing for the correlations among repeated measures over time. Timing adherence was used as the dependent measure in the analyses presented here. Between-groups differences in baseline adherence were assessed with the Kruskal-Wallis test.

Because of the non-normal distribution of our primary dependent variable (medication adherence) and the longitudinal structure of our data, a generalized estimating equation (GEE) model (Diggle, Liang, & Zeger, 1994) using Poisson regression with an independent correlation structure and a log linking function was chosen to evaluate the effects of the interventions while controlling for relevant potential confounders with repeated measures of adherence over time. Covariates originally hypothesized to be related to adherence included age, gender, language, general cognitive status, memory, mood, health literacy, and the presence or absence of a caregiver.

Participants provided data at monthly visits after randomization. We evaluated the relation of covariates including treatment group membership to these repeated measurements over time using a GEE model that allowed for correction of observed errors using robust (sandwich) estimators (Hardin & Hilbe, 2002). The form chosen for the correlation structure of the GEE model was determined by evaluating alternative structures, including autoregressive, unstructured, exchangeable, and independent, and choosing the form that resulted in the smallest value of the quasi-likelihood information criterion (QIC) as recommended by Hardin and Hilbe (2002). A full model was first estimated that included all potentially relevant covariates. They were chosen based on demographic (age, gender, language) considerations of previous research showing their effects on medication adherence (cognitive variables and health literacy, mood, and presence or absence of a

caregiver). All two-way interactions were included in a preliminary version of the full model. This full model was reduced through successively eliminating nonsignificant variables and then recalculating the model. Appropriateness of model changes was assessed through changes in variable significance and review of the quasi-likelihood information criterion corrected (QICC) also as recommended by Hardin and Hilbe (2002). The final model thus included relevant demographic variables as well as significant predictors of adherence.

RESULTS

Thirty participants were recruited for the study, all of whom contributed baseline cognitive and health literacy data. Of these, 27 provided baseline adherence data at the second study visit. These 27 were randomized to one of the treatment conditions. The three participants who were recruited and who provided written informed consent but who did not continue in the study each withdrew because of the time demands of the study. Twenty-four participants were evaluated on at least two occasions and provided baseline and post-intervention data for analysis in the models. These participants thus provided longitudinal data essential for evaluating the effect of the interventions or the control condition over time.

Because of missing data for the depression and health literacy measures, the preliminary full GEE model is based on only 23 participants. Of the 27 participants randomized, three withdrew consent because of the time demands of the study, and one patient was lost to follow-up after recruitment but before randomization after being hospitalized for a fall. Of the 27 participants randomized, 16 were men and 11 were women. Fifteen participated in English and 12 in Spanish; 15 had a primary caregiver who assisted with medication adherence (in these cases the caregiver either reminded the participant or actually opened the pill bottle for him or her) while 12 reported that they themselves assumed primary responsibility for taking their medications. Eleven participants were assigned to the control condition, 8 to automated reminding condition, and 8 to the tailored information condition. There were no significant differences among the groups in primary language, gender, or caregiver presence (all $ps > .20$). All patients had been prescribed donepezil (Aricept™), either 5 or 10 mg, once per day for treatment of memory impairment. All participants had been stable on their medications for at least 30 days at the time of their entry into the study.

Table 1 presents descriptive statistics for the continuous variables used in the study. Categorical variables are summarized above. Groups did not differ significantly at baseline in levels of adherence (Kruskal-Wallis $\chi^2 = 2.20$, $p = .33$).

Although specific diagnoses of mild cognitive impairment or Alzheimer's disease were not obtained as part of the study data collection, participants' scores on the ADAS-Cog allow characterization of the cognitive status of participants. The average total ADAS-Cog score of the sample was 22.7 ($SD = 11.4$; range 5–59; higher scores indicate poorer performance), and the average score on the supplemental delayed recall subtest was 7.9 ($SD = 2.4$; range 1–10). These scores are similar to those of persons diagnosed with either mild cognitive impairment or mild Alzheimer's disease in normative data reported by Pyo et al. (2006) who showed that patients with a clinical diagnosis of Alzheimer's disease and clear functional impairment as evidenced by a score of 1 on the Clinical Dementia Rating Scale had an average ADAS-Cog score of 15.72 ($SD = 6.34$). Current participants' scores are also consistent with a much poorer performance than normal elderly controls (mean age 72.1) whose average score was 4.98 ($SD = 2.25$) (Graham, Cully, Snow, Massman, & Doody, 2004).

Potential covariates for inclusion in GEE models were assessed with univariate tests of between-group differences via one-way analysis of variance (ANOVA). Models were developed based on demonstration of between-groups differences on covariates to be included in the models as well as on conceptual relevance. Covariates evaluated included age, gender, language, presence of a caregiver, and cognitive variables (general cognitive status, delayed recall, executive function, and health literacy) as well as mood. The model including all evaluated covariates is presented in Table 2. All two-way variable interactions were evaluated as well in light of the small size of each group and the potential for between-group differences that might affect results.

The model presented in Table 2 shows that language and gender were not related to medication adherence after including age, the presence of a caregiver and verbal memory (Delayed Recall) in the model. Measures of executive function (Mazes Time), health literacy (TOFHLA), and depression (HAM-D) were also not related to adherence. Model-corrected estimates of adherence are presented in Table 3, showing that both participants in the Reminding and Tailored Information conditions had higher levels of adherence compared to participants in the control group after taking relevant covariates into account.

As described above, nonsignificant effects in this full model were successively eliminated, the model was recalculated, and model fit was again evaluated at each iteration. The final model thus included general cognitive function (ADAS-Cog) and its interaction with group membership. Demographic variables, even when nonsignificant, are included in the final model due to their relevance. The reduced model is presented in Table 4. These data show that age was no longer a significant predictor of adherence after taking other variables and the interaction of group membership with general cognitive status into account. Data in Table 5 present model-corrected group estimates of adherence. In the final model, corrected estimates of each group's adherence mirrored the general pattern seen in the full model with both Reminding and Tailored Information groups showing higher levels of adherence than control participants. The estimate for Tailored Information was significantly greater than for control and Reminding participants.

DISCUSSION

The purpose of this study was to evaluate the effect of two interventions in improving medication adherence in individuals treated for memory problems. Results suggest that both of the interventions (automated telephone reminders or individually-tailored information) may improve medication adherence. Perhaps due to our small sample size, estimates in each model varied substantially, although both models produced results that suggested that both interventions may be useful in improving medication adherence. In the full model that included all possible covariates, both being older and having better long-term verbal memory were associated with better adherence. When the model was reduced based on evaluation of the significance of covariates and their interaction with group membership, only the presence of a caregiver and long-term memory were positively associated with better adherence.

These results highlight the role of caregivers in improving adherence in patients with memory problems. Our findings are also consistent with previous studies that have shown the importance of caregivers in adherence (Ben-Natan & Noselozich, 2011; Clark et al., 2010; McCurry et al., 2010). We note that personal circumstances dictate whether or not a patient seen in clinical practice has a caregiver who can assist with medications and that both interventions appear to have had an additional effect on adherence even after taking the presence of a caregiver into account.

Increasing age was associated with improved medication adherence. This finding is consistent with other studies that have shown that age, in itself, can be positively associated with adherence (Park et al., 1999). However, the results of the latter study also show that age-related declines in cognitive function may negatively influence adherence (Park et al., 1999). Age may thus be related to better adherence in elders with preserved memory function, but can itself be related to declines in memory functioning suggesting that an understanding of the effects of age on adherence may depend on an understanding of an individual's cognitive status.

Similarly, the association of adherence with better long-term verbal memory is not surprising, but emphasizes the role of basic cognitive skills in medication adherence (Ownby, 2006). Other studies have suggested that complex abilities such as working memory or executive skills may be related to medication adherence (Insel et al., 2006). Although one might expect that general cognitive status (as measured with the total score on the ADAS-Cog) and executive functions (as assessed by participants' performance on a maze solving task) would be related to adherence, we failed to find a relation. Given the small sample size employed in this study, it is possible that we simply did not have adequate statistical power to detect a relation that may have been present.

One purpose of this study was to evaluate the comparative effects of two distinct interventions on medication adherence. This was a goal because several studies have shown that interventions that combine several strategies may be effective in improving medication adherence, but few studies have allowed an evaluation of the interventions' distinct elements in promoting adherence. Such studies do not allow a determination of whether any single element of a combination strategy is by itself effective. This study suggests that both automated reminding and tailored information may be useful in promoting medication adherence. It is possible that a combination of the two strategies might have had additive effects. It is also possible that one treatment might have been superior based on patients' cognitive status. For example, automated reminding might be superior for patients without caregivers who have memory and other cognitive deficits, while tailored information may be helpful for patients with better cognitive function. It is possible that our small sample did not provide us sufficient statistical power to detect these possible relations. Future studies with larger sample sizes may allow an evaluation of the ways in which the effectiveness of different interventions may be related to patient characteristics.

Other researchers have also reported a relation between health literacy and adherence. We did not find this relation, but again small sample size may have resulted in lower power to detect the effect of this factor. It should also be noted that the tailored information application adjusted for participants' level of health literacy so that to an extent this factor was incorporated in the study design. Persons in the automated reminding condition might have been less affected by factors that required them to understand healthcare information, so the impact of health literacy on adherence in both groups may have been reduced. Whether health literacy might be related to medication adherence in other contexts is thus not clear. Patients' levels of health literacy may interact with how well they respond to adherence interventions.

Our results thus show that tailored information and automated reminding may be useful interventions to improve medication adherence in adults with memory problems. Although researchers have shown that a variety of interventions can enhance medication adherence, most of them are multifactorial and clinically intensive. The potential for computer-based interventions to reduce the cost of implementing adherence interventions thus merits further exploration.

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TABLE 1

Descriptive Statistics for Continuous Variables

Variable	N	Minimum	Maximum	Mean	SD
Age	30	71	92	79.93	5.34
TOFHLA total ^a	28	0	98	62.89	26.52
ADAS COG total ^b	29	5.00	59.00	22.72	11.44
Delayed Word Recall ^c	29	1	10	7.93	2.434
Maze time (seconds) ^d	27	25	240	125.78	92.16
HAM-D ^e	26	0	13	3.92	3.41
% Doses taken ^f	30	32	100	99.10	24.26
% Days correctly taken ^g	30	0	100	81.76	24.30
% Doses on schedule ^h	30	0	100	77.18	25.71

^aTest of Functional Health Literacy in Adults;

^bAlzheimer's Disease Assessment Scale, Cognitive Subscale;

^cDelayed Word Recall supplementary subtest of the ADAS-Cog;

^dMaze solving supplementary subtest of the ADAS-Cog;

^eHamilton Depression Rating Scale;

^fPercent of total doses taken over the interval (number of taken doses/number of days monitored times 100);

^gPercent of doses taken on the correct day (number of taken doses each day/number of days monitored times 100);

^hPercent of total doses taken at an interval between 18 and 30 hours after the previous dose (number of doses taken at the correct interval /number of intervals monitored times 100).

TABLE 2

Full Model Predicting Timing Adherence

Source	²	df	p
Intercept	352.39	1	<.001
Language	.29	1	.59
Gender	.27	1	.61
Age	9.57	1	.002
Caregiver	13.20	1	<.001
Delayed recall	7.22	1	.007
ADAS-Cog	.05	1	.83
Mazes time	.005	1	.95
TOFHLA	.37	1	.54
HAM-D	.50	1	.48
Treatment group	5.37	2	.07

TABLE 3

Estimated Marginal Means for Groups for the Full Model

Group	Mean	Std. Error	95% Confidence interval	
			Lower	Upper
Control	60.3	6.6	47.2	73.2
Reminding	75.7	5.5	65.0	86.5
Tailored information	78.6	3.4	70.9	84.2

Post-hoc tests (least significant difference); Control vs. Reminding, $p = .02$; Control vs. Tailored Information, $p = .04$; Reminding vs. Tailored Information, $p = .80$.

TABLE 4

Reduced Model

Source	²	df	p
Intercept	247.08	1	<.001
Gender	1.08	1	.30
Language	.07	1	.79
Age	.51	1	.47
Caregiver	14.82	1	<.001
Delayed recall	5.89	1	.02
ADAS-Cog	.21	1	.65
Treatment group X ADAS-Cog	7.12	2	.03
Treatment group	10.41	2	.005

TABLE 5

Estimated Marginal Means for Groups for the Reduced Model

Group	Mean	SE	95% Wald Confidence Interval	
			Lower	Upper
Control	60.0	6.1	48.1	72.0
Reminding	64.5	5.6	53.5	76.0
Tailored information	82.0	3.7	74.5	89.2

Post-hoc tests (least significant difference); Control vs. Reminding, $p = .48$; Control vs. Tailored Information, $p = .004$; Reminding vs. Tailored Information = .03.