

Multifaceted Prospective Memory Intervention to Improve Medication Adherence

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OBJECTIVES: To test whether a multifaceted prospective memory intervention improved adherence to antihypertensive medications and to assess whether executive function and working memory processes moderated the intervention effects.

DESIGN: Two-group longitudinal randomized control trial.

SETTING: Community.

PARTICIPANTS: Individuals aged 65 and older without signs of dementia or symptoms of severe depression who were self-managing prescribed medication.

MEASUREMENTS: After 4 weeks of initial adherence monitoring using a medication event monitoring system, individuals with 90% or less adherence were randomly assigned to groups.

INTERVENTION: The prospective memory intervention was designed to provide strategies that switch older adults from relying on executive function and working memory processes (that show effects of cognitive aging) to mostly automatic associative processes (that are relatively spared with normal aging) for remembering to take medications. Strategies included establishing a routine, establishing cues strongly associated with medication taking actions, performing the action immediately upon thinking about it, using a medication organizer, and imagining medication taking to enhance encoding and improve cuing.

RESULTS: There was significant improvement in adherence in the intervention group (57% at baseline to 78% after the intervention), but most of these gains were lost after 5 months. The control condition started at 68% and was stable during the intervention, but dropped to 62%. Executive function and working memory moderated the intervention effect, with the intervention producing greater

benefit for those with lower executive function and working memory.

CONCLUSION: The intervention improved adherence, but the benefits were not sustained. Further research is needed to determine how to sustain the substantial initial benefits. *J Am Geriatr Soc* 64:561–568, 2016.

Key words: medication adherence; intervention; prospective memory; elderly; hypertension

Medication adherence is critically important, yet typical adherence rates for prescribed medications are approximately 50%.¹ These rates are particularly low when medications are prescribed for chronic and asymptomatic conditions such as hypertension. People do not adhere to prescribed medications despite extensive interventions to educate, motivate, and support adherence behaviors.^{1,2} The purpose of this study was to examine the effects of a 4-week multifaceted prospective memory intervention on adherence to a daily prescribed antihypertensive agent in community-dwelling older adults (≥ 65) who were self-managing their medications. The immediate and long-term effects (6 months after initiation of the intervention) were examined. Another purpose of this study was to examine executive function and working memory, a set of cognitive abilities that are vulnerable to cognitive aging, as a moderator of the intervention effects on improving medication adherence.

Nonadherence prevents people from fully realizing the benefits of treatment, leading to substantial costs to individuals and society.³ Nonadherence to antihypertensive medication is associated with a significantly greater risk of major cardiovascular events and death.⁴ The need to control hypertension is clear, yet control is often inadequate. Past interventions to improve medication adherence have focused on knowledge, beliefs, and attitudes, including motivation,^{2,5} and a few studies have addressed forgetting through reminders.⁶ Knowledge, beliefs, self-monitoring, decreasing costs, and other strategies including ongoing

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reminders and once-a-day dosing have been shown to improve adherence, but the effects are often small and not sustained once the intervention is completed.^{7–9} On the basis of analyzing the cognitive processes involved in taking medications and how aging affects these processes, an intervention was designed to support the most-vulnerable processes.

An analysis of prospective memory-based tasks suggests that successful medication adherence involves five cognitive components (encoding the need to take medications and the conditions for taking them, retaining this information in memory, retrieving the intention to take the medicine at the appropriate time, executing the action of taking the medicine (often in the context of distraction), and monitoring that the medicine was taken (so as not to repeat a dose)),¹⁰ and research has shown that failure of any of these components can undermine adherence.¹¹ The multifaceted prospective memory (remembering to recall an intended activity planned for the future at the right time) intervention tested in this study targeted all five tasks with strategies that have been empirically demonstrated to improve prospective memory performance of older adults. An important and unique feature of the intervention was that it combined these strategies into a comprehensive package that can be easily administered and used.¹²

Given the complexity of the cognitive processes involved in successful medication adherence, it is not surprising that poor adherence is associated with poor cognitive function in general¹³ and particularly with poor executive function and working memory.^{14,15} Moreover, robust age-related cognitive declines¹⁶ make older adults particularly vulnerable to failures in adherence. An interesting feature of age-related cognitive decline is that normal aging tends to affect certain processes (e.g., executive function and working memory) more than other relatively automatic retrieval processes that depend on associative processes rather than more-effortful processes.^{17,18} Recent research shows that older adults with a history of hypertension show substantial deficits on laboratory prospective memory tasks that rely on the former but not the latter processes.¹⁹ Thus, the major focus of the intervention was to get older adults to rely on the relatively spared cognitive processes when taking medication. Generally, the intervention was aimed at switching dependence from self-initiated processes (processes that show large age-related deficits) that depend heavily on working memory and executive resources to environmentally supported and relatively automatic associative processes (processes that are thought to be spared with age).¹⁷ The hypothesis was that individuals in the multifaceted prospective memory intervention group would have greater adherence to antihypertensive medication than those in an education control group immediately and over 6 months. It was also hypothesized that the intervention would be more effective for those with poorer executive function and working memory, because these individuals should be less able to rely effectively on these processes to support their medication adherence.

METHOD

The University of Arizona Human Subjects Protection Program approved and monitored the study protocol. The

choice of antihypertensive medication to monitor was made by writing the name of each prescribed antihypertensive medication (with the exception of diuretics because sometimes individuals will intentionally withhold a diuretic) on separate slips of paper and randomly withdrawing a slip from an opaque envelope. All participants were asked to place the monitored medication in a medication container with a medication event monitoring system. After 4 weeks of baseline medication monitoring to establish the level of initial adherence for eligibility ($\leq 90\%$ adherence to the interdose interval), participants were randomly assigned to the multifaceted prospective memory intervention group or the educational comparison group (Figure 1).

Sample

The sample was selected from English-speaking, community-dwelling adults aged 65 and older who were self-managing at least one prescribed antihypertensive agent. Individuals residing in nursing homes, indicating symptoms of severe depression (Geriatric Depression Scale score >11),²⁰ or with signs of dementia (Mini-Mental State Examination (MMSE) score <24)²¹ were excluded from participation.

Random assignment occurred in blocks of two, with the first individual randomly assigned to one condition and the second individual assigned to the other condition. For the purpose of calculating the sample size, using an 18-percentage-point difference (80–62%), information obtained in a preliminary study,²² a standard deviation of 28 from the same preliminary study, a one-tailed alpha of .05, and a power of 0.90, it was determined that a final sample size of 43 per group, or a total sample size of 86, was needed. Anticipated attrition was 15%, so a target sample of 50 was anticipated for each arm.

Participants were recruited at meal sites for seniors, health fairs, and community talks. A complete description of the methods used for recruitment and efforts made to increase the comfort and security of participants are detailed elsewhere.²³ Of the 299 participants initially assessed, 134 were adherent to medication (adherence $>90\%$ during 4-week baseline period), and eight did not meet the inclusion criteria. Twenty-eight declined to participate after initial data collection or baseline monitoring, and one died, resulting in 128 individuals randomly assigned to the two conditions. After randomization, two individuals did not complete the allocated control condition, and two did not receive the allocated intervention. In total, 58 individuals in each condition continued to the end of the ongoing monitoring phase (Figure 1).

Intervention

The intervention provided older adults with strategies that helped establish a routine so that medication was taken at the same time under the same circumstances each day and associated the medication taking with a specific environmental cue such as having breakfast rather than a time (e.g., 8 a.m.). The idea is that time is not easily noticed but that a salient environmental event such as breakfast is and is hence more likely to cue relatively automatic

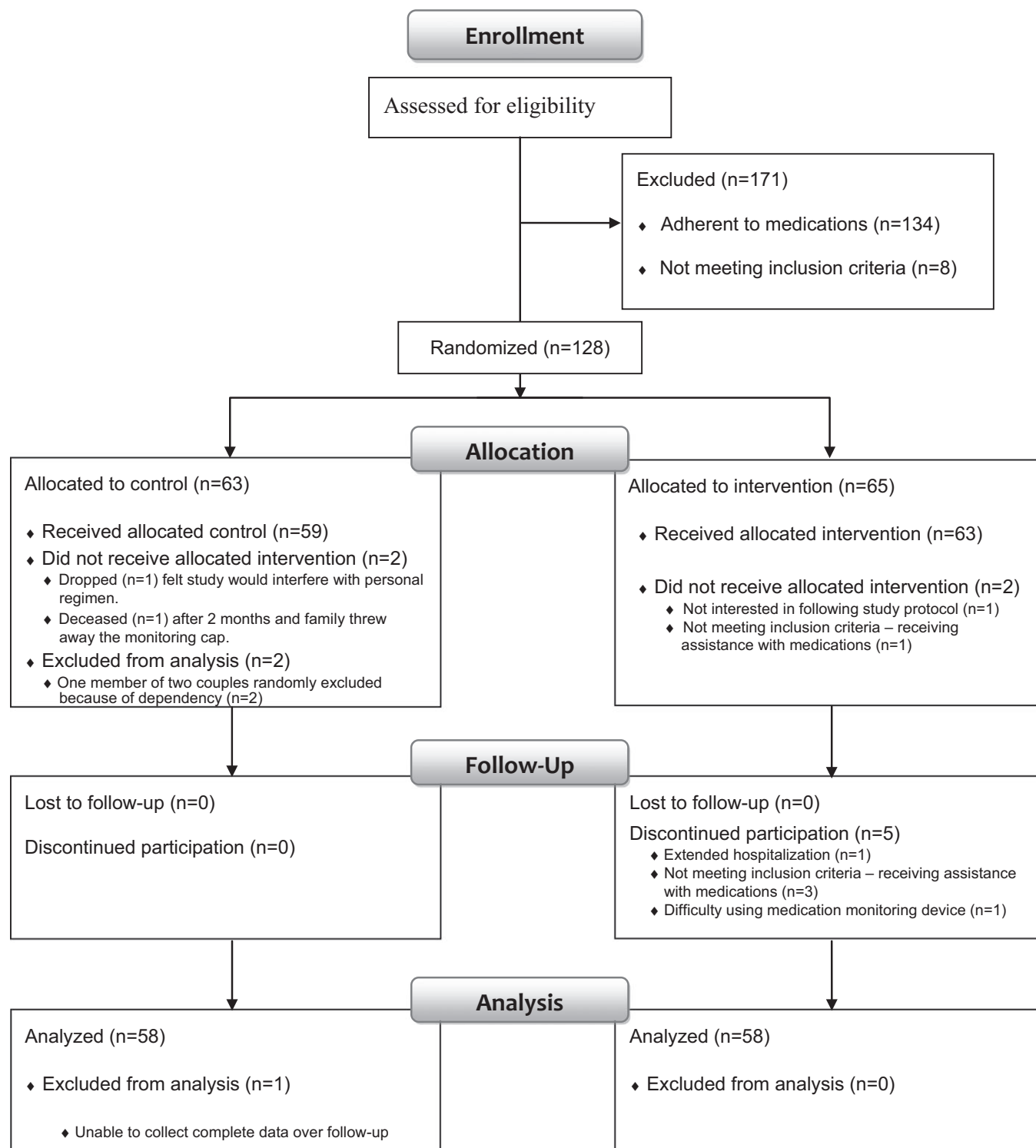


Figure 1. Flow diagram.

retrieval of the intention.^{24–26} Participants in the intervention condition were also asked to imagine where they will be when they need to take the medication because previous research has shown that forming this kind of implementation intention (consciously linking the action to a triggering cue) further automatizes retrieval.²⁷ The intervention also calls attention to the act of taking the medication (and specifically to elaborating the action) to make the event more memorable and uses an organizer to

provide a way to monitor whether the medication was taken as intended. These latter two steps were included, because too often and especially with frequent or habitual prospective memory tasks such as taking medication, the act of taking medication becomes routine and is performed without conscious thought.²⁸ The result is that the person may take the medication, but then not remember doing so, leaving open the possibility of repeating a dose. Participants were also encouraged to “do it now,” which was

intended to get them to perform the action soon as they recalled the intention to take the medication. This was included because previous research has shown that brief delays (as brief as 5 seconds) and interruptions after retrieving an intention (but before executing it) greatly interfere with remembering to perform the act, especially for older adults.²⁹

The education control group was aimed at establishing a relationship with the participants (as was the case in the intervention group) and received the same educational information on hypertension that was given to participants in the intervention group. Time and attention were also equated between the groups by including information on preventing falls and social interaction with the nurses for individuals in the control condition.

Procedure

Nurses delivered the intervention and control conditions at participants' homes. Participants were visited once a week for 4 weeks. The initial visit was approximately 90 minutes, and the following visits were 45 to 60 minutes. Participants in both groups received information about hypertension, the deleterious effects of uncontrolled hypertension, and antihypertensive medications. This education was designed to support the encoding and retention of information needed to take medication successfully. Participants in the intervention condition also received the strategy instructions that supported all components of prospective remembering in the first visit, and these were reviewed in each of the three other weekly visits. All participants in the intervention group were provided with a medication organizer, a box with slots labeled S, M, T, W, T, F, S for each day of the week and a medication container that could be moved from the slot for one day to the next. If the medication was to be taken twice a day, an additional organizer was provided.

Measures

Medication adherence was measured using a medication event monitoring system^{14,30} that consisted of a cap that keeps track of when it is opened.³¹ Adherence was defined according to percentage adherence to the interdose interval, which is 25% of the interval before and after the targeted prescribed time. If the dose is daily (24 hours), then the interdose interval is between 18 hours (24 – 6 hours) and 30 hours (24 + 6 hours) since the prior dose. If the dose is twice a day (12 hours), the interdose interval is between 9 (12 – 3) and 15 (12 + 3) hours from the prior dose. A cutoff point of 90% baseline adherence over the baseline 4 weeks was used to determine eligibility for the study.

Whether the intervention resulted in better medication adherence than the education control condition was initially examined. To do so, adherence (percentage adherence to the interdose interval) was computed for the baseline period (average over the last 2 weeks of the 4-week baseline), nurse-visit period (average over the 3 weeks from the first nurse visit to the fourth), and the additional 5-month monitoring period (average from the fourth nurse visit to the end of the study). The last

2 weeks of the 4-week baseline monitoring period was used because it has been shown that introducing a medication monitoring device may improve adherence but that the effect diminishes after 2 weeks.^{32,33} These data were included in a two-by-three mixed analysis of variance with the between-subject variable of condition (education control, intervention) and the within-subject variable of time (baseline, nurse-visit, monitoring).

A composite measure for executive function and working memory was created using perseveration errors and the number of categories correctly identified from the Wisconsin Card Sorting Test (WCST)³⁴ and absolute operation span score.^{35,36} The WCST assesses abstraction ability and ability to shift cognitive strategies in response to changing environmental conditions. Successful completion requires planning, organized searching, use of feedback to shift cognitive set, goal-oriented behavior, and ability to modulate impulsive responding.³⁴ Operation span assesses working memory capacity, which is a complex ability that involves holding on to information in the face of distraction and quickly retrieving recently activated information.³⁶ Scores from the WCST on perseveration errors and the number of categories correctly identified and absolute operation span scores were converted to z-scores and then summed and averaged to create the composite measure.

Strategy use for those in the intervention group was rated as 0 (not using this strategy), 1 (sometimes using this strategy), or 2 (always use this strategy). There were six strategies, with a maximum of 2 points for each strategy and 12 possible points for the total score.

RESULTS

Demographic information for participants who received the allocated intervention or control is presented in Table 1. Overall, mean age was 77.0 ± 7.4 and did not differ between the groups. Sex was also similarly distributed between groups, although the overall sample included more women ($n = 93$) than men ($n = 29$). There were no differences in education ($t(1,121) = 1.80$, $P = .07$).

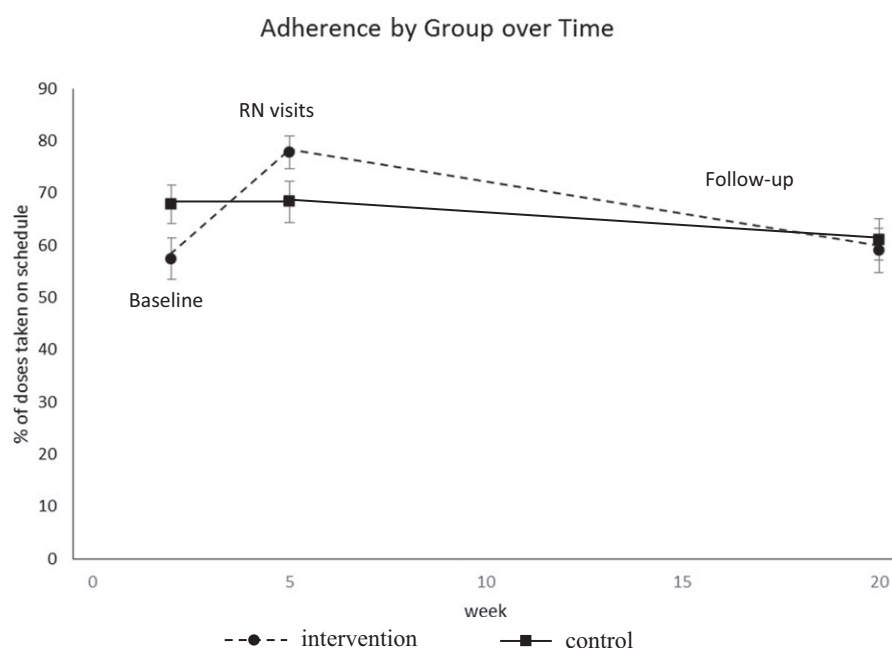
Intervention Effect on Adherence

A significant condition-by-time interaction (Wilks $\lambda = 0.887$, $F(2, 113) = 7.166$, $P = .001$) indicated that the pattern over time was different for the two groups. Adherence improved markedly in the intervention group, but this advantage was not sustained over the 5-month monitoring period (Figure 2). Adherence in the education control group, by contrast, declined slightly over the 5 months. The post hoc analyses probing the condition-by-time interaction supported this observation. The simple effect of time for the intervention group was significant (Wilks $\lambda = 0.715$, $F(2, 113) = 22.559$, $P < .001$). Pairwise comparisons for the intervention group indicated a significant increase in adherence from baseline (57.4 ± 29.8) to the end of the nurse visits (77.8 ± 24.4 , $P < .001$) and a significant decrease from the end of the nurse visits through the monitoring phase (59.0 ± 32.7 , $P < .001$). The simple effect of time for the control group was not significant (Wilks $\lambda = .951$, $F(2, 113) = 2.942$, $P = .06$). Pairwise

Table 1. Demographic Characteristics of Total Sample and Control and Intervention Groups

Characteristic	Total Sample	Control	Intervention	Statistic, <i>P</i> -Value
Starting enrollment, <i>n</i>	122	59	63	
Attrition over 6 months, <i>n</i>	6	1	5	
Age, mean $\pm$ SD (range)	77.0 $\pm$ 7.4 (65–94)	77.2 $\pm$ 7.6 (65–94)	76.8 $\pm$ 7.4 (65–91)	$t = 0.31, P = .76$
Sex, <i>n</i>				
Male	29	15	14	$\chi^2 = 0.17, P = .68$
Female	93	44	49	
Education, <i>n</i>				
<High school	11	2	9	$\chi^2 = 5.10, P = .16$
High school	17	8	9	
Some post–high school	34	16	18	
College degree	60	33	27	
Mini-Mental State Examination score, mean $\pm$ SD (range)	28.9 $\pm$ 1.4 (24–30)	29.1 $\pm$ 1.4 (24–30)	28.8 $\pm$ 1.5 (24–30)	$t = 1.25, P = .21$
Number of prescribed medications, mean $\pm$ SD (range)	8.1 $\pm$ 4.6 (2–33)	8.6 $\pm$ 5.4 (2–33)	4.6 $\pm$ 3.8 (3–24)	$t = 1.16, P = .25$
Number of antihypertensive medications, mean $\pm$ SD (range)	2.0 $\pm$ 1.1 (1–6)	2.0 $\pm$ 1.1 (1–6)	2.0 $\pm$ 1.1 (1–5)	$t = -0.35, P = .73$

SD = standard deviation; χ^2 = chi-square.

**Figure 2.** Adherence over time for intervention and control groups.

comparisons for the control group indicated a nonsignificant change from baseline (67.8 ± 28.5) to nurse visits ($68.3 \pm 30.2, P = .90$) and a significant decrease from the nurse visit to the end of the extended monitoring phase ($61.1 \pm 29.9, P = .02$).

To explore why adherence declined in the intervention group after the nurse visits, change in self-reported strategy use between the last intervention visit and the final visit at the end of the 5 months of additional monitoring was examined. There was a significant decline in strategy use overall, from a mean of 10.9 to a mean of 8.8 ($t(1,57) = 7.70, P < .001$). The following strategies showed a significant decline: cues for remembering ($t(1,57) = 3.79, P < .001$), “Do it now” ($t(1,57) = 2.03, P = .047$), “Elaborate the Action” ($t(1,57) = 4.05, P < .001$), and use of implementation intentions ($t(1,57) = 5.20, P < .001$). There were no significant differences for the strategies of establishing a routine or using an organizer.

Moderating Effect of Executive Function and Working Memory

Whether the intervention was more effective for those with lower executive function and working memory was next examined by assessing the interaction between the intervention and executive function and working memory using PROCESS,³⁷ a regression-based program that allows quantitative moderators to be assessed. Using the difference between baseline adherence and adherence during the intervention as the dependent variable and heteroskedasticity-consistent standard errors, a significant interaction was found ($t(1,118) = 2.24, P = .03$). That is, individuals with poorer executive function and working memory benefited more from the intervention than those with better executive function and working memory. This interaction is depicted in Figure 3, which shows that the regression lines predicting adherence from executive function for the

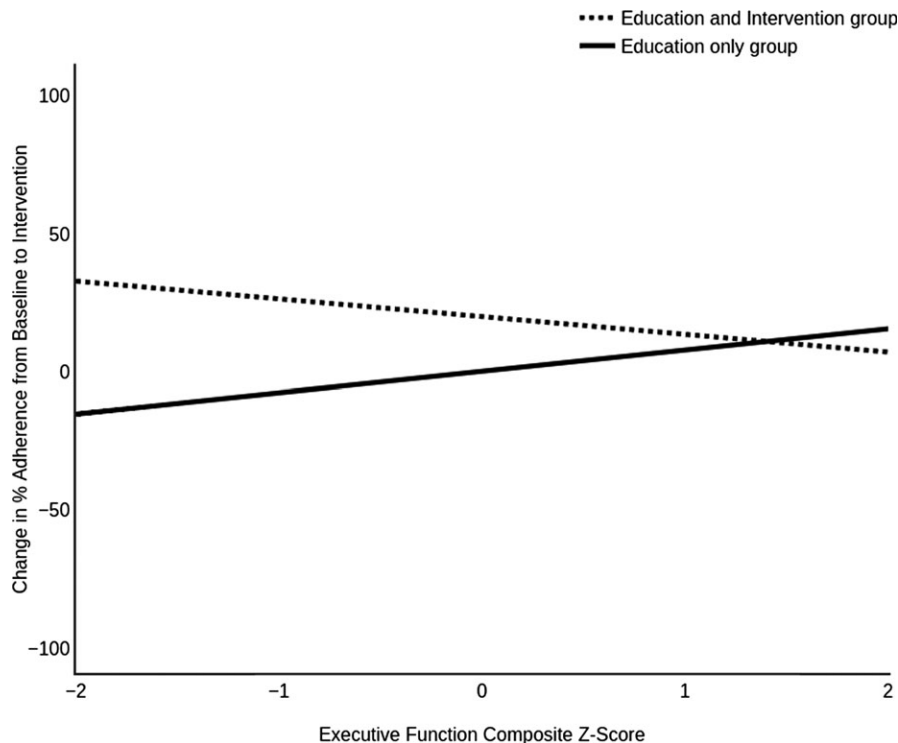


Figure 3. Experimental and control regression lines depicting the intervention-by-executive function interaction. The intervention group had significantly greater adherence when executive function z-score was less than 0.53.

intervention and control groups have different slopes. Predicted adherence for both groups is the same at the point where these lines intersect. For values of executive function to the left of the point of intersection, the intervention group had greater predicted adherence. Using the Johnson-Neyman technique, it was found that the intervention condition had significantly greater adherence than the control condition when the executive function–working memory composite was 0.53 or less. Because the executive function–working memory composite score was a standard score with a mean of 0 and a standard deviation of 1, participants in this sample who had a composite score of 0.53 standard deviations or less above the mean were especially likely to benefit from the intervention.

DISCUSSION

This study tested an intervention directed toward older adults (≥65) to improve adherence to prescribed antihypertensive medications. Older adults experience cognitive decline in the areas of executive function (inhibiting distractions, focusing and sustaining attention, shifting when needed, updating) and working memory (involved in the temporary storage and processing of information, keeping relevant information activated in the face of distraction).^{36,38,39} Executive function and working memory processes can be heavily involved in remembering to take medications as prescribed, such as when someone tries to keep in mind the intention to take medication while performing other activities associated with the demands of life. The intervention significantly improved adherence, presumably because it was designed to decrease the need

for effortful self-initiated processes in favor of more-automatic associative processes thought to be preserved with normal aging (e.g., associating medication taking with a specific cue such as having breakfast so that the occurrence of breakfast triggers retrieval of the intention). The results are consistent with those of past research showing that interventions that focus only on education have few benefits for adherence. Specifically, the education control condition showed no benefit from baseline to the nurse visits and a decline over the following 5 months.

A novel approach was developed for the current study that involved providing older adults with strategies for improving medication adherence. The strategies were ones that have been demonstrated in behavioral laboratories to improve prospective remembering in older adults, in part by promoting reliance on processes that tend to be spared with normal aging (e.g., relatively automatic associative retrieval processes) rather than on more-vulnerable executive function processes.⁴⁰ Some intervention studies have examined reminders, or single memory cues (e.g., automated telephone calls, postcards, text messaging) to help individuals adhere, with small effects. None have supported all components of successful prospective remembering (encoding, storage, retrieval of the intention to adhere at the right time, execution of the action of taking the medication so as not to forget over a delay, providing cues to give feedback about whether the medication was taken as intended). The intervention markedly improved medication adherence during the nurse visits. The finding that the intervention primarily benefitted participants with poorer executive function and working memory capacity suggests that it improved adherence by reducing reliance on these cognitive abilities.

It was expected that participants would integrate the trained strategies into their daily life and therefore have no need for continuing contact with the nurses, but intervention benefits were not sustained over the following 5 months, perhaps because the strategies learned during the intervention were not fully integrated into participants' daily routines. This drop in adherence suggests the need for continuing support for strategy use and converges with other studies demonstrating an improvement as long as the interventionist was in direct contact with the participants but not after.⁴¹ Support for this conclusion comes from a review of studies using reminders covering 1968 to 2011.⁶ All reminder interventions were based on continuous reminders, for example, telephone text messages or traditional telephone calls rather than the initial intervention described here to set up strategies for remembering, but without ongoing reminders. Ongoing reminders and ongoing coaching of strategy use could be necessary to continue the initial improvement seen in adherence.

A potentially critical feature of hypertension is that it is asymptomatic. This lack of symptoms surely adds to the difficulty of remembering to take medication because there are no physical cues (e.g., aches and pains) that can serve to remind people to take their medications. Research also shows that maintaining behavior change (e.g., use of the cognitive strategies implemented in this intervention) is more difficult when people do not receive salient feedback that the new behaviors are producing benefits.⁴² Thus, the asymptomatic nature of hypertension means that there was no feedback regarding improvements in health that resulted from enhanced medication adherence. At this point, further research is needed to determine how to sustain the use of the highly effective strategies in this cognitive intervention over the long term. This may involve regular self-monitoring of blood pressure so that individuals become more mindful of the health benefits of proper adherence. This approach has been used with success in other investigations.⁵ It is also possible that technology could be used to help sustain these strategies.^{43–46}

The current study demonstrates that executive function and working memory moderate the effect of the intervention on adherence. That is, the intervention was particularly effective for those with poorer executive function (executive function–working memory composite z-scores <0.53). Given that 70% of the population would have z-scores less than 0.53, the intervention could be significantly effective for 70% of those receiving it. Thus, the intervention has great potential to support medication adherence in populations most at risk of experiencing decline in executive function and working memory. These findings are consistent with the Institute of Medicine's recommendations to consider how cognitive aging in older adults affects performance of everyday activities and demonstrates that normal aging affects some cognitive processes more than others.⁴⁷ Given that other populations in addition to elderly adults with compromised executive function also have a decline in medication adherence,¹⁵ the intervention is likely to have general benefits. For example, chemotherapy treatment is associated with cognitive decline,⁴⁸ and lipid disorders and diabetes mellitus may accelerate vascular aging and hence decline in cognitive function consistent with what is seen in age-associated

decline.^{49–51} Hence, in addition to implications for promoting medication adherence in elderly adults, the findings of this study may be relevant for other populations.

The present study has limitations. The intervention focused solely on prospective memory strategies to address nonadherence that develops because of forgetting to take medications as intended. Medication adherence is multifactorial.⁵² Cost, lack of perceived benefit by the individual, and possible side effects have been identified as causal factors for nonadherence. Each of these factors is a possible causal pathway to nonadherence, but little attention has been paid to simple forgetting at the intended time as a reason for nonadherence except when addressed using single, albeit ongoing reminders such as telephone calls or postcards to sustain the action, and using single reminders, even when ongoing, does not always work.⁵³ Single reminders alone can be ineffective because they fail to address all of the component processes necessary for successful prospective remembering.

Little progress in improving medication adherence has been made since a review published a decade ago⁵⁴ in which forgetfulness was cited as the reason for nonadherence in 30% of individuals. The current study offers a new and unique approach to assisting older adults and others with asymptomatic diseases to improve adherence to medications so they are less likely to forget to take medications as intended. This multifaceted intervention produced pronounced improvements in medication adherence, especially for vulnerable individuals with poor executive function and working memory. Further research is needed to determine how to sustain the substantial initial benefits of this intervention technique.

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Conflict of Interest: The editor in chief has reviewed the conflict of interest checklist provided by the authors and has determined that the authors have no financial or any other kind of personal conflicts with this paper.

Author Contributions: Kathie Insel is the principal investigator of the study. Gil Einstein and Dan Morrow were Co-Investigators on the study since inception, throughout operationalization, data collection, and data analysis. This was the creative team. Joe Hepworth was the statistician. Kari Koerner was involved in data collection, continuous laboratory meetings, data analysis, and manuscript development.

Sponsor's Role: The National Institutes of Health was not involved in design, methods, subject recruitment, data collection, analysis, or preparation of the paper.

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