



Published in final edited form as:

J Aging Health. 2009 June ; 21(4): 567–580. doi:10.1177/0898264309332836.

Medication adherence in healthy elders: small cognitive changes make a big difference

Tamara L. Hayes, Ph.D.^{1,3}, Nicole Larimer, B.A.^{1,3}, Andre Adami, Ph.D.⁴, and Jeffrey A. Kaye, M.D.^{2,3}

¹ Division of Biomedical Engineering, Oregon Health & Sciences University, Portland, OR

² Department of Neurology, Oregon Health & Sciences University, Portland, OR

³ Oregon Center for Aging and Technology, Oregon Health & Sciences University, Portland, OR

⁴ Department of Computer Science, Universidade de Caxias do Sul

Abstract

Objectives—This was a cross-sectional study of the ability of independently living healthy elders to follow a medication regimen. Participants were divided into a group with High Cognitive Function (HCF) or Low Cognitive Function (LCF) based on their scores on the ADAS-Cog.

Methods—Thirty-eight participants aged 65 or older and living independently in the community followed a twice-daily vitamin C regimen for five weeks. Adherence was measured using an electronic 7-day pill box.

Results—The LCF group had significantly poorer total adherence than the HCF group (LCF: $63.9 \pm 11.2\%$, HCF: $86.8 \pm 4.3\%$, $t_{36}=2.57$, $p=0.007$), and there was a 4.1 relative risk of non-adherence in the LCF group as compared to the HCF group.

Discussion—This study provides strong evidence that even very mild cognitive impairment in healthy elderly living independently in the community has a detrimental and significant impact on adherence to a medication regimen. This study has important implications for the conduct of clinical drug trials in this population.

Keywords

cognitive impairment; medication; adherence

Correct medication use is an important part of healthy aging (Monane, Monane, & Semla, 1997). More than 75% of people aged 65 and older take prescription medication, and on average they take 3 or more medications a day (Helling et al., 1987; Ostrom, Hammarlund, Christensen, Plein, & Kethley, 1985). Unfortunately, more than 50% of these individuals are non-adherent to their medication regimen (Botelho & Dudrak, 1992; Kendrick & Bayne, 1982), which can have tremendous impact on their health. The financial cost of this medication mismanagement is also significant, since it leads to increased hospitalization and drug side-effects (Col, Fanale, & Kronholm, 1990). The importance of proper medication adherence is underscored by the fact that ability to manage medication is considered an

Address correspondence to: Dr. Tamara L. Hayes, Division of Biomedical Engineering, Oregon Health & Science University, 3303 SW Bond Avenue, Portland, OR 97239, Voice: 503-418-9315, Fax: 503-418-9311, hayesta@ohsu.edu.

Preliminary results of this work were presented at the 2006 Gerontological Society of America meeting.

instrumental activity of daily living (IADL), that is, a skill that is essential to maintaining independence in the elderly (Fillenbaum & Smyer, 1981).

There are many reasons why the elderly may be non-adherent (Fitten, Coleman, Siembieda, Yu, & Ganzell, 1995; Paes, Bakker, & Soe-Agnie, 1997; Salzman, 1995), including the high number of medications (and complexity of regimen) used by this population (Cramer, Mattson, Prevey, Scheyer, & Ouellette, 1989; Helling et al., 1987; Paes et al., 1997), increased sensitivity to side effects, the high cost of medications, and forgetting or confusion about dosage schedule. There is evidence that memory deficits can lead to a decrease in medication management abilities, reflecting the important role that memory may play in medication adherence. While most studies have looked at the correlation between medication adherence and MMSE scores, which is not a highly sensitive measure of small memory changes (Edelberg, Shallenberger, & Wei, 1999; Fitten et al., 1995; Morrell, Park, Kidder, & Martin, 1997; Patrick & Howell, 1998), Insel and colleagues found that a composite of memory and executive function scores was predictive of poor medication adherence in community-dwelling adults (Insel, Morrow, Brewer, & Figueredo, 2006). These findings would suggest that many apparently healthy elders living independently in the community may be at risk for poor medication adherence and its concomitant health risks, in spite of their apparent ability to manage their own medications. This has implications not only for the elders themselves, but also for clinical drug trials in which good adherence is essential to proper evaluation of the drug (Dunbar-Jacob, Burke, & Puczynski, 1995; Gorkin, Goldstein, Follick, & Lefrivre, 1990). The objective of the present study was to increase our understanding of how mild memory changes affect medication adherence.

Methods

Participants

Participants aged 65 or older with a Mini-Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975) score greater than 23 were recruited from two continuing care retirement communities in Oregon. All participants were living independently and were currently managing their own medication regimen on a daily basis. They were specifically asked to participate in a study of medication adherence, not cognitive decline or dementia. All participants provided written informed consent.

Clinical Assessments

Age, living status (alone or with another person), and years of schooling were collected for each participant. Cognitive function was assessed using a number of tests. There have been a wide range of tests developed to assess early cognitive loss, both clinically and for research purposes (Collie & Maruff, 2002). Since our goal was to identify individuals with very mild impairments, we chose tests that have shown construct validity for differentiating memory and cognitive loss in such individuals (Ihl, Frolich, Dierks, Martin, & Maurer, 1992). The Alzheimer's Disease Assessment Scale-Cognitive Subtest (ADAS-Cog (Graham, Cully, Snow, Massman, & Doody, 2004)) was used as a more comprehensive measure of cognitive function than is afforded by the MMSE and because it is widely used to assess cognitive function in clinical trials for dementia drugs. In addition to administering the ADAS-Cog, we also collected delayed Word List Recall scores (Welsh, Breitner, & Magruder-Habib, 1993), which are also sensitive to mild memory loss (Weaver Cargin, Maruff, Collie, & Masters, 2006). We used parts A and B of the Trail Making Test (Drane, Yuspeh, Huthwaite, & Klingler, 2002) which is used clinically to assess attention deficits (O'Donnell, Macgregor, Dabrowski, Oestreicher, & Romero, 1994). A Clinical Dementia Rating scale (Morris, 1993) score was assigned to each participant; this scale is often used clinically to

identify patients with Mild Cognitive Impairment. Finally, we also used the Instrumental Activities of Daily Living scale of the OARS questionnaire (Fillenbaum & Smyer, 1981) to assess functional abilities of the subjects. This test includes a measure of the assistance needed to manage medications, which was of direct relevance to our study.

In order to classify subjects into those with very mildly degraded cognitive function versus those that were relatively higher in function we first identified the age-adjusted norm for the ADAS-Cog scores, and the 95% confidence intervals around those norms (Graham et al., 2004). Scores greater than the value specified by the upper limit on the 95% confidence interval were considered to be significantly poorer than the age-adjusted norm (higher scores on the ADAS-Cog represented poorer performance). We then classified participants whose ADAS-Cog scores were above this limit as a “low cognitive function group (LCF)” (LCF: 18 subjects, 7 male, 11 female). The remainder of the participants were designated as a “higher cognitive function group” (HCF: 20 subjects, 5 male, 15 female). It is important to note that although the subjects in the HCF group had lower (better) ADAS-Cog scores, both groups of subjects were clinically healthy, community-dwelling elders who managed their own medications on a daily basis. By commonly used criteria for amnesic mild cognitive impairment (MCI) (Petersen, 2004) three of the 18 subjects in the LCF group had word-list recall scores worse than 1.5 standard deviations outside of the norms for their age, although 6 had a single test of the battery that was > 1.5 SD. None of the subjects complained of memory impairment. Thus, the LCF group represented a group of elders whose cognitive function was somewhat compromised as compared to healthy age-matched norms, but they were functioning independently in their community.

Procedures

We conducted a mock 5-week drug trial to estimate adherence in each group of subjects. During this trial, subjects took a 250mg Vitamin C supplement twice daily at predetermined times. Subjects were asked to identify two times at which they would take their vitamin supplement, as close to 12 hours apart as possible (e.g. 7am and 7pm). Medication adherence was measured using a 7-day reminder pillbox called the MedTracker (Figure 1) which we developed previously (Hayes, Hunt, Adami, & Kaye, 2006). Subjects loaded the pillbox with the vitamin supplements once a week. The first week of data was discarded; this initial period was intended to reduce error introduced by learning to use the MedTracker pillbox itself. Subjects were also asked to complete a self-assessment questionnaire about their adherence during the monitoring period.

Adherence to the vitamin regimen was measured in two ways, consistent with reporting of adherence in drug trials (Paes et al., 1997). Figure 2 shows how adherence was calculated. First, *total adherence* was estimated as the percentage of days in the trial period in which fewer than the prescribed two doses were taken. *Regimen adherence* was estimated as the percentage of doses that were not taken within 1 hour before, or 2 hours after, the prescribed time. An individual was considered to have poor adherence for a particular measure if their adherence by that measure was less than 80% (Ho, Magid, Masoudi, McClure, & Rumsfeld, 2006; Ho, Rumsfeld et al., 2006; Osterberg & Blaschke, 2005).

In addition to adherence numbers, we also looked at how closely the participants adhered to the time regimen, and the nature of missed doses. Because the instrumented pillbox reports the time at which each compartment is opened, we were able to track how late (or early) pills were taken, as well as when incorrect compartments was opened as well as when multiple compartments were opened. Determining what openings were errors required a heuristic approach, since there was no way of recording the participant’s intention. For example, if the person accidentally took a pill from the wrong compartment one day and then the next day recognized the mistake and “caught up” by taking the previous day’s pill,

this would appear as two errors rather than just the first error. Nonetheless, the patterns of errors have the potential to provide additional insight into issues of adherence. The heuristic used to interpret the error data were:

1. If all 7 compartments were opened within 10 minutes, the participant was assumed to be loading the device.
2. Otherwise, if a pill compartment was opened on the wrong day, this was considered an error. However, if this was the only compartment opened at the required time for the current dose, then the pill was considered to have been taken and was counted towards good adherence as well as being counted as an error. This situation could arise, for example, if the subject remembered to take their pill but forgot what day it was.
3. If multiple pill containers were opened during the same dose interval, then the incorrect days were all considered to be errors unless the participant was loading the device.

Analysis

Adherence data were analyzed using a Student's t-test for planned comparisons between groups. Relative risks of adherence were also calculated. Because the number of non-study medications taken differed between groups, the data were also analyzed using a 2-way ANOVA with group and number of medications as independent variables, and total adherence as the dependent variable. For the latter analysis, the number of medications was represented as an ordinal variable (6 or fewer medications, and more than 6 medications).

Results

Participants

Thirty-eight subjects (mean age 82.8 ± 5.5 years; 12 men, 26 women; mean education 16.4 ± 2.1 years) were recruited for the study. Demographic and clinical test scores for the two groups are shown in Table 1. There were no differences between groups in age or education level, or in their MMSE, IADL, or CDR scores. None of the subjects reported that they required assistance in managing their medications. By design, the LCF group had a higher mean ADAS-Cog score (poorer performance) than the HCF group (HCF: 6.0 ± 2.1 , LCF: 9.9 ± 2.1 , $t_{36} = -5.81$, $p < 0.001$). The LCF group also had a more missed words on the delayed Word List Recall (HCF: 3.4 ± 1.4 , LCF: 5.6 ± 2.7 , $t_{36} = -3.14$, $p < 0.002$). Delayed Word List Recall has been shown to be highly sensitive to early memory loss in older adults with no clinical impairments (Weaver Cargin et al., 2006), and therefore a poorer score on the delayed Word List Recall was not unexpected for this group. There were no significant differences between groups in their scores on the Trails A (HCF: 91.1 ± 1172.9 , LCF: 109.1 ± 3084.7 , $t_{27} = -1.191$, $p = 0.12$) or Trails B (HCF: 141.2 ± 2120.0 , LCF: 159.6 ± 6205.1 , $t_{27} = -0.865$, $p = 0.20$).

The LCF group took a somewhat greater number of non-study medications (HCF: 5.7 ± 2.5 , LCF: 6.9 ± 3.5 , $t_{36} = -1.26$, $p = 0.11$), although they did not differ in the frequency with which they took those medications (HCF: 2.5 ± 0.8 , LCF: 2.3 ± 1.0 times per day).

Adherence

Figure 3 shows the difference in adherence between the groups. Comparisons of both total adherence (taking the vitamins twice daily) and regimen adherence (meeting the predetermined dosage schedule) showed that the LCF group were significantly less adherent than the healthy elders. On average, the HCF group had excellent total adherence, unlike the

LCF group (HCF: $86.8 \pm 4.3\%$, LCF: $63.9 \pm 11.2\%$, $t_{36}=2.57$, $p=0.007$). There was also a significant difference in the regimen adherence, although the HCF group had somewhat lower adherence by this measure than by the total adherence measure (HCF: $76.9 \pm 6.2\%$, LCF: $62.1 \pm 7.0\%$, $t_{36}=1.78$, $p=0.04$). In order to determine if these differences in adherence were due primarily to poor adherence by the three participants in the LCF group who met the criteria for amnesic MCI, we repeated the analysis excluding those individuals. Excluding these subjects, the LCF group were still significantly less adherent than the HCF group on total adherence (HCF: $86.8 \pm 4.3\%$, LCF: $63.4 \pm 11.3\%$, $t_{33}=2.54$, $p=0.008$ for total adherence; HCF: $76.9 \pm 6.2\%$, LCF: $64.0 \pm 6.6\%$, $t_{33}=1.50$, $p=.07$ for regimen adherence).

Since the LCF group took somewhat more medications on average than the HCF group ($t=-1.26$, $p<0.11$), we also did an ANCOVA to control for this difference. Even controlling for the number of medications taken by each group, the total adherence of LCF group was still significantly worse than that of the HCF ($F_{1,35}=7.95$, $p=0.008$).

Subjects with at least 80% adherence were considered to have good adherence. Only 27.8% of the LCF group had good adherence to their regimen by this measure, as compared to 75% of the HCF (relative risk of poor adherence = 4.1, CI = [3.47, 4.78], $\chi^2 = 8.43$, $p<0.003$). In both groups, subjects had more trouble taking their medications in the evening than in the morning, with 65.8% achieving good adherence to the morning regimen, but only 39.5% achieving good adherence to the afternoon regimen. The pattern was the same for both groups.

Qualitative assessments

Self-report of medication taking revealed that subjects were not aware of how often they missed taking their vitamins. Ninety-three percent of subjects reported that they had “excellent adherence” (i.e. that they took their vitamins on time at least 80% of the time), although only 53% of subjects actual were adherent to regimen (across both groups). Furthermore, 12% of subjects believed that they had never missed a dose, when in fact only 5.3% of subjects had 100% adherence by this measure.

When subjects were asked to indicate reasons why they missed a pill, 62.2% reported that they were too busy to take it, and 59.5% reported that they were not home when they were supposed to take it. None of the participants reported that they missed a pill because they didn't want to take it, they didn't feel well enough to take it, or they weren't sure when they were supposed to take it. Interestingly, three participants (one HCF, two LCF) reported that they took the pill out of the box but forgot to take it, suggesting that even with detailed tracking of pill-taking, adherence may be overestimated in some cases.

Discussion

We have shown in this study that older people living independently and minding their own medication regimens have a wide range of medication adherence - some do well, and others adhere poorly to the regimen. Importantly, the characteristic that distinguished the ability to adhere to the regimen was relatively impaired cognitive function. None of these individuals was demented. The degree to which cognition was impaired or degraded in these subjects would not be apparent to a casual observer. Even in the LCF group only three could qualify for mild cognitive impairment and the results were not different with these individuals removed from the analysis. The participants themselves were also not fully aware of their inability to adhere to the regimen.

The pattern of cognitive deficit associated with being in the LCF did not map to a consistent cognitive domain across the study group. The LCF group scored significantly worse on the total ADAScog (a global cognitive measure) by design. Among the subtests of the ADAScog, the memory domain scores were significantly worse in the LCF group compared to the HCF group. However, the greatest difference between the groups was in the non-memory subtests. In theory deficits in memory or planning and executive function would be assumed to have the most impact on medication taking. There was no difference in Trails test performance suggesting that, at least to the degree that this test measures planning and executive function, there was not a difference based on this domain. Insel and colleagues recently reported that a composite of executive function and working memory was a significant predictor of reduced medication adherence in a population (Insel, Morrow, Brewer, & Figueredo). Although they did not report the raw scores of their participants, making it difficult to draw conclusions about the clinical level of functioning of their subjects, their study supports the hypothesis that the complex task of medication taking requires the efficient functioning of multiple cognitive processes in concert. This, coupled with our current study, would suggest that medication regimen adherence may be a very sensitive marker of early functional decline.

Our study had some limitations. We asked people to take a vitamin C tablet twice a day which is not a standard regimen. Participants also took only the study vitamins using the pillbox, and therefore had to follow the study protocol in addition to their daily medication regime. Participants may have not felt that it was important to take this non-essential supplement. However, the task itself was the same for all participants and at least 63% had good adherence to their regimen. We only followed their adherence behavior for five weeks. Although there may have been increased adherence seen after a longer time period of follow-up, there was no evidence in trends in the data to suggest this and the literature suggests that regimen adherence typically decreases over time in the absence of focused intervention (Osterberg & Blaschke, 2005; Weycker, Macarios, Edelsberg, & Oster, 2006). Of course we must be cautious in generalizing these results to all older persons and further study of different populations with different medication regimens in particular would be instructive.

This study has important implications for healthy aging. Population-based, longitudinal studies of medication adherence outcomes have shown significantly greater all-cause hospitalization and mortality for non-adherent patients, including those with diabetes mellitus and ischemic heart disease (Ho, Magid et al., 2006; Ho, Rumsfeld et al., 2006) and for survivors of acute myocardial infarction (Rasmussen, Chong, & Alter, 2007). In a study of 2169 community-dwelling elders, Yee and colleagues found that drug-related visits accounted for 12.6% of all emergency room visits, at a cost of \$1.5 million over a twelve-week period (Yee, Hasson, & Schreiber, 2005). Nineteen percent of these visits were directly related to medication non-adherence. Clearly, proper medication adherence is essential to maintaining health. The results of the current study suggest that within community-dwelling elders, adherence may relate more closely to cognitive status than has previously been shown. It is also possible that subtle cognitive impairments due to common chronic medical illnesses such as diabetes, COPD or heart failure may critically impair medication taking effectiveness.

Finally these results have important implications for clinical drug trials among the elderly. Rarely, except in studies of treatment of cognitive decline itself, is cognitive function assessed in any detail. Because the results of this study suggest that very mild cognitive deficits may have a profound impact on medication taking, it is important that adherence during the trial be monitored closely if cognitive function is even mildly compromised. Furthermore, the degree to which medication adherence in a clinical trial is assessed over

time, especially when the underlying condition itself (or the drug being studied) can affect cognition, needs to be reconsidered. Thus a drug's efficacy may be incorrectly judged because of a lack of presumed biological effect, when in fact the problem was an effect on cognition leading to poor adherence to the drug.

Acknowledgments

The authors gratefully acknowledge the support of the National Institute on Aging (P30AG024978, P30AG0801718, R01AG024059), the Office of Research and Development at the Department of Veterans Affairs, and Intel Corporation (loan of equipment). Dr. Kaye's time is partially supported by a Merit Review Grant, Office of Research and Development, Department of Veterans.

References

- Botelho RJ, Dudrak R 2nd. Home assessment of adherence to long-term medication in the elderly. *J Fam Pract* 1992;35(1):61–65. [PubMed: 1613477]
- Col N, Fanale JE, Kronholm P. The role of medication noncompliance and adverse drug reactions in hospitalizations of the elderly. *Arch Intern Med* 1990;150(4):841–845. [PubMed: 2327844]
- Collie A, Maruff P. An analysis of systems of classifying mild cognitive impairment in older people. *Aust N Z J Psychiatry* 2002;36(1):133–140. [PubMed: 11929450]
- Cramer JA, Mattson RH, Prevey ML, Scheyer RD, Ouellette VL. How often is medication taken as prescribed? A novel assessment technique. *Jama* 1989;261(22):3273–3277. [PubMed: 2716163]
- Drane DL, Yuspeh RL, Huthwaite JS, Klingler LK. Demographic characteristics and normative observations for derived-trail making test indices. *Neuropsychiatry Neuropsychol Behav Neurol* 2002;15(1):39–43. [PubMed: 11877550]
- Dunbar-Jacob, J.; Burke, LE.; Puczynski, S. Clinical assessment and management of adherence to medical regimens. In: Nicassio, PM.; Smith, TW., editors. *Managing Chronic Illness*. Washington, DC: American Psychological Association; 1995. p. 313-350.
- Edelberg HK, Shallenberger E, Wei JY. Medication management capacity in highly functioning community-living older adults: detection of early deficits. *J Am Geriatr Soc* 1999;47(5):592–596. [PubMed: 10323653]
- Fillenbaum G, Smyer M. The development, validity and reliability of the OARS multidimensional functional assessment questionnaire. *Journal of Gerontology* 1981;36:428–434. [PubMed: 7252074]
- Fitten LJ, Coleman L, Siembieda DW, Yu M, Ganzell S. Assessment of capacity to comply with medication regimens in older patients. *J Am Geriatr Soc* 1995;43(4):361–367. [PubMed: 7706624]
- Folstein M, Folstein S, McHugh P. "Mini-mental state" - a practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research* 1975;12:189–198. [PubMed: 1202204]
- Gorkin, L.; Goldstein, MG.; Follick, MJ.; Lefrbyvre, RC. Strategies for enhancing adherence in clinical trials. In: Shumaker, SA.; Schron, EB.; Ockene, JK., editors. *Handbook of Health Behavior Change*. New York: Springer; 1990. p. 361-375.
- Graham DP, Cully JA, Snow AL, Massman P, Doody R. The Alzheimer's Disease Assessment Scale-Cognitive subscale: normative data for older adult controls. *Alzheimer Dis Assoc Disord* 2004;18(4):236–240. [PubMed: 15592137]
- Hayes, TL.; Hunt, JM.; Adami, AM.; Kaye, J. An electronic pillbox for continuous monitoring of medication adherence. August 30-September 3, 2006; Paper presented at the 28th Annual International Conference of the IEEE Engineering in Medicine and Biology Society; New York, NY. 2006.
- Helling DK, Lemke JH, Semla TP, Wallace RB, Lipson DP, Cornoni-Huntley J. Medication use characteristics in the elderly: the Iowa 65+ Rural Health Study. *J Am Geriatr Soc* 1987;35(1):4–12. [PubMed: 3794145]
- Ho PM, Magid DJ, Masoudi FA, McClure DL, Rumsfeld JS. Adherence to cardioprotective medications and mortality among patients with diabetes and ischemic heart disease. *BMC Cardiovasc Disord* 2006;6:48. [PubMed: 17173679]

- Ho PM, Rumsfeld JS, Masoudi FA, McClure DL, Plomondon ME, Steiner JF, et al. Effect of medication nonadherence on hospitalization and mortality among patients with diabetes mellitus. *Arch Intern Med* 2006;166(17):1836–1841. [PubMed: 1700939]
- Ihl R, Frolich L, Dierks T, Martin EM, Maurer K. Differential validity of psychometric tests in dementia of the Alzheimer type. *Psychiatry Res* 1992;44(2):93–106. [PubMed: 1480682]
- Insel K, Morrow D, Brewer B, Figueredo A. Executive function, working memory, and medication adherence among older adults. *Journals of Gerontology Series B-Psychological Sciences & Social Sciences* 2006 Mar;61(2):102–7.
- Insel K, Morrow D, Brewer B, Figueredo A. Executive function, working memory, and medication adherence among older adults. *J Gerontol B Psychol Sci Soc Sci* 2006;61(2):102–107.
- Kendrick R, Bayne JR. Compliance with prescribed medication by elderly patients. *Can Med Assoc J* 1982;127(10):961–962. [PubMed: 7139444]
- Monane M, Monane S, Semla T. Optimal medication use in elders. Key to successful aging. *West J Med* 1997;167(4):233–237. [PubMed: 9348752]
- Morrell RW, Park DC, Kidder DP, Martin M. Adherence to antihypertensive medications across the life span. *Gerontologist* 1997;37(5):609–619. [PubMed: 9343911]
- Morris J. The clinical dementia rating (CDR): Current version and scoring rules. *Neurology* 1993;43:2412–2414. [PubMed: 8232972]
- O'Donnell JP, Macgregor LA, Dabrowski JJ, Oestreicher JM, Romero JJ. Construct validity of neuropsychological tests of conceptual and attentional abilities. *J Clin Psychol* 1994;50(4):596–600. [PubMed: 7983209]
- Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med* 2005;353(5):487–497. [PubMed: 16079372]
- Ostrom JR, Hammarlund ER, Christensen DB, Plein JB, Kethley AJ. Medication usage in an elderly population. *Med Care* 1985;23(2):157–164. [PubMed: 3974332]
- Paes AH, Bakker A, Soe-Agnie CJ. Impact of dosage frequency on patient compliance. *Diabetes Care* 1997;20(10):1512–1517. [PubMed: 9314626]
- Patrick L, Howell K. Mental status and self-medication ability in the hospitalized elderly. *Canadian Journal on Aging* 1998;17(4):425–439.
- Petersen RC. Mild cognitive impairment as a diagnostic entity. *J Intern Med* 2004;256(3):183–194. [PubMed: 15324362]
- Rasmussen JN, Chong A, Alter DA. Relationship between adherence to evidence-based pharmacotherapy and long-term mortality after acute myocardial infarction. *Jama* 2007;297(2):177–186. [PubMed: 17213401]
- Salzman C. Medication compliance in the elderly. *J Clin Psychiatry* 1995;56(Suppl 1):18–22. discussion 23. [PubMed: 7836347]
- Weaver Cargin J, Maruff P, Collie A, Masters C. Mild memory impairment in healthy older adults is distinct from normal aging. *Brain Cogn* 2006;60(2):146–155. [PubMed: 16446021]
- Welsh K, Breitner J, Magruder-Habib K. Detection of dementia in the elderly using telephone screening of cognitive status. *Neuroscience Letters (Neuropsychiatry, Neuropsychology and Behavioral Neurology)* 1993:103–110.
- Weycker D, Macarios D, Edelsberg J, Oster G. Compliance with drug therapy for postmenopausal osteoporosis. *Osteoporos Int* 2006;17(11):1645–1652. [PubMed: 16862397]
- Yee JL, Hasson NK, Schreiber DH. Drug-related emergency department visits in an elderly veteran population. *Ann Pharmacother* 2005;39(12):1990–1995. [PubMed: 16288080]

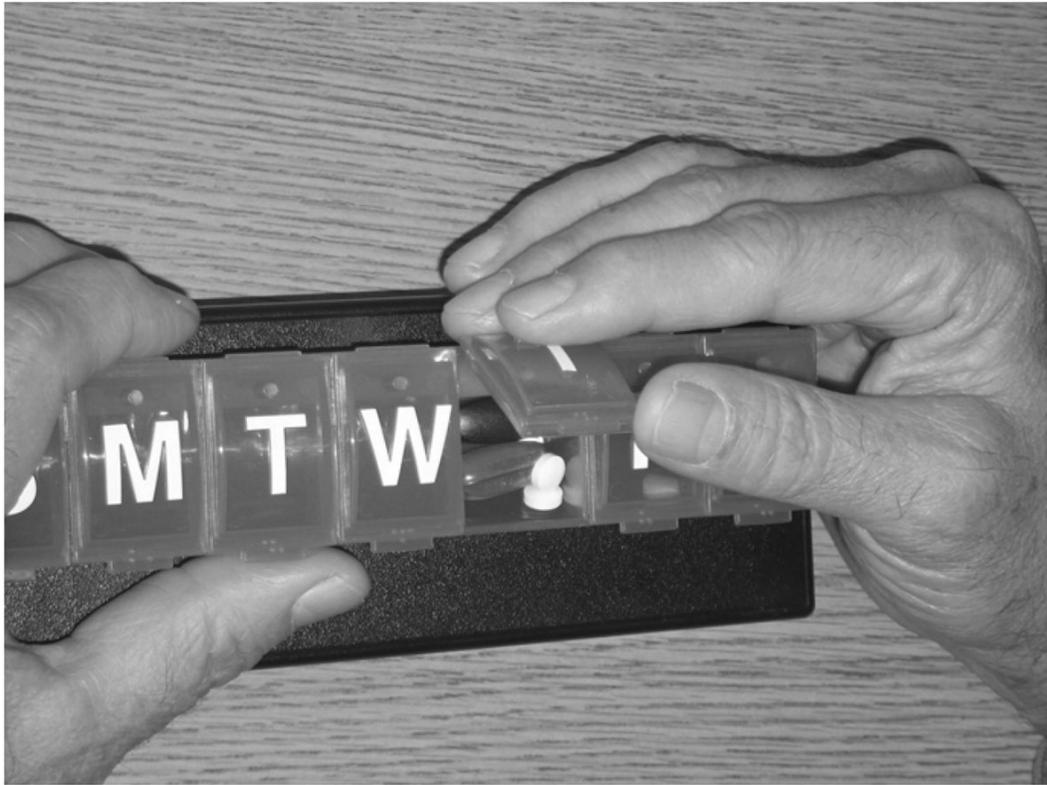


Figure 1.
The instrumented pillbox used in this study. The 7-day reminder box was identical to that used by many participants to manage their non-study medications.

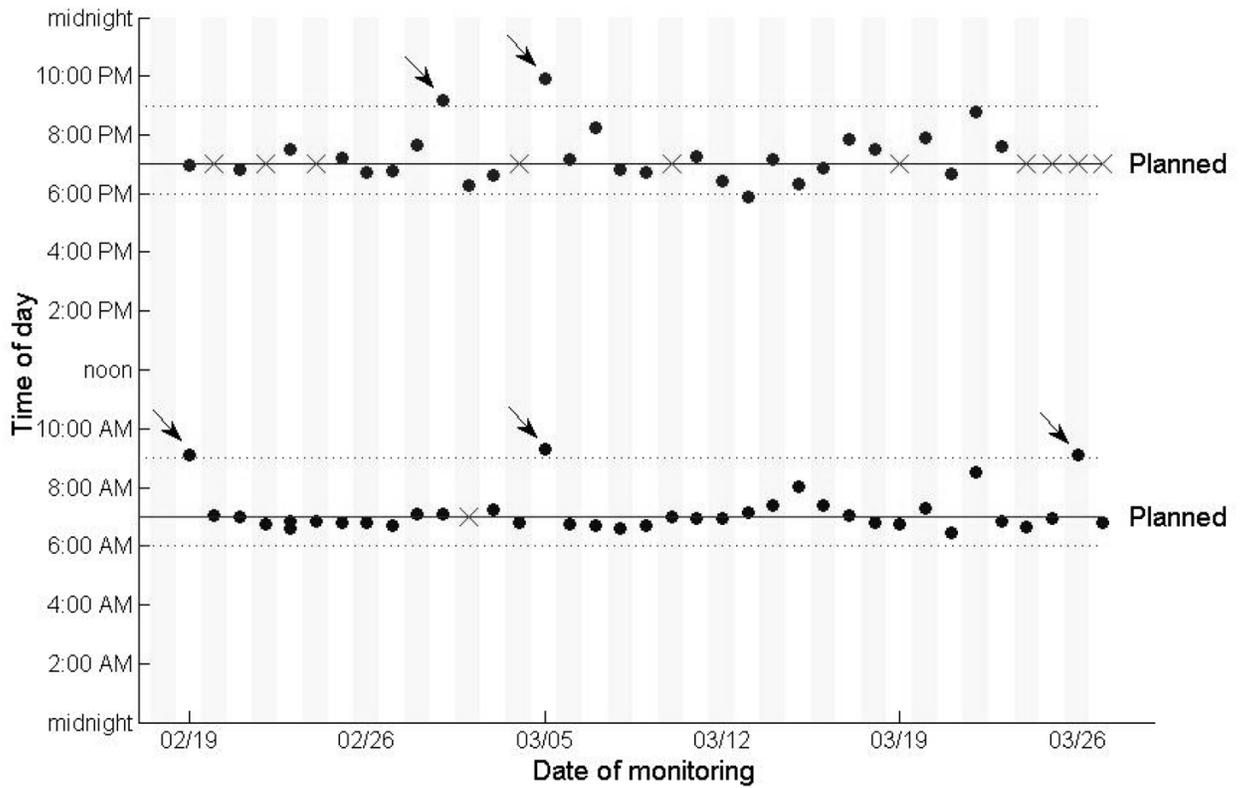


Figure 2. Plot of data from one subject. The abscissa is the date of monitoring (shaded bars show alternating days) and the ordinate shows the time of day the pill was taken. The dots indicate the times at which pills were taken. The solid horizontal lines indicate the morning and evening time at which pills were supposed to be taken; the dotted horizontal lines delineate one hour before this time and two hours after this time – that is, the window during which the participant was considered to be adherent to the regimen. The arrows show pills that were taken outside of this window. The X's indicate that a pill was missed. Total adherence is then calculated as the percentage of days in which two pills were taken (for this participant, 71.4%). Adherence to regimen is calculated as the percentage of days in which pills were taken within the specified window (78.6%). Regimen adherence can also be calculated for morning only (91.4%) or evening only (65.7%).

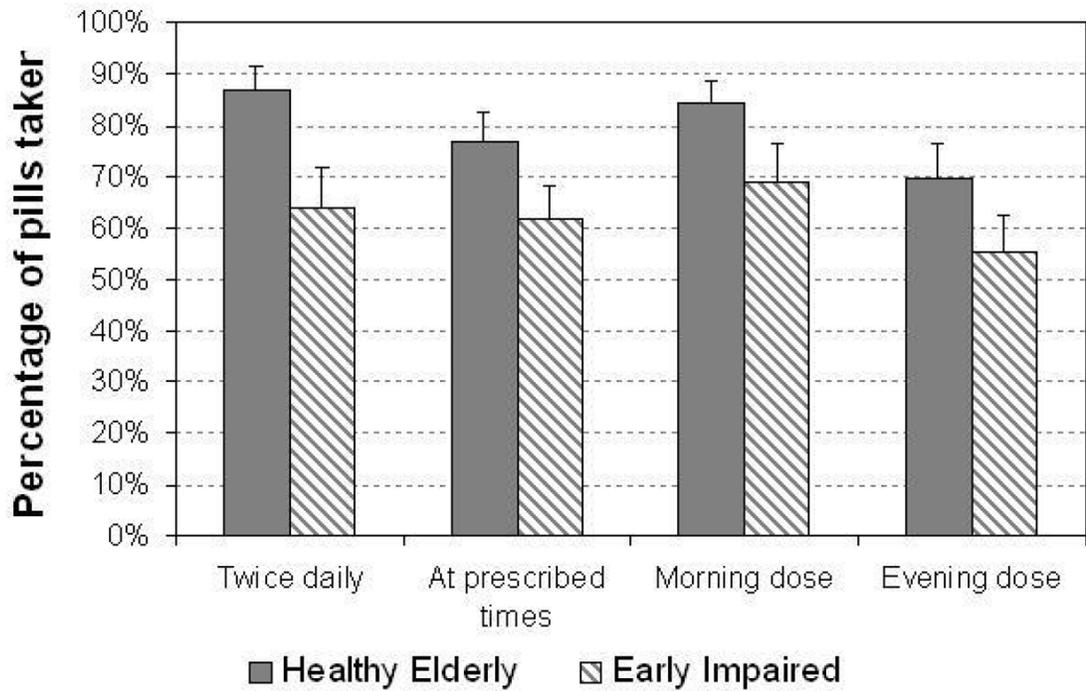


Figure 3. Means (with standard error bars) of adherence between the High Cognitive Function (gray bars) and Low Cognitive Function (hashed bars) groups, on four measures: adherence to a twice-daily schedule, adherence to the prescribed regimen (dose taken one hour before or two hours after the prescribed times), adherence to the morning regimen, and adherence to the afternoon regimen. All measures were significantly different between groups (see text)

Table 1

Group characteristics.

	High Cog. Function	Low Cog. Function
N subjects	20	18
ADAS-cog *	6.0 ± 2.1	9.9 ± 2.1
Memory subtests *	3.1 ± 1.4	4.5 ± 1.5
Non-memory subtests *	2.9 ± 2.1	5.4 ± 2.3
Education (years)	16.7 ± 2.1	16.1 ± 2.4
Age (years)	82.9 ± 5.5	82.8 ± 5.6
Delayed Word List Recall †	3.4 ± 1.4	5.6 ± 2.7
MMSE	28.8 ± 1.4	28.0 ± 1.7
OARS IADL	0.3 ± 0.8	0.2 ± 0.9
Number of Meds	5.7 ± 2.5	6.9 ± 3.5
Frequency of Meds	2.5 ± 0.8	2.3 ± 1.0
TMT-B (secs)	141.2 ± 46.0	159.6 ± 78.8
TMT-diff (secs)	50.2 ± 42.3	55.7 ± 55.2

Groups differ where indicated:

* p<0.001,

† p<0.002.

No other significant differences between groups were found.