



PRACTICE OF EPIDEMIOLOGY

Impact of Pill Organizers and Blister Packs on Adherence to Pill Taking in Two Vitamin Supplementation Trials

Han-Yao Huang,¹ Maureen G. Maguire,² Edgar R. Miller III,³ and Lawrence J. Appel^{1,3}

The impact of pill organizers on pill taking was determined in the Trial of Antioxidant Vitamins C and E (TRACE) Study, a factorial trial of vitamin C and vitamin E supplementation in 184 individuals. Participants were recruited in 1996–1997 and randomized to one of two groups (pill organizer or no organizer) and to one of four supplement groups for 2 months. The pill count (observed/expected X 100%) distribution was similar in the organizer and no organizer group for both vitamins. Mean differences in changes in serum vitamin levels between active and placebo groups did not differ by pill organizer use. The impact of pill organizers and blister packs was compared in another trial, the Vitamins, Teachers, and Longevity (VITAL) Study, in 297 individuals randomized in 1993–1994 to receive study pills either in blister packs or in pill organizers and to take one of two supplements. Among those with lower adherence, the pill count distribution in the blister-pack group exceeded that in the organizer group. Mean differences in serum vitamin E levels between active and placebo groups did not differ by types of pill packaging. In summary, use of blister packs, but not pill organizers, improved adherence as measured by pill counts among those with lower adherence. Neither pill delivery system improved adherence as measured by serum vitamin levels. *Am J Epidemiol* 2000;152:780–7.

controlled clinical trials; drug delivery systems; drug packaging; patient compliance

Adherence to pill taking is widely recognized as an essential feature of clinical trials that test the effects of medications provided in pills. Poor adherence, including underdosing, overdosing, and erratic dosing, may reduce internal validity and raise safety issues. For example, if the medication regimen is effective, lack of adherence may reduce the apparent effect size. In addition, poor clinical outcomes have been associated with partial medication adherence in patients with diabetes, hypercholesterolemia, and hypertension (1–3).

Several strategies and devices have been proposed to enhance medication adherence (4). Pill organizers and unit-dose blister packs are two systems that have been commonly used in clinical trials. One type of pill organizer is a container with seven compartments, one for each day of the week. Pill organizers may improve adherence by displaying pills to be taken on a daily basis and identifying missed pills.

These devices may also reduce confusion for persons taking multiple pills. Nonetheless, the use of pill organizers requires the active involvement of participants, who must place pills from bottles into the individual compartments. A unit-dose blister pack is a card with labeled blisters, each of which contains pills to be ingested at one time. As a type of ready-to-use packaging, blister packs eliminate the need for patients to transfer pills, e.g., from bottles to organizers.

Despite the intuitive appeal of these pill delivery systems, few studies have systematically assessed their utility. Two previous trials have shown a benefit of blister packs on adherence by pill counts, in comparison with pill bottles without an organizer, in elderly patients (5, 6). The sample sizes of these trials, however, were small—just seven and 84. A trial performed with 180 hypertension patients showed higher medication adherence, assessed by pill counts, in the group with blister packs than in the group with usual vials but found no difference in diastolic blood pressure (7). Another study of hypertensive patients (ages 20–80 years) demonstrated higher urinary excretion of the thiazide medication in the blister-pack group compared with those with the usual vials, but no difference in pill counts (8). One study of arthritis patients (mean age, 60 years) found that the use of 7-day pill organizers with compartments for different times of the day improved adherence to pill taking in comparison with the use of 7-day pill organizers with only one compartment for each day. However, the utility of the 7-day organizer itself was not assessed (9).

In this setting, we present results from two vitamin supplementation trials, TRACE (TRial of Antioxidant Vitamins

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Abbreviations: TRACE, Trial of Antioxidant Vitamins C and E; VITAL, Vitamins, Teachers, and Longevity.

¹Department of Epidemiology, School of Hygiene and Public Health, Johns Hopkins University, Baltimore, MD.

²Department of Ophthalmology, University of Pennsylvania, Philadelphia, PA.

³Department of Medicine, School of Medicine, Johns Hopkins University, Baltimore, MD.

Reprint requests to Dr. Han-Yao Huang, Department of Epidemiology, School of Hygiene and Public Health, Johns Hopkins University, 615 North Wolfe St., (Room E6006, Baltimore, MD 21205–2223 (e-mail: hyhuang@jhsp.edu).

C and E) and VITAL (VItamins, Teachers, And Longevity), in which we determined the impact of pill organizers and blister packs on adherence to pill taking, assessed by pill counts, serum vitamin levels, and self-reports.

MATERIALS AND METHODS

The institutional review boards of the Johns Hopkins Medical Institutions approved the TRACE and VITAL protocols. Each participant provided written informed consent.

Conduct of trials

TRACE was a placebo-controlled, double-masked, 2×2 factorial trial designed to assess the effects of vitamin C (500 mg/day of ascorbic acid) and vitamin E (400 IU/day of *d*- α -tocopheryl acetate) on lipid peroxidation in community-dwelling nonsmokers. Participants were recruited through local advertisements and word-of-mouth between February 1996 and June 1997. Inclusion criteria were 1) willingness to provide informed consent, 2) being a nonsmoker, 3) being a nonvegetarian, 4) not taking antioxidant vitamin supplements within 2 months before randomization, and 5) willingness to take study pills and not to take other vitamin supplements for 2 months. Each participant attended one screening visit at which baseline data were collected. Habitual dietary data were collected through semi-quantitative Block food frequency questionnaires.

Eligible and interested participants attended a randomization visit that included collection of a 12-hour fasting blood sample. Each participant was randomly assigned to one of two groups (pill organizer or no pill organizer) and to one of four supplementation groups. Randomization to use of an organizer was determined from a list of random numbers generated by a computer. Randomization of supplementation group was determined by a fixed randomization scheme generated by the Moses-Oakford algorithm (10), with a block size of eight and an allocation ratio of 1:1:1:1. Group assignment was issued by opening an opaque, sealed envelope, which contained a card indicating codes for use of pill organizer and for supplementation groups. Both study participants and personnel were masked to the assignment of supplementation groups. All participants received two pill bottles, one with 35 active or placebo vitamin C tablets and the other with 35 active or placebo vitamin E capsules. The 35 pills corresponded to an excess of approximately five pills for a 1-month supply. Bottles were labeled with randomization codes, instructions, and the date to start taking the pills. Participants assigned to the pill-organizer group also received a pill organizer with seven compartments, one for each day of the week, along with instructions on the use of the organizer. Participants were instructed to take two types of pills (vitamin C/placebo and vitamin E/placebo) each day and to avoid taking any vitamin supplements other than study pills during the study period.

One and 2 months after randomization, TRACE participants attended follow-up visits. At the first follow-up visit, a new set of pills was provided for the second month of supplementation. Adherence to pill taking was assessed by

the average of pill counts (observed/expected number of pills consumed \times 100 percent) at each follow-up visit, changes in serum levels of ascorbic acid and α -tocopherol from baseline, and self-reports. For those who dropped out after the first follow-up visit, pill counts were calculated from the pills remaining at the first follow-up visit. The observed number of consumed pills was calculated as 35 minus the number of pills remaining in the pill bottle and organizer, while the expected number of consumed pills was equivalent in absolute value to the number of days between the start date and the latest date of pill taking. Upon completion of the supplementation period, blood specimens were obtained and data on self-reported adherence to pill taking were collected through a self-administered questionnaire that contained questions about how frequently (never, rarely, sometimes, most of the time, all of the time) participants ever decided not to take study pills, forgot to take pills, skipped taking pills, took pills incorrectly because of carelessness, or took more than the assigned pills (11). Masking was assessed by querying participants about the types of pills that they thought they were taking and the reasons, if any, for their guess.

VITAL was a placebo-controlled, double-masked pilot trial designed to determine the feasibility of conducting a large-scale trial of antioxidant vitamin supplements by mail. In the fall of 1993, retired teachers in the Baltimore, Maryland, area were recruited through invitational mailings. Inclusion criteria were 1) a willingness to provide informed consent, 2) a willingness to discontinue any vitamin A, β -carotene, vitamin C, or vitamin E supplements, and 3) a willingness to replace their usual multivitamin (if any) with a standard multivitamin. Exclusion criteria were use of coumadin and participation in other trials. Baseline data, including age, gender, race, education, height, weight, alcohol consumption, exercise, medication use, and vitamin supplement use, were collected through mailed questionnaires without an in-person visit; in this fashion, the pilot study replicated the approach to data collection to be done in the main trial. In March 1994, eligible and interested participants were randomly assigned to one of two types of pill packaging (blister packs or pill bottles along with organizers) and to one of two supplement groups (placebo or an antioxidant vitamin preparation that provided 400 IU/day of vitamin E). Participants in the pill-organizer group received pills in four pill bottles labeled with the month's name (April, May, June, and July) and a pill organizer as described in the TRACE study. Participants in the blister-pack group received pills in monthly blister packs, each with 31 blisters labeled with dates. Participants were asked to start taking pills on April 1st and to indicate their actual start date. All participants received an instruction sheet about how to take pills. One month after the shipment of the pills, participants were scheduled for an in-person visit, during which adherence to pill taking was assessed by pill counts, serum α -tocopherol levels, and self-reports. Data on self-reported adherence and success of masking were collected by using the same questions described previously for the TRACE study.

Serum vitamin assays

In both trials, blood specimens were obtained after a 12-hour fast and were centrifuged at 2,000 g for 15 minutes. Serum specimens were aliquoted and stored at -70°C until assayed. In TRACE, measurement of serum ascorbic acid levels was based on the reduction of Fe (III) to Fe (II) by ascorbic acid, followed by chromogenic chelation of Fe (II) with ferrozine (12). Serum α -tocopherol level was measured by high performance liquid chromatography technique using a fluorescence detector to improve the sensitivity and specificity (13). In VITAL, the serum α -tocopherol level was measured by reverse-phase high performance liquid chromatography (14).

Statistical analysis

Comparisons of continuous baseline variables between randomized groups were performed by using the *t* test for variables with a Gaussian distribution and the Wilcoxon rank sum test for variables with a non-Gaussian distribution. Comparisons of discrete baseline variables between randomized groups were performed by using the Pearson χ^2 test. To display adherence data, we plotted the absolute levels of adherence (observed/expected \times 100 percent) against percentile of adherence. The Wilcoxon rank sum test was used to test for any difference in pill counts between the pill-organizer and no organizer groups in TRACE and between pill-organizer and blister-pack groups in VITAL.

Multiple linear regression models were used to estimate the main and interaction effects of pill organizers and active/placebo vitamin supplements on changes in serum levels of ascorbic acid and α -tocopherol in TRACE and to estimate the main and interaction effects of pill packaging and active/placebo antioxidant supplement on serum α -tocopherol levels at follow-up in VITAL.

All statistical tests were considered significant at a two-sided *p* value of less than 0.05.

RESULTS

Baseline characteristics of TRACE participants are summarized in table 1. Of the 318 individuals screened, a total of 184 participants were randomized (94 in the no pill-organizer group and 90 in the pill-organizer group); 97 percent of participants completed 1 month of supplementation (97 percent in the no organizer group and 98 percent in the organizer group), and 94 percent completed 2 months (90 percent in the no organizer group and 97 percent in the organizer group). None of the reasons for dropping out were related to use of a pill organizer. The mean age of the participants was 58 years (standard deviation = 14), 55.4 percent were female, and 50 percent were African American. The pill-organizer and no organizer groups were similar in age, gender, race, education, body mass index, alcohol consumption, exercise, fruit/vegetable consumption, disease history, medication use, and supplement use at baseline.

Except for those who dropped out of the trial, all participants returned study pills at the follow-up visits. Figures 1

TABLE 1. Baseline characteristics by use of pill organizer in the TRACE Study, 1996–1997

Characteristic*	Total (n = 184)	No organizer (n = 94)	Organizer (n = 90)
Age (mean (SD)†)	58 (14)	58 (13)	58 (14)
Female (%)	55.4	56.4	54.4
Race (%)			
White	45.6	48.9	42.2
Black	50.0	46.8	53.3
Others	4.4	4.3	4.5
Education (%)			
High school or less	20.6	18.1	23.3
Some college or college	55.4	54.3	56.7
Postgraduate	24.0	27.7	20.0
BMI† mean (SD)	28.8 (5.3)	29.2 (5.3)	28.3 (5.3)
Nondrinker (%)	56.0	52.1	60.0
Regular exercise‡ (%)	50.0	46.7	53.3
Fruits and vegetables§ (median)	3.7	3.7	3.4
Any disease history (%)	54.3	52.1	56.7
Any medication (%)	57.6	56.4	58.9
Supplement use¶ (%)	34.2	29.8	38.9
Any vitamin use# (%)	30.4	27.7	33.3
Any antioxidant use# (%)	18.5	18.1	18.9
Randomized group (%)			
Placebo	25.5	24.5	26.7
Vitamin C	25.0	25.5	24.4
Vitamin E	24.5	20.2	28.9
Vitamins C and E	25.0	29.8	20.0

* All *p* values from tests for differences between randomized groups are > 0.05 .

† SD, standard deviation; BMI, body mass index (kg/m^2).

‡ Currently engage in any activity long enough to work up a sweat at least once a week.

§ Fruits/vegetables intake (servings/day) from Block food frequency questionnaire.

¶ Use of any vitamin and mineral supplements at screening visit.

Use of supplements at screening visit.

and 2 displayed adherence as measured by pill counts. In figure 1, the first percentile (the lowest value) of adherence to the vitamin C study tablets was 67 percent in the no organizer group and 81 percent in the pill-organizer group. Median adherence by pill counts for the vitamin C study tablets was 99 percent (range, 67–119 percent) in the no organizer group and 100 percent (range, 81–108 percent) in the pill-organizer group ($p = 0.42$ for the difference between the groups). Similarly, in figure 2, median adherence to the vitamin E study capsules was 99 percent (range, 67–119 percent) in the no organizer group and 100 percent (range, 81–110 percent) in the pill-organizer group ($p = 0.34$ for the difference between groups). The percentage of participants who took 90 percent or more of the pills was 91 percent in the pill-organizer group and 94 percent in the no organizer group. The distributions of pill counts were similar in healthy individuals and in persons who had at least one chronic illness ($p = 0.63$). In both the pill-organizer and no organizer groups, serum vitamin levels in the active vitamin groups were significantly increased in comparison with the placebo groups (table 2). Mean differences in the changes in serum ascorbic acid levels between the active vitamin C and

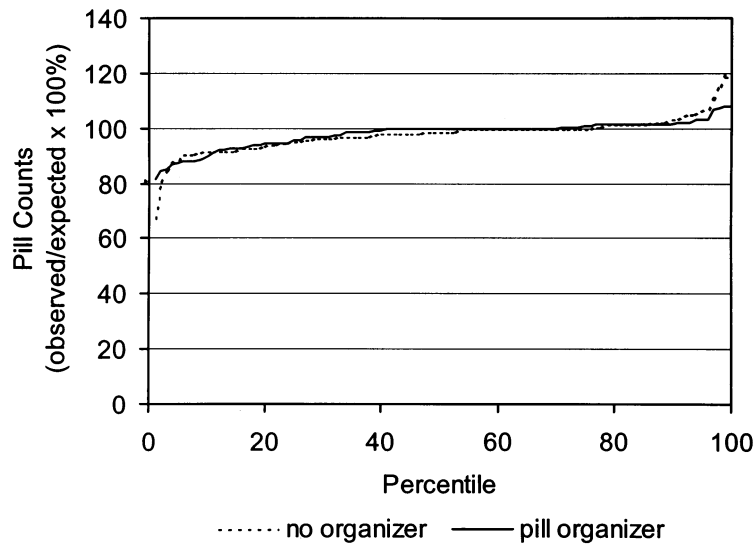


FIGURE 1. Adherence to the vitamin C study tablets (active and placebo) by percentiles in the pill-organizer and no organizer groups, TRACE Study, 1996–1997.

placebo groups were similar in the pill-organizer and no organizer group ($p = 0.47$ for the interaction term). The mean difference in the changes in serum α -tocopherol levels between the active vitamin E and placebo groups was somewhat higher in the no organizer group than in the pill-organizer group ($p = 0.06$ for the interaction term). The difference in adherence, either by changes in serum vitamin levels or by pill counts, between pill delivery groups did not differ by age (<65 vs. ≥ 65 years).

The overall pattern of self-reported adherence to pill taking was not different between pill-organizer and no organizer groups (table 3). About 53 percent of the participants

had correct answers to the questions about the types of pills they thought they were taking, with no difference between the active and placebo vitamin groups ($p = 0.33$ for vitamin C and $p = 0.80$ for vitamin E) and no difference between the organizer and no organizer groups ($p = 0.75$ for vitamin C and $p = 0.46$ for vitamin E). About 70 percent of participants did not have any particular reason for their answers to the questions about the types of pills they were taking, but just made a guess.

In VITAL, invitational mailings were sent to 4,774 retired teachers. Of these, 297 participants were randomized (148 in the organizer group and 149 in the blister-pack group). At

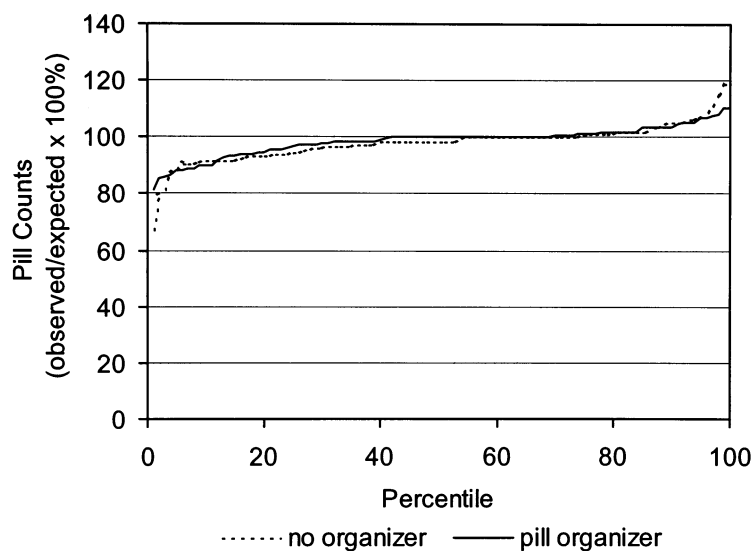


FIGURE 2. Adherence to the vitamin E study capsules (active and placebo) by percentiles in the pill-organizer and no organizer groups, TRACE Study, 1996–1997.

TABLE 2. Mean serum vitamin levels by supplement group and by use of pill organizer in the TRACE Study, 1996–1997

	No organizer		Pill organizer	
	Placebo (n = 42)	Active (n = 52)	Placebo (n = 49)	Active (n = 40)
Serum vitamin C (mg/dl) (mean (SD*,†))				
Baseline	10.2 (2.5)	11.5 (2.4)	10.8 (3.2)	11.1 (2.5)
Follow-up	10.1 (2.6)	15.6 (4.5)	11.3 (3.1)	14.7 (6.3)
Change	-0.1 (2.5)	3.9 (4.7)	0.5 (3.0)	3.6 (6.4)
Difference (95% CI)†‡	4.0 (2.4, 5.6)*		3.1 (1.1, 5.1)*	
Difference (95% CI)§	-0.9 (-3.4, 1.6)			
Serum vitamin E (mg/dl) (mean (SD*))				
Baseline	12.7 (3.8)	11.4 (2.8)	11.9 (3.1)	11.6 (3.2)
Follow-up	12.6 (3.7)	19.5 (6.4)	11.9 (3.4)	18.4 (9.0)
Change	-0.1 (1.7)	8.1 (5.5)	-0.01 (1.7)	5.8 (5.5)
Difference (95% CI)†‡	8.2 (6.4, 10.0)*		5.8 (4.0, 7.6)*	
Difference (95% CI)§	-2.4 (-4.8, 0.0)			

* $p < 0.0001$.

† SD, standard deviation; CI, confidence interval.

‡ Difference between placebo and active groups, separately within no organizer and pill organizer groups.

§ Interaction of organizer use and supplement use.

the end of pill taking, 294 participants (99 percent of the randomized participants) provided follow-up data; 289 participants attended an in-person visit, and five participants required a home visit. Counts of remaining pills were obtained from 291 participants.

Baseline characteristics of VITAL participants are summarized in table 4. The mean age was 65 years (standard deviation = 7), 58.2 percent were females, and 16.2 percent were non-Caucasians. Pill-organizer and blister-pack groups were similar in age, gender, race, education, body mass index, alcohol drinking, regular exercise, medication use, and vitamin supplement use at baseline.

As displayed in figure 3, adherence by pill counts ranged from 22 to 108 percent in the pill-organizer group and from 24 to 103 percent in the blister-pack group. The percentile

TABLE 3. Self-reported adherence to pill taking in the TRACE Study, 1996–1997

Self-report*	No organizer	Organizer	p value†
Decided not to take pills (%)	3.7	3.4	0.94
Forgot to take pills (%)	23.2	27.1	0.56
Skipped pills (%)	10.8	6.0	0.26
Took more than assigned pills (%)	2.4	0.0	0.15
Mistook pills due to carelessness (%)	12.1	11.9	0.95
Any of the above (%)	21.6	28.4	0.30

* Sample sizes ranged from 82 to 83 in the no pill organizer group and from 83 to 87 in the pill organizer group, depending on the number of participants who completed the second follow-up visit and answered the questions.

† From the Pearson χ^2 test.**TABLE 4. Baseline characteristics by types of pill packaging in the VITAL Study, 1993–1994**

Characteristic*	Total (n = 297)	Organizer (n = 148)	Blister pack (n = 149)
Age mean (SD)†	65 (7)	64 (7)	65 (7)
Female (%)	58.2	59.5	57.0
Non-Caucasian (%)	16.2	12.2	20.1
Education (%)			
Bachelor's degree	13.2	12.3	14.1
Master's degree	83.0	85.6	80.3
Doctorate	3.8	2.1	5.6
BMI† mean (SD)	27.3 (4.9)	26.8 (4.7)	27.7 (5.0)
Nondrinker (%)	50.2	45.3	55.0
Regular exercise‡ (%)	66.7	70.9	62.4
Medication (%) for			
Diabetes mellitus	6.0	4.7	7.4
Hypertension	30.6	26.3	34.9
Hypercholesterolemia	8.7	8.8	8.7
Vitamin use§ (%)			
Multivitamin	35.3	35.8	34.9
Antioxidant	26.9	29.7	24.2
Any vitamin	46.1	49.3	42.9
Randomized group (%)			
Placebo	50.0	50.0	50.3
Antioxidant	50.0	50.0	49.7

* All p values from tests for differences between randomization groups are > 0.05 .† SD, standard deviation; BMI, body mass index (kg/m^2).

‡ Currently engage in any activity long enough to work up a sweat at least once a week.

§ Use of vitamin supplements prior to randomization.

for 80 percent adherence in the pill-organizer group was greater than that in the blister-pack group, indicating that a larger proportion of participants in the pill-organizer group than in the blister-pack group had an adherence of less than 80 percent. The percentage of participants who took 90 percent or more of pills was 87 percent in the pill-organizer group and 93 percent in the blister-pack group. Although median adherence was the same (99 percent in both groups), adherence differed by types of packaging ($p = 0.05$). Specifically, among those in the lowest tertile of pill count distribution, adherence was higher in the blister-pack group. Distributions of pill counts were similar among healthy individuals and among persons who had at least one chronic medical condition ($p = 0.45$). In both the pill-organizer and the blister-pack groups, serum α -tocopherol levels in the active antioxidant group were significantly different from the levels in placebo group ($p = 0.0001$) at the follow-up visit (table 5). Mean differences in serum α -tocopherol levels between the active and the placebo groups were similar in the two types of packaging groups (p for the interaction term = 0.53). The difference in adherence, either by pill counts or by serum α -tocopherol levels, between pill delivery groups did not differ by age (<65 vs. ≥ 65 years).

The percentage of participants who reported any problem with pill taking was somewhat higher in the pill-organizer group than in the blister-pack group (39.3 vs. 28.7 percent, $p = 0.06$) (table 6). A higher percentage of persons assigned to the organizer group reported the problem of forgetting to take their pills (31.0 vs. 21.0 percent, $p = 0.05$). About 50 percent of the participants had correct answers to the ques-

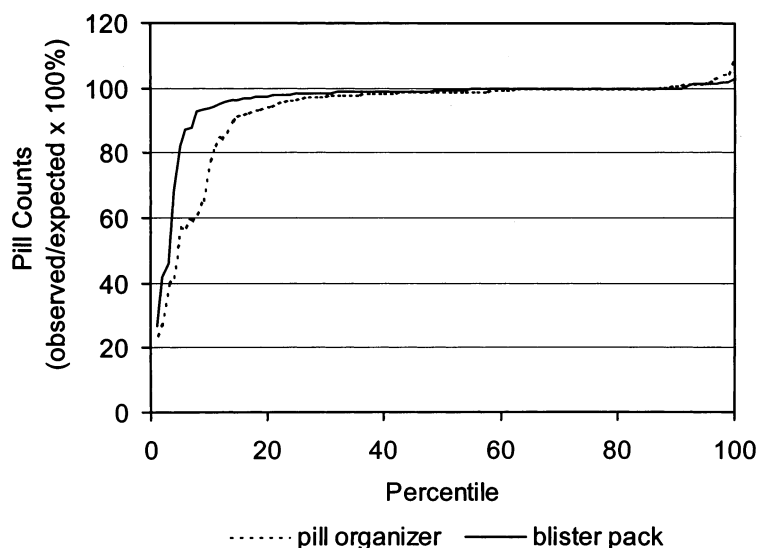


FIGURE 3. Adherence to pill taking by percentiles in the pill-organizer and blister-pack groups, VITAL Study, 1993-1994.

TABLE 5. Mean serum vitamin E levels and types of packaging by supplement group in the VITAL Study, 1993-1994

	Pill organizer		Blister pack	
	Placebo (n = 73)	Active (n = 73)	Placebo (n = 73)	Active (n = 72)
Serum vitamin E (mg/dl) (mean (SD)†)				
Follow-up	17.1 (3.9)	22.7 (7.1)	16.6 (6.3)	23.0 (7.5)
Difference (95% CI)‡	5.6 (3.8, 7.4)*		6.4 (4.2, 8.6)*	
Difference (95% CI)§	0.9 (-2.0, 3.8)			

* $p < 0.0001$.

† SD, standard deviation; CI, confidence interval.

‡ Difference between placebo and active groups, separately within no organizer and pill organizer groups.

§ Interaction of packaging (organizer/blister pack) and antioxidant supplement (active/placebo).

TABLE 6. Self-reported adherence to pill taking in the VITAL Study, 1993-1994

Self-report*	Pill organizer	Blister pack	p value†
Decided not to take pills (%)	7.6	5.6	0.51
Forgot to take pills (%)	31.0	21.0	0.05
Skipped pills (%)	11.7	7.0	0.17
Took more than assigned pills (%)	0.7	2.8	0.17
Mistook pills due to carelessness (%)	24.1	18.2	0.22
Any of the above (%)	39.3	28.7	0.06

* Sample size = 145 in the pill organizer group and ranged from 142 to 144 in the blister pack group, depending on the number of participants who answered the question.

† From the Pearson χ^2 test.

tion about the type of pills they were taking, with no difference between active and placebo vitamin groups ($p = 0.84$) and no difference between the blister-pack and pill-organizer groups ($p = 0.73$). About 56 percent of the participants did not have any particular reason for their answers to the questions about the types of pills they were taking, but just made a guess.

DISCUSSION

In contrast to previous trials that assessed adherence to medication use in patients with chronic illnesses, TRACE and VITAL were the first studies that determined the impact of pill organizers and blister packs on adherence to pill taking in a broad population. In TRACE, we documented that the use of pill organizers did not enhance adherence, whether assessed by serum vitamin levels, pill counts, or self-reports. This pattern of findings may have resulted from the key feature of organizers; that is, their use requires the active involvement of participants who must remove pills from bottles and place the pills in the organizer. In addition, it is possible that pill organizers would have been useful if the TRACE Study had enrolled more nonadherent individuals. In VITAL, adherence as measured by serum vitamin levels was similar in the blister-pack and the pill-organizer groups, while the pattern of adherence as measured by pill counts suggested that the use of blister packs may improve adherence, particularly among those with lower adherence. Self-reports of adherence corroborate the pill count results; that is, the percentage of VITAL participants who reported ever having forgotten to take study pills was lower in the blister-pack group than in the organizer group. This finding is not only consistent with pill count results, but is also a plausible explanation for the higher adherence in the blister-pack group.

The optimal approach to measure adherence remains uncertain. Direct observation on pill taking is the "gold standard," but, with the exception of direct observation therapy for tuberculosis (15), is impractical in clinical practice or in clinical trials conducted outside of medical facilities. Other methods of measurement, all of which are indirect, include interviews, self-reports, pill counts, biological markers, and electronic medication monitors. Interviews and self-reports are the simplest ways to assess adherence to pill taking, but tend to overestimate adherence and are not adequate measures, especially when used alone (16).

Pill counts remain a commonly used method to assess adherence to pill taking in research because the method is practical, inexpensive, and easy to implement. The accuracy of pill counts depends on participants' returning, not dumping, unused pills (17, 18). In both TRACE and VITAL, it is unlikely that "pill dumping" affected our results. It is noteworthy that excess pills were provided in each trial. In TRACE, at the first follow-up visit, of the 126 participants who had a supplementation period of less than 35 days between visits, only two participants (in the no pill organizer group) returned empty bottles and empty pill organizers. At the second follow-up visit, seven participants (one in the pill-organizer group and six in the no organizer group) returned empty bottles and empty pill organizers. Exclusion of these participants from statistical analyses did not materially alter the results. These findings suggest that pill dumping was uncommon and that, if it did occur, it did not affect the internal validity of this trial. In VITAL, for participants assigned to the blister-pack group, study pills were already packaged in each blister. This aspect of packaging makes pill dumping an unlikely explanation for our finding that adherence by pill counts appeared higher in the blister-pack group than in the organizer group. Because it is much easier to dump pills from bottles than from blister packs, one would expect that pill dumping would result in an opposite pattern. Furthermore, in both trials, participants did not know that pills that remained were counted.

Self-reports of adherence can potentially be misleading. To minimize this possibility, we used a standardized instrument (11). More important, there is little reason to suggest biased reports of adherence by types of pill packaging because participants did not appreciate that the types of pill packaging were under investigation. While the consent forms indicated that participants would be randomized to receive pills in different types of packaging, participants focused on vitamin supplementation as the main objective of the trials. In addition, there was no monetary reimbursement in either trial.

Biologic markers may be less vulnerable to participants' manipulation. Their use as adherence measures, however, depends on the pharmacokinetics and pharmacodynamics of the medication being administered. Electronic monitors are appealing because the number of pills removed is continuously recorded, and any side effect or problem after missed or excessive doses can be noted. However, in this method, one has to assume that pill bottle openings correspond to episodes of pill consumption. In view of these considerations, most trials that evaluate adherence to pill taking rely on more than one adherence measure.

Among the strengths of the VITAL and TRACE trials were the use of three measures of adherence: the large sample sizes, the high rates of follow-up, and the demographically heterogeneous study participants. Results from TRACE and VITAL should be relevant to other prevention-oriented trials. For people who do not routinely take pills, the packaging of pills into blister packs may remind them and prevent days of missed pills. Hence, blister packs may be particularly useful in healthy persons, such as participants in the Physicians' Health Study and Women's Health Study. Blister packs should be particularly useful in multi-factorial trials. A separate blister-pack card for each factor could be used. Alternatively, multiple types of pills could be packed on the same blister-pack card. In this case, distinct blisters contain study pills corresponding to each factor in the factorial design. Presumably, the benefits observed in the VITAL Study should extend to these more complex designs. However, blister packs may be impractical in trials that require frequent medication adjustment. In addition, packaging may be cumbersome for persons with arthritis and those who travel.

Results from VITAL raise the practical issue of whether the cost of blister packs justifies their expense (typically, 1 dollar for a 1-month blister pack). Such assessments will need to consider the nature of the dose-response relations, i.e., what level of adherence is required to achieve full effects and how much benefit occurs at lower levels of adherence. This information is rarely known.

In summary, the use of blister packs, but not pill organizers, improved adherence by pill counts, particularly among those with lower adherence. Neither pill delivery system improved adherence as measured by serum vitamin levels.

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REFERENCES

1. Ary DV, Toobert D, Wilson W, et al. Patient perspective on factors contributing to nonadherence to diabetes regimens. *Diabetes Care* 1986;9:168-72.
2. Lipids Research Clinics Program. The lipid research clinics coronary primary prevention trial results. *JAMA* 1984;251:351-64.
3. Inui TS, Yourtee EL, Williamson JW. Improved outcomes in hypertension after physician tutorials. *Ann Intern Med* 1976;84:646-51.
4. Bond WS, Hussar DA. Detection methods and strategies for improving medication compliance. *Am J Hosp Pharm* 1991;48:1978-88.
5. Wong BS, Norman DC. Evaluation of a novel medication aid, the calendar blister-pack, and its effect on drug compliance in a geriatric outpatient clinic. *J Am Geriatr Soc* 1987;35:21-6.

6. Ware GJ, Holford NH, Davison JG, et al. Unit dose calendar packaging and elderly patient compliance. *N Z Med J* 1991; 104:495-7.
7. Beckser LA, Glanz K, Sobel E, et al. A randomized trial of special packaging of antihypertensive medications. *J Fam Pract* 1986;22:357-61.
8. Eshelman FN, Fitzloff J. Effect of packaging on patient compliance with an antihypertensive medication. *Curr Ther Res* 1976;20:215-19.
9. Park DC, Morrell RW, Frieke D, et al. Cognitive factors and the use of over-the-counter medication organizers by arthritis patients. *Hum Factors* 1991;31:57-67.
10. Moses LE, Oakford RY. *Tables of random permutation*. Stanford, CA: Stanford University Press, 1963.
11. Morisky DE, Green LW, Levin DW. Concurrent and predictive validity of a self-reported measure of medication adherence. *Med Care* 1986;24:67-74.
12. McGown EL, Rusnak MG, Lewis CM, et al. Tissue ascorbic acid analysis using ferrozine compared with the dinitrophenylhydrazine method. *Anal Biochem* 1982;119:55-61.
13. Craft NE. High resolution HPLC method for the simultaneous analysis of carotenoids, retinoids, and tocopherols. *FASEB J* 1996;10:A527.
14. Bieri JG, Tolliver TJ, Catignani GL. Simultaneous determination of alpha-tocopherol and retinol in plasma or red cells by high pressure liquid chromatography. *Am J Clin Nutr* 1979; 32:2143-9.
15. Pozsik CJ. Compliance with tuberculosis therapy. *Med Clin North Am* 1993;77:289-301.
16. Burney KD, Krishnan K, Ruffin MT, et al. Adherence to single daily dose of aspirin in a chemoprevention trial. An evaluation of self-report and microelectronic monitoring. *Arch Fam Med* 1996;5:297-300.
17. Rudd P, Byyny RL, Zachary V, et al. Pill count measures of compliance in a drug trial: variability and suitability. *Am J Hypertens* 1988;1:309-12.
18. Pullar T, Kumar S, Tindall H, et al. Time to stop counting the tablets? *Clin Pharmacol Ther* 1989;46:163-8.