Placebo HAART Regimen as a Method for Teaching Medication Adherence Issues to Students

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Placebo medication regimens may help educate students about adherence issues. In this randomized trial, 23 third-year medical students took a 2-week placebo regimen mimicking highly active antiretroviral therapy (HAART) during their medicine clerkship; 15 students served as controls. Although no effect was demonstrated from this intervention on an evaluation instrument examining attitudes and beliefs about medication nonadherence, all 23 student-subjects agreed in postintervention interviews that the experience was useful and had learning value. Representative comments from the 19 subjects who expanded their interview responses portray this intervention as an eye-opening and unique method for teaching students about medication adherence issues.

KEY WORDS: adherence; experimental learning; medical students; patient compliance; placebos.

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Adherence (formerly compliance), the extent to which a patient's actions correspond with medical recommendations, affects provision of care in all fields but receives little attention in medical training. Many studies have shown that incomplete adherence is common, is underestimated by physicians, and cannot be predicted by demographic factors. Even highly selected groups such as physicians,¹ nurses,¹ and renal transplant recipients² achieve only about 80% adherence with medications. Treatment efficacy depends on accurate dosing of medications; even occasional lapses in adherence reduce drug levels, limit medication effectiveness, and can have major health consequences.

While physicians often assume nonadherent patients simply do not realize the health implications of not following advice, medication-taking behavior may be better explained by a cost-benefit model in which patients weigh multiple practical factors in deciding whether, when, and how to take prescribed medications.³ In one study, physicians listed medication side effects and number of daily doses as the most important barriers to adherence with highly active antiretroviral therapy (HAART), but their patients listed several factors that made it difficult to integrate HAART into daily life, including timing with respect to meals.⁴ In another study, individualized counseling and tailoring of HAART regimens to patients' lifestyles in one study improved adherence from 53% to 77% and reduced viral loads.⁵ While individualized attention to the patient's needs may improve adherence and outcomes, it requires empathic understanding and awareness of practical considerations on the part of the prescribing physician. Physicians do

not often inquire about medication-taking habits, however, asking patients closed-ended questions that presume adherence, if they inquire at all.^{6,7}

Patient-centered experiences, rarely offered in training, can have significant educational effects. In one study, physicians and nurses who took lactose pills every 4 hours as placebo for zidovudine reported after 7 days that the experience had been useful, harder than anticipated, and had increased their empathy for their patients' experiences; 2 years later, they reported strong recall of the experience and persistent effects on their interactions with patients.⁸ Several studies have examined the short-term experiences of students and physicians who took vitamins^{9,10} or candy¹¹ for 1 to 2 weeks as "medications" in teaching exercises. These studies documented limited adherence and were judged educational by the participants.^{9,10}

This paper describes a placebo HAART regimen given to third-year medical student volunteers in their core medicine clerkship as a patient-centered experiential educational technique to increase their awareness of difficulties faced by patients attempting to adhere to complex medication regimens. The study was intended to measure a change in the students' scores on an evaluation instrument designed to measure their attitudes and self-reported behaviors toward patients with adherence difficulties and in clinical situations in which adherence may be an issue. The study was also designed to gather the students' impressions of the effect of this intervention as an educational endeavor.

METHODS

Study Design and Sample Selection

This study was designed as a randomized controlled trial and was approved by the University of Washington Human Subjects Division under the condition that lactose-intolerant participants not be included in the intervention arm, because the placebo regimen contained lactose. Medical students were recruited during their third-year core internal medicine clerkship at the University of Washington School of Medicine. The recruiting physicians (ERT, ELS) announced the study to at least 6 groups of approximately 42 students each between July 1999 and February 2001, while the students were gathered for scheduled clerkship lectures. In this clerkship, students spend either 4 weeks in clinics and 8 weeks on inpatient wards, or 6 weeks on inpatient wards then 6 weeks with an internist in a smaller community within the 5-state region served by this medical school. There is no formal education on adherence during the clerkship.

Participation was voluntary, but students had to be willing to take a 2-week placebo HAART regimen if randomized to

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the intervention arm and to meet with researchers twice. Forty-seven study volunteers completed a short form reporting the number of chronic noncontraceptive medications they took, whether they were lactose intolerant (a criterion for exclusion from the intervention arm required by the Human Subjects Division, as the placebo regimen contained lactose), and whether they had any history of chronic renal failure (a criterion for exclusion as one placebo contained magnesium). Use of oral contraceptives and vitamins was not determined, because these are most commonly taken by healthy people to prevent unintended conditions rather than to treat active medical disease and thus the adherence experience may be different.

Development and Administration of Evaluation Instrument

Participants completed a 9-point Likert-type evaluation instrument (see Appendix available online) probing 6 domains around adherence. The instrument had been developed by two of the authors (ERT, DSP) based on a review of adherence literature and on interviews with students who participated in a pilot version of this project. (In the pilot study, designed and run by two of the authors [ESC, DSP], 16 students in the ambulatory portion of their medicine clerkship were given pill bottles containing candy [M&Ms[®], Mars, Inc.] and were counseled to take the "medications" as if they were HAART.) The instrument was pretested with 20 student volunteers to be sure the statements were not confusing or vague but was not otherwise validated. The instrument uses the term "compliance" rather than "adherence," as "compliance" was more commonly used in the medical literature at the time.

Group Assignment

After completion of the information form and evaluation instrument, the 39 lactose-tolerant participants were randomized into subject and control groups. Eight lactose-intolerant students participated as assigned members of the control group, but their data are excluded from the analysis because they participated outside the randomized controlled trial. Control students received no medications or counseling.

Preparation and Administration of the Placebo Regimen

Each of the subjects was given 3 full prescription bottles, prepared and labeled (as placebo) by the Investigational Drug Service of the University of Washington Medical Center Pharmacy, and was asked to take these as "prescribed" beginning the following morning. Each subject was counseled individually by a researcher using patient information sheets specific for indinavir, stavudine, and didanosine. The placebos mimicked standard doses of commercially available HAART medications in appearance. "Indinavir" was size 00 white gel capsules, each containing 1 g lactose, to be taken as 2 capsules by mouth every 8 hours on an empty stomach, separated by at least 1 hour from "didanosine." "Stavudine" was size 1 yellow and orange gel capsules, each containing 460 mg lactose, to be taken as 1 capsule by mouth twice daily, with or without food. "Didanosine" was unflavored chewable white tablets each containing aluminum hydroxide 160 mg and magnesium carbonate 105 mg (Gaviscon[®] Extra Strength Antacid

Tablets, GlaxoSmithKline, Philadelphia, PA), to be taken as 4 tablets chewed at bedtime on an empty stomach, at least 1 hour after "indinavir." Subjects were advised to drink at least 48 ounces of liquid daily while on "indinavir."

Data Collection at Study Exit

Two weeks later, while control and subject students were still participating in their core medicine clerkship, a researcher met with each participant to readminister the evaluation instrument. Subjects were asked to bring their pill bottles to this meeting; the remaining pills in each bottle were counted, and the count adjusted for the expected 13 days of use. The subjects were also interviewed by the researcher at this meeting using an interview template. The interview questions had been developed at the same time and in the same fashion as the evaluation instrument. The interview questions probed whether the subjects felt the exercise was useful, whether they learned anything not addressed in the evaluation instrument, whether the learning value of the exercise was worth the trouble involved, whether they had any suggestions to improve the exercise, and whether they had any other comments. Each subject's responses were written down on a copy of the template by the researcher as the subject answered and elaborated upon each interview question. The students in the control group were not interviewed.

Data Analysis

Responses from the evaluation instrument were evaluated using SPSS[®] 12.0 for Windows[®] (SPSS Inc., Chicago, IL), using nonparametric tests to compare the groups. Data from the lactose-intolerant students, who were not randomized and who did not take the placebo medications, are not included except where specifically mentioned. Interview responses were entered into a word processing system by two authors (ELS, ERT). The responses were then grouped by theme by one of the authors (ELS) and the groupings then reviewed by the other authors; no changes were suggested or made on the basis of this review.

RESULTS

The use of this placebo regimen generated a great deal of interest among the students, and the idea of taking such a regimen was discussed widely among the students. However, the possibility of randomization to the control group and the study requirement that participants meet twice with researchers during the medicine clerkship reduced enrollment. Some students asked to take the placebo regimen without enrolling in the study; this was not allowed. One subject did not return for follow-up and is not included in analysis, leaving 23 subjects and 15 randomized controls whose data are included. There were 15 men and 8 women in the subject group, and 9 men and 6 women in the control group. At entry, other than oral contraceptives and vitamins, 27 students (15 subjects and 12 controls) took no daily medication, 9 students (7 subjects and 2 controls) took 1–4 daily medications, and 2 students (1 subject and 1 control) did not report this information.

Evaluation Instrument Results

The instrument was scored so that higher values reflected more positive responses in each of the 6 domains. The domain

scores were not independent. Baseline scores in the domains Empathy, Flexibility, and Recognition were significantly correlated with the domain Insight (0.38, 0.45, 0.52, respectively; $P < .01$ for each pair) and with each other (Pearson correlation coefficients 0.33–0.37; $P < .05$ for each pair). The Total score was (necessarily) correlated with each of its domains. Mean scores from baseline administration of the instrument are shown in Table 1 for the subject and randomized control groups. Notably, the mean Total score at entry was higher in the subject group than the randomized control group. At entry, 3 of the 4 highest Total scores were from participants reporting chronic medication use, and 8 of the 9 participants reporting chronic medication use had Total scores above the mean for all students (data not shown).

Results of the final administration of the evaluation instrument are shown in Table 2 as the change in scores from pretest to posttest; changes in the scores in each domain and in the Total score were not significantly different between the subject and randomized control groups. Mean scores increased among the subjects more than controls in Counseling, Insight, Attitude, and Recognition, but the spread was very wide and no changes were significantly different between the 2 groups in this small sample. (Inclusion of the data from the 8 lactose-intolerant students assigned as controls brought the difference between the subject and control groups to significance at $P < .05$, with subjects' Total scores increasing more than randomized and assigned controls combined.) An outlier of note is the student who achieved by far the lowest adherence (46% of "indinavir," 50%–62% of the other "medications") but had the greatest change in Total score after the exercise (42 point increase, 1.9 SD above subjects' mean change of 15.3).

The additional statement "I felt this was a valuable exercise" was included at the end of the postintervention instrument given to the subjects and was answered by 21 out of the 23, with strong agreement (mean score 8.5 ± 0.9 out of 9). This question was not given to the controls.

Table 1. Baseline Scores on Evaluation Instrument

	Maximum Domain Score	Mean Baseline Score $\pm$ SD for Students Receiving Placebo Regimen (N=23)	Mean Baseline Score $\pm$ SD for Students Not Receiving Placebo Regimen (N=15)
Counsel	45	32.4 ± 5.2	29.7 ± 5.7
Insight	63	46.7 ± 5.5	45.1 ± 4.3
Attitude	54	34.9 ± 8.4	31.5 ± 6.9
Empathy	45	32.0 ± 5.6	27.7 ± 6.2
Flexibility	36	28.0 ± 3.7	25.9 ± 4.5
Recognition	45	36.3 ± 5.6	34.6 ± 4.1
Total*	297	210.3 ± 20.0	194.4 ± 18.1

Counsel: Self-assessed ability to counsel patients on medication adherence issues.

Insight: Insight into medication adherence issues.

Attitude: Attitudes about nonadherence and patients with difficulty adhering.

Empathy: Empathy for patients on complex medication regimens.

Recognition: Recognition of medication adherence-related issues as important.

Total: Total score of all 33 items.

* $P < .05$ for comparison between subjects and controls.

Table 2. Change in Scores on Evaluation Instrument

	Mean Change in Score $\pm$ SD for Students Receiving Placebo Regimen (N=23)	Mean Change in Score $\pm$ SD for Students Not Receiving Placebo Regimen (N=15)
Counsel	2.6 ± 4.4	0.7 ± 2.9
Insight	3.3 ± 6.9	-0.1 ± 4.2
Attitude	2.7 ± 5.7	1.8 ± 4.5
Empathy	2.8 ± 6.8	3.1 ± 4.0
Flexibility	2.1 ± 3.8	2.7 ± 4.1
Recognition	1.8 ± 3.9	0.5 ± 3.3
Total	15.3 ± 14.2	12.7 ± 14.6

See key of Table 1 for description of domains.

Differences between the 2 groups were not significant.

Placebo Medication Side Effects and Adherence Results

No side effects were reported beyond comments on palatability of "didanosine." Pill counts revealed that, on average, 75%–85% of the "prescribed" doses were taken for each of the 3 "medications" in the 13 days. One hundred percent compliance with all "prescribed" doses was achieved by 36% of the subjects for didanosine (once daily), 18% for "stavudine" (twice daily), and 14% for "indinavir" (3 times daily). Twenty-three percent of the subjects took at least 90% of "prescribed" doses. Subjects whose bottles were not empty returned on average 2–3 days' supply.

Interview Results

In the interviews, 23 of 23 subjects agreed this was "a useful exercise" and 23 of 23 agreed "the learning value of the exercise was worth the trouble involved." Nineteen subjects offered one or more observations about their personal experience, from general to specific, including 10 of the 14 who stated they had not learned things from the exercise that were not covered by the evaluation instrument. Of the 9 who indicated learning something beyond areas covered on the evaluation instrument, only 2 made unique comments (one learned more about antiretroviral drugs, one learned "things that are hard to articulate"). Table 3 lists excerpts showing common themes from the interview comments, including subjects' suggestions on how the exercise might be improved. The responses are grouped by themes identified on review of the responses, rather than by domains of the evaluation instrument, though many comments fall within 1 or more of the 6 domains. Overall, the subjects described the experience as valuable, educational, and eye opening. Many students reported becoming aware that their own medication-taking behavior did not meet the expectations they held for patients. Nineteen of the 23 subjects commented on their enhanced sense of the practical difficulties of following such a regimen. Attempting to follow the regimen was far more difficult than they had anticipated, even for those already on daily medication. Hospital call presented unique barriers to adherence. The subjects advised that this experience be offered on a volunteer basis during an outpatient portion of the medicine clerkship.

Table 3. Representative Interview Comments from Students Who Took the Placebo Regimen

General comments	Everybody should do it! It was really useful. I'd recommend it to people. Two weeks is long enough! I felt like I understood the complexity after 3 days! Needs to be at least 1 week. For the first few days, I felt it was no big deal. I could keep up. Ideally you'd take the real meds but I understand why that would be impossible to do.
Gained insight	Definitely very useful. I've never had to take medications for more than a few days at a time, but I prescribe them for patients all the time. Now I recognize this is something maybe I <i>wouldn't</i> take <i>even if</i> I had HIV. It really opened my eyes. I used to see someone with HIV who wasn't taking anything, and I'd think, "Why aren't you on medication?" I took all the pills but not at exactly the right time. There's compliance and there's compliance, I guess. Anything that puts a doctor in the role of a patient is useful. It creates some understanding of what patients go through, especially when asymptomatic.
Recognized difficulty	It sure was a pain to take all those pills. It was an eye opener because it was a lot harder than I anticipated. I thought I was aware of how difficult and just how complicated it was, but I wasn't. It was much, much harder than I thought it would be. Hard to remember the doses, timing the pills, bringing meds to work. I felt uncomfortable taking them in front of people. I don't think I realized how much that would influence me. I learned how hard it was to take medications on an empty stomach. I would have had to set an alarm for 2 AM to do q8 h on an empty stomach. I learned how much a regular daily routine would be necessary to keep up with medication regimen. It was very good. I had no idea how hard it was to manage all of these medications, especially the food issues and especially if you have a busy lifestyle. It really puts shackles on your life. If this was hard for me, think about the difficulty someone would have if they have mental status changes, or a lower education level, or cultural or language barriers. I learned how much some drug regimens dictate your lifestyle. I didn't think it would be a problem but found people really reacted to seeing a pill bottle in a social setting.
Increased empathy	I think everyone should have to do it. I empathized before but I didn't see how difficult it was. It was really hard. I missed a lot of doses. The white ones [chewable antacids] tasted awful. But now I totally empathize with the patients. It was a really good experience. I was explaining the difficulty of taking meds to one of my interns who has an AIDS patient about to die of PCP [pneumocystis carinii pneumonia] in the next few days. It was a real pain to take all those medications. I have a lot of sympathy now for patients who are taking a lot of medications. I don't see how you can do it [take 35 pills/day]. It gives you a lot more sympathy for your patients.
Enhanced communication	It helped me in talking with patients. Patients opened up more. I could elicit their issues better. As a doctor, based on this exercise, I would increase the time I spend talking about compliance. You need to ask about and discuss it, find nonjudgmental, brief ways to intervene, brainstorm, etc. Also this will help me to validate the difficulty of taking meds, and to empathize. You don't get much training in teaching people how to take meds. It's a deficit in our education, especially with HIV meds, or other regimented or inflexible med regimens.
Learned practical tips	It helped me think of ways to increase compliance. I can extend those ideas to other things too. I started to get some ideas of things that worked that I could help patients with. I learned a lot of little tips: setting an alarm, keeping the pills on my person all the time. I would recommend patients get little containers to carry their day's pills.
Suggested changes	Would definitely do this during outpatient rotation, not inpatient. If placebo contained <i>something</i> "good for you" like vitamin C, [students] would feel more inclined to take them and would feel more positive toward the medications. The antacid (placebo for didanosine) tasted bad! Smaller pills (for indinavir). Otherwise, no change. I'd like to know what other people thought of it.

DISCUSSION

Physicians must recognize the practical issues patients face with complicated medication regimens to support their patients' efforts at adherence and thus maximize the efficacy of treatment. At present, however, adherence issues are not often taught or demonstrated in medical education. The approach described here of "prescribing" a difficult placebo medication regimen seems to offer students an eye-opening educational experience, particularly useful in helping them understand and appreciate some of the difficulties patients face in trying to follow complicated medication regimens. This study did not show a difference in students' scores on the evaluation instrument from exposure to the placebo regimen, but the study was limited by the small sample size and by differences in the subject and control groups in gender, chronic medication use, and baseline scores on the evaluation instrument.

Whether and how to offer an educational placebo medication experience raises several issues. In this study, the participants were motivated volunteers from the larger clerkship

group, representing less than 20% of eligible third-year students approached, and thus they may differ from their peers in openness to learning from this type of experience. Whether there is educational benefit for unselected students, or long-term benefit for any participating student, has not been shown. Classroom discussion of students' experiences was not attempted in this study, but such discussion might facilitate further reflection, integration, and dissemination of this educational experience. In exit interviews in this study, several students advised that this experience be offered during the ambulatory portion of the clerkship, as taking overnight call in the hospital presented additional barriers to adherence that most patients would not face. Finally, while a placebo regimen of candy or vitamins would be simpler to provide (and to take), the easier or more pleasant experience might not carry the same educational impact as the more difficult regimen mimicking HAART or another complex multidrug regimen.

Awareness of the difficulties inherent in a complicated medication regimen will remain important for physicians to learn and retain as they endeavor to help their patients with

various chronic diseases. Students who took this placebo regimen learned first-hand how difficult it is for patients to follow such a regimen. Besides gaining this new appreciation, some students specifically described feeling more empathy for patients on these regimens, being more likely to discuss adherence (and nonadherence) with patients, and coming up with some practical ideas to help patients improve their medication adherence. Ideally, this and other methods to educate medical students about issues around adherence may improve their ability as physicians to recognize and address their patients' adherence difficulties and, ultimately, to improve their patients' outcomes.

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Supplementary Material

The following supplementary material is available for this article online:

Appendix 1. Evaluation Instrument.