*BEHAVIORAL CONTROL OF MEDICINE COMPLIANCE*LEONARD H. EPSTEIN¹ AND BRUCE J. MASEKUNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE AND
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This study examined the effectiveness of several behavioral techniques on compliance of college students taking vitamin C on q.i.d. regimen. Compliance was assessed by a new technique using a variation of the urine tracer procedure designed specifically for this study. Subjects were provided vitamin C tablets, with three tablets per week containing phenazopyridine, a drug that produces a bright red-orange urine discoloration. Subjects were requested to indicate when urine discolorations occurred, and compliance was assessed by comparing the time of their report to the time predicted on the basis of the scheduled sequence of vitamin C and phenazopyridine tablets. Baseline compliance was assessed for 72 subjects over a three-week period, with the 40 most noncompliant subjects randomly assigned to four groups for Treatment I. The groups were: self-monitoring, taste, taste and self-monitoring, and a no-treatment control group. The self-monitoring procedure involved recording the time medicine was taken; the taste procedure involved providing the subjects with flavored tablets to increase the saliency of tablet taking; and the self-monitoring and taste procedure involved providing subjects with flavored tablets and asking them to record the flavor of each tablet they ingested. At the end of six weeks, half the subjects in each of these groups participated in response-cost procedures while the remaining subjects continued with their previous procedures. Response-cost procedures were implemented by returning a portion of the subjects' deposit only if a preset compliance criterion was met. Treatment II procedures were implemented for an additional three weeks. Results indicated the self-monitoring and taste plus self-monitoring procedures were superior during Treatment I. The implementation of response cost during Treatment II was associated with a marked improvement in compliance, independent of the history of noncompliance. The effects of the taste plus self-monitoring procedure were maintained during Treatment II and results obtained by this procedure were not significantly different from effects of response cost.

DESCRIPTORS: medicine, compliance, response cost, self recording, humans

Patient compliance to prophylactic medication regimens is typically poor, with estimates of non-compliance ranging from 4% to 92% (Mars-ton, 1970) and averaging from 30% to 35% (Davis, 1966). Noncompliance may influence

the effectiveness of the medication, as irregular ingestion of the medication may be insufficient to maintain therapeutic blood levels. In addition, compliance may affect the results of clinical drug trials. Soutter and Kennedy (1974) indicated that 19% of 768 studies on drug effects used an objective measurement of patient compliance. This assessment is important, as poor compliance in a clinical trial may result in underestimation of the efficacy of the drug being studied.

Haynes and Sackett (Note 1) reviewed 246 studies dealing with patient noncompliance. Almost 60% of these studies involved methodological and epidemiological studies and reviews, with only 41% dealing with treatment strategies. Numerous models of medication taking

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have been advanced to identify variables that could have relevance to modification of noncompliance. For example, Becker, Drachman, and Kirscht (1972) presented an ambitious attempt to identify correlates of health motivations, perceptions, and attitudes of mothers in complying with medical regimens for their children. Gillum and Barsky (1974) identified four areas they consider related to medicine compliance, including psychological factors, environmental and social factors, therapeutic regimens, and the physician-patient interaction. In addition, Van Putten (1974) identified 46% of his sample of chronic schizophrenics reported they did not take medicine correctly to avoid the extrapyramidal symptom side effects of the antipsychotic medication. Haynes and Sackett (Note 1) listed 193 factors studied in relationship to compliance. Seventeen factors were studied at least 10 times, and only four of these factors had positive correlations in more than one-half of the studies. These factors are race, complexity of the therapeutic regimen, duration of therapy, and belief in the efficacy of therapy. Such factors as intelligence and severity of illness were not predictive of compliance. Caron and Roth (1968) showed how difficult it is even for a patient's attending physician to predict compliance. They found that resident physicians were unable to predict how well their patients complied with antacid intake, typically overestimating degree of compliance.

Strategies for improving compliance were assessed in approximately 40% of the studies reported by Haynes and Sackett (Note 1). Thirty-four different strategies were listed, with patient and health education as the most-studied procedure (17%). An illustrative report of educational strategies to influence compliance was completed by Sackett, Haynes, Gibson, Hackett, Taylor, Roberts, and Johnson (1975). These authors were interested in compliance to anti-hypertensive medications, a common clinical problem (Sackett *et al.*, 1975). Subjects were steelworkers who were provided treatment from their regular physicians or were treated in their factory as an augmented convenience. Half the

subjects in each group were also provided an educational package on facts about hypertension, the need for compliance to medication regimens, and some simple reminders to influence pill taking. Results assessed at six months showed approximately equivalent effects across all groups, with range from 50% to 56% compliance. Neither easier access to treatment nor mastery of hypertension information affected compliance rates.

Sackett *et al.* (1975) suggested that more direct attempts to modify behaviors involved in medicine intake be investigated. Zifferblatt (1975) indicated that patient noncompliance is primarily a behavioral problem, that of not taking medication in accordance with the physician's instructions. He advocated that solutions to medication compliance can come from applied behavioral analysis of medication-taking behavior. Actually, very little research has been conducted in the area of behavioral control of medicine compliance. Haynes (1973) developed a community based program for Antabuse intake in chronic alcoholics. Persons who were frequently arrested for public intoxication were given the opportunity of participating in Antabuse treatment as opposed to going to jail for 90 days. Treatment involved taking the medication twice per week at the municipal court. After a maximum of two missed meetings, the patients were returned to jail. Results for 138 patients indicated that almost half were still on the Antabuse program after 1 yr, and the mean number of arrests for the patient sample dropped from 3.8 to 0.3 arrests per year. Bigelow, Strickler, Leibson, and Griffiths (1976) used deposit contracts to influence Antabuse intake in a single group outcome study using 20 male outpatient alcoholics. The patients deposited an average of \$71.25, and \$5 to \$10 was forfeited when a patient did not attend a scheduled appointment. All patients were required to come each day for the first two weeks, and once every other day for the duration of the contract, which lasted a minimum of three months. Results indicated that patients were abstinent over 95% of the treatment

days, which was associated with a reported longer duration of abstinence for 80% of the subjects than experienced within the previous 3 yr. The results indicate impressive maintenance of compliance using procedures that required the subject to attend daily treatment sessions, during which medication ingestion was observed by a clinic staff member.

Medication typically is taken on an outpatient basis in which the patient and therapist are not in close contact. This separation makes measurement of compliance particularly difficult. The three most widely used procedures to assess compliance are patient self-report, tablet counts, and urine or serum tracers or tests. Self-report of compliance is the least accurate procedure (Park and Lipman, 1964; Rickels and Briscoe, 1970), with tablet counts slightly better but still not reliable (Roth, Caron, and Hsi, 1970), as not returning medication does not mean the patient has ingested it (Marston, 1970). The use of laboratory tests to detect a tracer or element of the target medication in urine or blood specimens can be accurate but is difficult to interpret. The tests have to be administered often to be sensitive to deviations in medicine intake; if they are administered on an intermittent basis, a patient may take medicine before the test and appear compliant when tested, even though possibly markedly noncompliant at other times. In addition, the testing is expensive, often requires laboratory assay, so that immediate feedback to the patient is not available, and optimum serum or urine levels have been difficult to specify (Soutter and Kennedy, 1974). The use of behavioral procedures to modify compliance requires reliable, ongoing measurement of medicine intake to reflect compliance accurately, as well as procedures that can be easily implemented in outpatient settings.

The present study was designed to develop reliable, easily implemented procedures for measurement and modification of medicine compliance. The compliance of college students taking vitamin C to prevent colds was assessed. The use of vitamin C (ascorbic acid) as a prophylaxis is

consistent with the use of medication in prevention, or possibly in asymptomatic disorders such as hypertension, in which symptoms may not be observed if patients are not compliant in medicine taking. Thus, it may serve as a useful analogue model for study of medication intake. Second, vitamin C may have many clinical uses. The most popular is as a preventative or treatment for colds (Pauling, 1970). Recent reviews on vitamin C and the common cold suggest that the effects of vitamin C are limited (Dykes and Meir, 1975), though results slightly favor vitamin C over placebos in terms of colds per year or duration of colds (Chalmers, 1975). Several other uses for vitamin C have been suggested. Ginter (1975) studied the effects of ascorbic acid on serum cholesterol levels. His results (Ginter, 1976) suggest that vitamin C deficits are related to cholesterol buildup in hyperlipemic subjects, and that prevention of a vitamin C deficiency may reduce the risk of hyperlipidemia. Another interesting use of vitamin C is in heat acclimatization (Strydom, Kotze, Van Der Walt, and Rogers, 1976). Physiological indices of heat stress were measured in three groups of mining recruits who were provided a placebo, 250 mg or 500 mg ascorbic acid during work in a hot climate over 10 days. Results indicated significantly better acclimatization for subjects provided vitamin C, with no differences between dosage levels. Finally, Schlegel (1975) suggested the use of ascorbic acid to prevent bladder cancer and reports his continued clinical use of vitamin C for patients with recurrent bladder cancer.

METHOD

Subjects

Subjects were recruited from undergraduate psychology classes to participate in a study on the effects of vitamin C as a prophylaxis for the common cold. Pre-experimental questionnaires filled out in class provided information on personal and medical history, which was used to exclude subjects from participation if they: (a) were taking anticoagulants or medication pro-

ducing side effects involving the respiratory system; (b) had a history of diabetes, gout, renal stones, respiratory symptoms of allergenic origin, kidney disease, urinary disease or dysfunction, or chronic gastrointestinal disturbance; (c) were taking psychotropic medications; (d) were pregnant; (e) had a history of elevated blood uric acid; (f) or had previously experienced adverse reactions to drugs used in this experiment. Eighty-five subjects began the study; 72 remained at the end of the initial three-week baseline. Ten subjects were terminated due to possible negative side effects of the medications used, primarily gastrointestinal disturbances; two subjects failed to return, and one contracted an unrelated illness.

Medications

Medications used were prepared by the Pharmaceutical Products Division of the Auburn University School of Pharmacy. Two types of tablets, identical in size, shape, and color, were prepared. One contained approximately 100 mg ascorbic acid, and the other, 100 mg ascorbic acid plus 200 mg phenazopyridine. Phenazopyridine is a urinary tract analgesic used for symptomatic relief of lower urinary tract irritations. Phenazopyridine was used in this study because it produces a reddish-orange discoloration of the urine, which was used to assess compliance. In addition, some of the tablets were flavored by the experimenters with quinine or extract of orange, which provided a salient taste to the tablets but did not produce any changes in size or color of the tablets.

Measurement of Compliance

Compliance was assessed in two ways. The first was a variation of the tracer technique, using phenazopyridine as the tracer. Each week, subjects were provided bottles of tablets, and instructed to take the medication on a q.i.d. (four times per day) basis, at 9:00 a.m., 1:00 p.m., 5:00 p.m., and 9:00 p.m., plus or minus 0.5 hr. This q.i.d. regimen is typical of medication regimens (Goodman and Gilman, 1975).

The tablet bottles were arranged so that the tablets were taken in a prearranged order, with three vitamin C and phenazopyridine tablets included each week. Nine different sequences of tracer tablets were developed, and subjects were presented a randomly chosen sequence each week. The sequencing of the tablets was determined by placing the tablets in three vials set in 16-dram childproof medicine bottles. The vials were acetate tubes wide enough in diameter to accommodate one tablet set in the bottle. Initially, two of the vials were plugged by cotton. After the tablets in the first vial were taken, tablets from a second marked vial were then taken, and then tablets from the remaining vial were used. Subjects were instructed to indicate on a data recording sheet when they observed urine discolorations. Compliance could be established by comparing the time reported for the first detectable discoloration by the subject with the projected time of urine discoloration if the tablet were taken as prescribed. A reported urine discoloration was acceptable if it occurred within 8 hr of the dose containing the tracer, except for the evening dosage, when a 12-hr period was used. For two subjects that indicated very low micturition rates, a 12-hr criterion was used for all doses. Single phenazopyridine doses may produce urinary discoloration for two to three urinations, and the tracers were scheduled at sufficiently long intervals to permit their complete metabolism and excretion before the next dose. A compliance score of three represented perfect agreement on all three tracers, and a score of zero indicated perfect noncompliance. The number of tablets available each week varied from 28 to 34, to decrease external feedback to subjects on their individual compliance, as well as to provide a second measure of compliance—tablet counts—determined by comparing the extra pills returned with the number of extra pills provided. Providing three tracers per week allowed for determination of noncompliance in scores ranging from one to three. For example, a score of three suggests all tablets were taken; two, between 67 and 99% of tablets were

taken; one, between 33 and 66%, and zero between none and 32% of tablets ingested.

The reliability of medication scheduling was established in the following manner. Each week, extra vials of tablets were developed, each vial having the scheduled sequence attached on a slip of paper. When a vial was given to a subject the sequence indication was removed and labelled with the subject's number. Remaining vials were used to test the reliability of scheduling. During baseline, an average of 10 vials per week was tested by selecting the three phenazopyridine tablets from the vials and distributing them to individuals not in the study for ingestion. In addition, during the six weeks of treatment, 90 more tracer tablets were tested from the tablets returned by subjects. These 90 pills represented 12% of the total number of tracer tablets dispensed. In all cases, persons testing the tablets reported urine coloration, indicating that all scheduled tracer tablets contained the tracer.

Procedure

The study was carried out in three, three-week phases. Phase I was the baseline phase. After subjects had filled out the pre-experimental questionnaires in class, they were contacted and scheduled for individual appointments weekly with the second author or an experienced research assistant. At this time, subjects were informed that some vitamin C tablets would contain phenazopyridine, were told the potential side effects, and provided with a handout from the Physicians' Desk Reference (1976). Before beginning the experiment each student deposited \$9.00, which was to be forfeited if data were not turned in weekly. At each weekly meeting, subjects' data sheets were turned in and they were provided the next week's supply of medicine. At the end of the three-week period, the 40 most noncompliant subjects were identified and randomly assigned to four treatment groups. Interactions with subjects during the weekly meetings were kept to a minimum, and did not

include verbal praise or reproof for compliant or noncompliant behavior.

The four groups during Treatment I were self-monitoring, taste, taste plus self-monitoring, and a no-treatment control that continued baseline procedures. The self-monitoring procedures required the subject to record, on the data sheets provided, the time at which each medicine dosage was taken. Each data sheet was arranged with four dosages by seven days, so that subjects had only to write in the time of medication intake. The taste group was provided the flavored tablets, to evaluate the importance of increasing the saliency of medicine taking on compliance. These subjects did not have any recording requirements. The taste plus self-monitoring group was requested to record on data sheets provided the flavor of each tablet ingested; these sheets were similar to data sheets of the self-monitoring group, except they required the subject to record the flavor and not the time the tablet was taken.

Due to insufficient control of compliance by the procedures in Treatment I, the effects of a response-cost procedure were evaluated in Treatment II. Response cost was implemented by exposing one-half of the subjects in each of the four Treatment I groups to response cost. Volunteers for the response-cost procedure were obtained from the first five subjects contacted during their regular appointment times from each group. Since subjects had originally been randomly assigned to groups, the first five subjects contacted did not constitute a particular subgroup. Only one subject from this initial sample of 20 did not agree, and another subject from the group was contacted. The response-cost subjects were instructed that they would be participating in procedures to increase reliability of medicine intake, as the effectiveness of the medicine could be evaluated only if medicine was taken as directed. All response-cost subjects signed a contractual agreement indicating that \$1.00 of their deposit would be forfeited each week in which they did not receive a compliance score of two or better. The remaining subjects

continued with the procedures implemented during Treatment I.

At the end of the study, subjects were provided debriefing information on the vitamin C-cold results, and informed of the compliance procedures used across groups. They were also provided a postexperimental questionnaire to determine if subjects understood the procedures used, participated appropriately in experimental conditions, and experienced no adverse side effects of the medications or recording procedures.

RESULTS

The baseline procedures were designed to identify a sample of noncompliant subjects, as well as providing pretreatment estimates of compliance for comparison to later treatment effects. Subjects were considered compliant if their mean compliance score over the three weeks was at least two, and if they were perfectly compliant for at least one week. Fifteen subjects fitted these criteria, with a mean compliance score of 2.4.

The mean compliance score for noncompliant subjects during baseline was 1.07, which is significantly less than that for compliant subjects, $F(1, 69) = 75.4, p < 0.001$. In addition, the mean extra-tablet score for the compliant subjects of 1.4 was significantly less than the mean of 4.5 for noncompliant subjects, $F(1, 69) = 12.3, p < 0.001$. The 40 most noncompliant subjects were randomly assigned to four treatment groups for Treatment I, and a two-factor, repeated measures on one-factor ANOVA was performed to ensure baseline equality of groups. The mean compliance score for each group was: self-monitoring, 1.03; taste, 0.93; taste plus self-monitoring, 1.10; and control group, 1.06. Analysis indicated that groups were not significantly different, $F(3, 36) = 0.17, p > 0.05$. A similar ANOVA performed on the pill counts also indicated no group effect, $F(3, 36) = 0.77, p > 0.05$.

The mean compliance scores for subjects in each group over the three phases of the experiment are presented in Figure I. During Treat-

Fig. 1. Mean compliance score for subjects in all groups during baseline and the two treatment phases.

ment I, the self-monitoring and taste plus self-monitoring treatments were associated with increases in compliance, with the compliance rates for taste and control groups decreasing slightly. A three-factor, repeated measures on two-factors ANOVA was performed on the first six weeks of data to assess statistically the reliability of the observed changes, Significant Trials, $F(2, 72) = 2.62$, $p < 0.05$, and Groups $\times$ Phases interaction were observed, $F(3, 72) = 3.24$, $p < 0.05$. Tukey's test for comparison of treatment means indicated that self-monitoring subjects were more compliant than control and taste subjects at the 0.01 level of significance; the taste plus self-monitoring subjects were superior to the taste and control at the 0.05 level of significance.

During Treatment II, the subjects that were provided response cost, independent of their treatment histories, showed marked improvement in compliance. Also, the taste plus self-monitoring groups appeared to improve over time, while the self-monitoring group decreased and the taste and control group remained unchanged. A two-factor, repeated measures on one-factor ANOVA for the Treatment II data showed a significant Group effect, $F(7, 32) = 8.30$, $p < 0.01$. The Group treatment means were then compared using Tukey's test for comparison among means. This analysis showed that subjects in the four response-cost groups and the taste plus self-monitoring group were significantly more compliant than subjects in the taste only and control group at the 0.05 level of significance. In addition, two of the response-cost groups were marginally superior to the self-monitoring group at the 0.10 significance level. The self-monitoring procedure, which was the best treatment during Phase II, was not durable and not significantly better than the taste or control procedures during Treatment II.

The extra-tablet measure was correlated with the compliance score during baseline, Treatment I, and Treatment II, and the correlations were -0.52 , -0.65 and -0.79 , each significant at the 0.01 level with 118 degrees of freedom.

Thus, the expected strong correlation between fewer extra pills and being compliant was observed. However, this correlation does not mean that extra pills is an equivalent measure of compliance to the phenazopyridine method, as the ANOVA's using extra-pills data were slightly different than when compliance scores were used. The ANOVA comparing baseline and Treatment I extra-pill data indicated significant Trials, $F(2, 36) = 10.76$, $p < 0.001$; and Phase X Trial, $F(2, 72) = 8.98$, $p < 0.001$ effects, but no Group effect. The ANOVA for extra pills in Treatment II did show a significant Group effect, $F(7, 32) = 3.98$, $p < 0.01$, similar to ANOVA on compliance scores. Duncan tests at the 0.05 significance level comparing treatment means indicated that all of the response-cost and the self-monitoring and taste plus self-monitoring groups were equivalent, and superior to the control and taste-only group in compliance. Thus, the results using pill counts during both Treatments were slightly different than results using the compliance scores.

DISCUSSION

The study was designed to evaluate several procedures for influencing compliance to medication regimens, as well as evaluating the potential for a new tracer technique measuring compliance. The treatment data indicated that the self-monitoring groups (self-monitoring and taste plus self-monitoring) in Treatment I were superior to the taste-only and the control groups. Subsequent implementation of response-cost procedures during Treatment II produced strong compliance for all subjects, independent of their history of noncompliance. These data replicate the results of Bigelow *et al.* (1976) and recommend the use of response-cost procedures. Also, the taste plus self-monitoring group appeared to improve over time, and the effects were statistically equivalent to the effects of response cost. Compliance of subjects in the self-monitoring group appeared to decelerate over time; however, these effects might be maintained by

greater attention to procedures that serve to increase the reactivity of self-monitoring (Kazdin, 1974).

The methodology developed to measure compliance was easily implemented and did not require laboratory analysis for assessment of compliance. A major advantage is that the measurement procedure provides a relatively continuous analysis of compliance, and is not subject to problems experienced when serum or urine tracers or analyses are used intermittently to assess compliance (Soutter and Kennedy, 1974). In addition, the system was inexpensive to implement, with the only costs being the initial preparation of the medicine. In clinical work, the cost of the medicine preparation may be absorbed by the patient. Discussions with local pharmacists indicate that these procedures could be used with many medicines, and Goodman and Gilman (1975) did not indicate negative side effects for formulating phenazopyridine with other medications.

The differences between measurement of compliance used in this study, and more traditional procedures such as tablet counts and periodic analysis of tracers or blood samples, makes comparison to other studies of compliance difficult. However, the 0 to 3 scoring system may be converted to a 0 to 100% compliance, assuming that scores of 0 to 3 are equivalent to 0 to 32% (0), 33 to 66% (1), 67 to 99% (2), and 100% (3), respectively. Conversion of the present compliance data to per cent compliance would show compliance rates of 80% for the subjects who were compliant during baseline and not included for further study, and compliance rates of 36% for noncompliant subjects during baseline who were continued. During Treatment II, the mean compliance of the 40 subjects who were provided response cost was 2.33, or 78%. Compliance of the taste plus self-monitoring group was 67%; compliance rates for the self-monitoring, taste, and control procedures were 49, 31, and 24% respectively. The per cent compliance of subjects in the response-cost procedures compares well to the criteria for

compliance of 80% established by Sackett *et al.* (1975).

The compliance measurement procedure used, however, may not be applicable to all subjects. It requires observation and recording of urinary discoloration, may be difficult to use with patients having irregular micturition, and may not effect compliance in patients that cannot monitor their behavior, as in some severely disabled psychiatric populations. A methodological concern at the outset of the present study was that the self-monitoring of urine discoloration that was a component of the compliance measurement might influence compliance. However, the results at the end of the baseline indicated that 79% of the population were noncompliant according to our compliance criteria. These data do not support the measurement procedure being particularly reactive.

A final measurement consideration involves the use of the taste procedure to measure fine-grained, tablet-by-tablet compliance. The scheduling of flavors could be compared to the self-reported intake to establish compliance for each individual dosage. In the present study, taste was used as a treatment to increase the saliency of taking medicine (Zifferblatt, 1975), but this technique could be easily adopted for accurate measurement of compliance.

In summary, the treatment data extend the use of response cost reported by Bigelow *et al.* (1976) to outpatient drug use. In addition, a new procedure for measuring ongoing compliance was presented. While these data on treatment and measurement are promising, they need to be replicated on other subject populations, for various disorders, and for longer durations until the strengths and limits of the procedures are well understood.

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