

Surreptitious Drug Use by Patients in a Panic Disorder Study

Duncan B. Clark, Ph.D., M.D., C. Barr Taylor, M.D.,
Walton T. Roth, M.D., Chris Hayward, M.D., M.P.H., Anke Ehlers, Ph.D.,
Jürgen Margraf, Ph.D., and W. Stewart Agras, M.D.

In a double-blind, placebo-controlled trial comparing alprazolam and imipramine for panic disorder, serum analysis revealed that a substantial proportion of the patients took explicitly prohibited anxiolytic medication. Excluding these patients changed the results.

(Am J Psychiatry 1990; 147:507-509)

While the psychological aspects of the placebo effect have been extensively analyzed and discussed (1) and surreptitious drug use has been noted in panic disorder research patients (2), the possibility that some placebo responders may be surreptitiously taking prohibited medications has not been addressed. When subjects' taking prohibited medications is acknowledged as a potential problem, experimenters usually rely on the patients themselves to report their use of these medications (3). The purpose of this study was to determine, by serum analysis, the frequency of surreptitious medication use in a placebo-controlled drug trial for panic disorder, to characterize patients who took prohibited medication, and to test whether or not inclusion of these patients changed the results. A more detailed report of the results with regard to cardiovascular side effects and clinical outcome is in press (4).

METHOD

Seventy-nine outpatients were recruited through the mass media to participate in a study comparing pharmacologic treatments for panic disorder. The mean \pm SD age of the patients was 35.1 ± 9.2 years; 21 (27%) were male and 58 (73%) were female. They were given the Structured Clinical Interview for *DSM-III* (5), medical histories were taken, and physical examinations, routine blood and urine tests, and thyroid func-

Presented at the 142nd annual meeting of the American Psychiatric Association, San Francisco, May 6-11, 1989. Received May 15, 1989; revision received Aug. 15, 1989; accepted Sept. 18, 1989. From the Department of Psychiatry, Stanford University Medical Center, Stanford, Calif. Address reprint requests to Dr. Clark, Western Psychiatric Institute and Clinic, University of Pittsburgh, 3811 O'Hara St., Pittsburgh, PA 15213-2593.

Supported by NIMH postdoctoral research training grant MH-16744 and a grant from the Upjohn Company.

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tion tests were performed. Patients were eligible for the study if they had at least some spontaneous panic attacks, had panic attacks with four symptoms occurring during an attack, or had had at least one panic attack each week for the past 3 weeks. Patients were excluded if they had diagnoses of primary affective disorder, alcohol or drug abuse, psychosis, or obsessive-compulsive disorder or if they were acutely suicidal, pregnant, or lactating or had a significant medical disorder. The procedures for the study were fully explained, and informed consent was obtained.

All patients were asked to be drug free for at least 2 weeks before baseline assessment and to take only prescribed study medication during treatment. Blood samples were taken and clinical measures were obtained for all patients at baseline and after 4 and 8 weeks of treatment. The serum analyses were for imipramine, desmethylimipramine, diazepam, desmethyldiazepam, and alprazolam; the results were available after all patients had completed the study.

Panic attacks and phobic avoidance were selected as the primary outcome measures. The mean number of panic episodes per week was determined from patient diaries and included anticipatory, situational, spontaneous, and limited-symptom panic attacks (6). A clinical measure of phobic avoidance was derived from questions from the Marks-Matthews Fear Inventory (7), with two added items (i.e., feeling trapped or caught in closed places and fear of being left alone). Data on a variety of other clinical measures were also collected.

Of the 79 patients beginning treatment, 26 were randomly assigned to placebo, 27 to imipramine, and 26 to alprazolam. Medications were dispensed in identical capsules of placebo, alprazolam (1 mg), or imipramine (30 mg). Medication was increased until patients were free of panic attacks, suffered from unpleasant side effects, or were taking 10 tablets per day. The average daily doses of medications at the end of 8 weeks of treatment were 3.7 (range = 1-8) mg of alprazolam and 147 (range = 30-270) mg of imipramine.

RESULTS

At baseline 17 (22%) of the 79 patients were found by serum analysis to have measurable blood levels of

TABLE 1. Study Completion Rates and Changes in Symptoms of 79 Panic Disorder Patients Who Did or Did Not Comply Fully With Their Prescribed Regimens in an 8-Week Drug Trial

Condition	Completers ^a		Change in Number of Panic Attacks per Week ^b		Change in Avoidance Score ^c	
	N	%	Mean	SD	Mean	SD
Noncompliers included in analysis						
Placebo (N=26)	20	77	-3.3	10.9	-3.2	4.0
Imipramine (N=27)	22	81	-5.9	4.5	-4.9	6.5
Alprazolam (N=26)	24	92	-7.5	7.4	-4.2	4.0
Noncompliers excluded from analysis						
Placebo (N=26)	15	58	0.4	11.7	-2.8	4.4
Imipramine (N=27)	17	63	-5.6	4.1	-5.4	7.0
Alprazolam (N=26)	23	88	-7.7	7.5	-4.5	4.1

^aFour patients with very low serum levels of prohibited medication at baseline and no other violations of the protocol were included here as completing the study. When noncompliers were included, there were no significant differences between conditions ($\chi^2=2.4$, df=1, n.s.); when noncompliers were excluded, there was a significant difference between the alprazolam condition and the imipramine and placebo conditions ($\chi^2=6.7$, df=1, p<0.05).

^bActive medication was compared with placebo by one-tailed t test. When noncompliers were included, there were no significant differences between conditions ($F=1.5$, df=2, 62, n.s.); when noncompliers were excluded, there were significant differences between conditions ($F=4.3$, df=2, 48, p<0.02); for imipramine versus placebo, $t=1.92$, df=27, p<0.05; for alprazolam versus placebo, $t=2.52$, df=33, p<0.01.

^cWhen noncompliers were included, there were no significant differences between conditions ($F=0.6$, df=2, 53, n.s.); when noncompliers were excluded, there were again no significant differences between conditions ($F=0.8$, df=2, 40, n.s.).

prohibited medication. Twelve had serum that was positive for diazepam and/or desmethyldiazepam, two for alprazolam, and three for desmethylimipramine. These serum-positive patients showed significantly higher phobic avoidance scores at baseline than the patients who were serum negative (mean \pm SD=12.0 \pm 5.6 and 7.9 \pm 6.0, respectively; $t=2.39$, df=71, p<0.02) but were not significantly different on frequency of panic attacks (9.0 \pm 5.2 and 7.3 \pm 6.0, respectively; $t=1.04$, df=77, n.s.). Of these 17 patients, five dropped out of the study and eight used prohibited medication while completing the study. The remaining four patients had either very low serum levels of diazepam and desmethyldiazepam (<100 ng/ml; N=3) or a low serum level of desmethyldesipramine (25.1 ng/ml; N=1) and otherwise completed the study without violating the protocol. Thus, only 24% (four of 17) of the serum-positive patients completed the protocol without using prohibited medication, a significantly smaller percentage than the 84% (N=52) of the 62 patients who were serum negative at baseline ($\chi^2=20.5$, df=1, p<0.0001).

During treatment, six patients in the placebo condition, four in the imipramine condition, and one in the alprazolam condition took prohibited medication. All but one of these patients completed the study. Of the patients assigned to the placebo condition, one patient had serum that tested positive for alprazolam, two for tricyclics, and two for both desmethyldiazepam and tricyclics. One placebo patient had serum that was positive for desmethyldiazepam at week 4 but dropped out before completing the study. Of those assigned to the imipramine condition, four patients had serum that tested positive for desmethyldiazepam. One patient assigned to the imipramine group had a serum imipramine level of zero and was therefore also considered to have violated the protocol. Of the patients assigned to

alprazolam, one patient had serum that was positive for desmethyldiazepam.

The results of the study, including and excluding noncompliant patients, are presented in table 1. For this analysis, patients whose serum tested positive for prohibited medication at baseline and/or during treatment and one patient who did not take the prescribed medication (i.e., whose imipramine level was zero) were considered to be "noncompliers" except where noted. When noncompliant patients were included, there were no significant differences between drug conditions in completion rate, change in frequency of panic attacks, or change in phobic avoidance. When treatment noncompliers were excluded, the completion rate was significantly lower for patients taking placebo and imipramine than for those taking alprazolam. Excluding all noncompliant patients, those in the imipramine and alprazolam conditions showed greater change in panic attack frequency than those taking placebo, but there were no significant differences in change in phobic avoidance. Four of the five placebo patients who completed the study while taking prohibited medication reported that they had no panic attacks at the endpoint of treatment.

DISCUSSION

A rather large proportion of patients in this study (i.e., 20 of 79 patients, or 25%) had serum that tested positive for prohibited medication during the "drug-free" baseline period and/or during the time they were supposed to be taking the assigned study medications. In four of these cases, it is possible that the patients discontinued medications as directed and, because of the relatively long half-lives of desmethyldiazepam (30–200 hours) (8) and desmethylimipramine (14–62 hours) (8), still had detectable levels of these active

metabolites. On the other hand, some patients may have taken alcohol, illicit drugs, or prescription medications other than those tested. Baseline noncompliers had more severe phobic avoidance than compliers and may have been reluctant to discontinue needed anxiolytic medication. Other patients may have found their study medication ineffective and therefore believed it necessary to add to their treatment.

This result suggests that the placebo response seen in some subjects in panic disorder research (9) may result from undetected surreptitious drug use. In our study, use of prohibited medication was apparently less important in the active medication conditions, as there was little impact in these groups on treatment outcome. Because only panic disorder patients were included, the findings cannot be generalized to research concerning other psychiatric disorders. Nevertheless, these results suggest that screening of urine or serum for relevant medications is necessary during all drug trials and that researchers should insist that patients have negative drug screens before being assigned to treatment conditions. Most of the patients who were serum positive at baseline either dropped out or continued to take prohibited medication throughout the study, indicating that in future studies it may be necessary to exclude some patients. However, noncompliance may be lessened if patients are aware that they are being monitored. The elimination of surreptitious drug

use by research patients would remove an important uncontrolled variable and, therefore, might allow researchers to conduct studies with smaller sample sizes.

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