

residents were each identified and openly discussed.

At one point the group focused on the new head nurse, citing her inability or unwillingness to structure ward activities and make nursing assignments. In her response, she indicated the staff was using her as a scapegoat for their feelings of hostility toward me and the program. The residents also came under fire for their absences and their continued unwillingness to consider staff observations and feelings. Staff were surprised to learn that the residents were required to attend seminars and other activities that took them away from the ward. For their part, the residents at last were able to grasp that somehow they were ignoring staff concerns.

Finally, a key male nursing assistant, hitherto reticent, voiced the opinion that "There has to be something better than what we are doing. If we pull together on this thing, we can make it work." With that declaration, five different views subsequently emerged from members of the staff about how the goals set for the program might be achieved. It seemed at last that the staff were going to take a closer look at community mental health and invest themselves in the program.

Staff members representing each of the five views were named to an ad hoc committee responsible for developing a ward program that would work with minimal strain on our resources, setting, and staff. The plan eventually evolved into one that emphasized staff control of most administrative decisions. The therapeutic community, which had given patients the responsibility for making some of the decisions, was abandoned. Because the ward was an admissions ward, and thus had a high transiency rate, and admitted both men and women, it could not, at least in the hands of the current staff, be operated as a more democratic therapeutic community. A schedule of ward activities was drawn up, and times were carefully established in which the patients could talk with the residents. Regular early morning rounds with nursing personnel kept the residents briefed on the events of the previous night, and many problems were aborted, thus easing the burden of nursing.

With the doctors back in clearer administrative control, staff seemed to relax, resumed more accustomed and time-tested roles, and appeared to be satisfied with the new structure. Because they had played a major role in developing a workable plan for the ward, they no longer felt impotent in dealing with and deciding their destiny. Daily I sensed a new atmosphere on the ward, one of a sense of community, collective effort, and newly liberated energies. We had learned, as the nursing assistant had urged, to "pull together on this thing."

Discontinuation of Chemotherapy for Chronic Schizophrenics

ROBERT F. PRIEN, Ph.D.

*Research Psychologist
Central Neuropsychiatric Laboratory
Veterans Administration Hospital
Perry Point, Maryland*

JEROME LEVINE, M.D.

*Chief, Psychopharmacology Research Branch
National Institute of Mental Health
Chevy Chase, Maryland*

RICHARD W. SWITALSKI, M.S.

*Senior Scientist, Biometric Laboratory
George Washington University
Washington, D.C.*

CONCERN ABOUT prolonged use of tranquilizing drugs has increased in recent years. Reports on oculocutaneous changes, persistent dyskinesia, and sudden deaths have focused attention on the potential dangers of prolonged ataractic treatment. There is also concern that long-term medication may contribute to institutionalization by reducing the chronic patient's drive, initiative, and planning ability.

Unfortunately the literature provides no consistent guidelines regarding withdrawal of tranquilizing drugs. Although a few studies report relatively low relapse rates of 20 to 25 per cent, most report significant regression in at least 40 per cent of the

Dr. Prien was formerly project coordinator of the NIMH psychopharmacology research branch collaborative studies on chronic schizophrenia at the biometric laboratory at George Washington University.

patients.⁹ Two large studies report relapse rates of more than 70 per cent.^{10, 11} However, it is obvious from the studies that some proportion of chronic schizophrenics are deriving no benefit from tranquilizing medication, although the percentage varies considerably among studies.

Efforts to identify patients who can tolerate long periods off medication have been largely unsuccessful. Length and severity of illness, duration of chemotherapy, and type of psychosis have been mentioned as possible predictors of relapse, but their significance has not been confirmed.

The investigation reported here was an attempt to identify subgroups of chronic schizophrenics with sufficiently low probability of relapse to warrant discontinuation of medication. Major emphasis was placed on the possible predictive value of such variables as length of hospitalization, age, severity of illness, and type and dose of previous medication.

The investigation of drug discontinuation was part of a multi-hospital collaborative project on the relative effectiveness of various dose levels of

phenothiazines in the treatment of chronic schizophrenia. The project was developed under the psychopharmacology program of the National Institute of Mental Health, and funded by Public Health Service grants. It consisted of two separate studies, both of which have been published elsewhere. The first study investigated the effectiveness of high doses of chlorpromazine,¹² and the second study the efficacy of high doses of trifluoperazine.¹³

FOR THE FIRST STUDY 60 men and 60 women were chosen from each of seven public mental hospitals, making a total sample of 840 patients. Criteria for selection were a primary diagnosis of schizophrenia, age between 19 and 55, continuous hospitalization for at least two years, and no evidence of organic brain disease, prefrontal lobotomy, mental deficiency, or medical conditions contraindicating the use of high doses. The upper age limit was established because of the possible toxic effects of high-dose therapy in elderly patients. The mean age of the patients selected was 41.6 years; 61 per cent were over 40 years. Length of hospitalization ranged from two to 34 years, with a mean of 14.5 years.

The patients were randomly assigned to one of four groups; each consisted of approximately 210 patients, 30 from each of the seven hospitals participating. Those in the first group were given a high dose, 2000 mg. of chlorpromazine per day; in the second, a low dose, 300 mg. of chlorpromazine per day; in the third, a placebo; and in the fourth, the physician's choice of medication, in whatever dose he chose to administer.

Patients were first observed in their normal hospital treatment for eight weeks. At the end of that baseline period, patients who had been assigned to high dose, low dose, and placebo were shifted to those medications. All medications were administered in liquid form under double-blind conditions. The study period was 24 weeks.

The clinical status of each patient was assessed in two ways. First, psychiatrists made over-all judgments of degree of improvement on the Global Change Scale, a seven-point scale devised for the studies that compared the patient's clinical condition during treatment with his previous condition. Second, specific psychopathology was rated by psychiatrists, nurses, and social workers. All patients were

⁹ H. L. Blackburn and J. L. Allen, "Behavioral Effects of Interrupting and Resuming Tranquilizing Medication Among Schizophrenics," *Journal of Nervous and Mental Disease*, Vol. 135, October 1961, pp. 303-308.

¹⁰ Eugene M. Caffey, Jr., Leon S. Diamond, Thomas V. Bank, Joseph C. Grasberger, Louis Herman, C. James Klett, and Charles Rothstein, "Discontinuation or Reduction of Chemotherapy in Chronic Schizophrenics," *Journal of Chronic Diseases*, Vol. 17, April 1964, pp. 347-358.

¹¹ Leslie S. Freeman and Eli Alson, "Prolonged Withdrawal of Chlorpromazine in Chronic Patients," *Diseases of the Nervous System*, Vol. 23, September 1962, pp. 522-525.

¹² Sol L. Garfield, Samuel Gershon, Ivan Sletten, Harry M. Marder, and Elizabeth Ferrell, "Withdrawal of Ataractic Medication in Schizophrenic Patients," *Diseases of the Nervous System*, Vol. 27, May 1966, pp. 321-325.

¹³ W. W. Good, Mac Sterling, and Wayne H. Holzman, "Termination of Chlorpromazine With Schizophrenic Patients," *American Journal of Psychiatry*, Vol. 115, November 1958, pp. 442-448.

¹⁴ S. Hughes and J. Crawford Little, "An Appraisal of the Continuing Practice of Prescribing Tranquilizing Drugs in Long-Stay Psychiatric Patients," *British Journal of Psychiatry*, Vol. 113, August 1967, pp. 867-873.

¹⁵ Charles Rothstein, "An Evaluation of the Effects of Discontinuation of Chlorpromazine," *New England Journal of Medicine*, Vol. 262, January 14, 1960, pp. 67-69.

¹⁶ C. B. Whitaker and R. M. Hoy, "Withdrawal of Perazine in Chronic Schizophrenia," *British Journal of Psychiatry*, Vol. 109, March 1963, pp. 422-427.

¹⁷ William W. Zeller, Paul N. Graffagnino, Chester F. Culbertson, and Herman Rietman, "Use of Chlorpromazine and Meprobamate in the Treatment of Emotional Disorders," *Journal of the American Medical Association*, Vol. 160, January 21, 1955, pp. 179-185.

¹⁸ Leopold N. Judah, Zelia M. Josephs, and O. D. Murphree, "Results of Simultaneous Withdrawal of Ataraxics in Chronic Psychotic Patients," *American Journal of Psychiatry*, Vol. 118, August 1961, pp. 156-158.

¹⁹ Gordon W. Olson and Donald B. Peterson, "Sudden Withdrawal of Tranquilizing Drugs From Chronic Psychiatric Patients," *Journal of Nervous and Mental Disease*, Vol. 131, December 1960, pp. 252-255.

¹² Robert F. Prien and Jonathan O. Cole, "High Dose Chlorpromazine Therapy in Chronic Schizophrenia," *Archives of General Psychiatry*, Vol. 18, April 1968, pp. 482-495.

¹³ Robert F. Prien, Jerome Levine, and Jonathan O. Cole, "High Dose Trifluoperazine Therapy in Chronic Schizophrenia," *American Journal of Psychiatry*, Vol. 126, September 1969, pp. 305-313.

evaluated just before the study and at eight-week intervals during the study. Patients terminated before the end of 24 weeks were evaluated at the time they left the study. A patient was considered relapsed if he regressed and had to be returned to prestudy medication before the end of the 24 weeks. The decision to terminate study medication was made jointly by the principal investigator and the treatment physician.

THE SECOND STUDY was conducted at six of the seven hospitals that had participated in the first study. Essentially the same design was used; the major difference was that the second study did not include a physician's-choice group. The 360 study patients were randomly assigned to one of three groups, each consisting of approximately 120 patients, 20 from each hospital. The high-dose group received 80 mg. of trifluoperazine per day, the low-dose group 15 mg. of trifluoperazine per day, and the third group a placebo. The mean age of the study group was 41.8 years, with 60 per cent over 40 years of age. Length of hospitalization ranged from two to 33 years, with a mean of 15.1 years.

In both studies, the placebo group had a significantly higher relapse rate than the groups receiving active medication. In the first study, 37 per cent of the patients on placebo relapsed, compared with only 13 per cent of the patients on low dose and 6 per cent of the patients on high dose. In the second study, relapse occurred in 50 per cent of the placebo group, 18 per cent of the low-dose group, and 15 per cent of the high-dose group. Chi-square analyses showed that the differences between the relapse rate of the placebo group and that of each of the other groups were significant at the .05 level.

Relatively few relapses, 12 per cent, occurred during the first five weeks on placebo. Most relapses, 73 per cent, occurred between the sixth and 16th weeks. Relapse was usually characterized by recurrence of hallucinations, delusions, and confusion, or by disruptive symptoms such as extreme hostility, excitement, and threatening or destructive behavior.

Analyses were conducted to determine whether the relapse rate of patients on placebo differed significantly among different subgroups of patients. The patients were grouped on the basis of a large number of variables including length of hospitalization, current age, age at onset of illness, severity and type of prestudy symptomatology, and dose and type of prestudy medication. Analysis was in the form of a sex-by-subgroup factorial design, with frequency of relapse as the criterion measure.

Relapse was found to be significantly related to

the dose of tranquilizing medication the patient was receiving before he was put on placebo—the higher the dose, the greater the probability of relapse. Table 1 shows the relapse rate for patients on low, moderate, and high doses of prestudy tranquilizing medication; all doses were converted to equivalent doses of chlorpromazine. In the first study, only 13 per cent of the patients on low prestudy doses relapsed when medication was discontinued, compared with 48 per cent of the patients on moderate doses and 59 per cent on high doses. The corresponding relapse rates in the second study were 32 per cent for low prestudy doses, 58 per cent for moderate prestudy doses, and 78 per cent for high prestudy doses.

In both studies, the difference in relapse rate between low dose and each of the other dose levels was significant at the .05 level. There was no significant difference between moderate and high dose levels. Table 1 also shows relapses by patients who received no tranquilizing medication before the study; in that subgroup, only one patient in each study failed to complete the 24 weeks on placebo.

In the first study, the relapse rates for the different prestudy dose levels were analyzed by hospital. In all but one of the seven hospitals, patients on low doses of prestudy medication had a lower relapse rate on placebo than patients on moderate or high doses. The incidence of relapse for patients on low prestudy doses was relatively low at each hospital, ranging from 13 to 25 per cent. However, the relapse rate for patients on moderate to high prestudy doses varied considerably between hospitals, ranging from 10 to 76 per cent. The possible explanation for that finding and its implications are discussed elsewhere.¹⁴ The sample in the second study was too small to permit a detailed analysis by hospital.

PROBABILITY OF RELAPSE was also related to length of current hospitalization. Table 2 gives relapse rates by length of hospitalization and dose of prestudy medication. Patients classified as long-stay had been hospitalized more than 15 years, and short-stay patients for less than 15 years. The table shows that long-stay patients on low doses of prestudy medication had a very low incidence of relapse. Only 15 per cent in the first study and 13 per cent in the second study were unable to complete the 24 weeks on placebo. In the first study, short-stay patients on low prestudy doses also had a low relapse rate, 23 per

¹⁴ Robert F. Prien, Jonathan O. Cole, and Naomi L. Belkin, "Relapse in Chronic Schizophrenics Following Abrupt Withdrawal of Tranquilizing Medication," *British Journal of Psychiatry*, Vol. 115, June 1969, pp. 679-686.

However, the same subgroup in the second study had a relapse rate of 47 per cent. In the other subgroups the proportion of relapsed patients ranged from 49 to 69 per cent.

Clinical deterioration was noticed in some patients on placebo who were not classified as relapsed. Approximately 12 per cent of the patients in the first study and 15 per cent in the second study regressed, though not severely enough to warrant resumption of prestudy medication. Regression was determined by the results shown on the Global Change Scale at the 24th week. Table 3 shows the percentage of patients in the placebo groups who were able to complete 24 weeks on placebo with no signs of regression. Again, long-stay patients receiving low prestudy doses showed relatively little regression when medication was withdrawn. Eighty per cent of the subgroup in the first study and 73 per cent in the second study showed no clinical deterioration after 24 weeks on placebo. The incidence of regression was relatively high in the other subgroups.

In the second study, the Global Change Scale was completed by the ward nurse as well as by the

TABLE 1
Relapses on Placebo
by Daily Dose of Prestudy Medication¹

	Study 1			Study 2		
	N on placebo	Relapses N	%	N on placebo	Relapses N	%
No medication	20	1	5	10	1	10
Under 300 mg.	65	12	18	34	11	32
300 to 500 mg.	60	29	48	31	18	58
Over 500 mg.	54	32	59	27	21	78

¹All doses were converted to equivalent doses of chlorpromazine.

TABLE 2
Relapses on Placebo by Daily Dose of Prestudy
Medication and Length of Hospitalization

		Study 1		Study 2	
		N	Re-lapses	N	Re-lapses
Under 300 mg.	Under 15 years	26	23%	19	47%
	Over 15 years	39	15%	15	13%
300 mg. and over	Under 15 years	73	56%	35	69%
	Over 15 years	41	49%	23	65%

TABLE 3

Percentage of Patients on Placebo Who Completed 24 Weeks With No Deterioration, by Daily Dose of Prestudy Medication and Length of Hospitalization

		Study 1	Study 2
Under 300 mg.	Under 15 years	58%	32%
	Over 15 years	80%	73%
300 mg. and over	Under 15 years	33%	14%
	Over 15 years	34%	22%

psychiatrist. Those ratings are particularly meaningful, because ward personnel are usually the first to notice negative changes in patients. Agreement between the psychiatrists and nurses was good; 32 per cent of the patients completing the 24th week were rated worse by the psychiatrists, compared with 30 per cent rated worse by the nurses.

The results indicate that the large majority of schizophrenics who have been hospitalized for more than 15 years and who are receiving low doses of tranquilizing medication can remain off drugs for six months without deleterious effects. That suggests drug discontinuation is a feasible treatment policy for long-stay patients who are receiving low doses of ataractic medication.

Long-stay patients on low prestudy doses of medication accounted for only about a fifth of the patients in both studies. However, both studies had an upper age limit of 55; more than a third of the patients between 50 and 55 were long-stay patients who had received low doses of prestudy medication. Had the studies included older schizophrenics, between age 56 and 65, for example, the proportion of patients in this subgroup might have been considerably higher.

Short-stay patients and patients receiving moderate or high doses showed relatively high relapse rates when drugs were discontinued. Probability of relapse appears too high to commend long-term drug withdrawal as a treatment policy for those groups of patients. It does not necessarily mean that these patients require all the medication they are receiving; many could possibly tolerate lower doses. That was illustrated in Study 1, where one of the treatment groups received 300 mg. of chlorpromazine per day. Most of the patients who had been receiving from 350 to 600 mg. of chlorpromazine before the study showed no significant regression on the 300 mg. dose. That finding suggests that public mental hospitals should pay more attention to determining the minimum dosage required by chronic schizophrenics. A workable dose-reduction program could result in sizable financial savings for the hospital and less risk of toxicity for the patient.