3

Int. Pharmacopsychiat. *13:* 100–111 (1978)

Are There Schizophrenics for Whom Drugs May be Unnecessary or Contraindicated?[1]

Maurice Rappaport, H. Kenneth Hopkins, Karyl Hall, Teodoro Belleza and Julian Silverman

Langley Porter Neuropsychiatric Institute, University of California, San Francisco, Calif.

Key Words. Schizophrenia · Antipsychotic medication utilization

Abstract. This study reports that there are schizophrenics who do relatively well long term without the routine or continuous use of antipsychotic medication. Specially selected young males undergoing an acute schizophrenic episode were followed, after hospitalization, for up to three years. While hospitalized they were assigned randomly to either placebo or chlorpromazine treatment. Many unmedicated-while-in-hospital patients showed greater long-term improvement, less pathology at follow-up, fewer rehospitalizations and better overall function in the community than patients who were given chlorpromazine while in the hospital. Factors related to post-hospital outcome were good premorbid history and short-lived paranoid characteristics. Considerations which may have an effect on the successful management of acute schizophrenic patients not on medication are mentioned. The findings underline the need for further study of how to utilize antipsychotic medication more selectively in the treatment of schizophrenia.

For most patients diagnosed as schizophrenic, antipsychotic medication is the treatment of choice. Several reports have indicated, however, that some patients do better or get along quite well long term without the use of antipsychotic medication (*Sullivan,* 1953; *Menninger,* 1959; *Perry,* 1962, 1976; *Dabrowski and Aronson,* 1964; *Goldberg et al.,* 1965; *Lehman,* 1967; *Mosher et al.,* 1974; *Silverman,* 1974; *Rappaport,* 1978). Other reports indicate that phenothiazines may have less than helpful effects on some patients (*Hartlage,* 1964; *Goldstein,* 1970; *Magaro and Vojtisek,* 1971).

[1] This research was supported primarily by the California Department of Mental Hygiene, Agnews State Hospital and the National Institute of Mental Health (Grant MH 16445). Additional support was obtained from the Wickes Foundation and Esalen Institute.

In this study clinical outcome was examined in young hospitalized patients after the onset of an acute schizophrenic episode and for up to three years after discharge. Of particular interest was the examination of patients who were off antipsychotic medication at follow-up but who, while hospitalized, had been assigned randomly to either a placebo or chlorpromazine medication condition.

Subjects, Procedures and Measures

Data are reported on 80 young male acute schizophrenics admitted to Agnews State Hospital (San Jose, California). Patients selected for the project met the following criteria: they were between 16 and 40 years old; they were referred from the community mental health program with a diagnosis of schizophrenia and also diagnosed independently as having an acute schizophrenic reaction at admission when examined by the hospital psychiatrist (who was not directly associated with the project) and by research personnel who evaluated patients using the Brief Psychiatric Rating Scale and a Global Assessment Scale; they had no serious adverse reaction to chlorpromazine; they had undergone no electroshock therapy within six months preceding admission; they had no gross organic impairment; they had no history of epilepsy; they had no known history of drug abuse immediately prior to admission; and they had no or few previous hospitalizations.

When a patient was accepted for the project he was assigned randomly to either a placebo or chlorpromazine condition. Over 80% were between 16 and 25 years of age, the two oldest patients were 38. Seventy-four percent had one or no previous hospitalization. Most were single and unemployed (83% and 57%, respectively).

Patient Assessment

At admission a patient received a physical and mental status examination. On that day, or the following two, trained research personnel also interviewed each patient and completed a modified form of the Brief Psychiatric Rating Scale (BPRS) by *Overall and Gorham* (1962), a Global Assessment (GA) Rating Scale, a premorbid history form based upon *Kantor*'s Process–Reactive Criteria (1966) and a paranoid-nonparanoid form based upon the *Venables and O'Connor* scale (1959). At discharge and at follow-up the administration of the BPRS and GA scales was repeated.

A composite measure based primarily on elements of the BPRS was designated as the experimental measure of severity of illness (SI). Elements of the BPRS were grouped to reflect thought disturbance, emotional disturbance, and functional disturbance. These three scores were combined with a global assessment rating (GA) to yield an overall SI score that ranged between 1 and 7 representing no disturbance to extremely severe disturbance.

A clinical change index (CI) was also used. It reflects change in clinical status over time obtained by recording improvement or worsening (as a plus or minus score respectively) that occurred between admission and discharge from the project as well as between admission and last follow-up contact. Direction of change was recorded for each measure and divided

by the number of measures available. This yielded scores ranging between +1.00 (improved on all items) through 0.00 (no change) to −1.00 (worse on all items).

Medication

All patients took nine tablets a day (three, three times a day). Those assigned to the chlorpromazine condition received a minimum of 300 mg a day. The physician could order up to 900 mg of chlorpromazine a day but he and the nursing staff remained blind as to whether the patient was receiving medication or placebos.

Follow-up

Follow-up measures consisted of BPRS and GA ratings obtained, whenever possible, at 1, 3, 6, 12, 18, 24, 30 and 36 months after discharge from the hospital portion of the project. Ratings were made by a trained research assistant who was unaware as to what the patient's medication condition was while he was hospitalized. A patient's medication status at follow-up was determined by asking the patient what medication he was on at the time he was being interviewed and also by checking his medication usage with a significant other if one was available.

Results

In this study it was not possible to control patient behavior or medication usage following discharge from the hospital. Since effect of medication was of paramount interest, patients were divided into four groups based on the medication condition randomly assigned while in the hospital and on the medication condition found at last follow-up contact. These four groups were designated as: PL-Off (i.e., *pl*acebo condition in the hospital and *off* anti-psychotic medication at last follow-up contact) and, similarly, CPZ-Off, PL-On, and CPZ-On, where CPZ refers to chlorpromazine.

These patient groupings reflected post-hospital medication utilization to the following extent: 39 (of 80) were found to be on major tranquilizer medication at last follow-up contact and reported being on such medication 65% of the time at previous contacts. Similarly, 41 patients found off medication at last follow-up contact reported they were off 71% of the time at previous contacts.

Admission

At admission SI scores were not significantly different for the four groups of patients. The four groups were similar in terms of age, education levels, marital status and employment status prior to admission.

Discharge

All groups, except the PL-On group, showed significant clinical improvement, using the CI score, between admission and discharge. In addition, chlorpromazine patients showed significantly less severity of illness than placebo patients ($t = 1.866$, $p < 0.05$, one-tailed). Analysis of functional disturbance scores did not reveal any significant differences.

Length of hospital stay also was not significantly different for patients assigned to chlorpromazine and placebo (means of 42.2 vs. 45.0 days respectively).

Follow-up

PL-Off patients had significantly lower SI scores (M = 1.74, SD = 0.863, N = 25) than did the CPZ-Off group (M = 2.79, SD = 1.788, N = 17), the PL-On group (M = 3.54, SD = 1.640, N - 17) and the CPZ-On group (M = 3.51, SD

Table I. Degree of improvement (CI scores[1]) between admission to the hospital project and last follow-up contact broken down by hospital/follow-up drug conditions, premorbid history and paranoid-nonparanoid status at admission

Drug status in hospital at FU		All pts.	Premorbid history		Diagnosis	
			good	poor	paranoid	nonparanoid
PL[2] – Off	M	0.92	0.92	0.92	0.98	0.85
	SD	0.164	0.177	0.098	0.055	0.205
	N	24	19	5	12	12
CPZ – On	M	0.48	0.74	0.11	0.53	0.45
	SD	0.668	0.460	0.743	0.566	0.728
	N	22	13	9	9	13
PL – On	M	0.29	0.26	0.32	–0.10	0.42
	SD	0.704	0.757	0.653	0.714	0.655
	N	17	8	9	4	13
CPZ – Off	M	0.52	0.57	0.40	0.47	0.64
	SD	0.669	0.687	0.607	0.639	0.720
	N	17	12	5	12	5

[1] CI scores based upon BPRS and Global Assessment changes between Day 2 and last follow-up contact. Scores ranged between –1.00 and +1.00, where –1.00 indicates worsening on all measures, 0.00 – no overall worsening or improvement and +1.00 indicates improvement on all measures.

[2] PL – placebo; CPZ – chlorpromazine.

Table II. t-test comparison between groups of schizophrenics shown in table I with different combined hospital/follow-up drug conditions

Drug group comparisons		All patients	Premorbid history				Diagnosis				
			df	good	df	poor	df	par.	df	non-par.	df
1. PL-Off	vs. CPZ-On	3.040***	44	1.492	30	2.243*	12	2.606**	19	1.799	23
2. PL-Off	vs. PL-On	4.090***	39	3.411***	25	1.884	12	4.875***	14	2.231*	23
3. PL-Off	vs. CPZ-Off	2.755***	39	2.048*	29	1.692	8	2.676**	22	0.885	15
4. CPZ-On	vs. PL-On	0.829	37	1.705	19	−0.604	16	1.576	11	0.110	24
5. CPZ-On	vs. CPZ-Off	−0.162	37	0.710	23	−0.687	12	0.234	19	−0.479	16
6. PL-On	vs. CPZ-Off	−0.921	32	0.883	18	−0.203	12	−0.567	14	−0.598	16

*p < 0.05. **p < 0.02. ***p < 0.01.

= 1.632, N = 21). t-tests were all significant at the $p < 0.02$ level, or better. Differences in SI scores between the latter three groups were not significant.

Clinical change (CI scores) between admission and follow-up were also examined for all four groups of patients and, in addition, scores were examined in terms of premorbid history and paranoid-nonparanoid diagnoses at admission. These data are shown in table I; t-tests of comparisons between groups appear in table II. The PL-Off group showed improvement that was significantly greater than that for the CPZ-Off group, the CPZ-On group and the PL-On group ($p < 0.001$ in all comparisons). Patients who accounted for the difference between the PL-Off and the CPZ-Off groups are those who showed good premorbid histories and paranoid characteristics at admission. No comparable differences were found between the PL-On and CPZ-On groups.

It was observed that 40% of patients at admission showed paranoid characteristics. At discharge and at last follow-up contact 20% and 18% respectively, showed paranoid characteristics.

Rehospitalization data are shown in table III. Those in the PL-Off group had the fewest rehospitalizations (8%); this can be compared with those in the CPZ-Off group where more individuals experienced rehospitalizations (47%). The chi-square analysis is significant as shown in table III. The PL-Off group of patients also showed fewer rehospitalizations than those either in the CPZ-On group (73%) or the PL-On group (53%). Chi-square also was significant when all placebo and all chlorpromazine patients were compared in terms of the numbers in each group that were rehospitalized ($\chi^2 = 8.425$, $p < 0.01$).

In terms of functional disturbance found at follow-up those in the PL-Off group showed less disturbance (M = 1.29, SD = 0.75, N = 24) than did those in

Table III. Rehospitalizations in relation to hospital/follow-up (FU) medication conditions

Medication group		Number of patients within each group that was rehospitalized		
in hosp.	At FU	n	patients rehospitalized	percent rehospitalized
PL	– Off	24	2	8
CPZ	– On	22	16	73
PL	– On	17	9	53
CPZ	– Off	17	8	47

PL-Off vs. CPZ-Off: $\chi^2 = 6.129$; $p < 0.02$.
PL-On vs. CPZ-On: $\chi^2 - 1.342$; NS.

the CPZ-Off group (M = 2.12, SD = 1.54, N = 17). The difference between means is significant ($t = -2.221$, $df = 39$, $p < 0.05$). Differences in mean functional disturbance scores between the CPZ-Off, PL-On and the CPZ-On groups are not significant.

Type-of-living-situation at follow-up was examined in terms of whether an individual was living alone, with family, with friends, etc. No differences were found between those who had been assigned to placebos and those assigned to chlorpromazine while hospitalized.

Patient Attrition

The 80 patients in this study represented 63% of the total sample (127) studied while in the hospital. It was noted that during the follow-up period, there was a significantly larger attrition of subjects from the group assigned to placebo while in the hospital than the group assigned to chlorpromazine (45% vs 26%). It was recognized that the significant findings reported above pertaining to post-discharge differences in severity of illness, rehospitalizations and overall functional disturbance might represent biased results due to differential attrition. Consequently an analysis was performed in which attrition was equalized artifically by reducing the number of subjects in the chlorpromazine group with the worst follow-up SI scores on the assumption that patients lost from the placebo group might also have been those who had the worst scores. Nine patients in the chlorpromazine group had to be eliminated, four in the CPZ-Off group and five in the CPZ-On group. When tests of significance were repeated with the smaller sample size using the worst case assumption condition, significant differences were no longer found between the PL-Off (N-24) and CPZ-Off (N-13) groups in terms of either severity of illness, rehospitalizations or overall functional disturbance in the community although differences were in the same direction as before.

Discussion

This study indicates that among young acute schizophrenic males there are those who do well long term without initial or continuous use of phenothiazine medication. Patients in the Pl-Off group showed greater clinical improvement and less pathology at follow-up, fewer rehospitalizations and less overall functional disturbance in the community than the other groups of patients studied,

including matched patients in the CPZ-Off group. It should be kept in mind, however, that these results may possibly reflect a differential attrition rate bias.

These findings nevertheless are in general agreement with the observations of other clinicians and investigators. *Lehman* (1967), citing *Kraepelin,* noted that many dementia praecox and schizophrenic patients recovered without deterioration or major defect in an era before the discovery of antipsychotic medication. More recently *Judd et al.* (1973) and *Mosher et al.* (1974) as well as *Davis et al.* (1976) and *Rappaport* (1978) have reported results indicating that some unmedicated schizophrenics do as well or better than similar patients who are given antipsychotic medication. A considerable body of literature, however, stresses the finding that phenothiazines are effective in the treatment of most schizophrenias. In this study also, at least between admission and discharge, those who received chlropromazine showed a faster and greater symptom reduction that did those who received placebos. Also, more patients on placebos than on chlorpromazine became more symptomatic between admission and discharge. This suggests that for most patients antipsychotic medication is the treatment of choice early in the course of schizophrenia, particularly if one is interested in symptom reduction. Our findings suggest, however, that antipsychotic medication is not the treatment of choice, at least for certain patients, if one is interested in long-term clinical improvement. Caution must be used in withholding medication until adequate information is available which specifies for whom this course is clearly indicated.

Routine and continuous use of phenothiazines may be contraindicated for some schizophrenics for several reasons. A number of clinicians have suggested that the period immediately following an acute schizophrenic break is critical and that how a patient is treated during this time is quite important. The stormy phase of schizophrenia can be looked upon as an attempt at reorientation, at solving problems of living. *Boisen* (1942), for example, states that in the acute schizophrenic episode 'there lies a problem to be solved. . . . there is an attempt at reconstruction that may or may not succeed'. In order to solve these basic problems of living, the acute schizophrenic needs to retain his sensitivity and awareness and must have full access to all his psychological resources. Phenothiazines, by reducing neurological sensitivity, may interfere with these problem-solving, reintegrative responses. Reports by *Goldstein* (1970), *Magaro and Vojtisek* (1971), and *Rappaport et al.* (1971) as well as observations reported by *Hollister* (1964) and *Rappaport* (1978) indicate that there are negative phenothiazine effects such as decreased sensory and psychological sensitivity, decreased problem-solving ability and a decreased ability to learn (*Hartlage,* 1964).

In another article *Silverman* (1974) has put forward theoretical consider-

ations of why some patients may be poor candidates for phenothiazine treatment. He postulated that some psychotics who are hypersensitive to stimulation attenuate the intensity of strong incoming stimuli. During the acute episode, this responsiveness is used as a defensive maneuver to prevent becoming overwhelmed by environmental information. He further postulates that this input attenuation maneuver provides a protected 'space' within which problem-solving activities can be completed. Antipsychotic medication makes it physiologically difficult (sometimes impossible) to maintain this stimulus attenuation maneuver.

From present data it would appear that patients who may benefit from *not* receiving phenothiazine medication routinely and continuously are likely to be found at least among young males at the onset of their first or second acute schizophrenic episode. (No comments can be made about females, chronic schizophrenics or other subgroups of schizophrenics, since they were not included in the study.) These patients are also more likely to be found among those with good rather than poor premorbid histories (*Valliant et al.*, 1964; *Goldstein*, 1970; *McCabe et al.*, 1972; *Evans et al.*, 1973; *Zigler and Levine*, 1973; *Bromet et al.*, 1974; *Strauss and Carpenter*, 1977) and among those who show time-limited paranoid characteristics at the onset of their break.

With respect to paranoia our results indicate that of all patients not receiving chlorpromazine while in the hospital those rated as paranoid at admission were significantly more likely to remain off medication and to show the greatest clinical improvement. Other clinical observations and reports also suggest that some paranoid individuals do well off medication long term. For example, *Goldberg et al.* (1967), on the basis of their results, speculated that 'after five weeks of treatment one might predict that . . . the placebo effects on paranoid symptoms might equal or perhaps exceed drug effects'. *Kellam et al.* (1967) suggest 'that paranoid symptoms respond to placebo treatment . . . because these are learned behaviors and, therefore, can be unlearned. . .'. *Freedman et al.* (1967) found that paranoid schizophrenics most likely to show symptom reduction within three months were those who met two out of the following three criteria: showed low cognitive differentiation, displayed high social isolation, and displayed low oppositionalism. Paranoid ideation is frequently 'localized', that is, some paranoid individuals can function well except when circumstances intrude upon their area of paranoia. Functional deficits in the nonparanoid individual are usually more widespread. Consequently it seems reasonable to expect some paranoid individuals to show a better functional outcome than some nonparanoid individuals. Also, as suggested by our analysis, it is likely that at times of acute exacerbation of schizophrenia some individuals demonstrate only a short-lived type of paranoia (that is, a paranoid state rather than trait). The lack of persis-

tence of paranoid symptoms may be a clue to identifying those who can show marked and persistent long-term overall clinical improvement with the use of little or no phenothiazines.

How should patients be managed when phenothiazines or other antipsychotic medications are contraindicated? This may be answered in part by procedures employed in this study. It is believed to be important to establish a treatment milieu with carefully selected and trained personnel. These individuals must be able to tolerate bizarre behavior without routinely calling for medication, to regard the acute schizophrenic episode as a period in which there is an opportunity to reintegrate and to return to a better personal and interpersonal level of functioning, to remain supportive under difficult conditions, and to be ready and willing to give considerable time and attention to a patient as he goes through crisis. A more detailed description of the treatment milieu employed in this study has been presented elsewhere (*Rappaport et al.*, 1974).

It remains a challenge to find ways of identifying patients who do better long term off rather than on phenothiazines, even though they undoubtedly represent a minority of the schizophrenic population. If such patients could be identified it would improve our diagnostic capabilities and increase our ability to choose the most effective treatment for each patient. It would also very likely contribute to a reduction in the incidence of antipsychotic drug-induced complications (*Crane*, 1973). These considerations are particularly important in light of the development of community mental health programs where there is emphasis on routine and long-term use of phenothiazines as well as emphasis on brief hospitalization – perhaps too brief in some instances (*Glick*, 1974).

References

Boisen, A.: The form and content of schizophrenic thinking. Psychiatry *5:* 23–33 (1942).

Bromet, E.; Harrow, M., and Kasl, S.: Premorbid functioning and outcome in schizophrenics and nonschizophrenics. Archs. gen. Psychiat. *30:* 203–207 (1974).

Crane, G.: Clinical psychopharmacology in its 25th year. Science *181:* 124–128 (1973).

Dabrowski, J. and Aronson, J.: Positive disintegration (Little, Brown 1964).

Davis, J.M.; Gosenfeld, L., and Tsai, C.C.: Maintenance antipsychotic drugs do prevent relapse: A reply to Tobias and MacDonald. Psychol. Bull. *83:* 431–447 (1976).

Evans, J.; Goldstein, M., and Rodnick, E.: Premorbid adjustment, paranoid diagnosis and remission. Archs. gen. Psychiat. *28:* 666–672 (1973).

Freedman, N.; Cutler, R.; Engelhardt, D., and Margolis, R.: On the modification of paranoid symptomatology. J. Nerv. Ment. Dis. *144:* 29–36 (1967).

Glick, I.; Hargreaves, W., and Goldfield, M.: Short vs. long hospitalization. Archs. gen. Psychiat. *30:* 363–369 (1974).

Goldberg, S.; Klerman, G., and Cole, J.: Changes in schizophrenic psychopathology and ward behavior as a function of phenothiazine treatment. Br. J. Psychiat. *111:* 120–133 (1965).

Goldberg, S.; Schooler, N., and Mattson, N.: Paranoid and withdrawal symptoms in schizophrenia: differential symptom reduction over time. J. Nerv. Ment. Dis. *145:* 158–162 (1967).

Goldstein, M.: Premorbid adjustment, paranoid status and patterns of response to phenothiazine in acute schizohprenics. Schizophrenia Bull. *3:* 24–37 (1970).

Hartlage, L.: Effects of chlorpromazine on learning. Psychol. Bull. *64:* 235–245 (1964).

Hogarty, G.; Schooler, N., and Goldberg, S.: Drug and sociotherapeutic interactive effects on tenure and adjustment among outpatient schizophrenics. Paper presented at the American College of Neuropsychopharmacology meeting, Palm Springs, December (1973).

Hollister, L.: Adverse reactions to phenothiazines. J. Am. med. Ass. *189:* 311–313 (1964).

Judd, L.; Goldstein, M.; Rodnick, E., and Jackson, N.: Phenothiazine effects in good premorbid schizophrenics divided into paranoid-nonparanoid status. Archs. gen. Psychiat. *29:* 207–211 (1973).

Kantor, R.E. and Herron, W.G.: Reactive and process schizophrenia (Science and Behavior Press, New York 1966).

Kellam, S.; Goldberg, S.C.; Schooler, N.R.; Berman, A., and Shmelzer, J.: Ward atmosphere and outcome of treatment of acute schizophrenia. J. psychiat. Res. *5:* 145–163 (1967).

Lehmann, H.E.: The clinical features of schizophrenia; in *Freeman and Kaplan* Comprehensive textbook of psychiatry (Williams and Wilkins, Baltimore 1967).

Magaro, P. and Vojtisek, J.: Embedded figure performance of schizophrenics as a function of chronicity, premorbid adjustment, diagnosis and medication. J. abnorm. Psychol. *77:* 184–191 (1971).

McCabe, M.S.; Fowler, R.C.; Cadoret, R.J., and Winokur, G.: Symptom differences in schizophrenia with good and poor prognosis. Am. J. Psychiat. *128:* 10 (1972).

Menninger, K.: Toward a unitary concept of mental illness. A psychiatrist's world (Viking, New York 1959).

Mosher, L.R.; Mann, A., and Matthers, S.M.: Soteria: A new treatment for schizophrenia – one year follow-up data. Presented at the 51st annual meeting of the American Orthopsychiatric Association, San Francisco, April (1974).

Overall, J. and Gorham, D.: The brief psychiatric rating scale. Psychol. Rep. *10:* 799 (1962).

Perry, J.E.: The reconstitutive process in the psychopathology of the self. Ann. N.Y. Acad. Sci. *96:* 853–876 (1962).

Perry, J.E.: The roots of renewal in myths and madness (Josey-Bass, San Francisco 1976).

Rappaport, M.; Hopkins, H.K.; Hall, K., and Silverman, J.: Phenothiazine effects on auditory signal detection in paranoid and nonparanoid schizophrenics. Science *174:* 723–725 (1971).

Rappaport, M.; Hopkins, H.K.; Hall, K.; Belleza, T., and Silverman, J.: NIMH Final Report. Selective drug utilization in the management of psychoses. Grant No. MH 16445, March (1974).

Rappaport, M.: Are drugs more than palliative in the management of schizophrenia?; Ch. 5

in *Brady and Brodie* Controversy in Psychiatry (Saunders & Co., Philadelphia, 1978).

Silverman, J.: 'Altered' states of consciousness: positive and negative outcomes. Paper presented at the annual meeting of the American Academy of Psychoanalysis (1974).

Strauss, J.S. and Carpenter, W.T.: Prediction of outcome in schizophrenia. Archs. gen. Psychiat. *34:* 159–163 (1977).

Sullivan, H.S.: Conceptions of modern psychiatry (Norton 1953).

Valliant, G.D.: Prospective prediction of schizophrenic remission. Archs. gen. Psychiat. *11:* 509–518 (1964).

Venables, P.H. and O'Connor, N.: A short scale for rating paranoid schizophrenia. J. ment. Sci. *105:* 815–818 (1959).

Zigler, E. and Levine, J.: Premorbid adjustment and paranoid-nonparanoid status in schizophrenia: a further investigation. J. abnorm. Psychol. *82:* 189–199 (1973).

M. Rappaport, MD, Research Department, Agnews State Hospital, *San Jose, CA 95114* (USA)