an appraisal of the long-term use of tranquilizing medication with hospitalized chronic schizophrenics: a review of the drug discontinuation literature

Robert F. Prien and C. James Klett

Physicians are often faced with the problem of determining whether hospitalized chronic schizophrenics require continuous treatment with tranquilizers. This is a difficult decision, particularly when the patient has shown no florid symptomatology for a long period of time. While discontinuation of medication may lead to recurrence or exacerbation of psychotic behavior, prolonged use of ataractic drugs also has several disadvantages. Reports on persistent dyskinesia, cardiovascular and hepatic complications, oculocutaneous changes, and sudden deaths have focused attention on the potential dangers of prolonged ataractic treatment. Reports on persistent dyskinesia, cardiovascular and hepatic complications, oculocutaneous changes, and sudden deaths have focused attention on the potential dangers of prolonged ataractic treatment (Alexander 1969, Bloom and Davis 1970, Cancro and Wilder 1970, Crane 1968, Crane and Paulson 1967, DeLong 1968, Forrest and Snow 1968, Hollister and Kosek 1965, Hunter, Earl, and Thornicroft 1964, Leetsma and Koenig 1968, Leming 1965, Margolis and Goble 1965, Prien et al. 1970, Richardson, Graupner, and Richardson 1966, Siddall 1965, Waltzkin and MacMahon 1962, Wendkos and Clay 1965, and Zelman and Guillan 1970). There is also concern that long-term medication may contribute to institutionalism by reducing drive, initiative, and planning ability in the chronic patient (Follin et al. 1961, Klerman 1963, and Porteus 1957). It has even been suggested that the prescription of drugs to patients who have shown no behavioral change in years may be more therapeutic for the physician than the patient. Believing that the drugs are beneficial, the physician’s conscience is stilled, and he is diverted from the need to search for alternative therapeutic and rehabilitative programs (Hughes and Little 1967). Finally, the cost of maintaining large numbers of patients indefinitely on ataractic drugs is a significant item in the hospital budget. Not only are drugs expensive but considerable staff time is spent in preparing and administering the medication. If continued ataractic treatment is unnecessary, this time and money could be used to implement other therapeutic programs.

The extent of this problem can be seen in a survey the senior author carried out at seven public mental hospitals in 1964. Approximately 85 percent of chronic schizophrenic patients were receiving phenothiazine medication, 54 percent in doses exceeding the equivalent of 250 mg. of chlorpromazine per day. Most of these patients had been receiving the same regimen for at least a year. Of the patients not on phenothiazines all but a few were receiving minor tranquilizers or antidepressants, and, indeed, only 6 percent were receiving no medication at all. Two years later a followup survey at three of the hospitals revealed no change in the proportion of patients receiving phenothiazine medication.

Drug Discontinuation Literature

Unfortunately, the literature provides no consistent guidelines regarding withdrawal of ataractic drugs. Although a few studies report relatively low relapse rates (5 to 25 percent) following drug discontinuation, most studies have found significant regression in at least 40 percent of patients taken off medication, and several studies report relapse rates exceeding 70 percent. These figures suggest that some proportion of chronic

1 A similar problem is faced by the physician who must decide whether the discharged psychotic requires prolonged maintenance treatment with tranquilizing medication. The literature on maintenance therapy for schizophrenic outpatients is as complex and contradictory as the literature for inpatients and will be the subject of a later review.

2 Unpublished data.
schizophrenics do not require continuous medication, but the percentage varies from one study to another.

The least favorable report on drug discontinuation was by Judah, Josephs, and Murphree (1961), who removed medication from 519 chronic schizophrenics for 90 days; during that period 72 percent of the patients regressed to a point requiring resumption of medication. When Olson and Peterson (1960) withdrew phenothiazines from 127 chronic schizophrenics, 54 percent required resumption of medication 3 months later. By the end of 6 months, the relapse rate had reached 74 percent. Greenberg and Roth (1966) found a relapse rate of 72 percent in 18 patients taken off chlorpromazine for a 20-week period. After interrupting chlorpromazine and reserpine treatment for 1 month in 40 psychotic patients, Zeller (1956) found that 68 percent had suffered relapses. Diamond and Marks (1960) removed phenothiazines from 20 chronic schizophrenics and substituted placebo. By the end of 6 months, 70 percent of the patients either required active medication or were judged to be significantly worse. Morton (1968) also found a 70 percent relapse rate in 20 patients after 6 months on placebo.

A less severe relapse rate was reported by Rassidakis et al. (1970), who removed medication from 43 chronic schizophrenics; 58 percent relapsed over a 9-month period. Caffey et al. (1964) substituted placebo for phenothiazines in 171 chronic schizophrenics and found that 45 percent had to be returned to active medication during a 16-week study period. Blackburn and Allen (1961) reported a similar relapse rate—43 percent—in 28 chronic schizophrenics over a 4-month period. After withdrawing perphenazine from 26 chronic schizophrenics, Whittaker and Hoy (1963) found that 38 percent required resumption of the drug within 10 weeks. Prien, Cole, and Belkin (1969) reported a relapse rate of 40 percent in 179 chronic schizophrenics treated with placebo over a 6-month period; a second study involving 92 chronic schizophrenics revealed a relapse rate of 45 percent (Prien, Levine, and Switalski, 1971). Rothstein, Zeltzman, and White (1962) put 18 chronic schizophrenics on placebo and found that 39 percent showed clinical signs of regression by the end of 6 months.

Some investigators report even lower relapse rates. When Freeman and Alson (1962) removed medication from 46 chronic psychotics and substituted placebo, only 28 percent relapsed over a 6-month period. Similarly, Garfield et al. (1966) administered placebo to 18 chronic schizophrenics for 6 months and reported that 22 percent had to be returned to active medication. Hughes and Little (1967) withdrew chlorpromazine from 21 psychotics and found that only 19 percent required resumption of medication during an 18-month period. Using a sample of 112 chronic schizophrenics, Good, Sterling, and Holtzman (1958) concluded that chlorpromazine could be withdrawn for a period of 3 months without noticeable regression, although withdrawal for longer periods produced a significant increase in pathology. Marjerrison, Irvine, and Steward (1964), Ekdawi (1966), and Ray, Ragland, and Clark (1964) also found that phenothiazines could be removed for up to 3 months without significant negative results. Gottschalk et al. (1970) found a relapse rate of only 5 percent in 74 chronic schizophrenics after 4 weeks off medication. Finally, Follin et al. (1961) removed chlorpromazine from 39 long-term psychotics and reported that only 5 percent regressed over a 9-month period.

How does one explain the diversity of findings from drug discontinuation studies? A number of factors may account for at least some of the variability among studies. First, some investigators substitute placebo after withdrawing medication. The effect this practice can have on results was demonstrated by Olson and Peterson (1962) in a study of intermittent therapy. One group was treated alternately with drugs and placebo; a second group was treated alternately with drugs and no pills. The group receiving placebo had a relapse rate of only 29 percent, while the group receiving no pills had a relapse rate of 85 percent. Whittaker and Hoy (1963) also compared placebo and no pills. Only 23 percent of the patients on placebo relapsed as compared to 54 percent on no pills. In contrast, Marjerrison, Irvine, and Steward (1964) reported no difference between placebo and no pills. After a 2-month period during which they administered placebo to 15 chronic schizophrenics and no pills to 16, they found no significant difference in the two groups’ clinical state.
Another factor is the criterion for assessing relapse. The definition of relapse may range from the first sign of deteriorated behavior to behavior so severe that it necessitates return to known medication. Furthermore, the behavior that one investigator will tolerate before resuming active medication may differ markedly from the behavior tolerated by another investigator, even within the same treatment setting. The lack of a standardized criterion of relapse obviously makes comparison of study results difficult.

The duration of time off medication also differs significantly from study to study. Some studies use withdrawal periods of only 1 month while others evaluate patients over a 12- to 18-month period. Since some patients don't relapse until they have been off medication for 3 or 4 months (Blackburn and Allen 1961, Caffey et al. 1964, Cancro and Wilder 1970, Diamond and Marks 1960, Ekdawi 1966, Freeman and Alson 1962, Olson and Peterson 1960, and Rothstein, Zeltzer, and White 1962), studies of less than 3 months' duration may have deceptively low relapse rates.

Finally, there is the question of treatment milieu. Judah, Josephs, and Murphree (1961) and Rothstein (1960) suggest that differing results stem, at least in part, from environmental effects. In particular, tolerance for deterioration may vary considerably from hospital to hospital and, conceivably, from ward to ward. It is possible that patients from wards placing major emphasis on chemotherapy may react differently than patients from wards which focus on nonsomatic therapies. Rathod's study (1958) comparing two wards on which discontinuation was carried out appears to support this view, and studies by Hamilton et al. (1960 and 1963), Barrett et al. (1967), Ekdawi (1966), Goldsmith and Drye (1963), Meszaros and Gallagher (1958), and Prien, Cole, and Belkin (1969) also suggest that drug effect is related to treatment milieu.

**Controlled Studies**

Several of the discontinuation studies utilized control groups. In most of these studies, the control group had a much lower relapse rate than the group receiving placebo or no medication. These studies are summarized in table 1.

**Recovery of Relapsed Patients**

In some of the early studies on drug withdrawal, the nursing and medical staff feared that relapsed patients would be extremely difficult to control and that recovery would be relatively slow. These fears proved unfounded. Discontinuation studies have shown that resumption of medication is quickly effective in reducing symptoms. In most cases, the relapsed patient rapidly returns to his prestudy level when medication is reinstated.

**Identifying the Relapse-Prone Patient**

Efforts at predicting patient response to drug discontinuation have been largely unsuccessful. Although duration of illness, severity of illness, age at onset of illness, chronological age, duration of chemotherapy, diagnosis, level of social adjustment, pattern of symptomatology, and drug-excretion rate have all been mentioned as possible predictors of relapse (Denber and Bird 1955 and 1957, Diamond and Marks 1960, Forrest and Forrest 1959, Freeman and Alson 1962, Gottschalk et al. 1970, Kamano 1966, Pollack 1958, Rassidakis et al. 1970, and Winkelman 1967), many studies have been unable to confirm the predictive value of these variables (Blackburn and Allen 1961, Caffey et al. 1964, Good, Sterling, and Holzman 1958, Judah, Josephs, and Murphee 1961, Mefferd et al. 1958, Morton 1968, Prien, Cole, and Belkin 1969, and Whitaker and Hoy 1963).

Two variables show promise as indicators of relapse. In a study by Prien, Cole, and Belkin (1969), relapse rate was significantly related to two variables: 1) the dose of phenothiazine medication the patient was receiving before the study and 2) length of hospitalization. Patients who had been hospitalized over 15 years and were receiving low doses of tranquilizing medication (i.e., the equivalent of 250 mg. or less of chlorpromazine) had a relapse rate of only 15 percent following withdrawal of medication, while patients hospitalized less than 15 years and receiving high doses of prestudy medication had a relapse rate of almost 60 percent. These findings were replicated in a second study (Prien, Levine, and Switalski 1971).

These results suggest that the criteria for patient selection may be another factor accounting for relapse.
for the diversity of findings from discontinuation studies. A study with a high proportion of long-stay patients on low maintenance doses would presumably have a lower relapse rate than a study using patients hospitalized for short periods and treated with high doses. Unfortunately, this is difficult to determine from the literature since no other studies have reported similar analyses.

**Intermittent Drug Therapy**

Several studies have investigated the feasibility of intermittent chemotherapy programs in which drug-free periods are alternated with medication periods. The most comprehensive study on intermittent therapy was conducted by Caffey et al. (1964). In this double-blind study, 348 chronic schizophrenics were randomly assigned to four groups: 1) chlorpromazine or thioridazine every Monday, Wednesday, and Friday with drug-free days in between; 2) chlorpromazine or thioridazine daily; 3) placebo every Monday, Wednesday, and Friday with drug-free days in between; and 4) placebo daily. At the end of 4 months, 45 percent of the placebo patients had relapsed, as compared to only 15 percent of the intermittent drug patients and 5 percent of the continuous treatment patients. In another large-scale study, Olson and Peterson (1962) alternated drugs and placebo monthly over a 6-month period and found that relapse occurred in 29 percent of the patients studied. In a control group to whom drugs had been administered continuously, 8 percent suffered relapses. Zocchi et al. (1969) administered medication to 51 patients on an intermittent schedule three times a week during the first 3 months and twice a week thereafter. Only 24 percent of the patients had to be returned to daily drug therapy over a 13-month period. Finally, Greenberg and Roth (1966) in a 42-patient study found no significant difference between a continuous chlorpromazine schedule and an intermittent schedule in which medication was omitted 1 to 6 days a week. These results suggest that intermittent treatment may be a good compromise between continuous treatment, with its physical and economic drawbacks, and complete withdrawal, with its high risk of relapse.

It is interesting to note that some hospitals have already adopted a modified intermittent schedule—the drug-free weekend—for patients on maintenance chemotherapy. This serves two purposes. First, it reduces staff workload at a time when fewer personnel are available and, second, it allows the patient to engage in weekend activities (e.g., weekend visits) without the inconvenience of medication. The weekend drug-free schedule has been evaluated by only one team of investigators. Chien and DiMascio (1971) withdrew weekend medication from 10 chronic schizophrenics and compared them with a control group receiving daily medication. At the end of 6 weeks, there was no significant difference between groups.

**Dose Reduction**

Thus far, we have been concerned only with drug withdrawal, but a related area also warrants discussion. Prien, Levine, and Cole (1970) found that most long-term schizophrenics receiving the equivalent of 350–600 mg of chlorpromazine showed no change in clinical condition when their dose was reduced to 300 mg. Complete withdrawal of medication, however, resulted in severe deterioration. This finding suggests that even patients who require ataractic drugs may be receiving more medication than they need. This finding is supported by Greenberg and Roth (1966), who gradually substituted placebo for active medication over a 48-week period. During the first 8 weeks, placebo was substituted for medication 1 day a week. Every 8 weeks thereafter, 1 placebo day was added to the weekly regimen. At the end of 48 weeks (when patients were receiving one-seventh of their original medication), only one of 21 patients had relapsed. When all active medication was withdrawn, however, clinical deterioration was relatively rapid; 12 patients (57 percent) had to be returned to known medication within a 20-week period. A control group of 18 patients received active medication 7 days a week. After 48 weeks, one patient had relapsed. When all active medication was then abruptly withdrawn, 13 patients (72 percent) relapsed within 20 weeks. Greenberg and Roth concluded that most patients need medication but that the majority are receiving higher doses than they actually require. They recommended that more attention be placed on the minimum dosage required by chronic schizophrenics in mental hospitals.
Table 1. Controlled drug discontinuation studies

<table>
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<th>Investigators</th>
<th>Sample</th>
<th>Design</th>
<th>Findings</th>
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| Adelson & Epstein (1962) | 288 schizophrenics hospitalized 2 to 10 years & under 50 years of age | Double-blind: 5 groups  
1) Chlorpromazine  
2) Perphenazine  
3) Prochlorperazine  
4) Trifluoperazine  
5) Placebo  
(n = 48 in each drug group & 96 in the placebo group) | After 5½ months, 18% of the placebo group & 3% of the drug groups were judged significantly worse. |
| Blackburn & Allen (1961)   | 53 male chronic schizophrenics under 40 years of age | Double-blind: 3 groups  
1) Drug (n = 25)  
2) Placebo (n = 14)  
3) Placebo-drug crossover (n = 14) | By end of 3 months, 43% of placebo groups & 12% of drug group required known medication or transfer to closed ward. |
| Caffey et al. (1964)    | 348 male schizophrenics hospitalized at least 2 years & less than 56 years of age | Double-blind: 4 groups  
1) Drug daily  
2) Intermittent drug  
3) Placebo daily  
4) Intermittent placebo  
(n = about 87 patients per group) | By end of 4 months, 45% of placebo groups, 15% of intermittent group, & 5% of daily drug group required known medication. |
| Diamond & Marks (1960) | 40 chronic schizophrenics on reserpine or chlorpromazine for at least 6 months | Double-blind: 4 groups  
Placebo substituted in half of patients receiving each drug (n = 10 per group) | By end of 6 months, 70% of placebo group & 25% of drug groups showed clinical deterioration. |
| Freeman & Alson (1962)   | 94 long-term male psychotics on chlorpromazine for at least 2 months | Double-blind: 2 groups  
1) Drug (n = 48)  
2) Placebo (n = 46) | By end of 6 months, 28% of placebo group & 17% of drug groups showed clinical deterioration. |
| Garfield et al. (1962)   | 27 schizophrenics hospitalized at least 9 months & less than 60 years of age | Double-blind: 2 groups  
1) Drug (n = 9)  
2) Placebo (n = 18) | By end of 6 months, 22% of placebo group & 0% of drug group required known medication. |
| Good, Sterling, & Holzman (1958) | 112 chronic schizophrenics on maintenance drugs | Double-blind: 4 groups  
1) Drug  
2) Placebo  
3) Drug-placebo crossover  
4) Placebo-drug crossover | At 3 months, no significant difference between groups. At 6 months, placebo group showed significantly more pathology than drug group. |
| Grinspoon, Ewalt, & Shader (1967) | 10 schizophrenics hospitalized 3 years or more & under 36 years of age | Double-blind: 2 groups  
1) Drug + psychotherapy  
2) Placebo + psychotherapy  
(n = 5 in each group) | After 6 weeks, placebo group showed significantly more pathology than drug group. |
<table>
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<tr>
<th>Study Details</th>
<th>Sample Size</th>
<th>Study Design</th>
<th>Outcomes</th>
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<tr>
<td>Melnyk, Worthington, &amp; Laverty (1966)</td>
<td>40 schizophrenics on phenothiazines</td>
<td>Double-blind: 2 groups 1) Drug (n = 20) 2) Placebo (n = 20)</td>
<td>By end of 6 weeks, 50% of placebo group &amp; 0% of drug group relapsed.</td>
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<td>Prien, Cole &amp; Belkin (1969)</td>
<td>720 schizophrenics hospitalized at least 2 years &amp; under 56 years of age</td>
<td>Double-blind: 4 groups 1) High daily dose of chlorpromazine 2) Low daily dose of chlorpromazine 3) Placebo 4) Physician's choice of treatment (n = about 180 patients per group)</td>
<td>By end of 6 months, 40% of placebo group, 13% of low-dose group, 6% of high-dose group, &amp; 1% of physician's-choice group relapsed &amp; required known medication.</td>
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<td>Prien, Levine, &amp; Switalski (1971)</td>
<td>275 schizophrenics hospitalized at least 2 years &amp; under 56 years of age</td>
<td>Double-blind: 3 groups 1) High daily dose of trifluoperazine 2) Low daily dose of trifluoperazine 3) Placebo (n = about 92 patients per group)</td>
<td>By end of 6 months, 45% of placebo group, 18% of low-dose group, &amp; 13% of high-dose group relapsed &amp; required known medication.</td>
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<td>Rassidakis et al. (1970)</td>
<td>84 schizophrenics hospitalized at least 3 years</td>
<td>Two groups: 1) Drug (n = 41) 2) No drug (n = 43)</td>
<td>By end of 9 months, 58% of no drug group &amp; 34% of drug group relapsed.</td>
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<td>Schiele, Vestre, &amp; Stein (1961)</td>
<td>80 male chronic schizophrenics</td>
<td>Double-blind: 4 groups 1) Thoridazine 2) Trifluoperazine 3) Chlorpromazine 4) Placebo (n = 20 in each group)</td>
<td>By end of 16 weeks, 60% of placebo group showed &quot;appreciable worsening&quot; as compared to 5% of drug groups.</td>
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<td>Shawver et al. (1959)</td>
<td>120 chronic schizophrenics under 50 years of age with at least 6 months on chlorpromazine</td>
<td>Three groups: 1) Chlorpromazine 2) Reserpine 3) Placebo (n = 40 in each group)</td>
<td>By end of 6 months, placebo group showed significantly more regression than either drug group.</td>
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<td>Whittaker &amp; Hoy (1963)</td>
<td>39 male schizophrenics with at least 1 year in hospital</td>
<td>Double-blind: 3 groups 1) Drug (n = 13) 2) Placebo (n = 13) 3) No pills (n = 13)</td>
<td>By end of 10 weeks, 54% of no-pill group, 23% of placebo group, &amp; 8% of drug group required known medication.</td>
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<tr>
<td>Zeller (1956)</td>
<td>80 chronic schizophrenics on phenothiazines</td>
<td>Two groups: 1) Drug (n = 40) 2) Placebo (n = 40)</td>
<td>By end of 1 month, 68% of placebo group &amp; 13% of drug group required known medication.</td>
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Frequency of Daily Dosage

Another procedure which warrants reevaluation is the time-honored practice of administering medication in equally divided doses three to six times a day. This practice is apparently based on the assumption that frequent administration of equally divided doses will minimize side effects and maximize therapeutic benefit. In a review of drug administration schedules, DiMascio and Shader (1969) claim that this practice has no scientific basis and is inconsistent with what is presently known about the pharmacology of psychotropic drugs. They advocate the use of daily or twice-daily schedules in which drugs with sedative-hypnotic activity are given primarily in the evening, while drugs with stimulating properties are administered in the morning. Other investigators also question the practice of administering drugs more than once or twice a day (Haden 1959, Hrushka, Broch, and Hsu 1966, Kris 1958, Peterson and Olson 1963, Roberts 1961, Tibbits 1958, and Vestre 1966). They claim that multiple-dose schedules are not only unnecessary but are inconvenient to both patients and staff.

Summary

Three major findings emerge from the rather extensive and complex literature on drug discontinuation.

(1) Indiscriminate withdrawal of ataractic medication for long periods of time carries a relatively high risk of relapse. Most studies indicate that 40 percent or more of the patients taken off medication relapse within 6 months. The probability of relapse appears too high to commend long-term drug withdrawal as a general treatment policy for chronic schizophrenics.

(2) Discontinuation is most feasible with patients who have been hospitalized for long periods and are already receiving low doses of phenothiazine medication. The risk of relapse with these patients is relatively low.

(3) Intermittent drug therapy appears to have considerable merit. All investigators who have used intermittent schedules feel that continuous ataractic treatment is unnecessary with the large majority of patients. Most of these investigators acknowledge, however, that more study is needed to develop criteria for predicting the length of drug-free periods individual patients can tolerate. Evidence indicates that this tolerance varies considerably from one patient to the next (Olson and Peterson 1962 and Wold 1960). Fortunately, however, the tolerance of the individual patient does not appear to change over time (Wold 1960). This suggests that, once an intermittent schedule is established for the individual patient, it can be maintained for a relatively long period.

Clearly, there is need for further research on long-term and intermittent drug withdrawal. In particular, it is necessary to develop criteria that will differentiate between the relapse-prone and nonrelapse-prone patient. It is also important to establish the length of time that the relapse-prone patient can remain off medication without regressing. Alternatives to drug withdrawal, such as dose reduction, should also be investigated. A workable withdrawal or dosage reduction program could result in less risk of toxicity for the patient, less workload for the staff, and reduced expenditure for the hospital.

References


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