

Maintenance Antipsychotic Therapy: Is the Cure Worse than the Disease?

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The serious long-term complications of maintenance antipsychotic therapy led the authors to undertake a critical review of outpatient withdrawal studies. Key findings included the following: 1) for at least 40% of outpatient schizophrenics, drugs seem to be essential for survival in the community; 2) the majority of patients who relapse after drug withdrawal recompensate fairly rapidly upon reinstatement of antipsychotic drug therapy; 3) placebo survivors seem to function as well as drug survivors—thus the benefit of maintenance drug therapy appears to be prevention of relapse; and 4) some cases of early relapse after drug withdrawal may be due to dyskinesia rather than psychotic decompensation. The authors urge clinicians to evaluate each patient on maintenance antipsychotic therapy in terms of feasibility of drug withdrawal and offer practical guidelines for withdrawal and subsequent management.

A SURVEY of the overall picture of the treatment of chronic schizophrenic patients indicates that the vast majority are receiving antipsychotic drug therapy. Most experts believe that drug therapy should be continued indefinitely in view of the substantial risk of relapse upon discontinuance (1). However, recent publications (2, 3) have pointed to the serious and often irreversible complications of prolonged antipsychotic therapy. Tardive dyskinesia in particular is becoming recognized as a major therapeutic challenge. This late-appearing, persistent neurological syndrome seems to be associated with the use of antipsychotic compounds. The prevalence of tardive dyskinesia among patients on long-term drug therapy is estimated to be between 0.5% and 40% (4). Unfortunately, there has been no effective treatment for tardive dyskinesia to date.

The seriousness of the long-term complications war-

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rants a reexamination of the evidence in favor of prolonged maintenance antipsychotic therapy. Traditionally, research dealing with maintenance antipsychotic therapy has focused on relapse rates. Typical studies evaluating the need for continued maintenance drug therapy compare a group of patients withdrawn from phenothiazines with a group maintained on drugs. The principal outcome measure is the number or percentage of patients who show clinical deterioration. If, as is usually the case, a substantial number of drug-withdrawn patients deteriorates in contrast to the drug-continued group, it is concluded that drug withdrawal is too risky and continued drug therapy is therefore essential. We feel that this approach has limitations and does not do justice to the complex clinical issues involved. The concept of the risk/benefit ratio, which often governs clinical decisions, should be accorded more attention. The clinician faced with a chronic schizophrenic patient on maintenance antipsychotic therapy ought to consider the following issues.

1. *The clinical impact of relapse.* Although it is important to know the likelihood of patient relapse following antipsychotic drug withdrawal, it is just as important to know how serious the consequences of such a relapse would be. Psychotic decompensation in the employed head of a household may lead to disastrous psychological and economic consequences for a whole family, while the same adverse change in a hospitalized chronic patient may result in much less upheaval. Thus drug discontinuance studies should emphasize the impact of relapse and the subsequent fate of relapsed patients in addition to assessing relapse rates. In particular, suicidal, self-destructive, or assaultive behavior should be noted.

2. *The benefits of continued drug therapy.* A most important theoretical aspect of maintenance antipsychotic therapy is whether these drugs are only prophylactic or are also therapeutic. The clinician needs to know whether by withdrawing drugs he simply deprives the patient of protection against future relapse or whether he is also depriving him of an active therapeutic agent, thereby circumventing continued improvement. This kind of information could be obtained if data on psychosocial functioning were reported separately for drug and placebo survivors (i.e., non-relapsers).

It is worth examining the drug discontinuance litera-

in order to determine the extent to which published studies provide information on the clinically relevant risk/benefit issues. In this article, we will focus on schizophrenic patients who are not hospitalized, since outpatients are the appropriate group for study of drug maintenance as opposed to drug treatment issues. Moreover, inpatients are shielded from many of the stresses experienced by patients in the community that might lead to relapse (5). Therefore, the study of outpatients more accurately reveals the extent to which drugs can protect patients from regression or decompensation under stress.

In our discussion of outpatient antipsychotic drug withdrawal studies, we will mention methodological problems, but we will not discuss them in detail.

REVIEW OF OUTPATIENT STUDIES

Tuteur and associates (6) substituted placebo for low doses of chlorpromazine (CPZ) in 57 socially recovered chronic female schizophrenic outpatients seen in a drug clinic. The relapse rate was 56% (N=32), compared to a rate of 13% in a similar group of patients who stayed on CPZ. In 3 placebo patients, relapse led to extended rehospitalization; 27 relapsed patients recompensated within days of resuming medication; and 2 patients recompensated after a brief readmission. No mention is made of the psychosocial adjustment of the placebo survivors.

In a placebo-controlled withdrawal study of chronic psychotic outpatients by Gross (7), 50 of 98 patients on placebo (51%) relapsed within 6 months as opposed to 6 of 46 (13%) in the drug-maintained control group. However, Gross noted that while 50% of clinic patients who relapsed on active medication had to be hospitalized, only 13% of drug-withdrawn relapsed patients needed rehospitalization—the rest regained stability under resumed medication. Unfortunately, the study population was not adequately described and the functioning of the placebo survivors was not presented.

In a longitudinal study involving 6 female schizophrenics who had been discharged for at least 1 year, Vold (8) substituted placebo for CPZ. Five patients relapsed and showed severe social disorganization. When CPZ was reinstated, these 5 patients improved. When placebo was reinstated, there was remarkable individual consistency; the 5 patients again relapsed after about the same amount of time. Despite the small sample, this study strongly suggests consistency of drug response for individual patients and raises the possibility that a patient's past response to drug withdrawal can be used to predict future behavior.

Troshinsky and associates (9) studied a group of stable chronic schizophrenics who had been discharged from a state hospital for at least 1 year. Patients were randomly assigned to continued phenothiazine therapy or to "exact replica placebo." Most

patients were on a low dosage (the equivalent of 150 to 200 mg of CPZ per day). During 10 months, 12 of 19 placebo patients deteriorated and 8 required rehospitalization. Only 1 patient on active medication got worse. The 7 placebo survivors and 23 drug survivors showed little or no change. To estimate the impact of contact with the aftercare clinic, the study included a control group of discharged schizophrenics not attending the clinic. A follow-up inquiry with relatives of the latter group yielded 27 usable responses, which indicated that 13 of 27 patients were not doing well; 6 of these 13 were on drugs and 7 were not. Fourteen patients were apparently doing well, 6 of them on drugs and 8 not receiving phenothiazines.

Wiener and associates (10) withdrew medication from 41 outpatients and compared them to a randomly selected group of 42 patients who continued medication. Twenty-six of the 41 were successfully withdrawn for the 3-month study period. The only negative result was an increase in depression scores on the Minnesota Multiphasic Personality Inventory. However, since the population was a mixture of psychotic and neurotic patients and the drugs included meprobamate as well as CPZ, the results are difficult to interpret.

Pasamanick and associates (11) studied home care of schizophrenics under drug and placebo conditions. Although this was not strictly a withdrawal study, the findings are relevant to our review. Sixty-five (83%) of drug-treated patients as opposed to 31 (55%) of the patients on placebo were successfully maintained at home for 6 to 18 months. However, the drug failure subjects spent an average of 168 days in the hospital, whereas the average stay of the placebo failures was 94 days.

In a controlled study by Engelhardt and associates (12), schizophrenic outpatients were assigned to CPZ, promazine, or placebo and were followed for 48 months. Hospitalization was required for 19.1% of 152 CPZ patients versus 31.0% of the 142 placebo patients. It was concluded that CPZ prevented rather than merely delayed hospitalization.

Leff and Wing (5) studied maintenance phenothiazine therapy of acute schizophrenics who had recovered and had been discharged from the hospital. Of 116 suitable patients, only 35 entered the trial; this group was randomly assigned to trifluoperazine, CPZ, or placebo. During the 1-year study, 12 of 15 placebo patients (80%) relapsed as opposed to 7 of the 20 drug-treated patients (35%). All 7 drug relapsers but only 6 of the 12 placebo relapsers were rehospitalized. Follow-up of the 81 patients who had not entered the trial revealed that their overall relapse rate was similar to the overall relapse rate of the study group (56.8% and 53.3%, respectively). Patients with good prognoses who were not on phenothiazines did rather well (27.3% relapse rate), while drug patients with poor prognoses did poorly (66.7% relapse rate). These two groups had been excluded from the controlled portion of the investigation on the grounds that they had been either too well or too sick for purposes of the study.

Hirsch and associates (13) substituted placebo injections in half of a group of 81 chronic schizophrenics maintained on fluphenazine decanoate. The relapse rates in 9 months were 66% for placebo patients and 8% for drug patients. However, since negative responders and relapsers on fluphenazine had been screened out before the study, the authors estimated that over 30% of unselected patients probably could not be maintained on fluphenazine injections. It was noteworthy that 89% of the drug patients received only one 25-mg injection of fluphenazine decanoate monthly, which was a very low but apparently quite effective maintenance dose. The patients who relapsed on placebo were found to be very difficult to restabilize (14).

In a controlled study of the posthospital treatment of 374 schizophrenics, Hogarty and Goldberg (15) compared CPZ with placebo and also studied the effects of "major role therapy," a form of intensive casework with rehabilitation counseling. Clinical deterioration on placebo as shown by cumulative relapse rates was substantial: 67% at the end of 1 year and 80% at the end of 2 years. However, the corresponding relapse rates for the CPZ group also tended to be high: 31% at 1 year and 48% at 2 years. Approximately 75% of relapsers required rehospitalization (16).

The drug relapse rates in the Hogarty and Goldberg study may be inflated, since an unknown number of patients may have discontinued medication on their own prior to relapse. The results clearly indicate the prophylactic value of CPZ: the drug prevented relapse and probably rehospitalization in at least a third and possibly more of the patients. Analysis of data for the survivors showed that drug-treated patients who survived in the community did not adjust any better than patients who managed to survive on placebo (17).

DISCUSSION

The studies we reviewed had some major deficiencies. A great deal of information was missing in terms of population characteristics, control for confounding variables, enumeration of side effects, clinical assessment of placebo survivors, and description of the subsequent fate of relapsed patients. Nevertheless, based on the reported findings, we have arrived at several tentative conclusions.

Relapse Rates Attributable to Drug Withdrawal

Since there was considerable variation in the percentage of patients who relapsed while on antipsychotic medication, the best estimate of deterioration attributable to drug discontinuance can be obtained from drug-placebo differences. Drug-placebo differences in relapse rates in the studies cited ranged between 12% and 59%, with a median value of 40%. Therefore, one can conclude that for at least 40% of outpatient schizophrenics, phenothiazines are essential for survival in the community.

A number of clinical implications can be derived from this conclusion. The question arises of what proportion of chronic schizophrenic outpatients may not need to be on antipsychotics, either because they would do well without medication or because they would not do well on drugs for reasons including failure to find optimal drug or dose level, noncompliance, or toxicity. Judging by this review, the proportion of such patients may be as high as 50%.

The suggestion that as many as half of schizophrenic patients might not be worse off if their maintenance antipsychotic medication were withdrawn will surely meet with some raised eyebrows. It is well to remember, however, that there may be a substantial difference between the efficacy of drug treatment actually given to patients and the theoretical optimal drug/dosage combination. The more the actual antipsychotic therapy approximates idealized optimal efficacy, the larger the drug-placebo differences could become following drug withdrawal. The longer a patient has been on maintenance antipsychotic therapy, the greater the likelihood that an effective drug/dosage combination has been found, and consequently, the less the likelihood of relapse on continued medication. While there were not adequate data in the reviewed withdrawal studies regarding length of prestudy pharmacotherapy, it was our distinct impression that the lowest drug relapse rates and the largest drug-placebo differences were obtained in populations who had been on maintenance antipsychotic therapy for the longest time (13). Conversely, patients recently discharged from the hospital tended to experience higher drug relapse rates and smaller drug-placebo differences (15). However, we believe that even in the most stable groups, a number of patients could be saved from the dangers of tardive dyskinesia as well as from the financial and social burdens of prolonged drug therapy.

Consequences of Relapse

Rehospitalization rates after placebo relapse varied between 10 and 75%. In some studies, relapsed patients recompensated quickly following return to medication (6, 7); in others, restabilization after relapse was difficult (13). An interesting trend emerged from three studies, in that drug failures appeared to have a considerably higher rehospitalization rate than placebo relapsers (5, 7, 11). The most obvious interpretation is that patients who relapse on medication are sicker than placebo relapsers. Leff and Wing's study (5) provides indirect support for this hypothesis. One of the outstanding methodological features of this study was the authors' ability to follow-up those suitable patients who did not enter the trial. Among patients who were on drugs but were judged to be too sick to be withdrawn, a substantial 67% relapse rate was found, confirming the clinical judgment that they were poor risks.

From the sparse data, one may tentatively infer that relapse following drug discontinuation can be reversed

the majority of cases by prompt resumption of drug therapy and that the best guide to the likelihood and timing of relapse and recovery is probably the patient's past behavior in a similar situation (8).

Outcome in Placebo Survivors

There was little information in the reviewed withdrawal studies on the comparative functioning of placebo survivors and drug survivors. However, none of the studies we have discussed showed placebo survivors to be doing any worse than patients maintained on drugs. In fact, the studies by Leff and Wing (5) and Hogarty and associates (17) suggest that there might be a subgroup of patients, albeit small, who function better without drugs than drug-maintained patients do. Thus the studies we reviewed tend to support the conclusion of Hogarty and Goldberg (15) that maintenance antipsychotic therapy is essentially prophylactic, i.e., it tends to prevent relapse.

The proportion of drug-free schizophrenics who function well may be underestimated in the literature, since many of these patients may not be in treatment as seen in private settings. Therefore, aftercare clinics may show lower proportions of patients successfully maintained without antipsychotics than do private psychotherapists. The study by Troshinsky and associates (9) tends to support this hypothesis in that a higher relapse rate was found in the placebo group than in schizophrenics not on medication who were not attending the clinic.

Mortality Resulting from Prolonged Drug Treatment

Withdrawal symptoms that are commonly observed during the first 10 to 14 days after phenothiazine discontinuance have been recognized (18), but they were not focused on in withdrawal studies. However, it appears that some patients who appear to deteriorate within a few weeks of drug withdrawal may in fact be developing dyskinesia rather than adverse clinical change. In an ongoing pilot study of antipsychotic withdrawal, we have observed increased dyskinesic movements in 4 of the first 5 placebo relapsers. Patients who show newly appearing dyskinesic movements after antipsychotic withdrawal can be assumed to have a covert form of persistent dyskinesia, previously suppressed by drugs and made overt by drug discontinuance. In our pilot study, it was quite difficult to assess the relative contributions of the two concurrent processes—increased dyskinesia and increased psychiatric symptoms—to the clinical decision to drop the patients from the study. Some patients appeared to react to a relatively sudden increase in dyskinesia with agitation, psychosomatic complaints, and miscellaneous symptoms seemingly unrelated to movement disorders. To observers such as family, foster parents, aftercare staff, or even physicians, these behavioral changes may have indicated clinical deterioration. This process has similarities to cases of pheno-

thiazine-induced decompensation reported by Van Putten and associates (19), wherein increased psychosis was associated with akathisia and was reversed by the administration of an anticholinergic. We believe that at least some relapses, especially during the first 4 to 6 weeks after antipsychotic withdrawal, are attributable to withdrawal emergent dyskinesia rather than to psychotic decompensation.

In view of the above findings and especially in view of the fact that it is almost impossible to predict accurately which patients will relapse when their antipsychotic medication is withdrawn (1), we tentatively offer the following guidelines to clinicians who wish to evaluate the need for continued maintenance therapy.

GUIDELINES

The major principle we wish to stress is that every chronic schizophrenic outpatient maintained on antipsychotic medication should have the benefit of an adequate trial without drugs.

When a patient's drug history reveals that discontinuance or reduction of antipsychotic drugs in the past was followed by clinical relapse, it is safe to assume that this patient has already been tested without medication with negative results, and any new attempt to withdraw drugs is likely to fail.

Withdrawal of antipsychotic medication could be implemented in accordance with the following principles: 1) gradual withdrawal is preferable to abrupt discontinuation; 2) if a patient is on several antipsychotics, they should be stopped one at a time; 3) if a patient is on an antiparkinson drug, it should be continued for 1 to 2 weeks after antipsychotic withdrawal to guard against cholinergic withdrawal symptoms; and 4) if discussion with the patient reveals that he is most reluctant to be without medication, reduction to a token amount is preferable to total withdrawal. Further course of action would naturally depend on what happens to the patient following drug discontinuation. There are four major possibilities.

1. There may be severe relapse, with or without rehospitalization. Obviously, in these situations return to antipsychotic medication in adequate doses is indicated. Perhaps a new attempt could be made at a later date to reduce dosage or to institute drug-free weekends or holidays as suggested by Prien and Klett (1).

2. In cases of lesser clinical deterioration, the best action would probably be prompt reestablishment of previous antipsychotic therapy to achieve recompensation. However, many of these patients may be good candidates for dosage reduction, and a subsequent attempt to reduce the dosage could be initiated.

3. If no adverse behavior change occurs, one can hope to have found an ideal candidate for antipsychotic drug withdrawal. However, these patients should be closely followed for at least 1 year, since clinical relapse may be expected to occur at any time during the first 12 months (20, 21).

4. Dyskinesia may appear or worsen. The expectation is that such a change would occur within 4 to 6 weeks of drug discontinuation and would precede psychotic decompensation. Judicious drug management of these patients would take into account both dyskinesia and behavioral deterioration. If both were severe, reinstatement of the former antipsychotic regimen might be wise, despite the possibility that the covert dyskinesia might in time be further aggravated by the antipsychotic drug. If the dyskinesia is severe but the recrudescing psychotic symptoms are not too troublesome, one may attempt to concentrate on controlling only the dyskinesic symptoms through treatment with promising drugs such as deanol (22) or papaverine (23). If these treatment efforts fail, one could later prescribe an antipsychotic to suppress symptoms. If both dyskinesia and psychotic relapse are comparatively mild, one could embark on a course of treatment with antipsychotics presumed to have few or no neurological side effects. Drugs that could be considered for this purpose include chlorprothixene, which has been shown to produce the least withdrawal emergent symptoms in children (24); thioridazine, which is known to have a low likelihood of producing extrapyramidal symptoms; and the investigational drug clozapine, which is an effective antipsychotic apparently without neurological side effects (25). Treatment with these agents would presumably benefit the psychotic symptoms and would prevent further dyskinesia. Finally, if the dyskinesia is mild and no psychotic relapse is observed, it may be best to hope for spontaneous long-term improvement of the dyskinesia and to refrain from reinstating drug therapy.

CONCLUSIONS

Our review of drug discontinuance studies in outpatient schizophrenics maintained on antipsychotics suggested that perhaps as many as 50% of such patients might not be worse off if their medications were withdrawn. In view of the long-term complications of antipsychotic drug therapy—primarily tardive dyskinesia—an attempt should be made to determine the feasibility of drug discontinuance in every patient. Close supervision during the postwithdrawal weeks may enable the clinician to differentiate withdrawal emergent dyskinesia from psychotic relapse so that the appropriate therapeutic measures can be instituted.

REFERENCES

1. Prien RF, Klett CJ: An appraisal of the long-term use of tranquilizing medication with hospitalized chronic schizophrenics. *Schizophrenia Bull* 5:64-73, 1972
2. Baldessarini RJ, Lipinski JF: Risks versus benefits of antipsychotic drugs. *N Engl J Med* 289:427-428, 1973
3. Crane GE: Clinical psychopharmacology in its 20th year. *Science* 181:124-128, 1973
4. Crane GE: Persistent dyskinesia. *Br J Psychiatry* 122:395-405, 1973
5. Leff JP, Wing JK: Trial of maintenance therapy in schizophrenia. *Br Med J* 3:559-604, 1971
6. Tuteur W, Stiller R, Glotzer J: The discharged mental hospital chlorpromazine patient. *Dis Nerv Syst* 20:512-517, 1959
7. Gross M: The impact of ataractic drugs on a mental hospital outpatient clinic. *Am J Psychiatry* 117:444-447, 1960
8. Wold PN: A long-term evaluation of chlorpromazine in schizophrenic patients. *J Nerv Ment Dis* 130:151-154, 1960
9. Troshinsky CH, Aaronson HG, Stone RK: Maintenance phenothiazines in aftercare of schizophrenic patients. *Pennsylvania Psychiatric Quarterly* 2:11-15, 1962
10. Wiener DN, Feinberg P, Nagobads IJ, et al: Effects of withdrawal of tranquilizers. *Arch Gen Psychiatry* 9:513-519, 1963
11. Pasamanick B, Scarpitti FR, Lefton M, et al: Home versus hospital care for schizophrenics. *JAMA* 187:177-181, 1964
12. Engelhardt DM, Rosen B, Freedman N, et al: Phenothiazines in prevention of psychiatric hospitalization. IV. Delay or prevention of hospitalization—a re-evaluation. *Arch Gen Psychiatry* 16:98-101, 1967
13. Hirsch SR, Gaid R, Rohde PE, et al: Outpatient maintenance of chronic schizophrenic patients with long-acting fluphenazine: double-blind placebo trial. *Br Med J* 1:633-637, 1973
14. Ridsdale BC: Personal communication, March 6, 1975
15. Hogarty GE, Goldberg SC: Drug and sociotherapy in the after care of schizophrenic patients: one-year relapse rates. *Arch Gen Psychiatry* 28:54-64, 1973
16. Hogarty GE, Goldberg SC, Schooler NR: Drug and sociotherapy in the aftercare of schizophrenic patients. II. Two-year relapse rates. *Arch Gen Psychiatry* 31:603-608, 1974
17. Hogarty GE, Goldberg SC, Schooler NR: Drug and sociotherapy in the after care of schizophrenic patients. III. Adjustment of nonrelapsed patients. *Arch Gen Psychiatry* 31:609-618, 1974
18. Brooks GW: Withdrawal from neuroleptic drugs. *Am J Psychiatry* 115:931-932, 1959
19. Van Putten T, Mutalipassi LR, Malkin MD: Phenothiazine induced decompensation. *Arch Gen Psychiatry* 30:102-105, 1974
20. Freeman HE, Simmons OG: *The Mental Patient Comes Home*. New York, John Wiley & Sons, 1963
21. Gardos G: Are antipsychotic drugs interchangeable? *J Nerv Ment Dis* 159:343-348, 1974
22. Miller E: Deanol: a solution for tardive dyskinesia. *N Engl J Med* 291:796, 1974
23. Gardos G, Cole JO: Papaverine for tardive dyskinesia? *N Engl J Med* 292:1355, 1975
24. Polizos P, Engelhardt DM, Hoffman SP, et al: Neurological consequences of psychotropic drug withdrawal in schizophrenic children. *J Autism Child Schizo* 3:247-253, 1973
25. Simpson GM, Varga E: Clozapine—a new antipsychotic agent. *Curr Ther Res* 16:679-686, 1974