Placebo Washout in Trials of Antipsychotic Drugs

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Abstract

For antipsychotic phase 3 clinical trials, we compare the relative merits of a placebo washout period with an alternate design strategy using a low-dose antipsychotic treatment. Evaluations are made with respect to the achievement of specific clinical trial design goals including the effect on power for detecting between-treatment and within-treatment pre-post differences. The relative merits of these two designs are discussed separately for those patients who enter the initial lead-in period after withdrawal from previous antipsychotic medication and for those not on medication immediately before that period.


In phase 3 clinical trials of antipsychotic agents for patients diagnosed with schizophrenia or schizoaffective disorder, it is current practice for all study participants to receive placebo during an initial period before they are randomized onto study medication. Various names have been used to describe this prerandomization period, including "baseline (placebo)" (Shopsin et al. 1972, 1979), "initial placebo (washout)" (Prien 1988), "placebo washout" (Marder and Meibach 1994), and "placebo lead-in." For the purpose of our article, we chose the term "placebo washout" because of its widespread use (although it has questionable meaning for patients who have not been receiving prescribed or unprescribed drugs before the trial).

The length of the prerandomization period is usually 1 week for an oral neuroleptic and 1 month for a slow-release injectable neuroleptic medication. The typical trial also includes a double-blind placebo treatment arm that follows the single-blind placebo washout. The ethical implications of use of this design feature have been discussed elsewhere (Addington 1995; Volavka 1995b) and are outside the scope of this article.

The ethical implications of the washout period in trials of antipsychotics have received little attention (Volavka 1995a). Some may believe that the washout period is not problematic since it is relatively short, patients are under close supervision in the hospital, and active antipsychotic medication can be restarted if needed.

However, the effects of denial of treatment to a patient in need of treatment must be considered. Clearly, patients eligible for participation in a trial of an antipsychotic drug need treatment, as this need is an important criterion for inclusion in the antipsychotic trial. The washout period interrupts or delays the needed treatment, symptoms may worsen, and for some groups of individuals the worsening may reach a level of statistical significance.

Reprint requests should be sent to Dr. J. Volavka, Director, Clinical Research Division, Nathan S. Kline Institute for Psychiatric Research, 140 Old Orangeburg Rd., Orangeburg, NY 10962.
(Volavka et al. 1992). Although first-person accounts of washout period experiences have not been published, many patients have published vivid descriptions of their experiences suffered during a psychotic exacerbation. An investigator is obligated to curtail the washout period if such clinical deterioration becomes obvious, but a patient’s increased suffering may not be easily recognized. Moreover, close supervision does not always prevent violent inpatient incidents, and patients may abscond from the hospital and do serious harm to themselves or to others. The safety of placebo treatment in schizophrenia is under increasing scrutiny, partly because of several suicides reported recently in the media. Although none of these patients were involved in a placebo washout, there is a potential for an unfortunate incident. From both the patient’s and the clinical investigator’s point of view, in designing a study, the risk-to-benefit ratio of a placebo washout period must be carefully appraised. To examine this risk, we contrast the use of the placebo approach with an alternative design strategy that we call the prerandomization treatment period (PRTP).

In the PRTP strategy, patients who are being treated with an antipsychotic at the time they are selected to enter the trial have their current treatment replaced by a standard antipsychotic at a clinically appropriate dosage. The dosage of this standard antipsychotic is tapered off to a predefined level (e.g., 10 mg of haloperidol a day for a week) (Hirsch and Barnes 1990). On the basis of recent data (McEvoy et al. 1991; Volavka et al. 1992, 1995), the dosage of haloperidol might be as low as 5 mg/day, corresponding to a plasma level of about 2 ng/mL. However, the available data do not permit us to make a firm recommendation of a specific dosage. Nevertheless, several objective criteria can be specified for choosing the low-dose level (dose X). One such criterion is that X should be the lowest dose that produces a mean change of zero in the severity of symptoms during the run-in period. That is, the severity at the beginning and at the end of the PRTP should be the same when averaged over subjects.

**Background**

The origin of the washout period in psychopharmacology is not clear. Although it was used quite early in the trials of antidepressants (Jones and Ainslie 1966), it apparently was not used in the classical antipsychotic drug trials of the 1960s and early 1970s (e.g., Cole et al. 1964; Goldberg et al. 1967, 1972). In antipsychotic trials, it may have originated at New York University’s Bellevue Hospital (Gershon et al. 1970) in a study design calling for a 3–7-day period during which recently admitted patients received placebo and possibly sedatives for behavioral control.

The washout period seems to have received scant attention in methodological publications. After an early description of the washout period was published (Gallant et al. 1971), with no mention of placebo, guidelines for clinical trials were developed by the American College of Neuropsychopharmacology (Wittenborn 1978), with a brief description of a “pretreatment washout” (still with no mention of placebo). Two paragraphs on a washout period appeared in a methodological paper by Prien (1988). Laska et al. (1994) suggested that the purpose of the washout period is “to eliminate or at least minimize the lingering effect of previous medication, to elicit the untreated severity of illness, and to establish a stable baseline from which to assess change over time” (p. 31). Kane et al. (1994) commented that the duration of a drug-free period is currently feasible in most research environments is too short to permit previous medication to be adequately washed out, although they concluded that whatever time is feasible is useful.

A single-blind washout period was used in three well-known large multicenter trials of new antipsychotics (clozapine [Kane et al. 1988] and risperidone [Marder and Meibach 1994; Peuskens 1995]), as well as in several trials whose results await publication (sertindole, seroquel [ICI 204,636], ziprasidone, and MAR 327). In all of these trials, the washout period was 1 week, but for individual patients, depending on the degree of clinical deterioration, the time could permissibly be shortened. An initial washout period of 1–2 weeks has been used in other clinical investigations of antipsychotics (e.g., haloperidol dose–response studies). Some of these trials used single-blind placebo during this period (Volavka et al. 1992, 1995), while others did not (Potkin et al. 1985; Santos et al. 1989; Van Putten et al. 1992; Palao et al. 1994).

In some research facilities, some patients entering the initial placebo period may not have received medication immediately before their enrollment, but the majority of patients entering contemporary phase 3 trials have to be withdrawn from their ongoing antipsychotic medication when they enter the washout period. Thus, 63 percent of the patients entering the European risperidone phase 3 trial (n = 1,362) had to be withdrawn from their previous antipsychotic medication (Peuskens 1995). In the North American risperi-
of the patients (» = 523) were withdrawn from previous neuroleptic medication; 13 percent were withdrawn from lithium (Janssen Research Foundation, unpublished data).

We will next attempt to systematically assess the extent to which the placebo washout period and the active prerandomization treatment period at dose level X meet specific clinical trial design goals, and contrast their benefits and risks. Where appropriate, we will emphasize the implications for the two main subpopulations of patients with schizophrenia usually studied in antipsychotic phase 3 trials—acutely exacerbated patients with a history of responding to typical antipsychotics (historical responders) and chronic patients with a history of treatment nonresponse to typical neuroleptics (historical nonresponders). Further, we will differentiate between patients who are withdrawn from their previous medication (treatment withdrawn) and those who were not receiving medication (treatment delayed) immediately before the start of the washout.

There are many possible objectives of a clinical trial, and an appropriate experimental design must accommodate them. In our assessment of the two run-in strategies, we will mostly limit considerations to implications of the effect on the patient and to the two common clinical trial objectives: (1) estimation and detection of differences in effects before and after receiving study treatment (within-treatment pre-post contrast); and (2) estimation and detection of differences in effects between study treatments (between-treatment contrast).

Goals of the Baseline Period, Problems, and Solutions

Goal 1. Minimize the Carryover Effects of Previous (Nonstudy) Drugs (Shopsin et al. 1972; Kane et al. 1994).

The problem. For treatment-withdrawn patients, residual levels of the antipsychotic medication may affect the outcome of the study. The nature of such pretrial/study treatment interactions may be pharmacodynamic (adding spurious antipsychotic, adverse, or withdrawal effects) or pharmacokinetic (interfering with the biotransformation or excretion of the study compound). The problem of residual antipsychotics is more important in trials involving historical responders than in those involving historical nonresponders, since the residual level of the drug in the system is not likely to be clinically effective in nonresponders.

In the rat, a single intraperitoneal injection of haloperidol hydrochloride produced pharmacologic activity whose apparent half-life was 12.8 days (Campbell and Baldessarini 1985); the brain elimination half-life under these conditions was 16.7 days (Cohen et al. 1988). In humans, the plasma half-life of haloperidol after a single oral dose may be as long as 21.2 days (Hubbard et al. 1987). Based on these observations, it would appear that several months may be required for oral haloperidol to be cleared from the body.

Sampath et al. (1992) followed 24 patients in a discontinuation study of maintenance fluphenazine decanoate after an initial observation period of 12 months. At the end of this period, the patients were randomly assigned to participate in a placebo group or to continue on their dose of fluphenazine. Monthly neuroleptic plasma levels were obtained; neuroleptic activity was demonstrated up to 8 months after the introduction of placebo.

Previous use of street drugs by patients entering the study may substantially affect the results in two ways. The phenomenology of acute toxic psychoses may be difficult to distinguish clinically from acute schizophrenia. Individuals with toxic psychoses are more likely to improve spontaneously than are those with schizophrenia. Further, withdrawal syndromes from street drugs may distort clinical outcomes. The heterogeneity introduced by these effects can inflate the variance and make the statistical distinction of study treatments more difficult. (The problem with street drugs is usually not important in patients who have been hospitalized for more than about a month, which is usually the case with historical nonresponders. By then the acute effects and the withdrawal syndrome have largely dissipated, and access to street drugs in the hospital is usually limited.)

For treatment-delayed patients, carryover effects of the previous antipsychotic treatment do not exist. Street drugs may pose a problem, however.

Solution 1. Placebo washout period. Although their levels are reduced, antipsychotics in the treatment-withdrawn patient's system are certainly not eliminated by a week-long washout period for oral medication or by a washout period of 1 month after parenteral decanoate fluphenazine or haloperidol. Adverse effects such as parkinsonian tremor or rigidity may persist for several months after the discontinuation of oral treatment (Klawans et al. 1973).
The carryover effects of pretrial medication are reduced but not prevented by this design strategy. On the other hand, the problem of prior use of street drugs is alleviated considerably by the placebo washout period.

For patients not on medication immediately before the washout period, the washout period means a delay of treatment rather than its interruption. As pointed out by others in the context of placebo treatments of longer duration (several months), “discontinuing treatment may not be equivalent to not treating” (Baldessarini and Viguera 1995, p. 191). It is likely that this statement also applies to the weeklong placebo washout period. This issue could be elucidated by analyses of unpublished data that have been collected in recent studies (Marder and Meibach 1994; Peuskens 1995).

Solution 2. Prerandomization treatment at dose level X. After the prerandomization treatment, the amount of residual antipsychotics in the treatment-withdrawn patient’s system and the effect on the results of the clinical trial cannot be any smaller—and probably will be greater—than they would be after a placebo washout period. The problem of prior use of street drugs would be addressed as adequately with a PRTP as with the placebo washout period.

For treatment-delayed patients, prerandomization treatment at dose level X could bring about clinical improvement that probably would be greater—than they would be after a placebo washout period. The problem of prior use of street drugs is alleviated considerably by this design strategy. On the other hand, the problem of prior use of street drugs is alleviated considerably by this design strategy. On the other hand, the problem of prior use of street drugs is alleviated considerably by this design strategy. On the other hand, the problem of prior use of street drugs is alleviated considerably by this design strategy.

Comparative evaluation of the placebo washout and prerandomization treatment at dose level X. Neither solution eliminates the carryover problem. However, since every patient switches to the same standard medication and the tapering-off period takes some time, the heterogeneity of residual antipsychotic medication and the resulting highly variable carryover are lessened. This would be true for either a placebo or a low-dose standard treatment period. A problem with the standard treatment period approach may arise if there are interactions among the residual antipsychotic, the standard drug, and the study drug. However, even in this remote case, unless there is an interaction with one but not both of the study drugs, randomization appears to minimize any bias in the estimation of the between-treatment contrast. In general, this contrast does not seem to be compromised by the use of a standard treatment period. However, since patients with low-dose standard treatment are likely to be less severely ill than they would have been with only a placebo, the within-treatment post contrast may have less power with this design approach. (We discuss this further below.)

Patients who are treatment withdrawn probably differ from those who are treatment delayed in their response to placebo washout and to prerandomization treatment at dose level X.


The problem. Regardless of whether they can be distinguished from one another, patients who remit spontaneously or who respond to placebo do not provide an adequate basis for testing the merits of a potential antipsychotic compound. The response of patients with toxic psychoses and those with brief psychotic disorder (American Psychiatric Association 1994) may be considered spontaneous remission. Indeed, some patients with schizophrenia improve even without antipsychotic treatment. Including such patients in a study would spuriously inflate the apparent efficacy of the test compounds.

We hypothesize that the likelihood of placebo response (and perhaps also of spontaneous remission) is greater in patients who have not been treated with antipsychotic medication immediately before the start of the washout period than in those who had to be withdrawn from such medication. Information suitable to test these hypotheses is in the unpublished data bases generated during recent drug studies (Marder and Meibach 1994; Peuskens 1995). Obviously, the issues of placebo response and particularly of spontaneous remission are more pertinent for historical responders than for historical nonresponders.

Solution 1. Placebo washout period. Two methods have been used to exclude spurious responders from clinical trials. In the first, a relative criterion is set that defines an upper limit on the allowed percentage of improvement from the beginning to the end of the washout period. If the limit is exceeded, the patient does not enter the randomization phase of the experiment. In the second approach, an absolute or threshold severity criterion is set. To qualify for entry into the randomization phase, a patient must exhibit at least moderately severe symptoms at the end of the washout period. Both relative and absolute criteria are defined quantitatively in advance and vary depending on the rating scale used. The absolute approach has been used in the recently reported major trials of antipsychotics (Kane et al. 1988; Marder and...
and in the yet-to-be reported trials of sertindole, seroquel (ICI 204,636), ziprasidone, and MAR 327.

**Solution 2. Prerandomization treatment at dose level X.** The approaches described above would prevent the inclusion of spontaneous remitters and placebo responders in prerandomization treatment to the same degree. However, patients who respond to the low-dose level treatment who might not have responded to placebo would also be excluded from the randomization phase.

**Comparative evaluation.** The prerandomization treatment at dose level X may lead to the exclusion of some patients who are very responsive to antipsychotics. Since those remaining have received an active, albeit low-dose, medication, the severity level of their symptomatology may be lower than if they were subject to a placebo washout period. Also, to achieve the same study sample size, more patients may have to enter the prerandomization phase under the standard treatment strategy than under the placebo washout approach. On the other hand, the prerandomization treatment may produce fewer dropouts because there may be fewer acute exacerbations among patients who were withdrawn from their previous antipsychotic medication. Such exacerbations may occur during the washout because of either a withdrawal syndrome (perhaps a supersensitivity psychosis) (Chouinard 1990) or a reduction in the antipsychotic effect of the previous treatment (with or without a withdrawal syndrome).

The question of which design strategy is best with respect to pre-post contrasts is complicated. A design that stratifies the randomization in terms of the severity entry criteria may ensure that the patients entering the treatment part of the study after a PRTP are, on average, as severely ill as those entering after a placebo washout without stratification. However, it is more likely that the placebo washout produces patients with more severe symptoms at randomization. Further, the mean improvement in the double-blind phase would probably be lower after a PRTP than after a placebo washout because the patients most likely to improve may have been excluded. At randomization, the PRTP sample is likely to contain a greater proportion of relatively poor responders. This is more likely to be true for treatment-delayed patients; during the PRTP, some of the responders among these patients may improve to the extent that they fail to meet severity criteria at randomization. It is less likely to be true for treatment-withdrawn patients because dose X will be less effective than the dose from which they were withdrawn. As reported above, the majority of patients who enter typical antipsychotic trials are treatment-withdrawn.

Taken together, these factors suggest that the apparent effect size of a treatment in a design using PRTP would be smaller than after a placebo washout period. As a result, the power to detect a pre-post difference may be reduced to some extent. However, the degree to which this would seriously compromise the apparent clinical value of the antipsychotic being tested does not seem substantial.

On the other hand, because the PRTP is likely to exclude more patients who are extremely good responders to antipsychotics, the power to detect differences between treatments may be improved. In a hypothetical study of two treatments, one of which is superior to another, patients who respond extremely well to both drugs add no discriminating ability to the trial. If the proportion of such individuals is reduced, the power to detect true treatment differences is increased to some extent. In any case, for comparisons between treatments, no bias seems to be introduced with either solution.

The effect of the placebo washout period on the power to detect treatment differences was tested by a metaanalysis of 101 double-blind studies of antidepressants, of which 50 had an initial placebo period and 51 did not (Trivedi and Rush 1994). The results of the metaanalysis indicated no significant effect of the initial placebo period on the power to detect differences in treatment efficacy in a subsequent double-blind part of the study.

**Goal 3. Establish a True Baseline** (Kane et al. 1994) and Enhance Diagnostic Precision (Shopsin et al. 1972).

**The problem.** Antipsychotic medication administered before the trial masks the patient's psychotic symptoms, thus obscuring the true level of disease. This problem is more serious for historically responding patients than for the historical nonresponders, who, by definition, do not improve substantially with pretrial antipsychotic medication. In addition to masking psychotic symptoms, the antipsychotic medication administered before the trial may mask movement disorders.

As formulated above, the problem of establishing true baseline exists only in the patients who were receiving antipsychotic medication immediately before the trial. However, one might argue that the baseline should be established to reflect the patient's behavior after some exposure to the hospital environment (since the drug trial will take place there).
would require an initial washout period even for patients who were not receiving antipsychotic medication immediately before the trial.

Solution 1. Placebo washout period. With respect to psychotic symptoms, we previously observed that historically responding schizophrenia patients who entered a 1-week placebo washout after being withdrawn from antipsychotic medication had a statistically significant amount of clinical deterioration as measured by the Brief Psychiatric Rating Scale (Overall and Gorham 1962) (Volavka et al. 1992). Extending the duration of the washout period beyond 1 week would undoubtedly have resulted in a further increase in symptom severity. The time course of the deterioration can be estimated from the attrition rate of patients assigned to the placebo arm in a recent antipsychotic trial whose subjects were mostly historical responders (Marder and Meibach 1994). Each week, additional patients will deteriorate to the point that they must receive rescue medication. Of course, unless the placebo washout period lasts an unacceptably long time, there is no way of knowing if a deteriorating patient has reached the "true level of disease."

Whether the goal of totally unmasking a patient's symptoms has any justification is questionable. It seems neither ethical nor practically necessary. An appropriate severity criterion for entry into the double-blind phase of the trial can be set that ensures that participants exhibit sufficient psychopathology (e.g., in positive symptoms) that they are representative of individuals with the disease for which the therapy is intended.

1. Movement disorders. The value of a washout period as a means to uncover "any preexisting movement disorders" (Kane et al. 1994, p. 349) is somewhat questionable if the period lasts only 1–2 weeks. After randomization, three factors affect the changes of the severity of dyskinesias: the pretreatment treatment, the effects of withdrawal from that treatment, and the effects of the test drug. Little is known about how these factors interact. Dyskinesia may be temporarily unmasked or enhanced by the discontinuation of antipsychotic treatment (Branchey et al. 1981) and the time course for an individual is not predictable. Further, since parkinsonian tremor and rigidity caused by antipsychotics may persist for several weeks after the discontinuation of oral treatment (Klawans et al. 1973), the currently practicable washout period of 1–2 weeks is not long enough for these adverse effects of the previous medication to subside.

2. Plasma homovanillic acid (pHVA). Long-term administration of antipsychotics reduces the dopaminergic transmission in the brain. Levels of pHVA are affected by the dopaminergic transmission in the brain. Therefore, the pHVA levels have been used to study the pharmacodynamic effects of antipsychotics. In general, the pHVA increases after the discontinuation of long-term antipsychotic treatment. Such increase was observed to continue throughout the drug-free period of 5 weeks after the discontinuation of oral fluphenazine (Pickar et al. 1986). In a similar study, the pHVA increase after antipsychotic withdrawal was more pronounced in patients who clinically decompensated during the 6-week drug-free period. These patients seemed to show a peak pHVA increase around 4 weeks after their antipsychotic treatment was discontinued (Davidson et al. 1991). Taken together, the pHVA data indicate that a washout period of 1–2 weeks causes large changes in the central dopaminergic transmission and that these changes may vary with the clinical effect of the drug withdrawal.

For treatment-delayed patients, the placebo washout period serves to establish the true baseline under the hospital conditions.

Solution 2. Prerandomization treatment at dose level X. In treatment-withdrawn patients, prerandomization treatment might also result in the unmasking of some previously controlled psychotic symptoms, depending on the dose level X. However, the unmasking would be less pronounced than that associated with placebo treatment. Prerandomization treatment may unmask tardive dyskinesia, but as in the case of psychotic symptoms, the unmasking probably would not be complete. A standard treatment period of 1 week would not be expected to have much effect on a preexisting parkinsonian tremor and rigidity.

For treatment-delayed patients, prerandomization treatment would obscure the true baseline and therefore it would be unacceptable.

Comparative evaluation of the placebo washout and prerandomization treatment at dose level X. For treatment-withdrawn patients, somewhat fewer symptoms would be unmasked by prerandomization treatment than by placebo, but this would not be likely to bias or otherwise affect the between-treatment contrast. As above, there might be some loss in power for the within-treatment contrast. If a lead-in period is used for treatment-delayed patients, then the placebo washout is clearly superior to treatment X.

Discussion

Many researchers have considered
the value of a run-in period, particularly as it relates to compliance in outpatient settings in other fields of medicine. For example, Davis et al. (1995) in an empirical study found that a placebo run-in period would have had little effect on the outcome and would have increased recruitment difficulties. Schechtman and Gordon (1993) studied the value of a placebo run-in period with respect to cost-effectiveness in a randomized clinical trial. Their results relate to the association between adherence and response to treatment. Brittain and Wittes (1990) gave a statistical model of adherence to the protocol and after simulation concluded that the value of a run-in period depends on the proportion of nonadherers and the ability to detect them during the prerandomization phase. With either a high degree of adherence or a poor ability to detect nonadherers, the run-in period is undesirable, especially when the cost of recruitment is high.

Covert noncompliance with treatment is not uncommon among psychiatric inpatients, including those who consent to participate in treatment trials. Some of that noncompliance is attributable to the unpleasant side effects of antipsychotic treatment. Thus, compliance might be better with placebo than with an active treatment. However, as discussed above, a weeklong placebo period may not be long enough to effect perceptible changes of side effects in the patients who are withdrawn from antipsychotics. In any event, we are not aware of any data on treatment compliance during placebo washout.

In the literature on antipsychotic trials, the prerandomization washout period has been justified by one or another of the three goals that we have reviewed. We have examined the extent to which these goals are attained by the washout period and by an alternative method—the low-dose PRTP. From the standpoint of the possibility of bias in the comparison of study treatments, the differences between the two methods are marginal. However, the PRTP may result in a loss in power for pre-post treatment contrasts and an underestimate of the magnitude of the effect size in a random sample of patients. This may be a worthwhile price to pay for ethical advantages and practical benefits. Clearly, the low-dose prerandomization treatment must be given serious consideration as an alternative to a washout period in phase 3 trials of antipsychotics.

Whether a placebo washout period or a low-dose PRTP is used, more use must be made of the statistical information obtained during this period to make the trial more efficient. Libiger et al. (1994a, 1994b) found a relationship between the change during a 1-week placebo washout period and short-term clinical response. Patients who deteriorated most during the washout period tended to show greater improvement after subsequent treatment with active medication. Thus, results obtained during the washout period may be used to good advantage at the time of randomization. By stratification, the random assignment of deteriorated patients should be balanced among the test treatments. Data collected during the prerandomization period may contain other predictors of treatment response, markers of disease subtypes (e.g., Kraepelinian [Kraepelin 1919/1961] vs. others), and perhaps other heuristically important features. These too may reduce variability and increase power.

There is some uncertainty as to the appropriate treatment and dosage to use in the proposed treatment replacing the placebo washout period. The requirement set up for dose X may possibly be met by haloperidol using dosages around 5 mg/day (Volavka et al. 1995). This suggestion is meant as a starting point for a discussion that, we hope, our article will elicit.

The literature on the run-in period ignores the differences between patients who enter the period after they are withdrawn from antipsychotic treatment and those who were not receiving such treatment immediately before that period. We hope that the effects of the run-in period on these two groups of patients will be studied. Until the results of such studies are available, it may be prudent to assume that they are different from each other. The use of stratification to balance on this factor should be considered in the design of future studies.

In conclusion, we recommend that investigators carefully consider the need for a placebo washout period in an experimental design and weigh its merits against alternatives such as the PRTP. The information on response during the prerandomization period may be useful, and researchers should include the analysis of such data in their publications. We believe that the response to a run-in period in treatment-withdrawn patients may be different from that in treatment-delayed patients, and we hope that this issue will be studied.

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