Commentary

Estimating the Impact of the Discontinuation of Medical Interventions on Health Outcomes

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The same study designs are used to document the magnitude of the influence of currently used and of previously used treatments on health outcomes. However, because randomized trials rarely are utilized to study cessation of treatment, most of what we know about the experience of former users of a given treatment comes from cohort and case-control studies. These studies generally compare former users with never users or current users, but occasionally different groups of former users are compared according to how long ago the treatment was stopped. The experience of whole populations following relatively rapid and widespread discontinuation of a previously common treatment sometimes can serve as a secondary source of data on the consequences of discontinuation of therapy.

Once begun, some medical interventions are administered over the remainder of a patient’s lifetime, but most are not. Stopping an intervention (e.g., a medication, radiation therapy, physical therapy) often leads to a reduction in or loss of the risks and benefits associated with actively receiving it. Documentation of the timing of such a reduction can produce insights into the means by which the intervention gives rise to these risks and benefits. For example, the relatively rapid decline in the excess risk of endometrial cancer that accompanies cessation of postmenopausal estrogen therapy (1) argues that such treatment influences a relatively late stage in the development of endometrial neoplasia. In a corresponding way, the extended reduction in risk of ovarian cancer following discontinuation of the use of oral contraceptives argues in support of the hypothesis that a relative deficiency of one or more gonadal hormones can act at an early stage in the genesis of this malignancy.

Nonetheless, the primary purpose of studying the impact of stopping therapy is a practical one: to inform patients and their providers of the duration of the altered risk of favorable and unfavorable health outcomes that had been present while the treatment was being used. Additionally, such research can identify outcomes whose occurrence is atypical only upon cessation (e.g., medication withdrawal phenomena). Ultimately, information from studies of the experience of persons following cessation of treatment bears on both the decision to use the treatment in the first place and the decision to continue or stop that treatment later on.

The epidemiologic approaches available to measure the consequences of cessation of treatment are largely the same as those available to measure the consequences of initiation of treatment. These approaches include randomized trials; cohort and case-control studies; and, at a population level, correlations of incidence trends in health outcomes with trends in utilization of the treatment.

RANDOMIZED TRIALS

Occasionally (although not very often), investigators will design a trial in which, among persons receiving a particular treatment, some will be invited at random to discontinue it. For example, of 1,013 patients who had been receiving antiepileptic drug treatment and had been free of seizures for at least 2 years, 59% of those randomized to have their medication gradually withdrawn remained seizure-free during the ensuing 2 years, in contrast to 78% of patients who continued the antiepileptic treatment as before (2).

Information relevant to the consequences of stopping therapy occasionally can be obtained from the further follow-up

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of participants in a randomized trial in which the intervention has been discontinued. For example, Heiss et al. (3) monitored the incidence of breast cancer and a variety of other health outcomes in women who had taken part in one component of the Women’s Health Initiative—the randomized trial comparing combined hormone therapy and placebo—during an average of 2.4 years after that trial had been concluded. Both the incidence of breast cancer in the women who had been assigned to receive combined hormone therapy (0.34 per 100 woman-years) and the 1.26-fold increase that such an incidence represented beyond that for women assigned to receive placebo were the same during the trial and the posttrial follow-up. These data argue that, for at least 2 years, the adverse influence of combined hormone therapy on breast cancer risk persists.

There are 3 potentially important limitations of using the posttrial experience of study participants to draw inferences regarding the impact of cessation of use of an intervention.

1. If the results of a randomized trial suggest that use of the intervention examined had benefits that exceeded its risks, it is likely that, at the conclusion of the trial, only a small portion of trial participants assigned to be given this therapy would in fact stop using it. The fact that the investigators involved in the hormone component of the Women’s Health Initiative trial could use posttrial data to gauge the consequences of hormone cessation was attributable to the very small fraction (just 4%) of women taking hormones at the end of the active phase who continued to do so after the trial had been stopped.

2. The duration of follow-up may be short, and any altered risk present during this period of time may not reflect that which exists over the longer term. Almost certainly, the reason that nonrandomized studies have obtained a very different result from the Women’s Health Initiative with regard to breast cancer incidence in former users of combined hormone therapy—researchers have observed little or no increased risk (4)—is that the results of the nonrandomized studies reflect the experience of many women beyond the first 2 years following cessation of therapy.

3. By the end of the active phase of a randomized trial, adherence to the intervention may not be high and almost certainly will be lower than at the start of the trial. For example, in the combined hormone arm of the Women’s Health Initiative trial, there was a gradual decrease in the percentage of women continuing to receive therapy during the 5.6-year duration of the study, with but 58% of women still adherent at the end. Thus, in an analysis based on “intent to treat,” a smaller difference in the incidence of a given health outcome between treatment and control groups in the postintervention phase compared with the experience during the trial may be as much attributable to a change in adherence over time during the trial as to the waning influence of the discontinued intervention.

Anticipating the limitations of an intent-to-treat approach, for selective outcomes Heiss et al. (3) also presented an analysis of the posttrial experience confined to participants who, as of the conclusion of the trial’s active phase, were at least 80% adherent to the assigned study medication and had been so during the entire study. To minimize the potential bias associated with failure to include about half the study population, the authors assessed the predictors of adherence during the active phase and weighted the statistical contribution of each woman by the inverse of the predicted likelihood of her adherence (5). For the incidence of hip fracture during the active phase of the study, they observed a 24% reduction in risk for women assigned to combined hormone therapy. During the 2.4-year posttrial follow-up, the corresponding reduction based on an intent-to-treat analysis was 9% and that based on the weighted analysis confined to medication-adherent women was 13%. As expected (based on prior trials of hormone use in relation to bone density and on nonrandomized studies of hormone use in relation to hip fracture), the skeletal benefit of combined hormonal therapy was observed to wane once treatment had been stopped, but probably not as much as would have been suggested by the intent-to-treat analysis.

**COHORT AND CASE-CONTROL STUDIES**

Because data from randomized trials bearing on the impact of stopping treatment are relatively sparse, we must rely heavily on the results of cohort and case-control studies.

**Bases for comparison with the incidence following treatment discontinuation**

In deciding to initiate use of a medication or other medical intervention, a patient and his or her provider want to know the size of the respective benefits and risks of that intervention, both while it is being used and after it has stopped being used. In many instances, this information can be obtained in cohort and case-control comparisons of current users with nonusers and of former users with nonusers. For example, on the basis of the results of a meta-analysis of primarily cohort and case-control studies, Lee et al. (4) estimated that a woman’s risk of breast cancer is increased by about 8% per year of use of combined hormone therapy while she is actively taking one of these preparations but only by about 1% per year of use after she has discontinued them.

Among persons who have already initiated a therapy or preventive intervention, data bearing on the decision to remain on it will come from direct comparisons of the experience of continuing and former recipients of the treatment. Occasionally, a comparison of continuing and former users actually is needed to obtain an unconfounded estimate of drug efficacy and/or safety in current users. That is, the incidence among former users is used to estimate the expected incidence in current users in the absence of a drug effect. For example, the occurrence of suicide was compared between current and former users of clozapine (an antipsychotic drug) in the United States because 1) no data were available on suicide mortality in a comparable group of psychotic individuals who were medication nonusers or users of other antipsychotic agents; and 2) rates in the US population at
large, a good basis for comparison in many cohort studies of Americans, would greatly underestimate the expected mortality from suicide among persons who would be candidates for clozapine treatment (6).

Finally, if it is expected that certain adverse effects are associated only in the short term following withdrawal of a medication, the incidence of those events can be compared between persons who recently stopped and those who stopped some time in the past. As an example, the drug clopidogrel often is used for a number of months by patients after they have undergone acute medical or surgical therapy for coronary disease. Ho et al. (7) observed that, among 1,568 persons treated at Veterans Affairs hospitals in the United States who completed a course of clopidogrel therapy, the occurrence of myocardial infarction and mortality during the first 90 days after cessation of use greatly exceeded the corresponding incidence afterward.

Potential limitations of cohort and case-control studies assessing the impact of treatment discontinuation

Two such limitations are as follows:

1. Misclassification of the timing of cessation of treatment: All of the various means of ascertaining the date of treatment discontinuation—interviews, medical records, and (increasingly) pharmacy databases—may be inaccurate to at least some degree. Errors of a few days or weeks are of little consequence when the time period in question is lengthy, for example, the incidence of breast cancer in the years to decades following cessation of use of combined hormone therapy. However, when investigating the potential short-term deleterious influence of cessation of such drugs as clopidogrel, being unable to reliably distinguish between current, very recent, and not-so-recent users will dull the ability of a given study to identify the existence and size of an association if one is truly present. Aware of this potential source of bias, the clopidogrel study investigators—who had ascertained use of this drug and its cessation exclusively from the Veterans Health Administration Pharmacy Benefits Management database—conducted a series of supplementary analyses in which, for a random sample of the study population, the initially estimated date of drug cessation was moved either forward or backward by as much as 30 days, and the results of these analyses were compared with those obtained in the principal analysis (7).

2. Confounding: The validity of assessing the consequence of stopping treatment by means of a cohort or case-control study rests heavily on the investigator’s ability to distinguish the influence of stopping from the reasons for stopping. The means available to accomplish this task—restriction, adjustment, and (in cohort studies) matching—are exactly those available in any non-randomized epidemiologic study. In the examples described earlier, particular efforts were made to examine subgroups of the study population in which there was little likelihood that cessation of treatment, or the timing of cessation, was related to the outcomes under study. For instance, one analysis of the clozapine study focused on persons who stopped using the drug for nonpsychiatric reasons, specifically the development of leucopenia, as a basis for comparison with current users. Current users had a low rate of suicide relative to that in both this former-user group and, to a similar degree, in the group of patients stopping clozapine for other reasons (presumably persistent psychiatric morbidity in many instances). These observations argue in favor of the hypothesis that use of clozapine leads to a lowered risk of suicide rather than that the inherent risk for patients who stop the drug is atypically high.

Of course, in these studies, confounding can be controlled only to the extent that one can identify and measure those factors that bear on the likelihood of both cessation of a given therapy and the particular outcome under consideration. In contemporary pharmacoepidemiology, administrative databases are a commonly used source of data, and these databases generally lack information pertaining to the reason(s) for treatment discontinuation. As a consequence, they may prove less than ideal when seeking to address the consequences of cessation of a number of forms of therapy.

In comparisons of the incidence of a given outcome between current and former users of a therapy, when should duration of use be considered a confounding factor? For treatment administered over a very brief period of time, or whose administration varies little from patient to patient (e.g., a 10-day course of an antibiotic), the issue of confounding by duration of treatment does not arise when examining the influence of stopping that treatment. Even if duration varies widely (e.g., for combined hormone therapy) and duration of use is related to the outcome under consideration, the means by which it is dealt with will be influenced by the specific question being posed. For example, if one wants to estimate the degree of reduction of breast cancer risk for former users of combined hormone therapy relative to that for current users, it is not appropriate to adjust for total duration of use; the additional duration accrued by a given current user, relative to her counterpart who quit, is a consequence of the decision to continue. Only if the goal of the study were one of prediction—To what degree does recency of use predict risk beyond total duration of use?—would it be appropriate to adjust for total duration. Further discussion of this issue has been provided by Weiss and Dublin (8).

The study of mortality from myocardial infarction in relation to recency of cessation of clopidogrel use dealt with yet another threat to validity arising from the fact that, during a several-month period following the cardiovascular event that led to initiation of clopidogrel, the rate of myocardial infarction and death would be expected to drop, even in the absence of effective therapy. If persons who stopped clopidogrel tended to do so relatively soon after starting to use the drug, the rate of myocardial infarction and death would be higher among recent than not-so-recent stoppers, even if cessation had no impact on the occurrence of these adverse outcomes. However, in this study, it was observed that the size of the transient excess risk was similar among persons who stopped early (within 90 days after the cardiovascular
event that prompted use of clopidogrel) and among those who stopped much later, that is, after 270 days. Because the rate of myocardial infarction/mortality is likely to become relatively stable once a number of months have elapsed following the cardiovascular event that leads to use of clopidogrel, confounding from this source is unlikely to be the sole explanation for the observed increase in myocardial infarction and mortality seen very soon after clopidogrel had been stopped.

POPULATION-LEVEL TRENDS

When a sizable fraction of users of a given treatment within a population abruptly stops using it, examination of time trends in the incidence of conditions influenced by current use of that treatment may shed some light on the consequences of cessation of use. For example, the decrease in the incidence of endometrial cancer in the United States in the mid-1970s that coincided with the large-scale decrease in the use of unopposed estrogen therapy (1) argues that at least some of the excess risk of this disease diminishes quickly once estrogen use is stopped. However, trends in reported incidence can be affected by a number of factors, including changes in diagnostic criteria and the prevalence and type of screening. An interpretation of a drop in incidence needs to consider these factors, as well as the possibility that other determinants of the health outcome in question (including the rate of initiation of the therapy) may be changing over time, too. In addition, it may be difficult to document accurately the timing and magnitude of a particular population’s abandonment of a form of therapy.

For all of these reasons, we generally cannot look to time trends in population incidence to quantify the size and speed of the expected change in risk for an individual who has stopped receiving a particular therapy. Results of cohort and case-control studies (and, in the uncommon instances in which they are available, results of randomized trials) generally will be a better guide to our understanding the consequences of the cessation of therapy, with the examination of time trends in incidence serving as but a blunt means of confirmation.

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