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Primary non-adherence and the new-user design

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1 | INTRODUCTION

The new-user design has been widely used in pharmaco-epidemiology.^{1,2} By following patients from the initiation of a treatment, the new-user design has several advantages over designs that begin follow-up on prevalent users. The new-user design allows study of the full time course of outcome risk after treatment initiation, with representation of early and late events.^{1,3,4} It also ensures appropriate temporal ordering of baseline confounders, exposures, and outcomes, avoiding adjustment for intermediate variables that may have been affected by treatment.¹ Coupled with an active-comparator design,⁵ new-user approaches can mitigate the potential for immortal time-bias⁶ and confounding by indication.⁷ The active comparator new-user design helps to articulate clearly a causal question about the benefits and harms of starting a particular intervention in a more real-world setting.⁸ These theoretical and conceptual advantages have led to the recommendation that such designs should be a default approach for comparative effectiveness research studies.^{2,9,10}

The new-user design is a special case of the treatment decision design,¹¹ which begins follow-up at the times when treatment decisions are made (Figure 1). Framing the research question and analysis in this way connects estimates to treatment decisions, providing information that is directly relevant to clinicians and patients. In the analysis, researchers often present an observational analog to the “intention-to-treat analysis,” in which patients are analyzed by their initial treatment (or assigned treatment) group, regardless of treatment changes and non-adherence that occur during follow-up. The use of the language from randomized controlled trials suggests that, under the assumption of no uncontrolled confounding, these adjusted estimates are similar to what one would obtain in parallel group randomized controlled trial conducted in the same population.

However, when treatment groups are inferred from the treatment actually started by patients, we are implicitly conducting our analysis among the “treatment compliers,” those patients who will follow the treatment decision made during their encounter with the clinician (Figure 1). Non-adherence to initial treatment decisions has been termed “primary non-adherence” or “primary non-compliance,”^{12,13} and has been found to be substantial in

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CONFLICT OF INTEREST

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several studies.^{13–15} Comparing prescription orders and filled claims using data linking electronic prescribing records and pharmacy claims, primary non-adherence ranged between 23% and 55% for new medications intended for chronic use among a large cohort of adult patients,¹³ and 15% and 17% for antidiabetics and antihypertensives, respectively.^{16,17} Using data from integrated health care delivery systems, primary non-adherence ranged between 5% and 13% for newly initiated oral medications for hypertension, diabetes, and/or hyperlipidemia.¹⁸ The higher rates of primary non-adherence in the first citation might be attributable to patients obtaining prescriptions outside of the context of their insurance (eg, paying out of pocket), which would have appeared as primary non-adherence as no pharmacy claim would have been generated. Multiple factors have been associated with primary non-adherence, including patient age, physician specialty, prescription copayments, prescription of brand-name drugs, medication class, and delivery route of prescriptions.^{13,14}

Non-adherence to treatment has been extensively studied. Undoubtedly, non-adherence can occur throughout the course of a treatment. Methods exist to estimate effects of treatment under full compliance and perfect adherence, including Robins' generalized methods.^{19,20} However, discussion of correction methods in the literature has typically focused on secondary non-adherence, which occurs later in the course of treatment relative to primary non-adherence (Figure 1). To our knowledge, primary non-adherence to initial treatment decisions has not been discussed as a methodological challenge in comparative effectiveness research, although several studies have examined ways to correct estimation of medication adherence when it is an outcome of interest.^{21–23}

In the presence of primary non-adherence, conditioning on starting treatment (eg, filling a prescription) changes the study sample from one that has been prescribed a treatment to the selected group of patients who were both prescribed treatment *and* were initially adherent to that treatment. This sample may be systematically different from the desired target population, which is (usually) individuals who were prescribed treatment. Although we are often interested in the effect of the decision to start a patient on treatment, we can often only identify the patients who adhered to the decision with the new-user design when inferring treatment groups from the treatment actually started by patients.

Consequently, by conditioning on initiating treatment, the new-user design yields an estimate of an average treatment effect in the population of primary compliers (Figure 1). While we are interested in the effect of the treatment decision, $E[Y^Z = 1 - Y^Z = 0]$, where Z denotes the assigned treatment and Y^Z denotes the counterfactual outcome of interest, we would be able to estimate this effect if we have treatment decision and factors contributing to such decision measured. However, conditioning on primary adherence as implicitly done with the standard implementation of a new-user design, the estimate changes to the effect of the treatment decision among adherers (who collect an initial prescription), $E[Y^Z = 1 - Y^Z = 0 | A = 1]$ where A indicates whether the patient filled the initial prescription. The interpretation of such effect estimates is complicated by 2 potential biases: sampling bias and selection bias. These 2 biases pose threats to different aspects of study validity despite the similarity it may seem at first glance.

Primary non-adherence could impair external validity in a specific target population via sampling bias.^{24,25} When new use is an eligibility criterion to identify the study sample and the propensity of primary adherence is affected by certain patient characteristics, the resulting study sample of primary compliers is not a random sample of the target population of interest. Imagine a target population that consists of 80% of males and 20% females who were prescribed a treatment, and all female patients initially adhered whereas only 50% of male patients initiated. When we identify the study sample by conditioning on initiating treatment with the new-user design, the male to female ratio in the study sample would be 2:1 instead of 4:1 in the target population. When the treatment effect is heterogeneous by gender, sampling bias occurs, where the estimate in such a study sample may not generalize to the target population.

Primary non-adherence could also impair internal validity via selection bias, similar to secondary non-adherence.²⁶ This could be viewed as a missing data problem as we only have information such as prescription fill data on adherers. Restricting to patients with complete data (as implicitly done by a new-user design) yields estimates in a selected subgroup of patients. It is common that factors such as socioeconomic status cause both primary adherence and outcomes. For example, if patients face high out-of-pocket costs for a therapy, new users of that therapy with prescription fill data may consist of patients of higher socioeconomic status who are less price sensitive. In such settings, conditioning on primary adherence (and restricting to those having prescription fill data) opens a back-door path from the treatment decision to the outcome through socioeconomic status, creating selection bias in estimates of the effect of the treatment decision (Figure 2).²⁶

The type of bias, sampling bias or selection bias or both, that primary non-adherence could cause depends on the target population of interest and missing data. There has been a lack of clarity in the literature as to the distinction between sampling bias due to a lack of generalizability (external validity) and selection bias due to missing data (internal validity).²⁴ This point is clarified by specifying a target population a priori.²⁵ Specifically, once a target population is well defined and eligibility criteria are used to identify the study sample, then patients excluded from a study sample due to ineligibility cannot affect internal validity and do not cause selection bias as it is generally construed. However, care must be taken to make inferences to the target population also defined by such exclusions, and a sampling bias may be present if results are generalized to other target populations. Of course, eligible patients removed from the study sample due to missing data may affect internal validity because their removal might cause a selection bias. Alternatively, one can alter the target population to exclude such people, and thereby trade sampling and selection biases. In doing so, one should be guided by a scientific rationale.

Fortunately, the increasing availability of electronic health record and e-prescribing data creates an opportunity to study the problem of primary non-adherence, specifically for prescriptions intended for chronic-use. Primary non-adherence for medications meant to be used sporadically should be treated differently and is beyond our scope. Characteristics of the overall sample prescribed the medication and the complier sample can be reported.^{13,18} If substantial differences were observed, using assumed models of the primary non-adherence mechanisms, results from the complier sample could be generalized to the target

population using, for example, inverse-probability weighting when all relevant factors contributing to primary non-adherence are measured.²⁴ Furthermore, the order date of the prescription by physicians can serve as a more meaningful index date, approximating that of the randomization date origin in randomized controlled trials. Such an approach could also potentially address the problem of missing exposure data caused by low-cost generics²⁷ or free medication samples.²⁸ Primary non-adherence also exists in trials when individuals assigned treatment do not take the treatment. Including the primary non-adherers in observational studies, thus, brings us closer to trials when patients are analyzed by their initial assigned treatment group. Augmenting the prescription fill data with treatment decisions as evidenced in the electronic health data or e-prescribing data, we would be able to study the predictors of primary non-adherence and better understand the population we are studying and to whom our results apply.

One limitation in the perspective that we have described herein arises when one considers the cause of primary non-adherence. Our discussion thus far has assumed that primary non-adherence is preventable, eg, patients declining treatment because of economic reasons. It is of interest to include such patients who are price-sensitive in the study population because we are interested in the effect of treatment among patients starting treatment and these patients are potential users when economic factors are removed. However, some primary non-adherence may not be preventable, eg, patients declining treatment because of religious or cultural belief. Clearly, patients who would never accept treatment should be excluded from the study population. The effect of treatment in such patients would not be estimable and would be of little clinical or policy relevance. To avoid including patients with non-preventable primary non-adherence in the study population, researchers should take steps to exclude these patients a priori, eg, by requiring that patients have some use of the health care system during a baseline period.

In summary, primary non-adherence to initial treatment decisions is substantial among patients newly prescribed medications but remains underappreciated in the literature relative to secondary non-adherence, which occurs later in the course of treatment. Discussion of primary non-adherence will help epidemiologists understand the population under study and to whom study results apply. In particular, having a precise definition of the study population of interest a priori will help minimize unnecessary biases.

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KEY POINTS

- Primary non-adherence to initial treatment decisions is substantial but remains underappreciated in the literature.
- Typical implementations of the common new-user design may not yield the desired effect estimate in the presence of primary non-adherence.
- Discussion of primary non-adherence will help epidemiologists understand the population under study and to whom study results apply.
- Having a precise definition of the study population of interest a priori will help to minimize selection bias or sampling bias.

FIGURE 1.

Study population by source of anchoring point. The choice of anchoring point determines the treatment effect being estimated. In the presence of primary non- adherence, studying a sample of treatment compliers yields a corrupted observational intention-to-treat effect. This effect is corrupted (differs) from one we would get from studying the prescribed treatment group

FIGURE 2.

Restricting to a level of a common effect (primary adherence) of treatment decision, factors, and a cause of outcome creates bias of the treatment decision and outcome relationship by opening a back-door path from the treatment decision to the outcome through these factors such as socioeconomic status (SES)