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Invited Commentary: The Prevalent New User Design in Pharmacoepidemiology: Challenges and Opportunities

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ABSTRACT

The prevalent new user design includes a broader study population than the traditional new user approach that is frequently used in pharmacoepidemiologic research. In an article appearing in this issue (Am J Epidemiol. XXXX;XXX(XX):XXXX–XXXX), Webster-Clark and colleagues describe the treatment initiator types included in the prevalent new user design and contrast the causal questions assessed using a prevalent new user design versus a new user design. They further applied a series of simulation studies showing the importance of accounting for treatment history in addition to time since initiation of the comparator in the prevalent new user design. In this commentary, we put their findings in the broader context with a discussion of the strengths and limitations of the prevalent new user design and settings where it may be most useful. The prevalent new user design and new user design both address unique questions of clinical and public health importance. Real-world evidence generated by pharmacoepidemiologic research is increasingly being used by regulators and other knowledge users to inform their decision making. Understanding the causal questions addressed by different designs is crucial in this process; the study by Webster-Clark and colleagues represents an important step in addressing this issue.

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The real-world evidence generated by pharmacoepidemiologic research is playing an increasing role in clinical and regulatory decision making. Indeed, as part of the 21st Century Cures Act of 2016, the U.S. Food and Drug Administration launched the framework for evaluating the potential use of real-world evidence to support the approval of new indications for already approved drugs and to support post-marketing surveillance(1). This act followed the creation of several national post-marketing drug safety networks that were created to support regulators and other government partners such as the US Sentinel System, the Canadian Network for Observational Drug Effect Studies (CNODES), and the Asian Pharmacoepidemiology Network (AsPEN)(2).

With trials often conducted in ideal conditions at academic centers with highly-selected patient populations, observational studies provide complementary evidence regarding the use, effectiveness, and safety of prescription drugs in actual clinical practice. The evidence provided by observational studies is thus highly generalizable. Despite this benefit, such studies are difficult to conduct given their observational nature, underscoring the need for robust study design and analytical approaches to reduce the biases common in pharmacoepidemiology. Historically, this has involved the use of a new user design(3), which avoids the biases associated with the study of prevalent users. The active comparator, new user design (ACNU)(4) builds upon this approach, reducing potential confounding by indication and providing a more clinically relevant comparison. However, these approaches require new users (i.e., individuals with no previous use of the treatment under investigation or its comparator), which may not be feasible when studying newly-marketed drugs, drugs used to treat conditions with dynamic, multi-staged treatments (e.g., type 2 diabetes), or in the presence of formulary restrictions, where the natural comparator is often used prior to the treatment of interest. In such situations, the use of a new user or ACNU design may exclude a large

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number of patients who received the drug of interest in clinical practice. This could greatly reduce the generalizability of study results, a key advantage of observational studies(5).

The prevalent new user design was developed for the study of prescription drugs in such scenarios(6). In this approach, new users of the treatment of interest are matched to users of a comparator treatment selected from time- or prescription-based exposure sets; these users are also often matched on time-conditional propensity scores. By matching on previous history, this approach reduces potential confounding by indication and the potential consequences of a depletion of susceptible patients (i.e., prevalent user bias).(7) It also allows for the inclusion of the large majority of users of the drug of interest. For example, in our recent prevalent new user study of the antidiabetic sodium-glucose cotransporter-2 (SGLT2) inhibitors and the risk of major adverse cardiovascular events, 77.5% of the new users of SGLT2 inhibitor were included in the final matched cohort; using an ACNU design, 50.5% of new users would have been excluded because of previous use of the comparator drug (dipeptidyl peptidase-4 inhibitor)(8). The prevalent new user design is increasingly being used in pharmacoepidemiologic studies.(9-14)

In this issue of the *American Journal of Epidemiology,* Webster-Clark and colleagues examine the prevalent new user design, describing its initiator types (new users, direct switchers, and delayed switchers)(15). In addition, they contrast the causal parameters of interest in the prevalent new user design ("what if initiators of treatment A had instead initiated, continued, or restarted treatment B at the time of their treatment initiation?") with that addressed by the ACNU design ("what if new users of treatment A naïve to treatment B had instead, counter to fact, started using treatment B?"). Finally, the authors conducted a simulation study with seven scenarios, demonstrating that conditioning on time since initiation of the comparator can bias treatment effects

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in some scenarios that depend on the association between treatment history and the risk of the outcome.

This study has several key strengths. First, by examining the types of users included and the causal parameters investigated, it provides a more explicit understanding of the study populations and facilitates the interpretation of results of studies that use ACNU and prevalent new user designs. Differences in included user types and causal parameters estimated represent potentially important yet underappreciated sources of heterogeneity among published studies. Given the increasing use of real-world evidence generated using these approaches by regulators and other knowledge users, this is particularly important. Second, through its simulation study, it highlights the need to properly consider treatment history when matching new users of the treatment of interest to their matched comparators. Although there remains a need to further examine this issue under conditions that reflect the complexities found in a real-world setting, these simulations provide initial evidence of some scenarios that represent potential threats to the validity of the prevalent new user design.

Despite these important contributions to the literature, there remains a need for further studies in this area. The authors focused their discussion of causal parameters and their simulation study on an exposure definition that is analogous to an intention-to-treat approach, while many of the studies that have implemented the prevalent new user design(8, 9) used an as-treated (or per protocol) exposure definition in which patients were censored upon treatment discontinuation. The differences in exposure definitions have important implications for the interpretations of the causal parameters(16). While the authors investigated seven scenarios in their simulation study, there is a need to explore other situations in future studies that represent the more complex circumstances found in the real world. First, changes in treatment status are often informative and may be affected

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by treatment history, disease progression, and the occurrence of side effects. For example, the decision to switch antidiabetic drugs or add a second antidiabetic agent may be due to not achieving the targeted HbA1c level, while switching or discontinuation may occur because of the occurrence of an adverse event. In addition, the choice of treatment may depend on the types of antidiabetics they have used in the past. In the present study, these issues were simplified, with treatment decisions only relying on a few covariates. It is also worthwhile to explore different analytic approaches under different data-generating mechanisms and under various magnitudes of the associations between treatment history with either treatment switching and the outcome that reflect the range of plausible values (e.g., when treatment history is a weak confounder but a strong instrumental variable for the treatment decision). Second, as mentioned by Webster-Clark and colleagues(15), the switching patterns and reasons for switching may be specific to the treatment and outcomes of interest; therefore, the magnitudes of bias and precision introduced by ignoring treatment history may vary by study. Future studies that utilize plasmode simulation(17), which generate simulated datasets that could reflect the treatment patterns and conserve the covariate correlation structures of the real-world datasets, may further increase our understanding of the different study design approaches. Finally, with its use of exposure sets and time-conditional propensity score matching, the implementation of the prevalent new user design may be complex (e.g., matching with and without replacement, issues of correlated data when patients contribute to both exposure groups), particularly in multi-database studies where differences in data structure also exist. There remains a need to examine the implications of these methodological issues and to facilitate the implementation of the prevalent new user design in modular programs and research platforms commonly used in pharmacoepidemiology.

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Webster-Clark and colleagues(15) focused on the use of the prevalent new user design for head-to-head comparisons of two treatments of interest. They also mentioned some other scenarios where it may be useful, including the study of treatment augmentation and discontinuation. This design may also offer some advantages when comparing an active treatment to an unexposed group among patients with the same underlying condition. For example, Tran and colleagues(14) examined the effectiveness of proton pump inhibitors among patients with idiopathic pulmonary fibrosis. From a base cohort of patients with idiopathic pulmonary fibrosis, the investigators matched a new user of a proton pump inhibitor to a patient with a physician visit within one month of the date of the proton pump inhibitor prescription who remained unexposed (these patients are said to be from the same 'exposure set'); patients were also matched on time-conditional propensity score. In doing so, there was a clear date of cohort entry, which can help to avoid immortal time bias(18). Defining the cohort entry date is usually challenging when implementing a new user design in such scenarios.

The causal question addressed in the prevalent new user design is a heterogeneous one because of the different user types included using this approach. While the inclusion of several user types may complicate the interpretation of results, it is also reflective of the wide variety of patients seen in clinical practice. The prevalent new user design thus provides an average treatment effect across user types. However, effect modification by previous history (or user type) is possible, and the inclusion of relevant subgroup analyses allows for the assessment of its presence. If no effect modification is present, this approach provides highly generalizable results by including the vast majority of relevant patients. If effect modification is found, these strata-specific treatment effects

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may allow for the identification of patients most likely to benefit from the initiation of the treatment of interest and potentially an additional step towards more personalized medicine.

A key challenge, however, is the identification of the most clinically and etiologically relevant user types. Many previous studies that used a prevalent new user design classified patients as either incident new users (i.e., those without a prior history of the treatment of interest and no use of its comparator over a predefined time period) or prevalent new users (i.e., those without a prior history of the treatment of interest but with previous use of its comparator)(8-12), with some subclassifying prevalent new users as switchers versus those augmenting treatment. However, a finer stratification may be useful. Webster-Clark and colleagues(15) subclassified prevalent new users as direct switchers and delayed switchers, but other patterns and user types are possible, particularly in databases with longer patient histories (e.g., Canadian provincial databases, Scandinavian databases). One potential solution to decrease potential bias is matching on several history-related variables. For example, in our study of SGLT2 inhibitors, we matched for level of antidiabetic treatment in the prior year, previous use of glucagon-like peptide-1 (GLP-1) receptor agonists, and calendar time (within 120 days), in addition to time on DPP-4 inhibitors (prevalent new users only)(8). This approach resulted in very well-balanced groups. Nonetheless, it is possible that there are some subgroups within the prevalent new users for which treatment effects differ that were not identified in this study. Ultimately, drug utilization studies and an assessment of formulary restrictions are needed prior to commencing such studies to better understand the patterns of use of corresponding user types included in the study population. The availability of clinical data (e.g., laboratory test results) that are used to inform treatment decisions may be particularly useful to reduce residual confounding.

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When selecting the most appropriate approach to conducting a pharmacoepidemiologic study, there are several key considerations. These include determining the causal question to be addressed. Another is the conduct of a drug utilization study to better understand the patterns of use of the drug of interest and its comparator in everyday clinical practice. Both the ACNU and prevalent new user designs have their strengths and limitations, and understanding these properties and the causal questions answered by each design are essential considerations. While there remains a need for additional research in this area, the study by Webster-Clark and colleagues(15) brings several of these issues to the forefront and provides important information as we seek to better understand the properties of these approaches to pharmacoepidemiologic research.

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