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Instantaneous Preference was a Stronger Instrumental Variable than Three- and Six-Month Prescribing Preference For NSAIDs

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Abstract

Objective—Prescriber preference has been used as an instrumental variable (IV) in a prior study of nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) versus selective cyclooxygenase-2 (COX-2) inhibitors, with preference expressed as the drug constituting the immediately preceding prescription by the same prescriber (instantaneous preference). We sought to compare the correlations between different IV measures with exposure.

Study Design & Setting—In an ambulatory electronic medical record database of university-based physicians, we compared correlations with exposure among three measures of prescriber preference: instantaneous preference, and the proportion of that prescriber's prescriptions in the past three and six months that were for a NSAID.

Results—We identified 37,934 initial NSAID/COX-2 prescriptions. The correlation with exposure was 0.283 (95% confidence interval 0.274 – 0.292) for instantaneous preference, 0.197 (0.187 – 0.206) for three-month preference, and 0.170 (0.160 – 0.180) for six-month preference.

Conclusion—Instantaneous NSAID/COX-2 prescribing preference was most strongly correlated, and therefore the strongest IV. Future research should focus on the robustness of IV methods to violations of underlying assumptions, extension of IV methods to more than two groups, ratio measures of association, second and subsequent prescriptions per person, and timevarying exposures.

Keywords

confounding factors (epidemiology); bias (epidemiology); models, statistical; pharmacoepidemiology

WHAT'S NEW

Key Finding

- While instrumental variables are used to control for unmeasured confounding, the precision of the resulting measures of association depends on the correlation between the instrument and exposure. We found that prescribing preference as indicated by

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CONFLICTS OF INTEREST

None.

the most recent prescription by that prescriber for a selective cyclooxygenase-2 (COX-2) inhibitor vs. a nonselective nonsteroidal anti-inflammatory drug (NSAID) exhibited a stronger correlation with current exposure than did prescribing preference over the past three months or past six months.

What this adds to what was known

- For studies comparing COX-2 inhibitors to NSAIDs, the immediately preceding prescription is a stronger instrumental variable, and thus should produce more precise estimates of exposure effects than the proportion of prescriptions over the past three or six months.

What is the implication, what should change now

- Researchers should examine different measures of prescribing preference before deciding on one for use as an instrumental variable.
- Physician preference measured by the immediately preceding prescription should be evaluated as a lead candidate for an instrumental variable in studies of other drug classes.

INTRODUCTION

Conventional methods to address confounding in non-randomized epidemiologic studies include restriction, stratification, matching, and regression. These methods address confounding by measured but not unmeasured factors, regardless of whether one uses directly-measured variables or propensity scores based on them. An alternative approach, known as instrumental variables (IV), has widespread use in economics and econometrics, and eliminates bias caused by measured and unmeasured confounding provided that certain critical assumptions (listed below) are met (1). The IV approach is also known as estimation of simultaneous regression equations and two-stage least squares regression (2).

The idea of IV analysis is that the effect of an exposure can be estimated without bias due to unmeasured confounders through use of a variable (i.e., an “instrument”) that is related to exposure, but unrelated to outcome except through its relationship to exposure (3,4). The IV approach involves fitting two regression models. The first model examines the association between exposure as the dependent variable and the IV as the independent variable, possibly controlling for baseline covariates. The second model uses the outcome as the dependent variable and uses as the independent variables exposure, residuals (i.e., differences between predicted and observed responses) from the first model, and possibly covariates. This procedure yields asymptotically unbiased estimates of the effect of exposure on outcome, provided that three assumptions are true (2). The first assumption is that the IV is correlated with exposure. The second assumption is that the relationships between the IV and the exposure and the IV and outcome are not confounded by unmeasured variables. The third assumption is that the IV is unassociated with the outcome except through its association with the exposure.

The IV approach is commonly used to reduce bias in the “as-treated” analyses of randomized trials, usually with intention-to-treat as the primary analysis. In such cases, randomization arm is the IV, which is associated with exposure, and associated with outcome only through its relationship with exposure, except possibly with un-blinding in general, and behavioral interventions in particular (5).

Use of the IV approach in observational epidemiologic studies has been limited because of a lack of evident IVs (6). Korn first proposed using individual physicians as instruments in settings in which there is variability in prescriber preference for different treatments under

study (7). Adapting this model, Brookhart and colleagues recently used an IV approach to study the relative gastrointestinal safety of non-specific nonsteroidal anti-inflammatory drugs (NSAIDs) vs. cyclooxygenase-2 (COX-2) specific inhibitors in an observational cohort study (8). As their conceptual IV, they used prescriber preference for NSAIDs vs. COX-2 inhibitors. They implemented this as a binary IV defined as the drug class (NSAID vs. COX-2) of the agent most recently prescribed by the prescriber of the prescription of interest (instantaneous preference). However, it is unclear whether we should expect exposure to be more strongly correlated with instantaneous preference, or with a more global preference, as would be manifest over a longer period (e.g., three to six months). In general, people expect short-term behavior to be a better predictor of current behavior, and expect global preference to be a better predictor of behavior in the distant future (9). Choosing an IV that is strongly correlated with exposure is important because, other things being equal, a stronger IV-exposure correlation will yield a more precise IV-adjusted association measure between the exposure and outcome (10), and thus reduce the risk of type-2 error.

In light of the possibility that long-term preference may be more strongly correlated with exposure than instantaneous preference and thus lead to more precise estimates of exposure effects with an IV approach, we wished to compare several measures of prescribing preference with regard to correlation with the exposure. In particular, we wished to examine instantaneous preference, three-month preference, and six-month preference.

MATERIALS AND METHODS

Study Design and Population

We conducted a cross-sectional study using data derived from the ambulatory electronic medical record (EMR) system of the University of Pennsylvania Health System. Implemented in October 1998, the EMR contains patient- and visit-level data such as demographics, medical history, vital signs, progress notes, visit diagnoses, medication orders, and laboratory results. It includes records on approximately 300,000 patients cared for by about 2,100 medical providers, 26 percent of whom are sub-specialists. University of Pennsylvania's Committee on Studies Involving Human Beings approved this study and granted waivers of informed consent and HIPAA authorization.

Prescription Identification and Assignment of Physician Preference as an Instrumental Variables

We identified all prescriptions for the five most commonly used drugs in the NSAID/COX-2 inhibitor class (excluding combination products such as ibuprofen with pseudoephedrine) from October 1, 1998 through January 10, 2007 that occurred on or following the six month anniversary date of the first recorded prescription for each provider. The first prescription for a NSAID/COX-2 inhibitor for each patient was the unit of observation, and the exposure variable was given a value of one if the prescription was for a NSAID and zero if it was for a COX-2 inhibitor.

The first measure of prescribing preference was whether the immediately preceding prescription for a NSAID/COX-2 inhibitor issued by that provider was for a NSAID (coded as one) or a COX-2 inhibitor (zero). The second measure was proportion of NSAID/COX-2 prescriptions issued by that prescriber in the immediately preceding three months that was for a NSAID. The third measure was proportion of NSAID/COX-2 prescriptions issued by that prescriber in the immediately preceding six months that was for a NSAID. We also measured the following potential confounding variables that one might measure in a study of the association between NSAIDs/COX-2 inhibitors and gastrointestinal bleeding: age, sex, history

of peptic ulcer disease, and past use of proton pump inhibitors. The diagnostic codes used to identify peptic ulcer disease are available from the authors.

Statistical Analysis

For each potential IV and each potential binary confounding factor, we calculated the tetrachoric correlation coefficient (11) (with 95 percent confidence intervals [CIs]) with exposure. For a given two-by-two frequency table involving two binary random variables, the tetrachoric correlation is the Pearson correlation between two unmeasured or latent normal random variables that have been dichotomized to yield the two observed dichotomous random variables. Such a correlation is a special case of the biserial correlation, calculated as the Pearson correlation, between an observed continuous variable and a latent variable underlying an observed binary variable (12). The relationships between continuous confounding factors and the potential IV's and exposure were analyzed as biserial correlations. We used SAS version 9 (SAS Institute Inc., Cary, North Carolina).

RESULTS

The five most commonly prescribed medications in the NSAID/COX-2 class during the study period were ibuprofen (N=26,706), naproxen (N=22,685), celecoxib (N=14,571), rofecoxib (N=8,842), and nabumetone (N=5,081). After excluding prescriptions occurring before each prescriber's six-month anniversary date for their first recorded prescription (N=11,775), and second and subsequent NSAID/COX-2 prescriptions for the same patient (N=28,176), there were 37,934 NSAID/COX-2 prescriptions, each of which constituted an observation. These prescriptions were written by 602 providers, 34 percent of whom were sub-specialists.

Correlation coefficients are presented in Table 1. Instantaneous preference had the highest correlation with exposure: 0.283 (95% CI, 0.274 to 0.292). The correlation of exposure with three-month preference was 0.197 (95% CI, 0.187 to 0.206) and with six-month preference was 0.170 (95% CI, 0.160 to 0.180).

Among the baseline factors that might predict risk of gastrointestinal complications, age was most strongly correlated with prescribing preference, particularly the six- and three-month measures: 0.268 (95% CI, 0.258 to 0.277) and 0.251 (95% CI, 0.241 to 0.260), respectively. Sex, past diagnosis of peptic ulcer disease, and past use of proton pump inhibitors were weakly only correlated with prescribing preference, with correlations of 0.018 to 0.059.

DISCUSSION

We found that the instantaneous preference had a stronger correlation with exposure than the three- and six-month preference. This lends support for using instantaneous preference, as Brookhart and colleagues have done.(8,13) Further, the three-month preference appears to be a stronger IV than the six-month preference. Although Brookhart et al. did not report the correlation between the IV and exposure, they found that the probability that the next prescription was a COX-2 inhibitor was 77 percent if the previous prescription was a COX-2 inhibitor, and 55 percent if the previous prescription was a NSAID (8). Using an arc sin transformation (14), this gives an approximate correlation coefficient of 0.23, which is quite similar to our results.

In the context of behavioral research, tetrachoric correlation is considered to be "small" if less than 0.15; "medium" if from 0.15 to 0.30; and "strong" if greater than 0.30.(11) All three IVs evaluated had "medium" correlation with the observed exposure. Although stronger correlations between the IV and exposure will yield more precise IV-adjusted measures of association (2), additional research is needed to characterize the strength of this relationship.

Although correlation between the IV and measured factors that predict outcome do not violate IV assumptions (if those factors are adjusted for), correlation with *unmeasured* predictors of outcome would. Because measured predictors of outcome, especially age, did correlate with the IVs, there may well be unmeasured predictors of outcome that correlate with the IV. Additional research is needed to assess the robustness of IV methods to violations of this assumption.

Another IV assumption that needs to be assessed is whether the IVs have direct effects on outcome apart from their indirect effect on outcome through exposure. Such direct effects may occur in our context by having long-term or instantaneous preference be related to clinician behavior that reduces the risk of gastrointestinal complications, such as co-prescription of gastroprotective agents. Methods for assessing this assumption are available (5).

This study's primary limitation is generalizability. In particular, these results may not be generalizable to other drug classes. Therefore, it seems wise to empirically examine several expressions of physician preference in the context of a pharmacoepidemiologic study using IV methods before deciding on one. Correlation with instantaneous preference might be weaker when the choice of agents is due more to individual patient characteristics and less to underlying prescriber preference. For example, if prescribers are more likely to use patient characteristics to guide choice of antihypertensive drugs than choice of a NSAID vs. a COX-2 inhibitor, then all IVs may be weaker, and the rank order of different preference measures might differ from the results seen here. It is also possible, but seems less likely, that results from university-based prescribers might differ substantially from those of community-based prescribers. The similarity of our results to earlier results using more heterogeneous prescribers (8) argues against this possibility.

The use of prescriber preference as an IV is an intriguing and promising approach to address confounding by indication in pharmacoepidemiology. Its use in pharmacoepidemiology is still novel, and additional methodologic research is needed. For example, the robustness of IV methods to violations of underlying assumptions needs to be examined. In addition, the few currently published examples (8,13) have compared only two groups, and have examined risk differences. Future methodologic research should focus on extending the approach to comparisons of more than two groups, to examining ratio measures of effect, such as the risk ratio, rate ratio, and hazard ratio. The use of IV methods to study second and subsequent prescriptions in the same patient, to address time-varying exposures, and to evaluate interactions between exposure and baseline factors also needs to be developed. Such extensions will require the use of multiple instrumental variables, such as the multiple preference measures. A multivariable regression model of exposure on the three preference variables revealed that the partial F statistics (df=1, 37002) were 226, 27, and 197, respectively, for instantaneous preference, three-month preference, and six-month preference. The corresponding partial correlation coefficients were 0.078, 0.027, 0.073, which are much smaller than the respective marginal correlations of 0.283, 0.197, and 0.170. This evidence of weak independent effects of the preference variables indicates that they may serve as weak instruments when used together in identifying multiple exposure effects on outcome.

Additional research is needed for assessing the accuracy of applying linear IV models to binary outcomes in comparison to alternative IV approaches developed for binary outcomes (15). Finally, it is not clear how the very low risks of events in this context affects the validity of IV methods in general.

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References

1. Zohoori N, et al. Econometric approaches to epidemiologic data: relating endogeneity and unobserved heterogeneity to confounding. *Annals of Epidemiology* 1997;7:251–257. [PubMed: 9177107]
2. Martens EP, et al. Instrumental variables: application and limitations. *Epidemiology* 2006;17:260–267. [PubMed: 16617274]
3. Greenland S. An introduction to instrumental variables for epidemiologists. *International Journal of Epidemiology* 2000;29:722–729. [PubMed: 10922351]
4. Newhouse JP, et al. Econometrics in outcomes research: the use of instrumental variables. *Annual Review of Public Health* 1998;19:17–34.
5. Ten Have TR, et al. Causal models for randomized physician encouragement trials in treating primary care depression. *Journal of the American Statistical Association* 2004;99:8–16.
6. McMahon AD. Approaches to combat with confounding by indication in observational studies of intended drug effects. *Pharmacoepidemiology & Drug Safety* 2003;12:551–558. [PubMed: 14558178]
7. Korn EL, Baumrind S. Clinical preferences and the estimation of causal treatment differences. *Statistical Science* 1998;13:209–235.
8. Brookhart MA, et al. Evaluating short-term drug effects using a physician-specific prescribing preference as an instrumental variable. *Epidemiology* 2006;17:268–275. [PubMed: 16617275]
9. Nussbaum S, et al. Creeping dispositionism: the temporal dynamics of behavior prediction. *Journal of Personality & Social Psychology* 2003;84:485–497. [PubMed: 12635911]
10. Straiger D, Stock J. Instrumental variables regression with weak instruments. *Econometrica* 1997;65:557–586.
11. Cohen, J. *Statistical power for behavioral sciences*. Hillsdale, NJ: Lawrence Erlbaum Associates; 1988.
12. Bobko, P. *Correlation and regression*. Thousand Oaks: Sage Publications, Inc; 2001.
13. Schneeweiss S, et al. Risk of death associated with the use of conventional versus atypical antipsychotic drugs among elderly patients. *CMAJ Canadian Medical Association Journal* 2007;176:627–632.
14. Mosteller F, Youtz C. Tables of the Freeman-Tukey transformations for the binomial and Poisson distributions. *Biometrika* 1961;48:433–440.
15. Nagelkerke N, et al. Estimating treatment effects in randomized clinical trials in the presence of non-compliance. *Statistics in Medicine* 2000;19:1849–1864. [PubMed: 10867675]

Table 1

Correlation Coefficients (with 95% Confidence Intervals) between Different Expressions of Prescriber Preference with Exposure with and Potential Confounding Variables

	Immediately preceding prescription	Prescriptions in past three months	Prescriptions in past six months
Exposure (binary)	0.283 (0.274 to 0.292)	0.197 (0.187 to 0.206)	0.170 (0.160 to 0.180)
Sex (binary)	0.023 (0.013 to 0.033)	0.054 (0.044 to 0.064)	0.059 (0.048 to 0.069)
Age (continuous)	0.123 (0.113 to 0.133)	0.251 (0.241 to 0.260)	0.268 (0.258 to 0.277)
Past diagnosis of peptic ulcer disease	0.019 (0.009 to 0.029)	0.018 (0.008 to 0.028)	0.022 (0.012 to 0.032)
Ever past use of proton pump inhibitors	0.026 (0.016 to 0.036)	0.051 (0.041 to 0.061)	0.056 (0.046 to 0.066)