ELSEVIER

Journal of Clinical Epidemiology 61 (2008) 1285−1288

Journal of Clinical Epidemiology

BRIEF REPORTS

Instantaneous preference was a stronger instrumental variable than 3- and 6-month prescribing preference for NSAIDs

Sean Hennessy[a,b,*], Charles E. Leonard[a,b], Cristin M. Palumbo[a,b], Xiaoli Shi[a,b], Thomas R. Ten Have[a,b]

[a]*Center for Clinical Epidemiology & Biostatistics, Department of Biostatistics & Epidemiology, University of Pennsylvania School of Medicine, Philadelphia, PA, USA*

[b]*Center for Education and Research on Therapeutics, University of Pennsylvania School of Medicine, Philadelphia, PA, USA*

Accepted 6 January 2008

Abstract

Objective: Prescriber preference has been used as an instrumental variable (IV) in a prior study of nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) vs. 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 and 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 3 and 6 months that were for an 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 3-month preference, and 0.170 (0.160−0.180) for 6-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 time-varying exposures.

Keywords: Confounding factors (epidemiology); Bias (epidemiology); Models, statistical; Pharmacoepidemiology; Anti-inflammatory agents; non-steroidal; Cyclooxygenase 2 inhibitors

1. Introduction

Conventional methods to address confounding in nonrandomized 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

* Corresponding author. Center for Clinical Epidemiology and Biostatistics, Department of Biostatistics and Epidemiology, University of Pennsylvania School of Medicine, 423 Guardian Drive, 803 Blockley Hall, Philadelphia, PA 19104-6021, USA. Tel.: +215-898-9112; fax: +215-573-5315.

E-mail address: hennessy@mail.med.upenn.edu (S. Hennessy).

0895-4356/08/$ − see front matter
doi: 10.1016/j.jclinepi.2008.01.003

What's new

Key Finding

- Although 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 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 3 months or past 6 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 3 or 6 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.

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 unblinding 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 nonspecific 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., 3–6 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, 3-month preference, and 6-month preference.

2. Materials and methods

2.1. Study design and population

We conducted a cross-sectional study using data derived from the ambulatory electronic medical record system of the University of Pennsylvania Health System. Implemented in October 1998, the electronic medical record 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% of whom are subspecialists. University of Pennsylvania's Committee on Studies Involving Human Beings approved this study and granted waivers of informed consent and HIPAA authorization.

2.2. Prescription identification and assignment of physician preference as an instrumental variable

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 6-month anniversary date of the first recorded prescription for each provider. The first prescription for an 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 an NSAID and zero if it was for a COX-2 inhibitor.