Evaluating the Validity of an Instrumental Variable Study of Neuroleptics

Can Between-Physician Differences in Prescribing Patterns Be Used to Estimate Treatment Effects?

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Background: Postmarketing studies of prescription drugs are challenging because prognostic variables that determine treatment choices are often unmeasured. In this setting, instrumental variable (IV) methods that exploit differences in prescribing patterns between physicians may be used to estimate treatment effects; however, IV methods require strong assumptions to yield consistent estimates. We sought to explore the validity of physician-level IV in a comparative study of short-term mortality risk among elderly users of conventional versus atypical antipsychotic medications (APM).

Methods: We studied a cohort of patients initiating APMs in Pennsylvania who were eligible for Medicare and a state-funded pharmaceutical benefit plan. The IV was defined as the type of the APM prescription written by each physician before the index prescription. To evaluate whether the IV was related to other therapeutic decisions that could affect mortality, we explored the association between the instrument and 2 types of potentially hazardous coprescriptions: a tricyclic antidepressant (TCA) not recommended for use in the elderly or a long-acting benzodiazepine. To insure that the IV analysis was not biased by case-mix differences between physicians, we examined the associations between the observed patient characteristics and the IV.

Results: The cohort consisted of 15,389 new users of APMs. Our multivariable model indicated that physicians who had most recently prescribed a conventional APM were not significantly more or less likely to coprescribe a potentially hazardous TCA [odds ratio (OR), 0.78; 95% confidence interval (CI), 0.58–1.02] but were less likely to prescribe a long-acting benzodiazepine (OR, 0.57; 95% CI, 0.45–0.72) with their current APM prescription. The association between long-acting benzodiazepine prescribing and APM preference was no longer significant when the analysis was restricted to primary care physicians (OR, 0.84; 95% CI, 0.62–1.15). Multivariable regression indicated that important medical comorbidities (eg, cancer, hypertension, stroke) were unrelated to the IV.

Conclusions: The previous APM prescription written by the physician was unassociated with major medical comorbidities in the current patient, suggesting that the IV estimates were not biased by case-mix differences between physicians. However, we did find that the IV was associated with the use of long-acting benzodiazepines. This association disappeared when the study was restricted to the patients treated by primary care physicians. Our study illustrates how internal validation approaches may be used to improve the design of quasi-experimental studies.

Key Words: instrumental variables, quasi-experimental design, anti-psychotic medications, confounding bias, pharmacoepidemiology, prescribing

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Observational studies are necessary to evaluate the safety and effectiveness of prescription medications as they are used in routine practice. Such studies are challenging, however, because prescribing decisions often depend on variables that are not available in typical pharmacoepidemiologic databases. If there are unmeasured variables that are independent risk factors for the study outcome and also influence treatment choice, standard statistical methods may result in biased estimates of exposure effects.

To illustrate this problem, consider a recent observational study that compared the risk of mortality among elderly users of conventional versus atypical antipsychotic medications (APMs).[1] Selective prescribing of APMs to the elderly is likely because the atypical APMs are thought to be less sedating and less likely to cause extra pyramidal side effects and arrhythmias. If atypical APMs are thought to be generally safer, it is likely that they are selectively prescribed to patients who are frail and perceived to be more vulnerable to the side effects of conventional APMs. The comparative APM study was conducted using health care claims data, and

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therefore was unable to make statistical adjustments for aspects of frailty such as measures of cognitive and physical impairment. Because these variables may both influence treatment choice and be independently related to mortality, unmeasured confounding may bias the traditional regression results reported in this article.

To address this problem, the authors of the APM study used an instrumental variable (IV) approach as a secondary analysis. Instrumental variable methods allow for the estimation and bounding of treatment effects in the presence of unobserved confounding provided that a suitable IV (or "instrument") is available.[2,3] An instrument is a factor that is related to the treatment assignment, but independently unrelated to the outcome under study. Instrumental variables are often associated with a natural or quasi-experiment.

The IV that was used in the APM study was a measure of a physician's APM preference for prescribing an atypical APM rather than a conventional APM.[4] The preference measure was defined to be the type of the most recent APM prescription initiated by each physician before the index (current) prescription. So, if a physician most recently started a patient on an atypical APM, he would be classified as an "atypical APM preferring physician" for his current patient, otherwise he would be classified as a "conventional APM preferring physician."

This factor will be a valid IV if: (1) physicians vary in their preference for using the 2 different classes of APMs, (2) a physician's APM preference as reflected in the last APM prescription written is unrelated to the risk factors in his current patient (independence assumption), and (3) a physician's APM preference is related to the current patient's outcome only through its influence on the type of APM prescribed (the exclusion restriction). These assumptions are depicted in Figure 1A.

Violations of the exclusion restriction can occur if physicians who more frequently use the older drugs (the conventional APMs) differ systematically in their overall skill or the quality of care they deliver (Fig. 1B).[5] For example, such physicians may be more likely to make prescribing errors and less likely to deliver preventive services, make necessary referrals, or order screening tests. Violations of the independence assumption can occur if physicians who more frequently prescribe conventional APMs are seeing patients with a different prognosis than patients of physicians who more frequently prescribe atypical APMs (Fig. 1C). Both the exclusion and independence assumptions are not empirically verifiable (ie, by examining data we can never be certain that they hold—but one can empirically explore the plausibility of both assumptions).

Within a cohort of elderly new users of APMs, we evaluated the defensibility of the exclusion restriction by testing whether the IV, a physician's previous APM prescription, was related to the concomitant prescribing of 2 types of medications that are potentially hazardous in elderly patients: a tricyclic antidepressant (TCA) not recommended for use in the elderly or a long-acting benzodiazepine. We evaluated the plausibility of the independence assumption by examining whether observed patient-level characteristics were related to the IV.

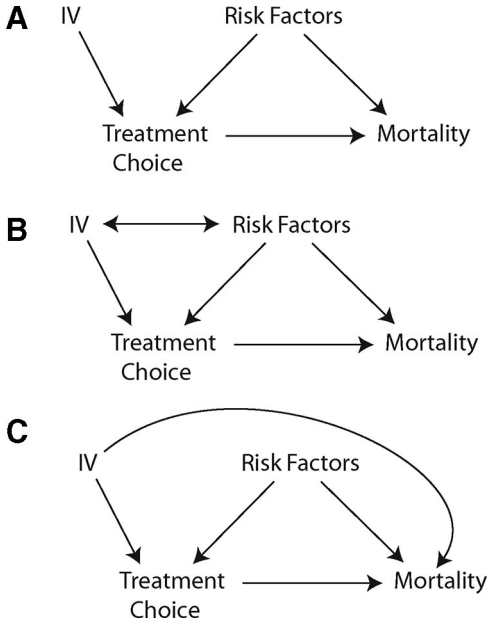

FIGURE 1. Causal diagrams depicting structural instrumental variable assumptions (A), a violation of the independence assumption (B), and a violation of the exclusion restriction (C). (Double headed arrow indicates an association due to a common cause.)

METHODS

Study Population and Data Sources

Our study was conducted in a population of Medicare beneficiaries who were also eligible for the Pharmaceutical Assistance Contract for the Elderly (PACE), a state-run drug benefit program in Pennsylvania. Beneficiaries of PACE have annual incomes between $10,000 and $20,000 and are 65 years or older. The PACE drug benefit pays for all outpatient drug treatment with a small copayment from $6 to $10.

For all members of this population, Medicare Part A and B claims are linked with pharmacy claims from PACE. Physicians were identified using the medical license number recorded in the pharmacy claim of the index APM prescription. This field has been found to accurately identify the prescribing physician in the PACE data.[6] Physician specialty information was obtained by linking the PACE pharmacy claim data to the American Medical Association's Masterfile of physicians using the medical license field. The AMA files have been found to be a reliable source of information on physician training and practice type.[7] Primary care physicians were defined to be those with a primary specialty code of internal medicine, family practice, or general practice. This category includes geriatricians. The specialty code was the only variable used from the AMA file.

Study Cohort

Within this population we studied an existing cohort of new users of APMs who initiated treatment during the years

1994–2003. To ensure a uniform 1-year eligibility period before filling the index APM prescription, we required all study subjects to have used more than 1 medical service and filled more than 1 prescription, in each of the two 6-month intervals before the index date. APM initiators were defined as having used no APM in the year before the index use. We restricted the analysis to just APM initiators to guard against selection bias among prevalent users from early symptom emergence, drug intolerance, or treatment failure.[8]

All personal identifiers were removed from the dataset before analysis to protect patient confidentiality. The Institutional Review Board of the Brigham and Women's Hospital approved this study and signed data use agreements with Medicare and PACE were in place.

Potentially Hazardous Concomitant Prescribing

We sought to determine whether a physician's surrogate APM preference was related to other prescriptions that were concomitant with the index APM prescription and that might affect mortality or be a general marker for lower quality of care. A concomitant prescription was defined to be a filled prescription within 3 days of the index APM prescription. The first potentially hazardous concomitant prescription that we considered was a long-acting benzodiazepine. Long-acting benzodiazepines are not recommended for use in the elderly as they have been associated with adverse outcomes such as cognitive impairment and falls.[8–10] For use in the elderly, shorter half-life benzodiazepines are considered to be safer.[10,11] The other potentially hazardous concomitant prescriptions that we considered were TCA agents not recommended for use in the elderly.[11,12] These include those with strong anticholinergic effects and others that are overly sedating, affect blood pressure, or potentially cause cardiac dysrhythmias.[12] If a TCA is required, desipramine or nortryptiline are considered to be the safest choices for older patients.[10] However, because there may be situations when a low dose of one of the potentially hazardous TCAs might be indicated, including pain or treatment failure on one of the safer TCAs, we considered a low dose of any TCA to be appropriate. We defined a low dose as any dose in the bottom quintile of the observed dose range. This definition yielded the lowest available dose form for each type of potentially hazardous TCA.

Exposure Definitions

Atypical APM agents were taken to be aripiprazole, clozapine, olanzapine, quetiapine, risperidone, and ziprasidone. Other APMs were considered conventional APMs, including acetophenazine, chlorpromazine, fluphenazine, mesoridazine, perphenazine, promazine, thioridazine, trifluoperazine, triflupromazine, chlorprothixene, haloperidol, loxapine, molindone, pimozide, and thiothixene. Coprescription of a long-acting benzodiazepine was defined as the filling of a prescription within 3 days of the index APM prescription for chlordiazepoxide, clonazepam, clorazepate, diazepam, or flurazepam. Coprescription of a potentially hazardous TCA was defined as the filling of a prescription within 3 days of the index APM prescription for amitripyline (>10 mg/d), clomipramine (>10 mg/d), doxepin (>10 mg/d), imipramine (>10 mg/d), protriptyline (>10 mg/d), and trimipramine (>12.5 mg/d).

Measurement of Physician APM Preference

Our IV, a physician's previous APM prescription, was defined as being the type of the most recent APM prescription initiated by each physician. If a physician's most recently recorded new APM prescription was for an atypical APM, then for the current (index) patient a physician is classified as an "atypical APM preferring physician." Similarly, if a physician's last recorded APM prescription was for a conventional APM, then the physician was classified as a "conventional APM preferring physician" for the index patient. This definition was used to allow a physician's APM preference to change quickly in time. This is necessary because the study period represents a relatively active period of research and debate related to the use of APMs. For the IV to be defined for each patient, we excluded each physician's first patient from the cohort. More details on the use of this instrument are given elsewhere.[4]

Statistical Methods

We explored the relationship between the measure of physician preference and each of the potentially hazardous coprescriptions using logistic regression models that adjusted for age, gender, and calendar year as a categorical variable. Because specialist physicians may be more likely to appropriately use potentially hazardous regimens in complicated or refractory patients, we repeated the analysis in a sample restricted to patients of primary care physicians. To explore whether the independence assumption was plausible, we examined the association between physician preference and each measured patient characteristic. These associations were estimated using a linear model of the patient characteristic that included the instrument and a calendar year term to correct for possible secular trends in prescribing or the use of diagnostic codes during the 10-year study period. This model yielded adjusted estimates of risk differences. These associations were compared with associations between the actual exposure and the instrument using the same statistical model. To account for the clustering of patient-level observations within physicians, the parameters and standard errors for all multivariable models were estimated robustly using a generalized estimating equation approach using a working variance-covariance matrix with an exchangeable structure.[13,14] All data analyses were performed in SAS V9.0 running on a Windows XP platform.

RESULTS

The cohort consisted of 15,389 new users of APMs of which 4905 initiated conventional APM therapy and 10,485 started on an atypical APM. The characteristics of the cohort are given in Table 1. These patients were treated by 6390 physicians.

In Table 2, we present the frequency of concomitant prescribing of any of the TCAs. Of the 15,389 new APM users, 692 (4.5%) received a concomitant prescription of a TCA of which 256 (37.0%) were considered to be potentially hazardous. In Table 3, we present the frequency of concom-

TABLE 1. Characteristics of Cohort

Patient Characteristics	N	%
Female patient	12,545	81.5
Age >80	10,750	70.0
History of		
Cerebrovascular disease	4661	30.3
Congestive heart failure	4918	32.0
Diabetes	1812	11.8
Hypertension	9685	62.9
Cardiac arrhythmia	223	1.5
Myocardial infarction	535	3.5
Other ischemic heart disease	3918	25.5
Other cardiovascular disorders	1910	12.4
Cancer	2198	14.3
Psychiatric disorder*	9299	60.4
Skilled nursing facility stay in previous 180 d	3149	20.5

*Includes mood disorders, dementia, delirium, and psychotic disorders.

itant prescribing of all benzodiazepines. Within our cohort of new APM users, 2854 (18.5%) received a concomitant prescription of a benzodiazepine of which 530 (18.6%) were for a long-acting benzodiazepine.

In Table 4, we present the association between the IV and potentially hazardous concomitant prescriptions. Adjusting for age, gender, and calendar year, physicians who have most recently prescribed a conventional APM were not statistically more likely to coprescribe a potentially hazardous TCA with their next APM prescription [odds ratio (OR), 0.78; 95% confidence interval (CI), 0.58–1.02], but they were less likely to coprescribe a long-acting benzodiazepine with their next APM prescription (OR, 0.57; 95% CI, 0.45–0.72). Among primary care physicians, conventional APM preference was not related to potentially hazardous TCA prescribing (OR, 0.98; 95% CI, 0.70–1.39) or long-acting benzodiazepine prescribing (OR, 0.84; 95% CI, 0.62–1.15).

In Table 5, we present the adjusted associations between the treatment and the patient risk factors (columns 2 and 3). The reported prevalence difference (PD) is the prevalence of the risk factor among patients started on an atypical APM minus the prevalence of the risk factor among patients started on a conventional APM. The prevalence statistics are adjusted for calendar year. The data in the table reveal that patients started on atypical APMs were significantly less likely to have a history of cancer (PD = −1.9%) and somewhat less likely to have a history of myocardial infarction (PD = −0.7%), ischemic heart disease (PD = −1.6%), and other cardiovascular disorders (PD = −1.6%). Atypical APM users were more likely to have a history of a skilled nursing facility stay (PD = 2.4%), hypertension (PD = 2.6%), psychiatric disorders (PD = 14.1%), and cerebrovascular disease (PD = 1.9%).

The associations between the IV and patient risk factors are also reported in Table 5 (columns 4 and 5). The reported PD for the IV is the prevalence of the risk factor among patients of physicians who have most recently prescribed an atypical APM minus the prevalence of the risk factor among patients of physicians who have most recently prescribed a conventional APM. The data in this table reveal that APM preference is only associated with a history of psychiatric disorders.

DISCUSSION

In our study, we found that many patient characteristics were associated with the actual APM treatment choice, suggesting the possibility of some residual bias due to unmeasured patient characteristics. Patients who were prescribed atypical APMs were much more likely to have spent time in a skilled nursing facility during the baseline period and also were more likely to have a history of psychiatric disorders, hypertension, and cerebrovascular disease. On the other hand, patients prescribed conventional APMs were more likely to have a history of cancer, possibly a result of conventional APMs being used in low doses as an antiemetic to control chemotherapy-induced nausea. Patients prescribed conventional APMs were also more likely to have a history of myocardial infarction, ischemic heart disease, and other cardiovascular conditions.

When we examined the association between the instrument and measured patient characteristics, the only association that persisted was between atypical APM preference and psychiatric diagnoses (eg, mood disorders, delirium). We speculate that this association is a result of mental health specialty care providers being both more likely to use atypical APMs and also more apt to recognize and diagnose psychiatric conditions. In such a situation, the observed violation of the independence assumption is more of an artifact rather than a real difference in prognosis across physician preference, and therefore not likely to be an important source of bias. The major medical comorbidities (eg, cancer, stroke, myocardial infarction) that are strong risk factors for short-term mortality were well-balanced across levels of the instrument.

We found that physicians who had most recently written a prescription for an atypical APM were not significantly more likely to coprescribe a potentially hazardous TCA, however they were more likely to write a prescription for a potentially hazardous benzodiazepine. This is likely to be a result of long-acting benzodiazepines being indicated for certain psychiatric conditions such as anxiety or panic disorders, and alcohol dependency that are typically treated by specialist physicians who are also more likely to use the newer APMs. However, if physicians who frequently prescribe atypical APMs were using more hazardous treatments, the bias would be conservative, tending to narrow the difference in risks between atypical and conventional APM exposure on short-term mortality.[1] When the study population was restricted to primary care physicians, this association was eliminated. Within this population of generalists, preference does not seem to be related to a proclivity to prescribe either of the 2 potentially hazardous medications that we studied, and supports the possibility that the IV exclusion restriction is approximately satisfied in this large subpopulation.

It is natural to assume that physicians who frequently prescribe the newer medications may be affecting the

TABLE 2. Frequency of Concomitant Prescribing of Tricyclic Antidepressants and Antipsychotic Medications

Drug (Dose)	Recommended for Use in the Elderly?	Frequency (All Physicians)	Frequency (PCPs Only)
Amitriptyline (≤10 mg)	Yes	58	43
Amitriptyline (>10 mg)	No	126	84
Clomipramine (≤10 mg)	Yes	0	0
Clomipramine (>10 mg)	No	10	2
Desipramine (all doses)	Yes	42	22
Doxepin (≤10 mg)	Yes	30	15
Doxepin (>10 mg)	No	89	60
Imipramine (≤10 mg)	Yes	10	6
Imipramine (>10 mg)	No	29	17
Nortriptyline (all doses)	Yes	293	150
Protriptyline (≤10 mg)	Yes	3	1
Protriptyline (>10 mg)	No	1	1
Trimipramine (≤12.5 mg)	Yes	0	0
Trimipramine (>12.5 mg)	No	1	1
Subtotal (all)		692	402
Subtotal (potentially hazardous)		256 (37%)	165 (41%)

PCP indicates primary care physician.

TABLE 3. Frequency of Concomitant Prescribing of Benzodiazepines and Antipsychotic Medications

Molecule	Recommended for Use in the Elderly?	Frequency (All Physicians)	Frequency (PCPs Only)
Alprazolam	Yes	706	507
Chlordiazepoxide	No	29	17
Clonazepam	No	348	139
Clorazepate	No	76	54
Diazepam	No	70	43
Estazolam	No	7	6
Flurazepam	Yes	23	18
Halazepam	Yes	1	1
Lorazepam	Yes	1391	931
Oxazepam	Yes	98	55
Quazepam	Yes	4	1
Temazepam	Yes	99	64
Triazolam	Yes	2	1
Subtotal (all)		2854	1837
Subtotal (potentially hazardous)		530 (18.5%)	259 (14.1%)

PCP indicates primary care physician.

outcome in a variety of other ways.[5] Therefore, violations of the exclusion restriction are a clear limitation for IV methods based on physician preference. In situations where the exclusion restriction is violated, however, traditional methods will also be biased because the treatment under study will be correlated with these other aspects of care that are independently related to the outcome. Although using an IV related to physician preference makes this potential bias more evident, the issue should be critically examined in all epidemiologic studies of medications used in real world settings.

One important limitation of our study concerns the generalizability of the results. We have studied a population of patients and physicians in a specific pharmacy benefit program and region in the United States. APM prescribing and preference may be quite different in other health care systems and geographic regions. Indeed, in a comparative safety study of APMs in a population of seniors in British Columbia, Canada, the associations between patient characteristics and APM type was very different.[15] This suggests that there are important differences in prescribing patterns between these 2 populations. It is possible for the exclusion

TABLE 4. Multivariable Adjusted Association Between a Physician's APM Preference and Coprescription of a Potentially Hazardous Medication

Drug Class	Population	Odds Ratio* [CI]	*P*
Potentially hazardous tricyclic anti-depressants	All patients	0.78 [0.58, 1.02]	0.07
	Patient of PCPs	0.98 [0.70, 1.39]	0.93
Long-acting benzodiazepines	All patients	0.57 [0.45, 0.72]	<0.01
	Patient of PCPs	0.84 [0.62, 1.15]	0.29

All associations adjusted for age, sex, and calendar year.
†Parameter standard errors estimated robustly to account for correlation of patient outcomes within physician.
PCP indicates primary care physician.

TABLE 5. Association Between Patient Characteristics and Both Treatment and Instrument (Type of Last Antipsychotic Medications Initiated by Physician)

	Actual APM Treatment Assignment		Last APM Assigned by Physician (IV)	
Patient Characteristics	Prevalence Difference† (%)	*P**	Prevalence Difference‡ (%)	*P**
Female patient	5.3	<0.01	0.9	0.20
Age >80 yr	2.0	<0.01	0.6	0.88
History of				
Cerebrovascular disease	1.9	0.04	0.5	0.54
Congestive heart failure	−1.2	0.22	−0.9	0.26
Diabetes	−0.3	0.79	−0.9	0.27
Hypertension	2.6	0.01	0.1	0.94
Cardiac arrhythmia	0.2	0.43	0.3	0.32
Myocardial infarction	−0.7	0.07	0.0	0.30
Other ischemic heart disease	−1.6	0.09	−0.5	0.50
Other cardiovascular disorders	−1.6	0.02	−0.5	0.43
Cancer	−1.9	0.01	−0.6	0.39
Psychiatric disorder§	14.1	<0.01	7.5	<0.01
Skilled nursing facility stay in previous 180 d	2.4	0.01	0.5	0.51

*Computed using a GEE approach that adjusts standard errors for within-physician clustering using a correlation matrix with an exchangeable structure.
†Prevalence of risk factor among atypical users minus prevalence of risk factor among conventional users estimated in a linear model adjusting for calendar year.
‡Prevalence of risk factor among patients of physicians who most recently prescribed an atypical APM minus prevalence among patients of physicians who most recently prescribed a conventional APM estimated in a linear model adjusting for calendar year.
§Includes mood disorders, dementia, delirium, and psychotic disorders.

restriction and independence assumptions to hold in 1 population but not in others, and therefore, our validation study in Pennsylvania tells us little about the validity of the study that was conducted in British Columbia.

In this article, we have evaluated the plausibility of the conditions necessary for an estimate of a physician's APM preference to be considered a valid IV. Even if these conditions are met, however, IV methods can result in biased estimates of treatment effects. For example, if treatment effect heterogeneity exists, then a further assumption, such as "monotonicity," is required to justify the use of conventional IV estimators[2] and in such cases the estimate is only generalizable to the population of patients whose treatment status is affected by the IV. Furthermore, the physician-preference IV method that we have described, attempts to control confounding bias in the initial treatment assignment, but it does not address confounding caused by informative censoring, treatment switching, or discontinuation. Therefore, the method is most appropriately used to assess very short-term drug effects in which such bias is minimal. Finally, although physician information is often available in pharmacoepidemiologic databases, in many settings it will not be practical or even feasible to use the physician as the basis of an IV. For example, if there is little variation in prescribing patterns across physicians, the physician preference IV will be weak and may yield highly inefficient and biased estimates of a treatment effect. If a good IV is unavailable, sensitivity analysis can be used to explore the possible direction and magnitude of the bias.[16,17] External information about the relationship between suspected unmeasured confounders and the study outcome or exposure can also be used to guide sensitivity analyses or be used to adjust effect estimates.[18,19]

Our study supplies evidence suggesting that a physician's preference for APM type may approximately satisfy

the independence assumption in that it is not related to important risk factors for death. However, we have found that the study needs to be restricted to primary care physicians in order for the exclusion restriction to be more plausible. Further work in this area should focus on the development of standard diagnostic methods and study design techniques that can be used to improve the validity of quasi-experimental studies that are conducted in heterogeneous populations of physicians and patients.

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