Potentially Inappropriate Medication and Health Care Outcomes: An Instrumental Variable Approach

Chi-Chen Chen and Shou-Hsia Cheng

Objective. To examine the effects of potentially inappropriate medication (PIM) use on health care outcomes in elderly individuals using an instrumental variable (IV) approach.

Data Sources/Study Setting. Representative claim data from the universal health insurance program in Taiwan from 2007 to 2010.

Study Design. We employed a panel study design to examine the relationship between PIM and hospitalization. We applied both the naive generalized estimating equation (GEE) model, which controlled for the observed patient and hospital characteristics, and the two-stage residual inclusion (2SRI) GEE model, which further accounted for the unobserved confounding factors. The PIM prescription rate of the physician most frequently visited by each patient was used as the IV.

Principal Findings. The naive GEE models indicated that patient PIM use was associated with a higher likelihood of hospitalization (odds ratio [OR], 1.399; 95 percent confidence interval [CI], 1.363–1.435). Using the physician PIM prescribing rate as an IV, we identified a stronger significant association between PIM and hospitalization (OR, 1.990; 95 percent CI, 1.647–2.403).

Conclusions. PIM use is associated with increased hospitalization in elderly individuals. Adjusting for unobserved confounders is needed to obtain unbiased estimates of the relationship between PIM and health care outcomes.

Key Words. Potentially inappropriate medication, health care outcomes, hospitalization, instrumental variable approach

Patients aged 65 years or older often suffer from chronic medical conditions and depend on medications to manage these conditions (Avorn and Shrank 2008). In an aging society with increasing drug consumption in elderly patients, the appropriate prescription of drugs is a worldwide concern. Unfortunately, suboptimal medication prescription is a common phenomenon in this population because of overprescription, underprescription,

and mis-prescription (Spinewine et al. 2007). Mis-prescription, especially regarding drugs to avoid, also known as potentially inappropriate medication (PIM), has been the most widely investigated of these practices. A number of studies have reported that PIM use in older adults is highly prevalent in industrialized countries and has a prevalence of up to 40 percent in community-dwelling, elderly managed care enrollees (Fick et al. 2001, 2008; Hanlon et al. 2002; Fillenbaum et al. 2004; Fu, Liu, and Christensen 2004; Klarin, Wimo, and Fastbom 2005; Espino et al. 2006; Franic and Jiang 2006; Zuckerman et al. 2006; Fu et al. 2007); up to 44 percent in hospitalized patients (Onder et al. 2005; Raivio et al. 2006; Mansur, Weiss, and Beloosesky 2009); and up to 50 percent in nursing home patients (Gupta, Rappaport, and Bennett 1996; Lau et al. 2005; Perri et al. 2005; Raivio et al. 2006; Barnett et al. 2011).

PIM increases the probability of adverse drug events, which may increase the risk for poor health care outcomes, such as hospitalizations, emergency department (ED) visits, or death. Previous studies have examined the association between PIM use and health care outcomes; however, the findings have tended to be inconclusive. Some studies have found that PIM use is associated with adverse drug reactions (Chang et al. 2005; Passarelli, Jacob-Filho, and Figueras 2005; Fick et al. 2008; Stockl et al. 2010), hospital admissions (Fick et al. 2001; Klarin, Wimo, and Fastbom 2005; Perri et al. 2005; Lin et al. 2008; Chen et al. 2009; Lai et al. 2009), ED visits (Fick et al. 2001; Fillenbaum et al. 2004; Perri et al. 2005; Chen et al. 2009; Lai et al. 2009), nursing home entry (Fillenbaum et al. 2004; Zuckerman et al. 2006), poor health-related quality of life (Chin et al. 1999; Franic and Jiang 2006), and mortality (Perri et al. 2005). However, other studies have reported mixed findings (Lau et al. 2005; Lin et al. 2008) or nonsignificant results (Gupta, Rappaport, and Bennett 1996; Chin et al. 1999; Hanlon et al. 2002; Aparasu and Mort 2004; Klarin, Wimo, and Fastbom 2005; Onder et al. 2005; Espino et al. 2006; Raivio et al. 2006; Lin et al. 2008; Mansur, Weiss, and Beloosesky 2009; Barnett et al. 2011).

Discrepancies in the results of empirical studies are primarily attributable to variations in the criteria used to identify PIM, the sample selection, or the health care settings. Moreover, previous studies of the effects of PIM use on health care outcomes suffer from methodological pitfalls that may have

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biased the validity of their results. For example, previous studies have failed to adjust for important observed or unobserved patient characteristics, failed to address the temporal relationship between PIM and health care outcomes, or had insufficient follow-up times or small sample sizes (Jano and Aparasu 2007; Spinewine et al. 2007). It has been suggested that rigorous study designs and analytical methods are needed to establish a causal relationship between PIM use and health care outcomes.

This study contributes to the existing literature in three ways. First, most previous studies have employed cross-sectional or retrospective cohort designs and have applied traditional analytical techniques, which are subject to the problem of endogeneity. When certain observed or unobserved patient characteristics are related to both PIM and health care outcomes, the characteristics that are not controlled for in the analysis may bias the study results. For example, patients with poor health status may require more medication and, therefore, are at an increased risk of receiving an inappropriate drug. However, patients with poor health status may experience worse health care outcomes irrespective of the effect of PIM. In this study, we incorporated two strategies to minimize the bias attributed to unobserved characteristics. We used a panel study design to account for the unobserved time-invariant patient characteristics. In addition, we employed an instrumental variable (IV) approach to address the imbalance in the unobserved covariates (Wooldridge 2010). Second, PIM use, health care outcomes, and other covariates were treated as time-variant variables within the panel study design. A panel study design can capture the changes over time in outcome measures, PIM use, or other covariates that influence outcomes, whereas a cross-sectional design cannot (Fitzmaurice, Laird, and Ware 2004). Finally, many previous studies were based on specific groups, such as a limited number of geographic areas (Hanlon et al. 2002; Fillenbaum et al. 2004; Espino et al. 2006; Barnett et al. 2011), hospitals and nursing homes (Chin et al. 1999; Chang et al. 2005; Onder et al. 2005; Passarelli, Jacob-Filho, and Figueras 2005; Perri et al. 2005; Raivio et al. 2006; Lin et al. 2008), or health maintenance organizations (Fick et al. 2001, 2008; Stockl et al. 2010). This study used a nationally representative sample to examine the effects of PIM use on health care outcomes in elderly individuals.

Health Care Services in Taiwan

Taiwan is a rapidly aging society. In 2009, adults aged 65 years or older accounted for 10.6 percent of the population of 23 million. Following the

introduction of the universal National Health Insurance (NHI) program in 1995, individuals have enjoyed a high degree of access to health care services based on personal preferences and without referral requirements (Cheng 2003). Therefore, the system differs from those with referral systems, which are characterized by general practitioners acting as gatekeepers (e.g., the systems in the United Kingdom and the United States). The average number of annual physician visits in Taiwan is among the highest in the world, with approximately 13 visits per individual; in 2009, the annual figure was 28 visits for the elderly. Unsurprisingly, patients in Taiwan are often criticized for their doctor-shopping behaviors (Chen, Chou, and Hwang 2006).

The characteristics of the health care system in Taiwan, such as easy access and no referral requirement, lead to more frequent and fragmented physician visits, which may increase the risk of PIM use. Piecoro et al. (2000) reported that having more prescribers increased the risk for PIM use in patients. For elderly patients, frequent physician visits are associated with polypharmacy (i.e., prescribing five or more drugs), in part, because of the comprehensive drug coverage and low drug copayment under Taiwan's NHI program (Chan, Hao, and Wu 2009), which might increase the risk of PIM use. Similar evidence has been found in the United States; previous studies indicated that the Medicare Part D benefit could result in more PIM use in older enrollees compared with nonenrollees under better accessibility to prescription medications scheme (Fu et al. 2010). Therefore, examining the effects of PIM on health care outcomes might be of value to countries with easy access to prescription drugs.

METHODS

Data Source

The data used in the analysis were obtained from the Longitudinal Health Insurance Database (LHID), which was provided by the National Health Research Institute in Taiwan. The LHID consisted of multiyear claim records for 1 million randomly selected NHI enrollees at the end of 2005. There were no significant differences in the distributions of age, sex, or average premiums paid between the LHID and the nationwide population databases. Using a representative sample, we obtained information on the basic demographic characteristics of the subjects and their physician visits, hospital admissions, and prescribed medications.

Study Design and Study Samples

We employed a panel study design with a 4-year (2007–2010) panel of NHI claim records. Subjects were included in the analysis if they (1) were 65 years of age or older at the beginning of 2007; (2) were alive during the study period to ensure comprehensive follow-up observations; and (3) had a minimum of three physician visits with prescriptions in any of the years during the study period to fulfill the purpose of analyzing their prescription drug use. We used the claim data of 2007 as baseline information and incorporated the data from the subsequent 3 years, 2008–2010, for analysis. There were 76,270 patients, and 228,810 patient years were included in the analysis; the unit of analysis was patient years.

Measures of Study Variables

Independent Variable: PIM. The independent variable was whether the patient had been prescribed at least one PIM in an outpatient setting per year. The PIMs were defined according to a list of drugs to avoid (i.e., drugs that should be avoided because of their ineffectiveness or potentially high risk for older adults). The Beers criteria provided the most widely used explicit list for evaluating the appropriateness of prescribed drugs for the elderly (Spinewine et al. 2007). We adopted the modified Beers criteria developed by Fick et al. (2003) for our analysis.

These modified criteria comprise two lists of inappropriate medications: (1) individual medications and classes of medications regarded as drugs-to-avoid for the elderly population; and (2) medications that should not be used by older adults known to one or more of 20 specific diseases or conditions. The first list, which was independent of diseases or conditions, was used in this study. We followed the inclusion and exclusion criteria adopted by researchers in Taiwan (Lai et al. 2009). First, inappropriate medications were categorized by the severity level according to the likelihood of a clinically significant adverse event. We only considered drugs in the analysis that had the potential to cause adverse outcomes of high severity. Second, we excluded drugs that were unavailable in Taiwan, including pentazocine, trimethobenzamide, amphetamines, guanadrel, mesoridazine, mineral oil, and desiccated thyroid. Finally, short-acting benzodiazepines, which are classified as inappropriate over a certain dosage, were excluded because of the lack of information on the prescribed daily doses of each medication. Because the medications used varied over the study period, the PIM variable was treated as time-variant each year.

Dependent Variables. The outcome variable was whether a subject had been hospitalized each year from 2008 to 2010; the outcome measure was coded as a dichotomous variable. To ensure the outcome measure was rigorous, if a hospital admission was unlikely to be associated with PIM use, we did not consider the hospitalization as an outcome event in the analysis. Therefore, in defining an outcome event, we did not include hospital admissions with the following diagnostic codes: nonmedical or poisoning events (ICD-9-CM codes: 980–995) or supplementary classifications (V-codes), such as chemotherapy. Thus, if a patient was admitted to a hospital for chemotherapy, for example, this case was not treated as a hospitalization event in the analysis.

Covariates. We incorporated a number of covariates in our analysis that may have influenced the relationship between PIM use and hospital admission. The patient characteristics included age, sex, NHI enrollment category, health status, and continuity of care. We used the NHI enrollment category as a proxy for individual socioeconomic status. The subjects with a well-defined monthly wage, such as full-time employees of public agencies or private companies, were classified into two categories, monthly salary under or over NTD 40,000 (with 1 US dollar equivalent to approximately 30 New Taiwan dollars in 2010). The remaining subjects were classified as farmers, fishermen, or members of occupational unions; low-income household members; and others. If an elderly individual was not a policyholder (i.e., a dependent), the enrollment category of the NHI policyholder was used.

Health status is a significant predictor of hospitalization; we employed three proxy variables in the model to represent a patient's health status: (1) hospitalization in the previous year; (2) a modified Charlson comorbidity index score (D'Hoore, Bouckaert, and Tilquin 1996); and (3) the average number of medications per prescription. The level of physician continuity of care was measured by the usual provider continuity (UPC) index. This index is defined as the number of physician visits by a patient to the doctor they saw most frequently divided by the total number of physician visits (Jee and Cabana 2006). The UPC index value has no inherent clinical meaning and was categorized into three equal tertiles. The accreditation level of the health care institution most frequently visited by a given patient was incorporated into the analysis to account for the characteristics of the health care providers. The four accreditation levels (in descending order) included medical center

hospital, regional hospital, district hospital, and community clinic (Huang et al. 2000). The NHI division area, for example, Taipei, Northern, Central, Southern, Kao-ping, and Eastern division, of a patient's most frequently visited institution was incorporated into the analysis to control for regional differences. In addition, time dummies were included for each year to control for the time trend.

Statistical Analyses

The analyses were performed in a sequential two-step process: naive generalized estimating equation (GEE) models and the IV approach.

Naive GEE Models. We fitted the GEE model to a panel study design that considered the unobserved time-invariant characteristics and accounted for the correlation between the repeated observations for the same subject (Fitzmaurice, Laird, and Ware 2004). The likelihood of hospitalization was analyzed using a logit link function and had a binominal distribution. The abovementioned naive GEE models did not consider whether a patient's PIM use was endogenous because of the unobserved time-variant characteristics, which were simultaneously related to both PIM use and health care outcomes. When endogeneity is present, unobserved characteristics can lead to bias in the results.

IV Approach. We employed the IV approach to address the issue of endogeneity because of the unobserved selection bias between the PIM and non-PIM groups. Previous studies have used physician prescribing preferences as an IV when the effectiveness of drug treatment on mortality and morbidity outcomes was assessed (Brookhart et al. 2006, 2007). In this study, we employed the PIM prescription rate of the physician most frequently visited by a patient as the IV for each patient's PIM use.

A valid IV should be highly correlated with the endogenous explanatory variable (patient's PIM use) and not correlated with the outcome of interest (hospitalization), except through the effect of the endogenous explanatory variable. For the IV being strongly associated with the endogenous variable, we considered that physicians' PIM rates are correlated with patients' PIM use. It is reasonable to say that a patient's suboptimal medication use is strongly associated with his/her physician's prescribing preference. A patient

is more likely to receive a PIM prescription from a physician with a high PIM rate compared with a physician with a low PIM rate. Therefore, we considered that the physician's PIM rate was positively associated with patient PIM use.

Then, we must be certain that the physician's PIM rate is uncorrelated with the patient's outcome. We considered that the physician PIM rate may be an invalid IV when the following two situations exist: the physician's quality is associated with physician PIM rate (violations of the exclusion restriction), and the patient characteristics were unbalanced between the physician groups with high and low PIM rates (violations of the independence assumption) (Brookhart et al. 2007).

Violations of the exclusion restriction may occur if the physicians with high average PIM rate have low quality, which leads to their patients' worse outcomes. For example, if physicians with high PIM rate were less likely to keep up with new practice guidelines, then their patients tended to have worse outcome. We have examined the possibility by using physician's service volume as a proxy of quality and found no relationship between physician PIM rate and physician service volume (detailed in the Results section). In addition, the Beer's drugs-to-avoid criteria were developed only for elderly patients; in this study, we constructed the physician's PIM rate in the patients under 65 years of age as the IV. We considered that the physician's PIM rate in patients under 65 was reflective of that physician's prescribing preference and were not correlated with the outcomes of the elderly patients aged 65 or over.

Violations of the independence assumption may occur when the characteristics of patients simultaneously correlated with their physicians' PIM rate and their outcome. This would make physicians' average PIM endogenous. For example, if physicians with higher PIM rates were more likely to take care of elderly patients or patients with more comorbidities, then their patients were more likely to have worse outcome than their counterparts. We have examined the plausibility of both the exclusion restriction and independence assumption in the results sections.

In this study, the PIM rate of an individual physician was calculated as the number of prescriptions classified as PIM divided by the total number of the physician's prescriptions for each year in patients less than 65 years of age. In addition, physicians with at least 10 claim records per year were included to avoid an unstable estimation of their PIM rates. Because the distribution of a physician's PIM rate was right-skewed, we used the log-transformed values in the analysis.

For the IV analysis, we employed the two-stage residual inclusion (2SRI) model suggested by Terza, Basu, and Rathouz (2008). The 2SRI model is a consistent estimate that corrects for endogeneity bias in a variety of nonlinear regression models. In the first stage of the 2SRI model, the patient's PIM use was regressed on the physician's PIM rate (IV), which was controlled for all observed patient- and institution-level covariates during the patient-year observation, as well as for year effect. The specification for the model is as follows:

$$\text{logit } X_{it} = \alpha_0 + \alpha_1 \log(\text{IV}_{it}) + \alpha_2 Z_{it} + \alpha_3 Z_{it} + \varepsilon_{it} \quad (1)$$

In the model, X_{it} represents the binary endogenous patient PIM use for individual i at year t . IV represents the instrument variable (the physician's PIM rate). Z_{it} represents a vector of variables that measure patient characteristics (e.g., age, NHI enrollment category, hospitalization in the previous year, a modified Charlson comorbidity index score, the average number of medications per prescription, and continuity of care during the patient year), provider characteristics (accreditation level of their institutions), and regional dummies. Z_i represents the patient's sex. We also included the year fixed effects (e_t).

The second-stage equation of the 2SRI model is identical to the naive GEE model with the exception that the estimated residuals from equation (1) are also included in equation (2). Therefore, in the second stage of the 2SRI model, the likelihood of hospitalization was regressed on the patient's PIM use, and the residual was estimated from the first stage and other observed covariates. The specification is as follows:

$$\text{logit } Y_{it} = \beta_0 + \beta_1 X_{it} + \beta_2 \hat{\varepsilon}_{it} + \beta_3 Z_{it} + \beta_4 Z_i + e_t \quad (2)$$

In the model, Y_{it} represents the likelihood of hospitalization for individual i at year t . X_{it} is the patient's PIM use for individual i at year t . We incorporated the residual, $\hat{\varepsilon}_{it}$, for each patient in each year by calculating the difference between the patient's actual PIM use and the predicted probability of the patient's PIM use in equation (1). Z_{it} , Z_i , and e_t include the same independent variables listed in equation (1). In addition, we also considered the correlation between the repeated measures for each patient by using the GEE models, which were identical to the naive GEE model. The analysis was performed using statistical software (SAS, version 9.3; SAS Institute, Cary, NC, USA).

EMPIRICAL RESULTS

Descriptive Analyses

Table 1 presents the baseline characteristics of the study subjects in 2008. The mean subject age was 74 years. Approximately 47.54 percent of the study subjects had Charlson comorbidity index scores of 0, whereas 23.12 percent had scores of 2 or higher. The average number of medications per prescription was 3.31 (standard deviation [SD]: 1.25). Community clinics were the most frequently visited health care institution (47.38 percent). Two-thirds (66.64 percent) of the patients received at least one PIM in 2008. The physician-level PIM rate was 0.14 (SD: 0.14). The likelihood of hospitalization in the subjects was 18.14 percent.

The First Stage of 2SRI

The validity of an IV relies on a number of assumptions: (1) the nonzero average causal effect of the IV on the patient's PIM use; (2) the monotonicity assumption; (3) the exclusion restriction; and (4) the independence assumption (Angrist, Imbens, and Rubin 1996; Brookhart et al. 2007). First, regarding the nonzero effect of the IV on a patient's PIM use, the results showed a significant positive relationship between the physicians' PIM rates and the likelihood of PIM use by patients (odds ratio [OR], 1.311; 95 percent confidence interval [CI], 1.299–1.323) (Table 2). Second, regarding the monotonicity assumption, we tested the gradient effects of physician PIM rates on patient PIM use by dividing the physicians' PIM rates into five groups in the model. The monotonicity assumption was supported by the significant gradient effects of the physicians' PIM rates on the likelihood of the patients' PIM use (Table 2).

Third, the assumption of the exclusion restriction and independence assumption indicates that a valid IV should be uncorrelated with the outcome of interest. In this study, we were unable to conduct the overidentification test because the IV estimation was exactly identified. We examined the plausibility of the two criteria, respectively. In terms of the exclusion restriction, the physician's PIM rate was not a valid IV if the prescribing preference was associated with patient outcome (not through patient's PIM use); for instance, physicians with high PIM rates were poor-quality doctors and their patients tended to have worse outcome. We used physician's service volume as a proxy for quality to examine the association as the relationship between volume and outcome has been well established (Halm, Lee, and Chassin 2002). We used each

Table 1: Characteristics of the Study Sample in 2008 ($N = 76,270$)

<i>Characteristics</i>	<i>Value</i>	
Dependent variable: Hospitalization ($N, \%$)	13,835	18.14
Independent variable: Patient's PIM use ($N, \%$)		
Covariates	50,826	66.64
Female ($N, \%$)	40,999	53.76
Age (years) (mean, SD)	73.99	6.31
Age groups		
<70	25,048	32.84
70–80	37,131	48.68
80+	14,091	18.48
NHI enrollment category ($N, \%$)		
<NTD 40,000	9,212	12.08
NTD 40,000 +	10,158	13.32
Farmers and fishermen/members of occupational unions	34,876	45.73
Low-income household	618	0.81
Others	21,406	28.07
Hospitalization in the previous year ($N, \%$)	12,902	16.92
Charlson comorbidity index score ($N, \%$)		
Score 0	36,258	47.54
Score 1	22,375	29.34
Score 2+	17,637	23.12
Average number of medications per prescription (mean, SD)	3.31	1.25
Average UPC index by physician (mean, SD)	0.50	0.22
Level of most frequently visited institution ($N, \%$)		
Medical center hospital	13,308	17.45
Regional hospital	15,744	20.64
District hospital	11,079	14.53
Community clinic	36,139	47.38
Area of most frequently visited institution ($N, \%$)		
Taipei area	23,338	30.60
Northern area	10,589	13.88
Central area	14,191	18.61
Southern	13,106	17.18
Kao-ping area	12,856	16.86
Eastern area	2,190	2.87
Instrument: Physicians' PIM rate (mean, SD)	0.14	0.14

NHI, National Health Insurance; PIM, potentially inappropriate medication; UPC index, usual provider care index.

physician's total number of visits as the measure of physician volume. We found that the Pearson's correlation coefficient was 0.07 among the observations in the 3 years (2008–2010) (data not shown). The low Pearson's correlation coefficients indicated little or no relationship (Portney and Watkins, 2000) between the physician PIM rate and the service volume, which implied that a physician's PIM rate was not associated with his/her quality of care.

Table 2: First-Stage Results: Adjusted GEE Estimations of the Effects of a Physician's PIM Rate on PIM Use in Patients

<i>Characteristics</i>	<i>OR</i>	<i>95% CI</i>		<i>OR</i>	<i>95% CI</i>	
Log (physician's PIM rate)	1.311***	1.299	1.323	—	—	—
Grouped physicians' PIM rates (reference group: quintile 1)						
Quintile 2	—	—	—	1.154***	1.123	1.186
Quintile 3	—	—	—	1.337***	1.299	1.376
Quintile 4	—	—	—	1.638***	1.591	1.687
Quintile 5	—	—	—	2.523***	2.442	2.606
Female	1.140***	1.115	1.166	1.137***	1.111	1.163
Age groups (reference group: <70)						
70–80	0.995	0.971	1.020	0.994	0.970	1.019
80+	0.919***	0.891	0.949	0.918***	0.889	0.947
NHI enrollment category (reference group: NTD 40,000+)						
<NTD 40,000	1.053**	1.010	1.098	1.052**	1.009	1.097
Farmers and fishermen/member of occupational unions	1.139***	1.101	1.179	1.141***	1.103	1.182
Low-income household	1.434***	1.259	1.634	1.422***	1.248	1.621
Others	1.054**	1.017	1.093	1.053***	1.016	1.091
Hospitalization in the previous year	1.065***	1.041	1.090	1.066***	1.041	1.091
Charlson comorbidity index score (reference group: score 0)						
Score 1	1.068***	1.043	1.094	1.080***	1.054	1.106
Score 2	1.207***	1.175	1.241	1.220***	1.187	1.254
Average number of medications per prescription	1.180***	1.169	1.192	1.185***	1.174	1.197
UPC index by physician (reference group: low)						
Intermediate	0.569***	0.556	0.583	0.573***	0.560	0.587
High	0.294***	0.286	0.301	0.297***	0.289	0.304
Level of most frequently visited institution (reference group: community clinic)						
Medical center hospital	0.583***	0.565	0.601	0.595***	0.577	0.614
Regional hospital	0.622***	0.605	0.640	0.640***	0.622	0.658
District hospital	0.723***	0.700	0.747	0.738***	0.715	0.762
Area of most frequently visited institution (reference group: Taipei area)						
Northern area	1.127***	1.088	1.167	1.108***	1.069	1.147
Central area	1.203***	1.162	1.245	1.196***	1.156	1.239
Southern	1.217***	1.134	1.306	1.222***	1.138	1.312
Kao-ping area	0.976**	0.958	0.994	0.965**	0.948	0.983
Eastern area	0.964**	0.946	0.983	0.945***	0.927	0.964
Year effect (reference group: 2008)						
2009	1.034*	0.998	1.072	1.033*	0.997	1.071
2010	1.051**	1.016	1.086	1.046***	1.011	1.081

GEE, generalized estimating estimation; NHI, National Health Insurance; OR, odds ratio; PIM, potentially inappropriate medication; UPC index, usual provider care index; 95% CI, 95% confidence interval.

*** $p < .01$, ** $p < .05$, * $p < .1$.

Fourth, the independence assumption may be violated if patient characteristics were unbalanced between the two physician groups with high and low PIM rates. A common approach adopted in previous studies was to test whether there was a lack of correlation between the IV and the observed characteristics that affected the error term of the second-stage analysis (Grabowski et al. 2013; Kahn et al. 2013). Therefore, we divided the variables used in this study by the observations that were below or above the median physician's PIM rate. We determined that most characteristics were similar between the two groups (Table 3). In general, the main assumptions of a valid instrumental variable were maintained in this study.

Naive GEE Models and 2SRI Estimation with GEE Models

Table 4 presents the estimates of the effects of patient PIM use on health care outcomes. We present two sets of results: (1) the naive GEE model that treated patient PIM use as exogenous and (2) the 2SRI estimation with the GEE model that treated patient PIM use as endogenous. The naive GEE models revealed that PIM use was significantly associated with an increased likelihood of hospitalization (OR, 1.399; 95 percent CI, 1.363–1.435). The 2SRI estimates indicate that PIM use was also significantly associated with an increased likelihood of hospitalization (OR, 1.990; 95 percent CI, 1.647–2.403). The coefficient of the effect of patient's PIM use on the likelihood of hospitalization using the 2SRI model was larger compared with the naive GEE model. Moreover, the coefficient of the residual (from the first-stage equation) was highly significant ($p < .0001$), which indicates an endogeneity bias in the estimates of the naive GEE model.

We conducted a variety of sensitivity analyses of our baseline models (Table 5). First, instead of using 2SRI, we employed the propensity score adjustment by using the inverse probability of treatment weightings to reduce potential differences in the observed characteristics of the patients who received at least one PIM (the PIM group) and the patients who did not (the non-PIM group) (Austin 2011; Rosenbaum and Rubin 1983). We determined that the model with propensity score adjustments yielded results similar compared with the 2SRI model. Second, to minimize an unstable estimate of the PIM rate for physicians with low service volume, the physicians with fewer than 10 claim records per year were excluded from the calculation of the physician's PIM rate as the IV. We performed a sensitivity analysis using various minimum amounts of claim records for physicians (a minimum of 20, 30,

Table 3: Examination of the Exclusion Restriction Assumption for the Instrumental Variable (2008 Data)

<i>Characteristics</i>	<i>Physicians'</i> <i>PIM Rates < Median</i>		<i>Physicians' PIM</i> <i>Rates ≥ Median</i>	
Total	40,525		35,745	
Female (<i>N</i> , %)	21,564	53.21	19,435	54.37
Age (mean, SD)				
<70	13,102	32.33	11,946	33.42
70–79	19,767	48.78	17,364	48.58
80+	7,656	18.89	6,435	18.00
NHI enrollment category (<i>N</i> , %)				
<NTD 40,000	4,961	12.24	4,251	11.89
NTD 40,000+	5,741	14.17	4,417	12.36
Farmers and fishermen/ members of occupational unions	16,959	41.85	17,917	50.12
Low-income household	299	0.74	319	0.89
Others	12,565	31.01	8,841	24.73
Hospitalization in the previous year (<i>N</i> , %)	6,941	17.13	5,961	16.68
Charlson comorbidity index (<i>N</i> , %)				
Score 0	18,084	44.62	18,174	50.84
Score 1	11,952	29.49	10,423	29.16
Score 2+	10,489	25.88	7,148	20.00
Average number of medications per prescription (mean, SD)	3.23	1.25	3.41	1.24
UPC index by physician (<i>N</i> , %)				
Low	14,034	34.63	11,147	31.18
Intermediate	13,226	32.64	11,657	32.61
High	13,265	32.73	12,941	36.20
Level of most frequently visited institution (<i>N</i> , %)				
Medical center hospital	9,292	22.93	4,016	11.24
Regional hospital	9,195	22.69	6,549	18.32
District hospital	5,876	14.50	5,203	14.56
Community clinics	16,162	39.88	19,977	55.89
Area of most frequently visited institution (<i>N</i> , %)				
Taipei area	14,340	35.39	8,998	25.17
Northern area	5,559	13.72	5,030	14.07
Central area	7,180	17.72	7,011	19.61
Southern	6,102	15.06	7,004	19.59
Kao-ping area	6,388	15.76	6,468	18.09
Eastern area	956	2.36	1,234	3.45

NHI, national health insurance; PIM, potentially inappropriate medication; SD, standard deviation; UPC index, usual provider care index.

40, and 50 claim records) each year. We determined that the results tended to be robust across the various thresholds. Third, instead of clustering standard errors at the subject level, we further considered the clustering effect of

Table 4: Adjusted GEE Model Estimations of the Effects of Patients’ PIM Use on Health Care Outcomes

<i>Characteristics</i>	<i>Naive GEE Model</i>			<i>2SRI Model</i>		
	<i>OR</i>	<i>95% CI</i>		<i>OR</i>	<i>95% CI</i>	
Patients’ PIM use	1.399***	1.363	1.435	1.990***	1.647	2.403
Residual from stage 1	—	—	—	0.699***	0.578	0.845
Female	0.896***	0.875	0.917	0.888***	0.866	0.909
Age groups (reference group: <70)						
70–80	1.198***	1.163	1.233	1.198***	1.163	1.233
80+	1.612***	1.558	1.668	1.621***	1.567	1.677
NHI enrollment category (reference group: NTD 40,000 +)						
<NTD 40,000	1.061*	1.012	1.113	1.057**	1.008	1.108
Farmers and fishermen/member of occupational unions	1.209***	1.164	1.255	1.196***	1.151	1.243
Low-income household	1.885***	1.672	2.125	1.836***	1.628	2.072
Others	1.045**	1.005	1.087	1.042**	1.002	1.084
Hospitalization in the previous year	1.635***	1.590	1.682	1.629***	1.584	1.676
Charlson comorbidity index (reference group: score 0)						
Score 1	1.528***	1.484	1.574	1.523***	1.478	1.568
Score 2+	2.778***	2.697	2.862	2.749***	2.667	2.833
Average number of medications per prescription ≥4	1.097***	1.087	1.108	1.082***	1.069	1.095
UPC index by physician (reference group: low)						
Intermediate	0.734***	0.715	0.753	0.763***	0.738	0.788
High	0.427***	0.413	0.440	0.467***	0.441	0.494
Level of most frequently visited institution (reference group: community clinic)						
Medical center hospital	1.617***	1.563	1.672	1.694***	1.625	1.767
Regional hospital	1.786***	1.733	1.842	1.854***	1.787	1.922
District hospital	1.535	1.482	1.589	1.574***	1.516	1.634
Area of most frequently visited institution (reference group: Taipei area)						
Northern area	1.015	0.977	1.054	1.010	0.972	1.049
Central area	0.998	0.963	1.034	0.991	0.957	1.027
Southern	0.987	0.951	1.024	0.975	0.939	1.012
Kao-ping area	1.090***	1.052	1.130	1.072***	1.033	1.113
Eastern area	1.164***	1.086	1.249	1.143***	1.065	1.226
Year effect (reference groups: 2008)						
Year 2009	1.013	0.987	1.040	1.016	0.989	1.043
Year 2010	1.097***	1.069	1.125	1.101***	1.073	1.130

GEE, generalized estimating equation; 2SRI, two-stage residual inclusion; NHI, National Health Insurance; OR, odds ratio; PIM, potentially inappropriate medication; UPC index, usual provider care index; 95% CI, 95% confidence interval.
*** $p < .01$, ** $p < .05$, * $p < .1$.

patients within the specific physicians to control for unobserved characteristics that may have existed among subjects visiting the same physician. This analysis also yielded similar results to our baseline model.

Table 5: Sensitivity Analyses

Characteristics	Naive GEE Model			2SRI Model		
	OR	95% CI		OR	95% CI	
(1) Propensity score adjustment	1.400***	1.364	1.437	—	—	—
(2) Excluding physicians with low service volume (minimum of 20 claim records)	1.398***	1.363	1.435	2.010***	1.664	2.428
(3) Excluding physicians with low service volume (minimum of 30 claim records)	1.399***	1.363	1.435	2.038***	1.686	2.464
(4) Excluding physicians with low service volume (minimum of 40 claim records)	1.396***	1.361	1.433	2.039***	1.685	2.467
(5) Excluding physicians with low service volume (minimum of 50 claim records)	1.398***	1.362	1.435	2.089***	1.725	2.529
(6) Clustering patients within a particular physician	1.392***	1.357	1.428	1.931***	1.635	2.281

GEE, generalized estimating equation; 2SRI, two-stage residual inclusion; OR, odds ratio; 95% CI, 95% confidence interval.

All models controlled for sex, age groups, NHI enrollment category, hospitalization in the previous year, Charlson comorbidity index, average number of medications per prescription, UPC index, level of health care institution, area of health care institution, and year effect.

*** $p < .01$.

DISCUSSION

Although the linkages between PIM and health care outcomes have been reported, this study adds to the literature by providing the first empirical evidence of causal inference using a design and an IV approach with a nationwide representative sample of elderly patients. This study supports the conclusion that PIM use increases the likelihood of hospitalization in the elderly.

During the study period from 2008 to 2010, approximately 66.64 percent of elderly patients received at least one medication from a list of drugs to avoid, which is consistent with the findings of Lai et al. (2009) in Taiwan. The prevalence of PIM use was substantially higher compared with the prevalence reported by other studies that used the Beers 2003 modified criteria for community-dwelling elderly or managed care enrollees in the United States and European countries; these studies ranged from 15 to 41 percent (Franic and Jiang 2006; Zuckerman et al. 2006; Fu et al. 2007; Fick et al. 2008; Barnett et al. 2011). The higher prevalence of PIM use may be attributable to frequent

physician visits without a referral and the low drug copayment under Taiwan's universal health insurance program.

Our findings support the conclusion drawn from the majority of previous studies that PIM use is associated with increased hospitalizations (Fick et al. 2001; Klarin, Wimo, and Fastbom 2005; Lin et al. 2008). However, Aparasu and Mort (2004) did not identify an association between the use of potentially inappropriate psychotropic agents and the number of hospitalizations in older adults. In addition, the findings from another study that examined elderly patients in an ED setting indicated that PIM was not associated with 3-month follow-up hospital admissions (Chin et al. 1999). These findings may be attributed to the fact that only a single hospital was included and less comprehensive outcome measures were used, such as whether patients transferred to other hospitals. It is reasonable to infer that PIM use may lead to increased adverse drug reactions (Chang et al. 2005; Fick et al. 2008) or other complications, which further increase the need for hospitalizations. However, the causal relationship between PIM use and health care outcomes has been questioned (Jano and Aparasu 2007; Spinewine et al. 2007), and the findings must be explained with caution because of potential unobserved confounders. Using the IV technique to account for the unobserved confounders, this current study enhanced the robustness of the findings. This study also suggests that adjusting for unobserved confounders is necessary to obtain unbiased estimates of the relationship between PIM and health care outcomes.

Our study has several limitations. First, the study used NHI claims data, which did not contain certain unobserved (such as health literacy) or unavailable characteristics (such as socioeconomic status or severity of illness) in the regression models that could have simultaneously affected PIM use and outcome measures. However, this study used a panel study design and an IV approach, which considered the influence of unobserved subject characteristics and thus mitigated this concern to some extent (Fitzmaurice, Laird, and Ware 2004; Wooldridge 2010). In addition, we included three proxy indicators to represent health status (i.e., hospitalization in the previous year, the modified Charlson comorbidity index score, and the average number of medications per prescription) and a proxy indicator for socioeconomic status (NHI enrollment status) in the regression models, which may have also lessened the bias from confounders not incorporated in the model. The second limitation was the healthy survivor effect that occurred due to the exclusion of deceased subjects who may have been hospitalized and would have consumed an extremely high amount of resources prior to death (Scitovsky 1984; Liu and Yang 2002) that were not directly attributable to PIM. Because the cause of death

was not available in the NHI claim data, we could not explore these possibilities; therefore, we restricted our study subjects to patients who had complete follow-up coverage over the 4-year observation period. Third, no information on the daily dosage of each medication was available in the NHI claims data. Inappropriate medication prescribing in this study was confined to medications that appeared on the drugs-to-avoid list. Therefore, this study may have underestimated the likelihood of PIM use in the elderly. Moreover, investigating the other types of inappropriate medication use, such as drug–drug interactions, warrants further exploration. Finally, the results of this study were obtained from a health care system under a universal coverage program without referral arrangements; thus, the findings may not be generalizable to other health care systems.

We concluded that PIM use is a common problem in outpatient settings in elderly patients in Taiwan, and PIM use is associated with an increased likelihood of hospitalization. Identifying methods to reduce PIM use in elderly individuals is an important task for health authorities in industrialized countries. We suggest that implementing educational programs to increase physician awareness of the risks of PIM use and improving patient continuity of care are potential strategies to prevent PIM use. In addition, using PIM as a performance measure for physicians and excluding certain drugs-to-avoid from the benefit packages for elderly individuals represent other strategies that health policy makers should consider.

ACKNOWLEDGMENTS

Joint Acknowledgment/Disclosure Statement: The study was supported by grants from the Ministry of Science and Technology (MOST103-2410-H-002-202) and the National Health Research Institute (NHRI-EX104-10225PI) in Taiwan. The funding source had no role in the study.

Disclosures: None.

Disclaimers: None.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article:

Appendix SA1: Author Matrix.