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RESEARCH ARTICLE

Does Increased Medication Use among Seniors Increase Risk of Hospitalization and Emergency Department Visits?

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Objective. To examine the extent of the health risks of consuming multiple medications among the older population.

Data Sources/Study Setting. Secondary data from the period 2004–2006. The study setting was the province of Ontario, Canada, and the sample consisted of individuals aged 65 years or older who responded to a national health survey.

Study Design. We estimated a system of equations for inpatient and emergency department (ED) services to test the marginal effect of medication use on hospital services. We controlled for endogeneity in medication use with a two-stage residual inclusion approach appropriate for nonlinear models.

Principal Findings. Increased prescription drug use has the effect of increasing the likelihood of both being admitted into hospital and visiting a hospital ED. Each additional medication is associated with a 2–3 percent increase in the likelihood of hospitalization and a 3–4 percent increase in the likelihood of an ED visit, after controlling for past utilization, health status, the endogeneity of medication use, and the unobserved factors that may affect the use of both services.

Conclusions. Multiple medications appear to increase the risk of hospitalization among seniors covered by a universal prescription drug plan. These results raise questions about the appropriateness of medication use and the need for increased oversight of current prescribing practices.

Key Words. Prescription drugs, hospitalization, instrumental variable, seniors, Ontario

Pharmaceutical expenditures are showing signs of slowing in high-income countries; however, the consumption of pharmaceuticals continues to increase over time (OECD 2015). Among three of the most common drug categories—antihypertensives, antidepressants, and antibiotics—consumption has nearly doubled between 2000 and 2011 across OECD countries, while the consumption of anticholesterol medications has tripled over this same time period

(OECD 2013). More than half of the populations in 9 of 11 high-income countries surveyed by the Commonwealth Fund reported taking at least one prescription drug regularly (52 percent in the United Kingdom, 56 percent in Canada and the Netherlands, and 61 percent in the United States) (Squires 2011).

The continued increase in pharmaceutical consumption raises concerns about adverse health effects and the related costs to the health system. While there are clear health benefits of prescription therapies, multiple-medication use may also have deleterious consequences for health. A number of studies have found an increased risk of adverse drug events associated with an increase in the number of drugs taken (Lazarou, Pomeranz, and Corey 1998; Patel et al. 2007; Zed et al. 2008; CIHI 2013). The risks associated with multiple-medication use are well documented (Kroenke and Pinholt 1990; Tamblyn et al. 1994), especially among older people where it is more common (Ramage-Morin 2009). However, the challenge with estimating the effects of additional drugs on health outcomes is that the variable of interest, the number of different drugs, is likely to be endogenous: there are likely to be characteristics related to the health of the individual that simultaneously predict both the number of drugs he or she consumes and his or her use of other health services and broader health outcomes.

Some studies in the U.S. context have attempted to address this methodological challenge by using difference-in-difference, matched cohorts, and instrumental variables (IVs) approaches. These studies have found that, contrary to what we might expect given the risks of increased drug use, increased drug coverage, and consumption had a negative effect on hospital service utilization. For instance, Afendulis et al. (2011) considered the impact of Medicare Part D—which increased the share of Medicare beneficiaries with prescription drug coverage—on hospitalization rates. Using a difference-in-difference approach on the implementation of Medicare Part D, the authors found increased drug coverage associated with Medicare Part D reduced hospital admissions. Meanwhile, Soumerai et al. (1991) used a matched cohorts approach and found that decreased Medicaid coverage increased admission to nursing homes, but it had no effect on risk of hospitalization. The effect of

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holding drug coverage may be to convert people who needed medications from nonusers to users. However, another recent study in the United States looked at the actual number of different drugs taken by a population of older adults and found similar protective effects. Specifically, Stuart, Doshi, and Terza (2009) analyzed the impact of prescription drug use on hospitalization costs for Medicare beneficiaries. The authors utilized a two-part model to estimate hospital admission and hospital spending and found that drug use is associated with reduced hospital costs.

It is possible that these findings are related to institutional factors associated with insurance for prescription drugs in the United States. In this study, we aim to build on the existing literature by quantifying the health risks of multiple-medication use on the use of inpatient and emergency department (ED) services among seniors in Ontario, Canada (Canada's most populous province). We focus on Ontario because health care funding and delivery is a provincial responsibility, and coverage can vary across provincial jurisdictions. In Ontario, physician and hospital care is free at the point of service, and universal drug coverage is provided to all residents who are 65 years of age or older with minimal cost sharing. In this study, we focus specifically on this population.

Canada is an ideal context in which to study the risks associated with multiple-medication use. In Canada, prescription drug consumption is particularly high compared to other countries. Between 1999 and 2009, the number of prescription medications dispensed by community pharmacies nearly doubled (Health Council of Canada 2010). In 2011, the OECD reported that Canada consumed above the OECD average amount of hypertension drugs, anticholesterols, and antidiabetics; and the consumption of antidepressants in Canada is the third highest among OECD countries (OECD 2013a,b). Furthermore, 17 percent of Canadians report taking four or more prescription drugs regularly—higher than most European countries surveyed, but lower than the United States, which is at 25 percent (Squires 2011). As in other countries, the use of prescription drugs increases significantly with age. While nearly all seniors living in institutions were taking at least one type of medication, over three quarters of those living in a private household were taking at least one type of medication (Ramage-Morin 2009). In 2012, about 60 percent of seniors in Canada were taking five or more different drugs, while 27 percent were taking 10 or more drugs and over 8 percent were taking 15 or more different drugs in that year (CIHI 2014).

While previous studies have demonstrated the risks of multiple-medication use in the Canadian context, this study innovates in three ways. First, it

examines the marginal risk of hospitalization and ED visits among a population of seniors who are universally covered with prescription drug insurance. Second, we follow previous U.S. studies by controlling for the endogeneity of drug utilization with a two-stage IV approach. Third, we estimate a system of equations for hospitalization and ED utilization in order to account for unobservable factors that may simultaneously explain the likelihood of both being hospitalized and visiting an ED.

We find that multiple-medication use is indeed associated with increased likelihood of utilization of hospital services, and that this effect is robust to a series of sensitivity analyses. We estimate that the average marginal effect of each additional prescription is between a 2–3 percent increase in the likelihood of hospitalization and a 3–4 percent increase in the likelihood of an ED visit. This modest but significant effect of taking an additional drug on hospital use signals the need for greater oversight of current prescribing practices among the senior population. It also suggests the need for further work using more detailed clinical data to disentangle the reasons for increased risk of drug use and possible interventions to reduce multiple-medication use.

METHODS

Data

The data for this study come from two linked sources that capture individual-level information. We used the 2005 Canadian Community Health Survey (CCHS), which is collected by Statistics Canada—the statistics and analytics agency of the Canadian federal government—and is a random and representative survey of the Canadian population 12 years and older, living in private dwellings. The 2005 survey was chosen because it contained information on insurance coverage, which we tested as an IV. The CCHS excluded those living on Indian Reserves or Crown lands, residents of institutions, full-time members of the Canadian Armed Forces, and residents of some remote regions. However, these exclusions comprised approximately 2 percent of the Canadian population. The CCHS captured a wide range of self-reported information, including demographic, socioeconomic, health, and behavioral variables.

Approximately 87 percent of CCHS respondents provided their government-issued health insurance number, which allowed their survey responses to be linked with administrative health data. We used linked administrative data at the Institute for Clinical Evaluative Sciences (ICES)—a government-funded, arm’s-length research institute in Toronto, Ontario, which

houses administrative health data for the province. We used records on physician, hospital, and pharmaceutical claims for 1 year before and 1 year after the 2005 CCHS was administered. Pharmaceutical claims data were obtained from the Ontario Drug Benefit (ODB) program, which provides universal drug coverage to Ontario residents who are 65 years of age or older. Our study sample focused on the ODB eligible population, and it included all Ontarians 65 years of age and older who were captured by the 2005 CCHS and were linkable to administrative data via a health insurance number. This study was approved through the ICES research ethics approval process.

Empirical Model and Estimation Strategy

Our dependent variables were the following: ED = 1 if the individual had at least one ED visit in the past year, and 0 if not; hospitalization = 1 if there was at least one hospitalization in the past year, and 0 if not. We listed our independent variables in Table 1. Our key variable of interest was the number of unique prescriptions assigned to an individual. One of the key empirical issues that we needed to address in our study was the potential endogeneity of this variable. We suspected that there was a simultaneous relationship between outcome variables (utilization of hospital services) and the number of unique drugs prescribed. One of the most effective methods for addressing potential endogeneity of regressors is to use an IV (Grootendorst 2007). However, given our model was nonlinear, typical two-stage predictor substitution (2SPS) methods for estimating IV models was not appropriate. Terza, Basu, and Rathouz (2008) demonstrated that 2SPS is not consistent when estimating nonlinear outcomes. Instead, these authors recommend a two-stage residual inclusion (2SRI) approach, which they demonstrate is consistent in the nonlinear context. The 2SRI method involves the estimation of a two-stage model, where the residuals from the first stage are included as regressors in the second stage.

The 2SRI approach still requires the identification of a suitable IV. In order for our IV to be suitable, it had to be both strong (i.e., highly predictive of the endogenous regressor) and valid (not correlated with the unobserved component of the error term in the outcome model) (Staiger and Stock 1997). A systematic review of the use of IVs in prescription drug research identified 26 studies and five types of IVs, including regional variation, facility prescribing patterns, physician preference, patient medical history, financial status (including insurance coverage), and calendar time (Chen and Briesacher 2011). A U.S. study by Stuart, Doshi, and Terza (2009) used private medical

Table 1: Variable Definitions and Descriptive Statistics

<i>Variable</i>	<i>Definition</i>	<i>Mean</i>	<i>SD</i>
<i>Dependent variables</i>			
Hospitalization	Hospitalization = 1, otherwise = 0	0.14	0.35
ED visit	ED visit = 1, otherwise = 0	0.30	0.46
<i>Instrumental variables</i>			
Prescriber volume	Standardized prescriber volume quintile		
	1	0.18	0.39
	2	0.18	0.39
	3	0.18	0.39
	4	0.18	0.39
	5	0.18	0.39
Prescriber volume missing	Missing observations for prescriber volume	0.09	0.28
Number of prescribers	Number of unique prescribers assigned to each patient	2.27	1.46
<i>Independent variables</i>			
Unique drugs	Number of unique drugs prescribed to each individual	6.92	4.99
Income quartile	Individuals' neighborhood income quintile		
	1	0.19	0.39
	2	0.17	0.38
	3	0.18	0.38
	4	0.17	0.38
Income missing	Missing observations for neighborhood income	0.10	0.30
Low-income drug program	Individual is in low-income drug program = 1, otherwise = 0	0.19	0.39
Postsecondary education	Postsecondary education = 1, otherwise = 0	0.44	0.5
Home ownership	Home ownership = 1, otherwise = 0	0.77	0.42
Married	Married = 1, otherwise = 0	0.49	0.5
Poor self-reported health	Poor self-reported health = 1, otherwise = 0	0.24	0.43
ADG	Number of ADGs assigned to each patient	4.76	2.93
Overweight	Overweight = 1, otherwise = 0 (based on self-reported height and weight)	0.44	0.5
Never smoked	Self-reported never smoked = 1, otherwise = 0	0.35	0.48
Private insurance	Self-reported private insurance = 1, otherwise = 0	0.31	0.46
Previous hospitalizations	Number of hospitalizations in the previous year	0.15	0.48
Previous ED visits	Number of ED visits in the previous year	0.5	1.15
Previous physician claims	Number of physician claims in the previous year	24.28	23.05
Female	Female = 1, male = 0	0.6	0.49
Age group			
	66–74	0.53	0.50
	75–84	0.39	0.49
	85+	0.08	0.27
LHIN	14 dummies (one for each LHIN)	–	–
Canadian born	Canadian born = 1, otherwise = 0	0.73	0.44

ADG, aggregated diagnostic group; ED, emergency department; LHIN, Local Health Integration Network.

insurance as an instrument for medication use. However, we tested the suitability of insurance coverage and found that it was not significantly associated with the endogenous variable, controlling for other factors. This may be because private insurance serves as a top-up insurance to the public plan in the Ontario context, and it largely covers the copayments of publicly funded drugs and the cost of drugs that are not listed on the provincial formulary (Paterson et al. 2008).

Instead, we considered two measures of prescribing patterns as our instrument. Previous studies have used similar instruments for prescription drug use (Salkever, Slade, and Karakus 2006; Dudl et al. 2009). The first was prescriber volume, or the total number of unique drugs prescribed by each patient's most responsible prescribing physician in the previous year, standardized by the total number of patients seen by that provider in a year. The most responsible prescribing physician was determined by assigning each patient to the physician that most frequently prescribed drugs to that patient in a year. The rationale for prescriber volume was that the prescribing behavior of an individual's most responsible physician is likely correlated with the number of unique drugs consumed; however, it should not directly impact non-drug health service utilization. The assumption was that individuals do not choose their physician based on their prescribing behavior. We believed this was a reasonable assumption as information about prescribing volume was not accessible to the patient. If some physicians specialize by treating patients at higher risk of nondrug utilization, then the correlation between physician prescribing volume and the observed and unobserved health of their patients may bias the second-stage coefficient on the number of drugs the patient takes. However, the majority of Ontario's primary care physicians—who do the majority of prescribing in Canada (Health Council of Canada 2010)—provide care to a geographic population and do not specialize in providing care to sicker populations. To demonstrate this, we used data on all primary care physicians in Ontario for the 2010/11 fiscal year to find physicians with a disproportionate number of patients with high Resource Utilization Band scores—a measure of expected utilization based on the Johns Hopkins Adjusted Clinical Group (ACG) system—and 10 or more aggregated diagnostic groups (ADGs)—a measure that groups ACGs into diagnosis categories (The Johns Hopkins University 1997). We found 5–7 percent of physicians at points greater than 1.5 times the interquartile range. This suggests that the primary care physician population in Ontario is fairly homogenous in its care for sicker patient populations. It is also worth noting that there are some specialized primary care models in Ontario (e.g., Community Health Centres); however,

these models capture less than 5 percent of the population (Glazier, Zagorski, and Rayner 2012).

The second IV we considered was the number of prescribing physicians assigned to each patient in a year. The rationale for this IV was that it should be highly correlated with polypharmacy, particularly if multiple providers are uncoordinated in their use of prescriptions, which could create greater opportunities for error. However, the number of prescribers a patient has should not be directly related to his or her risk of ED visits and hospitalizations. In addition, unlike prescriber volume, we do not have the same concerns about unobserved prescriber characteristics that may be associated with our outcomes (e.g., disproportionately treating sick/high-risk patients). As a sensitivity and robustness check, we report the results for both IVs in our analysis.

Econometric Model

The dependent variable in our first stage is a count variable for the number of unique prescription drugs. We estimated the following model using a negative binomial estimator:

$$d_i = \exp(\alpha + p_i'\beta + s_i'\lambda + h_i'\gamma + x_i'\delta + \omega_i)$$

where d_i denotes the distributional mean for the count of unique drugs, p denotes the IV (either a vector of dummy variables for prescriber volume quartiles, or the number of prescribers), s denotes a vector of socioeconomic variables, h denotes a vector of health and health behavior variables, and x denotes a vector of demographic variables. We estimated this model using the *glm* command in *Stata 13*.

Socioeconomic variables included income quintile, which was based on self-reported total household income. We also included a dummy variable for whether an individual was enrolled in the low-income drug program, which is an annual government program that provides benefits to Ontario residents who have total household incomes below a set threshold (during the time of the analysis, the threshold was set at \$16,018 for a single person, and \$24,175 for a couple). We also included a dummy variable for postsecondary education, home ownership, and whether the individual is married; these variables were obtained from the self-reported CCHS.

The health status and health behavior variables included a dummy variable for poor self-reported health obtained from the CCHS and a categorical variable for the number of ADGs assigned to each patient. ADGs were based on the ACGs developed at Johns Hopkins University. The ACG system

groups patients into clinically consistent categories based on diagnoses. The ADG assigns ACGs into 32 diagnosis categories. We also included dummy variables for whether individuals were overweight, had never smoked, and had access to private medical insurance for services not covered by the public health insurance plan. These variables were obtained from the CCHS. From the administrative dataset, we were able to obtain information on past utilization of health care services, including the number of hospitalizations, ED visits, and physician claims in the previous year.

Finally, we included a number of demographic characteristics, including the following: female, age group, the region—or Local Health Integration Network—where the individual is located, and whether he or she was born in Canada.

In our second-stage estimation, we adopted Zellner's Seemingly Unrelated Regression (SUR) model (Zellner 1962) approach and estimated a bivariate probit model using the user-generated command, *biprobit* in Stata 13.

$$y_{i,j} = \Phi(\alpha_j + d_i\beta_j + s'_i\lambda_j + h'_i\gamma_j + x'_i\delta_j + \hat{w}_i\psi_j + \varepsilon_{ij}) \begin{pmatrix} i = 1, 2, \dots, n \\ j = 1, 2 \end{pmatrix}$$

where j represents the equation number, and $\hat{w}$ represents the residuals from the first-stage regression. This two-stage approach allowed us to simultaneously estimate our outcome variables: probability of a hospitalization and ED visit. We used a SUR model because we wanted to account for possible correlation between the error terms (ε_{ij}) as the unobservables affecting ED visits and hospitalization may be highly correlated. Although the coefficient parameters in these models can be consistently estimated using separate probit regressions, if there is correlation between them, taking account of it by estimating them jointly via the bivariate probit method will increase the efficiency of the estimates (Greene 2003; Bhattacharya 2004). We included all of the exogenous variables as well as the stored residuals from our first-stage estimation in our second-stage estimation. In all estimations, we used bootstrapping with 300 iterations to obtain the standard errors.

RESULTS

Descriptive Statistics

Our sample included 6,181 observations (Table 1 provides descriptive statistics for this sample). With respect to our outcome variables 30 percent of our

sample had at least one ED visit and 14 percent had at least one hospitalization in the 12-month period following the CCHS survey. In addition, individuals in our sample consumed nearly seven unique drugs, on average, over this same period. This observed average drug use is consistent with what has been documented in other studies and in other Canadian jurisdictions (in 2012, seniors consumed an average of seven unique drugs) (CIHI 2014).

First-Stage Estimation

Our first-stage estimates are listed in Table 2. The results of this model suggest that both of our IVs were significant predictors of the number of unique drugs. We computed a Wald statistic of 433.90 ($p < .001$) for prescriber volume and 968.27 ($p < .001$) for the number of prescribers. This suggests our IVs are strong predictors of the number of unique drugs prescribed (Staiger and Stock 1997). All levels of prescriber volume were positive and statistically significant, with the coefficients increasing in magnitude with increasing prescriber volume. In addition, the number of prescribers was also positive and statistically significant. Being in the low-income drug program, the number of physician claims in the previous year, being female, age, being overweight, and having poor self-assessed and diagnosed health were all associated with increased drug consumption. Meanwhile, education, home ownership, hospital utilization in the previous year, and having never smoked were negatively associated with the number of unique drugs consumed.

Second-Stage Estimation

Our key result of interest was that the number of unique drugs consumed was found to be a significant predictor of ED visits and hospitalization. We computed average marginal effects (see Table 3) and found that each additional unique drug increased the probability of ED visit by between 3 and 4 percent. The effect was smaller for hospitalization, at 2–3 percent. To test whether this effect varies with the number of drugs taken, we also calculated the average marginal effects for each number of different drugs. Table S1 provides the detailed results for our second-stage estimation for the bivariate probit. It is important to note that individual responses to our IVs were heterogeneous (i.e., individuals vary in their reaction to prescriber volume and/or the number of prescribers). Therefore, our results should be interpreted as “local” to those who were affected by our IVs.

Table 2: First-Stage Estimates (Outcome = Number of Unique Drugs)

<i>Variables</i>	<i>IV= Prescriber Volume</i>			<i>IV= Number of Unique Prescribers</i>		
	<i>Coefficient</i>	<i>Robust SE</i>	<i>p</i>	<i>Coefficient</i>	<i>Robust SE</i>	<i>p</i>
Number of prescribers	—	—	—	0.159	0.005	<.001
Prescriber volume quintile						
1 (reference)	—	—	—	—	—	—
2	0.059	0.023	.012	—	—	—
3	0.072	0.024	.002	—	—	—
4	0.135	0.023	<.001	—	—	—
5	0.175	0.024	<.001	—	—	—
Prescriber volume missing	−1.671	0.092	<.001	—	—	—
Low-income drug program	0.206	0.031	<.001	0.179	0.025	<.001
Income quartile						
1	0.06	0.030	.042	0.093	0.025	<.001
2	0.022	0.030	.45	0.045	0.024	.062
3	0.039	0.028	.155	0.048	0.023	.037
4 (reference)	—	—	—	—	—	—
Income missing	−0.011	0.032	.723	0.03	0.028	.286
Postsecondary	−0.064	0.017	<.001	−0.077	0.014	<.001
Home owner	−0.035	0.021	.091	−0.035	0.017	.041
Married	−0.019	0.018	.308	−0.029	0.016	.066
Private insurance	0.032	0.018	.085	0.024	0.015	.113
Poor self-assessed health	0.337	0.020	<.001	0.253	0.015	<.001
ADG	0.062	0.004	<.001	0.039	0.003	<.001
Number of physician claims $t - 1$	0.0065	0.0004	<.001	0.0048	0.0004	<.001
Number of ED visits $t - 1$	−0.012	0.007	.114	−0.025	0.006	<.001
Number of hospitalizations $t - 1$	−0.143	0.018	<.001	−0.074	0.016	<.001
Overweight	0.112	0.017	<.001	0.112	0.014	<.001
Never smoked	−0.046	0.018	.011	−0.041	0.015	.005
Female	0.036	0.019	.059	0.037	0.016	.020
Age group						
66–74 (reference)	—	—	—	—	—	—
75–84	0.116	0.018	<.001	0.095	0.014	<.001
85+	0.167	0.031	<.001	0.171	0.027	<.001
LHIN						
1 (reference)	—	—	—	—	—	—
2	−0.116	0.036	.001	−0.076	0.029	.010
3	−0.073	0.046	.118	−0.058	0.040	.147
4	−0.081	0.037	.027	−0.081	0.029	.006
5	−0.079	0.072	.276	−0.102	0.054	.060
6	−0.069	0.054	.200	−0.086	0.041	.036
7	−0.066	0.066	.321	−0.045	0.052	.384
8	−0.114	0.049	.021	−0.052	0.041	.201

continued

Table 2. *Continued*

<i>Variables</i>	<i>IV= Prescriber Volume</i>			<i>IV= Number of Unique Prescribers</i>		
	<i>Coefficient</i>	<i>Robust SE</i>	<i>p</i>	<i>Coefficient</i>	<i>Robust SE</i>	<i>p</i>
9	−0.079	0.039	.044	−0.038	0.031	.232
10	−0.078	0.041	.060	−0.017	0.034	.62
11	−0.123	0.039	.002	−0.101	0.032	.002
12	−0.099	0.049	.044	−0.086	0.039	.027
13	−0.088	0.036	.016	−0.053	0.031	.083
14	−0.21	0.048	<.001	−0.169	0.044	<.001
Canadian born	−0.005	0.020	.818	−0.024	0.016	.147
Log likelihood	−17,713.66			−16,924.12		
AIC	35,505.32			33,918.23		
BIC	35,767.76			34,150.5		
Wald statistic IV	433.90 ($p < .001$)			968.27 ($p < .001$)		

ADG, aggregated diagnostic group; ED, emergency department; IV, instrumental variable; LHIN, Local Health Integration Network.

Figure 1 shows that the annual risk of an ED visit increases steadily as individuals take additional drugs until 12 different drugs (average marginal effect of an additional drug at 12 drugs is 5 percent).

The incremental risk of being hospitalized is similar: Figure S1 shows that the annual risk of an individual being hospitalized increases until 17 drugs (average marginal effect of an additional drug at 17 drugs is 5 percent).

The second-stage results also suggest there is no independent relationship between our income variables and the use of hospital services. Our health variables were significant predictors of utilization in some estimations, but not consistently so. Poor self-assessed health was a significant predictor of ED visits in Model 1, but not in Model 2; however, the number of ADGs was a significant predictor of hospitalization in Model 2. Unsurprisingly, previous utilization was strongly associated with current utilization. Finally, being in the oldest age group was generally a significant predictor of ED visits and hospitalization.

Postestimation and Sensitivity Tests

To test the fit of our models, we calculated positive predictive values (PPVs) and negative predictive values (NPVs). The PPV for our estimation of the probability of an ED visit and hospitalization were between 66.83 and 69.90 percent and between 62.50 and 63.40 percent, respectively. Meanwhile, the NPV were 74.22–75.61 percent and 87.05–87.96 percent, respectively (see

Table 3: Effect of Number of Prescribed Drugs on Probability of ED Visit and Hospitalization

IV	IV= Standard Prescriber Volume				IV= Number of Unique Prescribers				No IV	
	2SRI		2SLS		2SRI		2SLS		Bivariate Probit	
	AME	SE	Coef	SE	AME	SE	Coef	SE	AME	SE
Model Estimate										
Probability ED visit = 1	0.0258	0.0048	0.0299	0.0038	0.0443	0.0042	0.0689	0.0038	0.0262	0.0018
Probability hospitalization = 1	0.0158	0.0030	0.0167	0.0025	0.0255	0.0024	0.0521	0.0033	0.0201	0.0011
Probability ED visit = 1, hospitalization = 1	0.0138	0.0020	—	—	0.0226	0.0016	—	—	0.0165	0.0008

Notes. All estimates are statistically significant at $p < .001$. All standard errors are bootstrapped with 300 replications. Marginal effects were calculated using the margins command in Stata 13 (see Appendix SA2). 2SRI, two-stage residual inclusion; 2SLS, two-stage least squares; AME, average marginal effect; Coef, coefficient (linear probability); IV, instrumental variable; SE, standard error).

Figure 1: Average Marginal Effect of Number of Unique Drugs on the Probability of an ED Visit, with 95 percent Confidence Intervals

Table S2). We also computed a correlation matrix on our independent variables to determine if there was any evidence of multicollinearity; however, there were no strong (>0.7) correlations between any of the independent variables in our models.

We also estimated our model using linear two-stage least squares (2SLS) and interpreted our second-stage estimation as a linear probability model. This did not alter our conclusions, but it did increase the magnitude of the effect of polypharmacy on the probability of an ED visit and hospitalization (see Table 3). In particular, when the IV was standardized prescriber volume, the estimated probability of an ED visit was 16 percent higher and the estimated probability of a hospitalization was 6 percent higher than the 2SRI estimates. When the IV was number of unique prescribers, the estimated probability of an ED visit was 56 percent higher and the estimated probability of a hospitalization was 104 percent higher. Given the 2SRI is more consistent in predicting nonlinear outcomes, we decided to interpret the more conservative estimates produced by the 2SRI.

We also estimated a bivariate probit without instruments to determine the impact this had on our second-stage estimation (see Table 3). The magnitude of the effects remained within the bounds of our two IV estimates.

Compared to our 2SRI estimates with standardized prescriber volume as the IV, the probability of an ED visit was 2 percent higher and the probability of a hospitalization was 27 percent higher. Compared to our 2SRI estimates with the number of unique prescribers as the IV, the probability of an ED visit was 41 percent lower and the probability of a hospitalization was 21 percent lower. Finally, in all estimations, the bivariate probit model produced significant rho statistics ($p < .001$), which suggests our outcomes are related and that the simultaneous model was appropriate.

DISCUSSION

Our findings suggest that increased prescription drug use among older Ontarians has the effect of increasing the likelihood of both being admitted to hospital and visiting a hospital ED. On average, seniors consume seven different medications in a given year, which is consistent with national estimates (CIHI 2014). Each additional medication is associated with between (on average) a 2–3 percent increase in the likelihood of hospitalization. This effect increases until the seventeenth drug prescribed where the marginal effect is 5 percent. Each additional medication is associated with a 3–4 percent increase in the likelihood of an ED visit. This effect increases until the twelfth drug prescribed where the marginal effect is 5 percent. It is important to note that these effects are conditional on the other patient and physician characteristics included in the model.

These findings are consistent with the literature that has demonstrated the health risks of multiple-medication use, but it is inconsistent with findings from the United States. It is possible that the contradiction with the U.S. findings is due to institutional differences in the U.S. and Canadian health care systems. In 2011, approximately 16 percent of the U.S. population was uninsured (nearly 50 million residents), and 30 million of those who are insured are considered “underinsured” with high out-of-pocket expenses relative to income (Thomson et al. 2013). Meanwhile, in Canada, provincial governments provide coverage of “medically necessary” physician, diagnostic, and hospital services, which includes inpatient prescription drugs (Thomson et al. 2013). In Ontario, residents also receive public universal insurance for prescription drugs if they are 65 years of age or older, live in a long-term care home, are enrolled in a home care program, have high drug costs relative to income, and/or receive social assistance. The impact of cost barriers on the appropriate

use of prescription drugs can also be measured by surveying the population about cost-related nonadherence. The U.S. population reports much higher rates of cost-related nonadherence than the Canadian population (23 percent vs. 8 percent), and even though cost barriers are significantly reduced for seniors in both countries the rate of cost-related nonadherence is still twice as high in the United States as in Canada (9.2 percent vs. 4.6 percent) (Kennedy and Morgan 2009). Therefore, it is possible that the differential effect we see in Canada and the United States is a result of access to affordable prescription drugs. In the United States, improved access through programs like Medicare Part D reduced hospital service utilization and costs, while in Canada increased consumption may have the effect we would predict based on the adverse drug reaction literature.

Our study has some important limitations. First, this analysis was conducted on a cross-sectional basis. While we did have 2 years of data on some variables (e.g., past utilization), our estimates may be more reliable and efficient if we were able to take advantage of longitudinal data. In any study that uses cross-sectional data, it is always difficult to make causal claims about the relationships between variables; however, we hope that by using an IV approach we can be more confident in the relationship between drug consumption and hospital service utilization. Finally, we were not able to include physician utilization in our analysis. While we had physician data, there was very little variability in this outcome (given that we included only seniors in our analysis), and we did not have a suitable IV.

In spite of these limitations, this study provides further support for the hypothesis that multiple-medication use is associated with net risks. It will be important for future research to identify the causes of increased risk of hospitalization due to multiple drug use and to disentangle the effects of specific drug categories that are inherently risky from interactions between different drugs, which would have different implications for prescribing practices. For instance, previous studies have found some drug categories such as anticoagulants and opioids to be most important in explaining hospitalizations due to adverse events than others (CIHI 2013). Also there are well-established lists of potentially inappropriate medications, such as the Beers list that was recently updated by the American Geriatric Society (AGS) (2015). Regular monitoring of the use of medications on this list and establishing protocols for reducing the prescribing of these drugs will likely help to reduce the risks of drug use among the senior population.

CONCLUSIONS

Overall there appear to be health risks associated with the use of medications among the older population, as indicated by the modest but significantly elevated risk of hospitalization and ED visits with increasing medications in the Ontario population. The risk appears to increase steadily with increasing prescriptions; the highest marginal risk for an ED visit appears among those who take over 12 drugs, while the highest marginal risk for hospitalization appears among those who take over 17 different drugs in a year. With respect to broader policy implications, our results raise questions about the appropriateness of medication use among seniors and the need for increased oversight of current prescribing practices. There is emerging evidence that not only is it possible to reduce the number of different drugs taken by seniors but also that drug discontinuation can lead to health benefits (Garfinkel and Mangin 2010). However, in most jurisdictions, prescribing of pharmaceuticals is at the discretion of the health care provider, and self-governing bodies handle incidents of malpractice. It may also be beneficial to increase public education about the consequences of the overconsumption of pharmaceuticals so patients can have more intelligent conversations with their providers.

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REFERENCES

- Afendulis, C. C., Y. He, A. M. Zaslavsky, and M. E. Chernew. 2011. "The Impact of Medicare Part D on Hospitalization Rates." *Health Services Research* 46: 1022–38.
- American Geriatric Society (AGS). 2015. "American Geriatric Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults." *Journal of the American Geriatrics Society* 63: 2227–46.
- Chen, Y., and B. A. Briesacher. 2011. "Use of Instrumental Variable in Prescription Drug Research with Observational Data: A Systematic Review." *Journal of Clinical Epidemiology* 64: 687–700.
- CIHI. 2013. *Adverse Drug Reaction-Related Hospitalizations among Seniors, 2006 to 2011*. Ottawa: CIHI.
- CIHI. 2014. *Drug Use among Seniors on Public Drug Programs in Canada, 2012*. Ottawa: CIHI.
- Dudl, R. J., M. C. Wang, M. Wong, and J. Bellows. 2009. "Preventing Myocardial Infarction and Stroke with a Simplified Bundle of Cardioprotective Medications." *The American Journal of Managed Care* 15: e88–94.
- Garfinkel, D., and D. Mangin. 2010. "Feasibility Study of a Systematic Approach for Discontinuation of Multiple Medications in Older Adults: Addressing Polypharmacy." *Archives of Internal Medicine* 170: 1648–54.
- Glazier, R. H., B. M. Zagorski, and J. Rayner. 2012. *Comparison of Primary Care Models in Ontario by Demographics, Case Mix and Emergency Department Use, 2008/09 to 2009/10*. Toronto: Institute for Clinical Evaluative Sciences.
- Greene, W. H. 2012. *Econometric Analysis*. New York: Prentice Hall Inc.
- Grootendorst, P. 2007. "A Review of Instrumental Variables Estimation of Treatment Effects in the Applied Health Sciences." *Health Services and Outcomes Research Methodology* 7 (3–4): 159–79.
- Health Council of Canada. 2010. *Decisions, Decisions: Family Doctors as Gatekeepers to Prescription Drugs and Diagnostic Imaging in Canada*. Toronto: Health Council of Canada.
- The Johns Hopkins University. 1997. *ACG Case-Mix Adjustment System [computer program]*. Baltimore, MD: Johns Hopkins University School of Hygiene and Public Health.
- Kennedy, J., and S. Morgan. 2009. "Cost-Related Prescription Nonadherence in the United States and Canada: A System-Level Comparison Using the 2007

- International Health Policy Survey in Seven Countries." *Clinical Therapeutics* 31 (1): 213–9.
- Kroenke, K., and E. M. Pinholt. 1990. "Reducing Polypharmacy in the Elderly. A Controlled Trial of Physician Feedback." *Journal of the American Geriatrics Society* 38: 31–6.
- Lazarou, J., B. H. Pomeranz, and P. N. Corey. 1998. "Incidence of Adverse Drug Reactions in Hospitalized Patients: A Meta-Analysis of Prospective Studies." *Journal of the American Medical Association* 279 (15): 1200–5.
- OECD. 2013. *Health Statistics*. Paris: OECD.
- OECD. 2015. *OECD Health at a Glance: 2015*. Paris: OECD.
- Patel, H., D. Bell, M. Molokhia, J. Srishanmuganathan, M. Patel, J. Car, and A. Majeed. 2007. "Trends in Hospital Admissions for Adverse Drug Reactions in England: Analysis of National Hospital Episode Statistics 1998-2005." *BMC Clinical Pharmacology* 7: 9.
- Paterson, J. M., A. Suleiman, J. E. Hux, and C. Bell. 2008. "How Complete are Drug History Profiles that are Based on Public Drug Benefit Claims?" *Canadian Journal of Clinical Pharmacology* 15 (1): e108–16.
- Ramage-Morin, P. L. 2009. "Medication Use among Senior Canadians." *Health Reports* 20: 37–44.
- Salkever, D., E. Slade, and M. Karakus. 2006. "Differential Effects of Atypical versus Typical Antipsychotic Medication on Earnings of Schizophrenia Patients: Estimates from a Prospective Naturalistic Study." *Pharmacoeconomics* 24: 123–39.
- Soumerai, S. B., D. Ross-Degnan, J. Avorn, T. J. McLaughlin, and I. Chodnovskiy. 1991. "Effects of Medicaid Drug-Payment Limits on Admission to Hospitals and Nursing Homes." *New England Journal of Medicine* 325: 1072–7.
- Squires, D. A. 2011. *The U.S. Health System in Perspective: A Comparison of Twelve Industrialized Nations*. New York: Commonwealth Fund. Available at http://www.commonwealthfund.org/~media/Files/Publications/Issue%20Brief/2011/Jul/1532_Squires_US_hlt_sys_comparison_12_nations_intl_brief_v2.pdf
- Staiger, D., and J. H. J. Stock. 1997. "Instrumental Variables Regression with Weak Instruments." *Econometrica* 65: 557–86.
- Stuart, B. C., J. A. Doshi, and J. V. Terza. 2009. "Assessing the Impact of Drug Use on Hospital Costs." *Health Services Research* 44: 128–44.
- Tamblyn, R. M., P. J. McLeod, M. Abrahamowicz, J. Monette, D. C. Gayton, L. Berkson, W. D. Dauphinee, R. M. Grad, A. R. Huang, and L. M. Isaac. 1994. "Questionable Prescribing for Elderly Patients in Quebec." *Canadian Medical Association Journal* 150: 1801–9.
- Terza, J., A. Basu, and P. Rathouz. 2008. "Two-Stage Residual Inclusion Estimation: Addressing Endogeneity in Health Econometric Modeling." *Journal of Health Economics* 27: 531–43.
- Thomson, S., R. Osborn, D. Squires, and M. Jun. 2013. *International Profiles of Health Care Systems*. New York: Commonwealth Fund, pp. 6–136.
- Zed, P., R. B. Abu-Laban, R. M. Balen, P. S. Loewen, C. M. Hohl, J. R. Brubacher, K. Wilbur, M. O. Wiens, L. J. Samoy, K. Lacaria, and R. A. Purssell. 2008. "Incidence, Severity and Preventability of Medication-Related Visits to the

- Emergency Department: A Prospective Study.” *Canadian Medical Association Journal* 178 (12): 1563–9.
- Zellner, A. 1962. “An Efficient Method of Estimating Seemingly Unrelated Regressions and Tests for Aggregation Bias.” *Journal of American Statistical Association* 57: 348–68.

SUPPORTING INFORMATION

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

- Appendix SA1: Author Matrix.
- Appendix SA2. Calculation of Marginal Effects.
- Table S1. Results of the Bivariate Probit Models.
- Table S2. Negative and Positive Predictive Values.
- Figure S1. Average Marginal Effect of Number of Unique Drugs on the Probability of Hospitalization, with 95 Percent Confidence Interval.