Association of out-of-pocket costs on adherence to common neurologic medications

Evan L. Reynolds, PhD, James F. Burke, MD, MS, Mousumi Banerjee, PhD, Kevin A. Kerber, MD, MS, Lesli E. Skolarus, MD, MS, Brandon Magliocco, MPH, Gregory J. Esper, MD, MBA, and Brian C. Callaghan, MD, MS

Correspondence

Dr. Callaghan
bcallagh@med.umich.edu

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Abstract

Objective

To determine the association between out-of-pocket costs and medication adherence in 3 common neurologic diseases.

Methods

Utilizing privately insured claims from 2001 to 2016, we identified patients with incident neuropathy, dementia, or Parkinson disease (PD). We selected patients who were prescribed medications with similar efficacy and tolerability, but differential out-of-pocket costs (neuropathy with gabapentinoids or mixed serotonin/norepinephrine reuptake inhibitors [SNRIs], dementia with cholinesterase inhibitors, PD with dopamine agonists). Medication adherence was defined as the number of days supplied in the first 6 months. Instrumental variable analysis was used to estimate the association of out-of-pocket costs and other patient factors on medication adherence.

Results

We identified 52,249 patients with neuropathy on gabapentinoids, 5,246 patients with neuropathy on SNRIs, 19,820 patients with dementia on cholinesterase inhibitors, and 3,130 patients with PD on dopamine agonists. Increasing out-of-pocket costs by \$50 was associated with significantly lower medication adherence for patients with neuropathy on gabapentinoids (adjusted incidence rate ratio [IRR] 0.91, 0.89–0.93) and dementia (adjusted IRR 0.88, 0.86–0.91). Increased out-of-pocket costs for patients with neuropathy on SNRIs (adjusted IRR 0.97, 0.88–1.08) and patients with PD (adjusted IRR 0.90, 0.81–1.00) were not significantly associated with medication adherence. Minority populations had lower adherence with gabapentinoids and cholinesterase inhibitors compared to white patients.

Conclusions

Higher out-of-pocket costs were associated with lower medication adherence in 3 common neurologic conditions. When prescribing medications, physicians should consider these costs in order to increase adherence, especially as out-of-pocket costs continue to rise. Racial/ethnic disparities were also observed; therefore, minority populations should receive additional focus in future intervention efforts to improve adherence.

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From the Health Services Research Program, Department of Neurology (E.L.R., J.F.B., K.A.K., L.E.S., B.C.C.), and School of Public Health (M.B.), University of Michigan; Veterans Affairs Healthcare System (J.F.B., B.C.C.), Ann Arbor, MI; American Academy of Neurology (B.M.), Minneapolis, MN; and the Department of Neurology (G.J.E.), Emory University, Atlanta, GA.

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Glossary

CCI = Charlson comorbidity index; CDSS = clinical decision support systems; ICD-9 = International Classification of Diseases–9; ICD-10 = International Classification of Diseases–10; IRR = incidence rate ratio; MPR = medication possession ratio; OOP = out-of-pocket; PD = Parkinson disease; SMD = standardized mean difference; SNRI = serotonin/norepinephrine reuptake inhibitor.

Prescription drug costs continue to rise in the United States, with an increasing amount of the financial burden being shifted to patients through out-of-pocket (OOP) costs.¹ Neurologist-prescribed medications accounted for approximately \$5 billion in Medicare Part D payments in 2013 (4.8% of total payments), an amount likely to climb as new, high-priced neurologic medications become available.² Previously, we demonstrated that patient OOP costs are increasing for frequently prescribed neurologic medications, especially for patients in high-deductible health plans.³ However, the effect of OOP costs on adherence to neurologic medications, outside of multiple sclerosis, is unknown.^{4–6}

Previous studies have revealed an association between OOP costs and nonadherence in patients with rheumatoid arthritis and in those with diabetes.^{7,8} Pertaining to neurologic medications, 3 studies have found associations between OOP costs and lower adherence to disease-modifying therapies for multiple sclerosis.^{4–6} However, many of these studies were small, did not account for the choice of medication, had selection bias, or had the potential for residual confounding. Furthermore, the effect of OOP costs for less expensive neurologic medications has not been studied.

We aimed to determine the association of OOP costs and medication adherence for patients with neuropathy, dementia, and Parkinson disease (PD). These conditions were selected because they are common and have sets of neurologic medications with similar efficacy and tolerability but variation in OOP costs. These scenarios allowed us to employ an instrumental variable modeling approach. This approach can mitigate the effect of unmeasured confounders and thus may identify the most reliable estimate of causal effects using observational data.^{9,10} We also investigated the association between demographic and other patient factors on medication adherence.

Methods

Population

We utilized the deidentified Clinformatics Datamart (OptumInsight, Eden Prairie, MN) database, which contains detailed medical and pharmaceutical claims on more than 73 million individuals insured by United Healthcare from 2001 to 2016. The pharmaceutical claims included information on medication name, number of prescription days supplied, and cost. We identified patients who had an outpatient visit linked

to 1 of 3 neurologic disease diagnoses and had a relevant neurologic medication prescribed within the following 12 months. Outpatient visits were determined using place of service codes. Diagnoses were identified using ICD-9/ICD-10 codes; specifically, peripheral neuropathy (356 [all-inclusive], 357 [except 357.0, 357.81], G60, G62, G63, G652), dementia (331 except for 331.3/4/5, G30, G31), and PD (332, G20, G21).¹¹ Previous studies have reported high specificities using similar neurologic ICD-9 coding algorithms to identify neurologic conditions.¹²

We identified 4 sets of relevant medications that have similar efficacy, tolerability, and mechanisms of action, but differential OOP costs. Differential OOP costs were determined by using data from our previous study.³ Neuropathy has 2 such sets of medications that fulfill these criteria from 2005 to 2016: pregabalin/gabapentin (gabapentinoids) and duloxetine/venlafaxine (mixed serotonin/norepinephrine reuptake inhibitors [SNRIs]).^{13–15} A meta-analysis found no significant differences in efficacy (pain scale, standardized mean difference [SMD]) for duloxetine/venlafaxine (SMD: 0.21, –0.81 to 1.21) and pregabalin/gabapentin (SMD: 0.19, –0.69 to 1.07).^{13,14} There were also no clear differences in rates of common adverse events among the drug pairs.¹³ In dementia, galantamine/rivastigmine and donepezil (cholinesterase inhibitors) demonstrated similar levels of efficacy (Mini-Mental State Examination or Bristol Activities of Daily Living Scale) with differential OOP costs from 2012 to 2016.^{16,17} There were no differences in rates of serious adverse events between the cholinesterase inhibitors.¹⁶ In PD, ropinirole and pramipexole (dopamine agonists) fulfill these criteria from 2009 to 2016.¹⁷ Specifically, a meta-analysis found no difference in efficacy (using the Unified Parkinson's Disease Rating Scale, mean difference: 3.19, –10.28 to 16.71) and tolerability (withdrawal odds ratio: 0.67, 0.34–1.28) between ropinirole and pramipexole.¹⁷

Our previous study found that the average OOP cost for a 30-day supply was different between each of the medication pairs (average 2016 OOP cost for a 30-day supply: gabapentinoids: pregabalin \$65.70, gabapentin \$8.40; SNRIs: duloxetine \$32.10, venlafaxine \$10.00; cholinesterase inhibitors: rivastigmine \$79.30, galantamine \$59.40, donepezil \$3.10; dopamine agonists: pramipexole \$35.90, ropinirole \$12.40).³

The population was restricted to patients with at least 24 months of continuous enrollment before the first neurologic

diagnosis, to capture incident diagnoses. To further limit the population to those with a first prescription in a particular class, we excluded patients who had one of the disease-specific medications prescribed in the 24+ months prior to diagnosis. After initial neurologic diagnosis, we restricted our analysis to patients who had the medication prescribed within 12 months and required patients to be continuously enrolled in their insurance plan for at least an additional 6 months after their first prescription.

Demographics and clinical variables

The database included information on patient age, sex, race/ethnicity, geographic region, education level, household income, insurance plan type, high-deductible health plan status, and Charlson comorbidity index (CCI).¹⁸ We also calculated the OOP costs by combining the copay and deductible payments for the initial medication prescription. OOP costs were scaled to represent costs for a 30-day medication supply.

Outcomes

Medication adherence was a continuous variable of the total number of days the specific medication was supplied in the first 6 months following the initial prescription. The medication possession ratio (MPR) was also calculated as the proportion of days-supply the specific medication was prescribed in the first 6 months following initial prescription.¹⁹

Statistical analysis

Descriptive statistics were used to characterize the patients taking the medications of interest in the 3 neurologic diseases. We utilized negative binomial regression to model the number of days the medication was supplied to the patient during the first half year of follow-up as a function of OOP cost, choice of medication, demographic (including sex, age, race, education, household income, geographic location), and patient factors (insurance type, high-deductible health plan, and CCI). Negative binomial regression is a standard approach when modeling overdispersed count data, such as medication days-supply. In each regression analysis, OOP costs were scaled to represent a \$50 increase for a 30-day supply of the medication.

Instrumental variable approach

To take into account the likely unmeasured confounding in the relationship with adherence, our primary analysis utilized an instrumental variable regression approach.^{9,10} Instrumental variable approaches can be used to estimate the causal effect of OOP cost on adherence even when not directly adjusting for unmeasured confounders if 2 key assumptions are met: (1) the instrument is strongly associated with the exposure of interest and (2) there is no relationship between the instrument and the outcome, other than through the key exposure (the exclusion restriction).

In this case, we used choice of individual medications for the same condition with similar efficacy and tolerability as an instrument. We knew, from prior work, that individual

medications are strongly associated with OOP costs, thereby satisfying the first instrumental variable assumption.³ While the exclusion restriction cannot be tested directly, it is reasonable within these groups of medications that the primary determinants of adherence—efficacy and tolerability—are similar across our selected medications. Specifically, we utilized the 2-stage residual inclusion approach.¹⁰ The standard errors for the negative binomial regression models were estimated from 1,000 bootstrap samples.

The secondary analysis utilized the conventional regression approach by fitting fully adjusted negative binomial regression models for the days-supply outcome as a function of OOP cost, medication choice, and demographic and other patient factors. In the fully adjusted model, we also evaluated the interaction between medication choice and OOP cost.

Data management was completed using SAS version 9.4 (SAS Institute, Cary, NC). Regression analysis and figures were completed using R version 3.4.2.

Standard protocol approvals, registrations, and patient consents

The University of Michigan institutional review board determined that this study was exempt.

The Clinformatics Datamart (OptumInsight) database is commercially available.

Results

We identified 52,249 patients with neuropathy and gabapentinoids (7,648 pregabalin, 44,601 gabapentin), 5,246 patients with neuropathy and SNRIs (1,499 venlafaxine, 3,747 duloxetine), 19,820 patients with dementia and cholinesterase inhibitors (18,679 donepezil, 1,141 galantamine/rivastigmine), and 3,130 patients with PD and dopamine agonists (1,510 pramipexole, 1,813 ropinirole) who met all selection criteria. Few patients switched medications during the 6 months of follow-up (neuropathy–gabapentinoids: 5.0%, neuropathy–SNRIs: 2.1%, dementia: 8.9%, PD: 4.7%). Demographic and other patient factors are provided in tables 1–3. Typically, patient OOP costs did not change during the 6 months of follow-up. For each medication scenario, the median difference in OOP cost between the first and last prescription was \$0.

Neuropathy: Gabapentin vs pregabalin

In each year after 2007, the average MPR was higher for gabapentin than it was for pregabalin (2008 pregabalin: 0.418, gabapentin: 0.457; 2016 pregabalin: 0.470, 2016 gabapentin: 0.522) (figure 1A). Each year between 2005 and 2016, the average OOP cost for pregabalin (2005: \$49.50 [37.90] and 2016: \$65.70 [90.20]) was higher than gabapentin (2005: \$13.10 [28.60] and 2016: \$8.40 [11.80]) (figure 1B).

Based on instrumental variable analyses, we found that a \$50 increase in OOP cost for a 30-day medication supply was

Table 1 Demographic and clinical characteristics of the neurologic patient groups

Demographics and clinical variables	Neuropathy: gabapentin vs pregabalin (n = 52,249)	Neuropathy: venlafaxine vs duloxetine (n = 5,246)	Dementia (n = 19,820)	Parkinson disease (n = 3,130)
Age, y, mean (SD)	65.2 (14.2)	60.4 (15.0)	79.0 (7.3)	70.6 (10.8)
Sex				
Female	27,955 (53.5)	3,193 (60.9)	12,092 (61.0)	1,353 (43.2)
Male	24,289 (46.5)	2,052 (39.1)	7,726 (39.0)	1,776 (56.7)
Missing	5 (0.01)	0 (0)	2 (0.01)	1 (0.03)
Race/ethnicity				
Asian	1,196 (2.3)	78 (1.5)	530 (2.7)	86 (2.9)
Black	6,263 (12.0)	496 (9.5)	1,710 (8.6)	195 (6.5)
Hispanic	6,421 (12.3)	532 (10.1)	2,333 (11.8)	312 (10.4)
White	35,208 (67.4)	3,784 (72.1)	13,934 (70.3)	2,351 (78.7)
Unknown	3,161 (6.1)	356 (6.8)	1,313 (6.6)	186 (6.2)
Geographic region				
East north central	5,646 (10.8)	562 (10.7)	2,575 (13.0)	311 (10.4)
East south central	2,246 (4.3)	235 (4.5)	730 (3.7)	110 (3.7)
Middle Atlantic	2,444 (4.7)	293 (5.6)	1,244 (6.3)	125 (4.2)
Mountain	5,751 (11.0)	543 (10.4)	2,596 (13.1)	449 (15.0)
New England	1,438 (2.8)	170 (3.2)	1,002 (5.1)	67 (2.2)
Pacific	9,221 (17.7)	627 (12.0)	4,564 (23.0)	700 (23.4)
South Atlantic	12,637 (24.2)	1,443 (27.5)	3,611 (18.2)	714 (23.9)
West north central	3,575 (6.8)	404 (7.7)	1,072 (5.4)	208 (7.0)
West south central	9,149 (17.5)	959 (18.3)	2,373 (12.0)	441 (14.8)
Missing	142 (0.3)	10 (0.2)	53 (0.3)	5 (0.2)
Education level				
Less than 12th grade	601 (1.2)	34 (0.7)	191 (1.0)	17 (0.6)
High school diploma	17,889 (34.2)	1,568 (29.9)	5,687 (28.7)	852 (28.5)
Less than bachelor's degree	26,371 (50.5)	2,689 (51.3)	10,716 (54.1)	1,720 (57.5)
Bachelor's degree plus	5,607 (10.7)	767 (14.6)	2,453 (12.4)	449 (15.0)
Missing	1,781 (3.4)	188 (3.6)	773 (3.9)	92 (3.1)
Household income				
<\$40,000	15,027 (28.8)	1,101 (21.0)	7,667 (38.7)	809 (27.1)
\$40,000–\$49,000	4,430 (8.5)	362 (6.9)	1,868 (9.4)	276 (9.2)
\$50,000–\$59,000	3,931 (7.5)	367 (7)	1,480 (7.5)	239 (8.0)
\$60,000–\$74,000	4,815 (9.2)	465 (8.9)	1,709 (8.6)	287 (9.6)
\$75,000–\$99,000	5,891 (11.3)	631 (12.0)	1,905 (9.6)	381 (12.6)
\$100,000+	9,734 (18.6)	1,202 (22.9)	2,420 (12.2)	711 (23.8)
Missing	8,421 (16.1)	1118 (21.3)	2,771 (14.0)	427 (14.3)

Continued

Table 1 Demographic and clinical characteristics of the neurologic patient groups (*continued*)

Demographics and clinical variables	Neuropathy: gabapentin vs pregabalin (n = 52,249)	Neuropathy: venlafaxine vs duloxetine (n = 5,246)	Dementia (n = 19,820)	Parkinson disease (n = 3,130)
Insurance plan type				
EPO	2,683 (5.1)	336 (6.4)	150 (0.8)	106 (3.6)
HMO	25,857 (49.5)	2,335 (44.5)	12,182 (61.5)	1,695 (56.7)
IND	1,185 (2.3)	121 (2.3)	639 (3.2)	85 (2.8)
POS	4,357 (8.3)	326 (6.2)	3,787 (19.1)	287 (9.6)
PPO	10,911 (20.9)	1201 (22.9)	822 (4.2)	523 (17.5)
Other	7,256 (13.9)	927 (17.7)	2,240 (11.3)	434 (14.5)
High-deductible health plan	1,610 (3.1)	162 (3.1)	118 (0.6)	91 (3.0)
CCI score, mean (SD)	2.4 (2.0)	2.21 (2.0)	3.0 (2.2)	2.4 (2.2)

Abbreviations: CCI = Charlson comorbidity index; EPO = exclusive provider organization; HMO = health maintenance organization; IND = indemnity; POS = point of service; PPO = preferred provider organization. Values are n (%) unless indicated otherwise.

significantly associated with lower adherence of pregabalin/gabapentin (adjusted incidence rate ratio [IRR] 0.91, 0.89–0.93). The predicted medication days-supply over the range of observed OOP costs for patients in the most common demographic and health plan groups is displayed in figure 1. Asian (adjusted IRR: 0.85, 0.82–0.96), black (adjusted IRR: 0.89, 0.87–0.91), and Hispanic (adjusted IRR: 0.87, 0.85–0.89) patients had significantly lower medication adherence rates compared to white patients. Higher age (adjusted IRR: 1.01, 1.01–1.01), CCI (adjusted IRR: 1.02, 1.02–1.02), and education level (having a high school diploma IRR: 1.07, 1.01–1.14, and $\leq$ bachelor's degree, 1.08, 1.02–1.15, ref = less than 12th grade education) were associated with increased adherence.

The OOP effect estimates were similar in the fully adjusted model (adjusted IRR: 0.93, 0.91–0.94). There was not a significant interaction effect between the medication choice and OOP cost, suggesting that the OOP effect on adherence was not significantly different among the 2 medications.

Neuropathy: Venlafaxine vs duloxetine

The MPRs for the 2 medications were similar between 2005 and 2012, with MPR differences ranging between 0.0 and 0.04 (figure 1C). From 2013 to 2016, the MPR was higher for venlafaxine than duloxetine (2013 venlafaxine: 0.58, duloxetine: 0.52; 2016 venlafaxine: 0.60, 2016 duloxetine: 0.52) (figure 2). The average OOP cost for a 30-day supply of duloxetine was larger than venlafaxine in each study year between 2004 and 2016 (2004 venlafaxine: \$25.40 [19.20], duloxetine: \$40.20 [23.20]; 2016 venlafaxine: \$10.00 [12.70], 2016 duloxetine: \$32.10 [31.60]) (figure 1D).

Based on instrumental variable analyses, we found that a \$50 increase in OOP cost for a 30-day medication supply was

associated with slightly lower rates of adherence (adjusted IRR: 0.97, 0.88–1.08), though the result was not significant. The regression model found that Hispanic patients had significantly lower adherence compared to white patients (adjusted IRR: 0.84, 0.76–0.92). Asian (adjusted IRR: 0.80, 0.96–1.07) and black (adjusted IRR: 0.93, 0.85, 1.02) patients also had lower rates of adherence compared to white patients, though the differences were not statistically significant. The instrumental variable regression found higher age (adjusted IRR: 0.98, 0.97–1.00) was significantly associated with lower adherence, and increased CCI score was associated with increased adherence (adjusted IRR: 1.02, 1.01–1.03).

The fully adjusted negative binomial regression estimated a statistically significant association between increased OOP cost and lower medication adherence (adjusted IRR: 0.92, 0.89–0.96). Similar to the instrumental variable approach, the fully adjusted model found significant age (adjusted IRR: 0.98, 0.97, 1.00), race/ethnicity (Asian: 0.79, 0.63–0.99, black: 0.93, 0.85–1.02, Hispanic: 0.83, 0.76–0.91, ref = white), and CCI score (adjusted IRR: 1.02, 1.00–1.03) associations with adherence. There was not a significant interaction effect between OOP cost and medication choice.

Dementia: Galantamine/rivastigmine vs donepezil

In each year between 2006 and 2016, the average MPR for patients taking donepezil was higher than the MPR for those patients taking rivastigmine or galantamine (2006 donepezil: 0.72, rivastigmine/galantamine: 0.69; 2016 donepezil: 0.71, rivastigmine/galantamine: 0.59) (figure 1E). When the average OOP costs for the 3 medications was similar (2004–2010) (figure 1F), the MPR remained close (between 0.0 and 0.06). After 2011, as the typical OOP costs for the 3 medications diverged, the MPR gap grew (between 0.10 and 0.22).

Table 2 Results of multivariable instrumental variable approach to evaluate the association of out-of-pocket costs with medication adherence

	Neuropathy: gabapentin vs pregabalin	Neuropathy: venlafaxine vs duloxetine	Dementia	Parkinson disease
Out-of-pocket cost (\$50)	0.91 (0.89, 0.93) ^a	0.97 (0.88, 1.08)	0.88 (0.86, 0.91) ^a	0.90 (0.81, 1.00)
Female (ref = male)	0.94 (0.93, 0.96) ^a	1.01 (0.96, 1.07)	0.98 (0.96, 0.99) ^a	0.98 (0.94, 1.02)
Age	1.01 (1.01, 1.01) ^a	0.98 (0.97, 1.00) ^a	1.00 (1.00, 1.01) ^a	1.00 (0.99, 1.01)
Race (ref = white)				
Asian	0.85 (0.82, 0.89) ^a	0.80 (0.61, 1.04)	0.90 (0.86, 0.95) ^a	0.99 (0.88, 1.12)
Black	0.89 (0.87, 0.91) ^a	0.93 (0.85, 1.02)	0.96 (0.94, 0.99) ^a	0.99 (0.90, 1.08)
Hispanic	0.87 (0.85, 0.89) ^a	0.84 (0.76, 0.92) ^a	0.94 (0.92, 0.97) ^a	0.96 (0.89, 1.03)
Education (ref = <12th grade)				
High school diploma	1.07 (1.01, 1.14) ^a	0.85 (0.63, 1.14)	1.00 (0.92, 1.08)	1.13 (0.80, 1.58)
Less than bachelor's degree	1.08 (1.02, 1.15) ^a	0.86 (0.64, 1.16)	1.01 (0.93, 1.10)	1.14 (0.81, 1.61)
Bachelor's degree plus	1.01 (0.96, 1.09)	0.84 (0.62, 1.14)	1.01 (0.93, 1.10)	1.19 (0.84, 1.68)
Household income (ref = <\$40,000)				
\$40,000–\$49,000	0.99 (0.97, 1.02)	0.93 (0.84, 1.03)	1.00 (0.98, 1.03)	1.00 (0.92, 1.09)
\$50,000–\$59,000	1.00 (0.98, 1.03)	1.08 (0.99, 1.18)	1.01 (0.98, 1.03)	1.04 (0.95, 1.13)
\$60,000–\$74,000	0.98 (0.96, 1.00)	0.97 (0.88, 1.07)	1.03 (1.00, 1.05) ^a	1.00 (0.92, 1.09)
\$75,000–\$99,000	1.00 (0.98, 1.02)	1.01 (0.93, 1.10)	1.03 (1.01, 1.06) ^a	1.06 (0.98, 1.14)
\$100,000+	1.00 (0.98, 1.02)	1.08 (0.99, 1.17)	1.01 (0.99, 1.04)	1.09 (1.02, 1.17) ^a
CCI score	1.02 (1.02, 1.02) ^a	1.02 (1.01, 1.03) ^a	1.00 (0.99, 1.00)	0.98 (0.97, 0.99) ^a
Insurance type (ref = PPO)				
EPO	0.94 (0.91, 0.97) ^a	0.98 (0.86, 1.10)	1.05 (0.98, 1.13)	0.96 (0.84, 1.09)
HMO	0.99 (0.97, 1.01)	0.96 (0.88, 1.04)	0.98 (0.96, 1.01)	0.98 (0.92, 1.05)
IND	1.05 (1.01, 1.10) ^a	0.99 (0.81, 1.22)	1.03 (0.99, 1.07)	1.10 (0.95, 1.26)
Other	1.01 (0.98, 1.04)	0.99 (0.89, 1.11)	0.99 (0.96, 1.01)	1.02 (0.92, 1.12)
POS	0.93 (0.91, 0.96) ^a	0.93 (0.85, 1.01)	1.00 (0.96, 1.05)	1.01 (0.94, 1.09)
High-deductible health plan	1.02 (0.98, 1.06)	1.07 (0.95, 1.21)	1.02 (0.98, 1.06)	0.94 (0.82, 1.06)
Division (ref = west south central)				
East north central	1.03 (1.01, 1.06) ^a	1.02 (0.93, 1.13)	1.04 (1.01, 1.07) ^a	0.99 (0.91, 1.07)
East south central	1.00 (0.97, 1.03)	1.00 (0.87, 1.14)	0.97 (0.92, 1.01)	0.93 (0.83, 1.05)
Middle Atlantic	0.93 (0.90, 0.96) ^a	0.92 (0.81, 1.05)	0.98 (0.95, 1.02)	1.00 (0.88, 1.13)
Mountain	1.02 (1.00, 1.09) ^a	1.04 (0.95, 1.14)	1.01 (0.98, 1.03)	0.94 (0.86, 1.02)
New England	1.04 (1.00, 1.09) ^a	0.95 (0.81, 1.12)	1.03 (0.99, 1.07)	0.98 (0.84, 1.15)
Pacific	0.99 (0.97, 1.02)	0.94 (0.85, 1.03)	1.00 (0.97, 1.02)	0.92 (0.85, 0.99) ^a
South Atlantic	0.98 (0.96, 1.00) ^a	0.94 (0.87, 1.03)	0.99 (0.96, 1.02)	0.97 (0.9, 1.04)
West north central	1.06 (1.03, 1.09) ^a	1.09 (0.97, 1.22)	1.03 (1.00, 1.07) ^a	1.01 (0.92, 1.11)

Abbreviations: CCI = Charlson comorbidity index; EPO = exclusive provider organization; HMO = health maintenance organization; IND = indemnity; POS = point of service; PPO = preferred provider organization.
Values are incident rate ratio (95% confidence interval).

^a $p < 0.05$.

Table 3 Results of conventional multivariable negative binomial regression approach to evaluate the association of out-of-pocket (OOP) costs with medication adherence

	Neuropathy drug = pregabalin; ref = gabapentin	Neuropathy drug = duloxetine; ref = venlafaxine	Dementia drug = galantamine or rivastigmine; ref = donepezil	Parkinson disease drug = pramipexole; ref = ropinirole
OOP cost (\$50)	0.93 (0.91, 0.94) ^a	0.92 (0.89, 0.96) ^a	0.87 (0.81, 0.94) ^a	0.96 (0.93, 0.99) ^a
Drug	0.99 (0.96, 1.01)	1.03 (0.97, 1.10)	0.87 (0.83, 0.92) ^a	0.97 (0.92, 1.03)
OOP × drug	NS	NS	1.10 (1.02, 1.19) ^a	NS
Female (ref = male)	0.94 (0.93, 0.96) ^a	1.01 (0.95, 1.07)	0.98 (0.96, 0.99) ^a	0.98 (0.93, 1.03)
Age	1.01 (1.01, 1.01) ^a	0.98 (0.97, 1.00) ^a	1.00 (0.99, 1.01)	1.00 (0.99, 1.01)
Race (ref = white)				
Asian	0.85 (0.82, 0.89) ^a	0.79 (0.63, 0.99) ^a	0.90 (0.85, 0.95) ^a	1.00 (0.86, 1.16)
Black	0.89 (0.87, 0.91) ^a	0.93 (0.85, 1.02)	0.97 (0.94, 1.00) ^a	0.99 (0.89, 1.10)
Hispanic	0.87 (0.85, 0.89) ^a	0.83 (0.76, 0.91) ^a	0.95 (0.92, 0.97) ^a	0.97 (0.89, 1.06)
Education (ref = <12th grade)				
High school diploma	1.07 (1.00, 1.14) ^a	0.85 (0.59, 1.21)	1.00 (0.91, 1.09)	1.14 (0.81, 1.60)
Less than bachelor's degree	1.08 (1.02, 1.16) ^a	0.86 (0.60, 1.23)	1.01 (0.93, 1.11)	1.15 (0.82, 1.62)
Bachelor's degree plus	1.02 (0.95, 1.10)	0.84 (0.58, 1.22)	1.02 (0.92, 1.12)	1.19 (0.84, 1.69)
Household income (ref = <\$40,000)				
\$40,000–\$49,000	0.99 (0.97, 1.02)	0.93 (0.84, 1.03)	1.00 (0.97, 1.03)	1.00 (0.92, 1.10)
\$50,000–\$59,000	1.00 (0.98, 1.03)	1.08 (0.97, 1.20)	1.01 (0.98, 1.04)	1.03 (0.93, 1.13)
\$60,000–\$74,000	0.98 (0.96, 1.00)	0.98 (0.88, 1.08)	1.03 (1.00, 1.06)	0.99 (0.90, 1.09)
\$75,000–\$99,000	1.00 (0.98, 1.02)	1.01 (0.92, 1.11)	1.03 (1.00, 1.06) ^a	1.06 (0.97, 1.15)
\$100,000+	1.00 (0.98, 1.02)	1.07 (0.98, 1.18)	1.01 (0.98, 1.04)	1.09 (1.01, 1.18) ^a
CCI score	1.02 (1.02, 1.02) ^a	1.02 (1.00, 1.03) ^a	1.00 (0.99, 1.00)	0.98 (0.97, 0.99) ^a
Insurance type (ref = PPO)				
EPO	0.94 (0.90, 0.97) ^a	0.98 (0.85, 1.12)	1.06 (0.96, 1.17)	0.96 (0.83, 1.12)
HMO	0.99 (0.97, 1.01)	0.95 (0.86, 1.04)	0.98 (0.95, 1.01)	0.99 (0.91, 1.08)
IND	1.05 (1.00, 1.11) ^a	0.99 (0.79, 1.24)	1.03 (0.98, 1.09)	1.12 (0.94, 1.33)
Other	1.01 (0.98, 1.04)	0.98 (0.88, 1.10)	0.99 (0.95, 1.02)	1.02 (0.91, 1.13)
POS	0.93 (0.91, 0.96) ^a	0.93 (0.84, 1.02)	1.01 (0.96, 1.06)	1.02 (0.93, 1.13)
High-deductible health plan	1.02 (0.98, 1.06)	1.07 (0.94, 1.23)	0.95 (0.85, 1.07)	0.94 (0.80, 1.09)
Division (ref = west south central)				
East north central	1.03 (1.00, 1.06) ^a	1.02 (0.92, 1.14)	1.04 (1, 1.07)	1.00 (0.90, 1.11)
East south central	1.00 (0.96, 1.04)	1.01 (0.87, 1.17)	0.96 (0.92, 1.02)	0.94 (0.81, 1.09)
Middle Atlantic	0.93 (0.90, 0.97) ^a	0.92 (0.80, 1.05)	0.98 (0.94, 1.03)	1.01 (0.87, 1.17)
Mountain	1.02 (1.00, 1.05)	1.04 (0.94, 1.16)	1.01 (0.97, 1.04)	0.94 (0.85, 1.03)
New England	1.04 (1.00, 1.09)	0.95 (0.80, 1.12)	1.03 (0.98, 1.08)	0.98 (0.81, 1.18)
Pacific	0.99 (0.97, 1.02)	0.93 (0.84, 1.04)	1 (0.97, 1.03)	0.92 (0.84, 1.01)
South Atlantic	0.98 (0.96, 1.00) ^a	0.94 (0.86, 1.03)	0.99 (0.96, 1.03)	0.97 (0.89, 1.06)
West north central	1.06 (1.03, 1.09) ^a	1.08 (0.94, 1.24)	1.03 (0.99, 1.08)	1.02 (0.90, 1.14)

Abbreviations: CCI = Charlson comorbidity index; EPO = exclusive provider organization; HMO = health maintenance organization; IND = indemnity; POS = point of service; PPO = preferred provider organization. Values are incident rate ratio (95% confidence interval).

^a $p < 0.05$.

Figure 1 Medication possession ratio (MPR) and out-of-pocket (OOP) costs for peripheral neuropathy, dementia, and Parkinson disease (PD)

Mean MPR in the first 6 months after initial prescription of the following: gabapentin and pregabalin for peripheral neuropathy (A) and corresponding OOP costs (B), duloxetine and venlafaxine for peripheral neuropathy (C) and corresponding OOP costs (D), donepezil and galantamine/rivastigmine for dementia (E) and corresponding OOP costs (F), and pramipexole and ropinirole for PD (G) and corresponding OOP costs (H).

The instrumental variable regression estimated that a \$50 increase in OOP cost for a 30-day medication supply was significantly associated with lower adherence with dementia medications (adjusted IRR: 0.88, 0.86–0.91). The instrumental variable approach estimated that Asian (adjusted IRR: 0.90,

0.86–0.95), black (adjusted IRR: 0.96, 0.94–0.99), and Hispanic patients (adjusted IRR: 0.94, 0.92–0.97) had lower rates of adherence compared to white patients. There were also significant effects for age (adjusted IRR: 1.00, 1.00–1.01), sex (female adjusted IRR: 0.98, 0.96–0.99), and household income.

Figure 2 Predicted medication days supplied in first 6 months for a typical patient based on instrumental variable regression results

The results from the fully adjusted negative binomial model found both OOP cost and medication choice were significantly associated with adherence. The interaction between medication and OOP cost was also significant, meaning that the OOP cost effect sizes were different between the patients taking donepezil (IRR: 0.96, 0.83–1.11) and rivastigmine/galantamine (IRR: 0.87, 0.81, 0.94). Similar to the instrumental variable regression, the fully adjusted model found Asian (adjusted IRR: 0.90, 0.85–0.95), black (adjusted IRR: 0.97, 0.94–1.00), and Hispanic patients (adjusted IRR: 0.95, 0.92–0.97) had lower rates of adherence compared to white patients.

PD: Pramipexole vs ropinirole

In years when OOP costs for the 2 drugs were similar (2004–2007), MPR differences were small (between 0.003 and 0.052) (figure 1G). However, in years when OOP costs were the most different (2013–2016), the MPR differences were larger (between 0.03 and 0.09). From 2008 to 2016, the average OOP cost for a 30-day supply was larger for patients taking pramipexole compared to ropinirole (2008 pramipexole: \$48.90 [61.00], 2008 ropinirole: \$35.80 [53.10], 2016 pramipexole: \$35.90 [47.10], 2016 ropinirole: \$12.40 [24.20]) (figure 1H).

Results from the instrumental variable regression model estimated that \$50 increases in 30-day supply OOP costs were

associated with lower medication adherence (adjusted IRR: 0.90, 0.81–1.00), but the result was not statistically significant ($p = 0.052$). In contrast to the other disease comparisons, adherence was not significantly different among Asian (adjusted IRR: 0.99, 0.88–1.12), black (adjusted IRR: 0.99, 0.90–1.08), Hispanic (adjusted IRR: 0.96, 0.89–1.03), and white patients. CCI score (adjusted IRR: 0.98, 0.97–0.99) and having $\geq \$100,000$ household income (adjusted IRR: 1.09, 1.02–1.17, ref < \$40,000) were significantly associated with medication adherence for patients with PD.

The fully adjusted regression model found a significant association between \$50 increases in 30-day supply OOP costs and adherence (adjusted IRR: 0.96, 0.93–0.99). Similar to the instrumental variable approach, the only other factors that were significantly associated with adherence were CCI score (adjusted IRR: 0.98, 0.97–0.99) and having a $\geq \$100,000$ household income (adjusted IRR: 1.09, 1.01–1.18, ref = <\$40,000). There was not a significant interaction between medication choice and OOP cost on adherence.

The predicted adherence by OOP cost from the instrumental variable regression for the typical patient in each of the 4 medication scenarios are displayed in figure 2. Adherence decreases as OOP costs increase for all 4 medication scenarios.

Discussion

Using an instrumental variable regression approach based on a large, nationally representative, privately insured claims database, we found that higher OOP costs are associated with lower medication adherence in neuropathy, PD, and dementia. These findings were statistically significant for 2 of the 4 medication sets and borderline significant for a third. Reassuringly, the association between higher OOP cost and lower medication adherence was also seen for all 4 medication sets when using a more conventional modeling approach. The neurologic conditions and corresponding medications identified in this research are highly prevalent, accounting for over 5 million supply-months prescribed in 2013 through Medicare part D.² We also found that Asian, black, and Hispanic patients consistently had lower medication adherence than white patients across the 3 neurologic diseases and 4 medication scenarios. Therefore, interventions to increase medication adherence in these populations is critically important to reducing health care disparities.

Previous studies found associations between higher OOP cost and lower medication adherence for patients with multiple sclerosis, but when the OOP cost ranges were small, this association did not persist.^{5,6} In contrast, we found significant associations between OOP cost and adherence with the relatively inexpensive medications for neuropathy, dementia, and PD. Our results are similar to what has been demonstrated with small changes in OOP costs for patients with diabetes.⁷ Compared to previous studies, our instrumental variable analytic approach allowed us to best estimate the causal relationship between OOP costs and medication adherence by limiting selection bias, residual confounding, and the confounding inherent to medication choice. We were able to more granularly measure adherence by modelling days-supply through a negative binomial regression. Interestingly, the predicted adherence for the most typical patients based on OOP costs followed similar and overlapping trends across different disease and medication scenarios (figure 2). These results indicate that OOP costs have a highly predictable effect on medication adherence that has little to do with the indication or medication choice.

Though many factors that give rise to high OOP costs are not in the physician's control, providers can influence medication choice in a substantial way. When choosing among medications with differential OOP costs, prescribing the medication with lower OOP expense will likely improve medication adherence while reducing overall costs. For example, prescribing gabapentin or venlafaxine to patients with newly diagnosed neuropathy is likely to lead to higher adherence compared with pregabalin or duloxetine, and therefore, there is a higher likelihood of relief from neuropathic pain. Given that systematic reviews of medications for painful diabetic neuropathy demonstrate similar efficacy of these medications, cost becomes an important factor.^{13–15} Although associations between improved care coordination and increased adherence have been

inconsistent, future studies should assess whether better care coordination can improve adherence, even in those with high OOP costs.^{20–22} Patients increasingly identify lower costs as a top health care priority, emphasizing the importance for physicians to be mindful of the direct effects on patients' pocketbooks.²³ Furthermore, because dementia (associated with cardiovascular diseases and diabetes) and neuropathy (associated with diabetes) are associated with other conditions that require medication, the effect of OOP costs on drug adherence may be magnified.^{24–26}

Interestingly, combination pills and extended-release formulations are marketed to increase medication adherence, but whether the higher OOP costs of these medications mitigates or reverses any advantage to the original formulation is unclear and deserves further study. Whereas the effectiveness of extended-release formulations has been studied in a handful of epilepsy medications, no studies have taken into account the effect of OOP costs, as most are performed as part of clinical trials where patients do not bear the cost of the medications.²⁷ Future studies are needed to determine if combination pills and extended-release formulations improve real-world medication adherence, taking into account OOP costs.

While physicians should consider OOP costs as a possible way to maximize patient medication adherence, patient cost information is generally not readily available at the time medication decisions are made. Embedding OOP cost information in the electronic health record is one approach. While providing total costs in the electronic health record has been shown to reduce laboratory testing utilization, the effect of providing OOP cost information has not been studied.^{28–30} The frequency of patient insurance changes and the complexity of how drugs are tiered in the hundreds of available plans are challenges to implementing this method. Another approach is clinical decision support systems (CDSS) aimed at improving prescription patterns. Previous studies have shown that CDSS can be successful in altering prescribing behavior, especially in scenarios where the prescription system initiated the decision support.^{31,32} While many CDSS interventions have successfully improved patient and pharmaceutical outcomes, most systems have yet to include patient OOP cost factors. Including patient OOP cost information in the pharmaceutical CDSS is challenging, as the CDSS would need to obtain specific information about each patient's health plan and pharmacy, whereas typical pharmaceutical CDSS only utilize non-patient-specific information such as drug interactions. Adding medication OOP cost information would likely reduce patient cost burden in scenarios where suitable alternative medications are available.

In 3 of 4 disease–medication comparisons, Asian, black, and Hispanic patients had significantly lower medication adherence than white patients. Neurologic health care disparities are not only limited to decreased access to outpatient neurologists, but also spill over to medication adherence.³³ Though our study was the first to find associations between neurologic

medication adherence and race, previous literature has found minority patients to have lower medication adherence in several diseases. For example, lower adherence rates have been found for black patients in cardiovascular disease.³⁴ Similarly, Hispanic patients with diabetes had lower adherence rates than white patients in all English proficiency groups.³⁵ Moreover, white patients had higher adherence compared to nonwhite patients treated for hypertension, depression, hyperlipidemia, asthma/chronic obstructive pulmonary disease, diabetes, and osteoporosis.³⁶ The consistency of these results with our data highlights the importance of targeted interventions to improve medication adherence in nonwhite populations.

We found that medication adherence was low across all disease and medication scenarios. The mean MPR across the 3 conditions was 0.55, indicating that prescribed medications are underused by 45% of optimal adherence within the first 6 months after initiation of evidence-based treatments for common neurologic disorders. Adherence varied by scenario, with the lowest adherence for gabapentinoids and SNRIs for neuropathy (0.49 and 0.55) and the highest adherence for cholinesterase inhibitors for dementia (0.70) and dopamine agonists in PD (0.64). The high adherence for donepezil was surprising since the health benefit of cholinesterase inhibitors is small and the population by definition has memory impairment.¹⁶ However, the presence of caregivers for these patients may have ultimately improved medication adherence.³⁷ The lack of adherence seen in our study is not surprising, as even when OOP costs are low, drug adherence may be suboptimal. Studies have shown that even after life-threatening diseases take place, such as myocardial infarction, medication adherence rates geared to prevent subsequent events are poor.³⁸ Previous work has demonstrated that reminder mailings and other behavioral incentives may improve adherence, but whether these interventions would increase adherence in patients with neurologic diseases remains uncertain.^{39,40} Further studies regarding behavioral interventions are needed to explore why medication adherence varies so much by condition, which may provide insight into interventions to improve adherence.

Limitations include possible disease misclassification of ICD-9/ICD-10 codes. Furthermore, the smaller sample sizes of the venlafaxine/duloxetine and pramipexole/ropinirole comparisons may have reduced our power to detect associations between OOP costs and adherence in the instrumental variable regression. On the other hand, we were able to find significant associations with both of our modeling approaches. We were unable to directly adjust for adverse events in our analysis. We were unable to measure immediate nonadherence for patients who did not fill their first prescription following a diagnosis, which could also relate to OOP costs. This could underestimate the effect OOP costs have on medication adherence. There are many reasons a patient may not start a medication; therefore, it is difficult to estimate which patients had immediate nonadherence due to OOP costs. We assumed that patients used all medication days supplied, which could overestimate medication adherence. One of the strong assumptions for the instrumental

variable approach is that the instrument (medication choice) can only be related to the outcome (adherence) through OOP cost. If this assumption is violated, we will incorrectly overestimate the OOP cost effects. The results of traditional modeling approaches yielded similar results, which mitigated this limitation. This study was performed in a privately insured population; therefore, generalizability of results to other populations is unclear. However, this study has clear implications on out-of-pocket costs in the Medicare and Medicaid populations. Since greater health care disparities are seen in those populations, we would expect the results presented here to be amplified.

We found significant associations between higher OOP costs and decreased medication adherence for patients with 3 neurologic diseases and 4 different medication scenarios. As cost-shifting strategies and the development of new medications lead to increased patient OOP costs through copays and deductibles, it is important for physicians to have access to OOP cost information to inform their medical decision-making when choosing among similar medications. Finding the medication with the lowest OOP cost has the potential to increase medication adherence and ultimately improve patient care. Racial and ethnic disparities exist in medication adherence, which warrants further study and interventions.

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Appendix Authors

Name	Location	Role	Contribution
Evan L. Reynolds, PhD	University of Michigan, Ann Arbor	Author	Study design, interpretation of the statistical analysis, wrote the manuscript
James F. Burke, MD, MS	University of Michigan, Ann Arbor	Author	Study design, interpretation of the statistical analysis, wrote the manuscript
Mousumi Banerjee, PhD	University of Michigan, Ann Arbor	Author	Statistical analyses, interpretation and presentation of the results, critical revisions of the manuscript
Kevin A. Kerber, MD, MS	University of Michigan, Ann Arbor	Author	Interpretation of the data, critical revisions of the manuscript
Lesli E. Skolarus MD, MS	University of Michigan, Ann Arbor	Author	Interpretation of the data, critical revisions of the manuscript
Brandon Magliocco, MPH	The American Academy of Neurology, Minneapolis, MN	Author	Interpretation of the data, critical revisions of the manuscript
Gregory J. Esper, MD, MBA	Emory University, Department of Neurology, Atlanta, GA	Author	Interpretation of the data, critical revisions of the manuscript
Brian C. Callaghan, MD, MS	University of Michigan, Ann Arbor	Author	Study design, interpretation of the statistical analysis, wrote the manuscript

References

- Claxton G, Rae M, Long M, Damico A, Whitmore H, Foster G. Health benefits in 2016: family premiums rose modestly, and offer rates remained stable. *Health Aff* 2016;35:1908–1917.
- De Lott LB, Burke JF, Kerber KA, Skolarus LE, Callaghan BC. Medicare part D payments for neurologist-prescribed drugs. *Neurology* 2016;86:1491–1498.
- Callaghan BC, Reynolds E, Banerjee M, et al. Out-of-pocket costs are on the rise for commonly prescribed neurologic medications. *Neurology* 2019;92:e2604–e2613.
- Dor A, Lage MJ, Tarrant ML, Castelli-Haley J. Cost sharing, benefit design, and adherence: the case of multiple sclerosis. In: *Pharmaceutical Markets and Insurance Worldwide*. Bingley, UK: Emerald Group Publishing Limited; 2010:175–193.
- Gleason P, Starner CI, Gunderson BW, Schafer JA, Saran HS. Association of prescription abandonment with cost share for high-cost specialty pharmacy medications. *J Manag Care Pharm* 2009;15:648–658.
- Shao H, Stoecker C, Monnette AM, Shi L. Cost sharing of disease-modifying treatments (DMTs) as policy lever to improve DMTs' access in multiple sclerosis. *Value Health* 2018;21:1083–1089.
- Karter AJ, Parker MM, Solomon MD, et al. Effect of out-of-pocket cost on medication initiation, adherence, and persistence among patients with type 2 diabetes: the diabetes study of Northern California (DISTANCE). *Health Serv Res* 2018;53:1227–1247.
- Hopson S, Saverio K, Liu LZ, et al. Impact of out-of-pocket costs on prescription fills among new initiators of biologic therapies for rheumatoid arthritis. *J Manag Care Spec Pharm* 2016;22:122–130.
- Baiocchi M, Cheng J, Small DS. Instrumental variable methods for causal inference. *Stat Med* 2014;33:2297–2340.
- Terza JV, Basu A, Rathouz PJ. Two-stage residual inclusion estimation: addressing endogeneity in health econometric modeling. *J Health Econ* 2008;27:531–543.

- Hoffman EM, Staff NP, Robb JM, St Sauver JL, Dyck PJ, Klein CJ. Impairments and comorbidities of polyneuropathy revealed by population-based analyses. *Neurology* 2015;84:1644–1651.
- Germaine-Smith C, Metcalfe A, Pringsheim T, et al. Recommendations for optimal ICD codes to study neurologic conditions: a systematic review. *Neurology* 2012;79:1049–1055.
- Griebeler ML, Morey-Vargas OL, Brito JP, et al. Pharmacologic interventions for painful diabetic neuropathy: an umbrella systematic review and comparative effectiveness network meta-analysis. *Ann Intern Med* 2014;161:639–649.
- Finnerup NB, Attal N, Haroutounian S, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. *Lancet Neurol* 2015;14:162–173.
- Finnerup NB, Sindrup SH, Jensen TS. The evidence for pharmacological treatment of neuropathic pain. *Pain* 2010;150:573–581.
- Raina P, Santaguida P, Ismail A, et al. Effectiveness of cholinesterase inhibitors and memantine for treating dementia: evidence review for a clinical practice guideline. *Ann Intern Med* 2008;148:379–397.
- Zhuo C, Zhu X, Jiang R, et al. Comparison for efficacy and tolerability among ten drugs for treatment of Parkinson's disease: a network meta-analysis. *Sci Rep* 2017;7:45865.
- Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care* 2005;43:1130–1139.
- Sperber CM, Samarasinghe SR, Lomax GP. An upper and lower bound of the medication possession ratio. *Patient Prefer Adherence* 2017;11:1469–1478.
- Costa E, Pecorelli S, Giardini A, et al. Interventional tools to improve medication adherence: review of literature. *Patient Prefer Adherence* 2015;9:1303–1314.
- Peikes D, Chen A, Schore J, Brown R. Effects of care coordination on hospitalization, quality of care, and health care expenditures among Medicare beneficiaries: 15 randomized trials. *JAMA* 2009;301:603.
- Lee JK, Grace KA, Taylor AJ. Effect of a pharmacy care program on medication adherence and persistence, blood pressure, and low-density lipoprotein cholesterol: a randomized controlled trial. *JAMA* 2006;296:2563.
- Schleifer D, Friedman W, Diep A. Where Americans See Eye to Eye on Health Care. Public Agenda and the Kettering Foundation; 2018. Available at: [hiddencommon-ground.org](https://www.hiddencommon-ground.org). Accessed May 2019.
- Ninomiya T. Diabetes mellitus and dementia. *Curr Diab Rep* 2014;14:487.
- Ott A, Breteler MM, de Bruyne MC, van Harskamp F, Grobbee DE, Hofman A. Atrial fibrillation and dementia in a population-based study: The Rotterdam Study. *Stroke* 1997;28:316–321.
- Kivipelto M, Helkala EL, Laakso MP, et al. Midlife vascular risk factors and Alzheimer's disease in later life: longitudinal, population based study. *BMJ* 2001;322:1447–1451.
- Brandt C, May TW. Extended-release drug formulations for the treatment of epilepsy. *Expert Opin Pharmacother* 2018;19:843–850.
- Feldman LS, Shihab HM, Thiemann D, et al. Impact of providing fee data on laboratory test ordering: a controlled clinical trial. *JAMA Intern Med* 2013;173:903–908.
- Horn DM, Koplan KE, Senese MD, Orav EJ, Sequist TD. The impact of cost displays on primary care physician laboratory test ordering. *J Gen Intern Med* 2014;29:708–714.
- Tierney WM, Miller ME, McDonald CJ. The effect on test ordering of informing physicians of the charges for outpatient diagnostic tests. *N Engl J Med* 1990;322:1499–1504.
- Pearson SA, Moxey A, Robertson J, et al. Do computerised clinical decision support systems for prescribing change practice? A systematic review of the literature (1990–2007). *BMC Health Serv Res* 2009;9:154.
- Garg AX, Adhikari NK, McDonald H, et al. Effects of computerized clinical decision support systems on practitioner performance and patient outcomes: a systematic review. *JAMA* 2005;293:1223–1238.
- Saadi A, Himmelstein DU, Woolhandler S, Mejia NI. Racial disparities in neurologic health care access and utilization in the United States. *Neurology* 2017;88:2268–2275.
- Ferdinand KC, Yadav K, Nasser SA, et al. Disparities in hypertension and cardiovascular disease in blacks: the critical role of medication adherence. *J Clin Hypertens* 2017;19:1015–1024.
- Fernández A, Quan J, Moffet H, Parker MM, Schillinger D, Karter AJ. Adherence to newly prescribed diabetes medications among insured Latino and white patients with diabetes. *JAMA Intern Med* 2017;177:371–379.
- Rolnick SJ, Pawloski PA, Hedblom BD, Asche SE, Bruzek RJ. Patient characteristics associated with medication adherence. *Clin Med Res* 2013;11:54–65.
- El-Saifi N, Moyle W, Jones C, Tuffaha H. Medication adherence in older patients with dementia: a systematic literature review. *J Pharm Pract* 2018;31:322–334.
- Volpp KG, Troxel AB, Mehta SJ, et al. Effect of electronic reminders, financial incentives, and social support on outcomes after myocardial infarction: the Heart-Strong randomized clinical trial. *JAMA Intern Med* 2017;177:1093–1101.
- Dai H, Mao D, Volpp KG, et al. The effect of interactive reminders on medication adherence: a randomized trial. *Prev Med* 2017;103:98–102.
- Asch DA, Troxel AB, Stewart WF, et al. Effect of financial incentives to physicians, patients, or both on lipid levels: a randomized clinical trial. *JAMA* 2015;314:1926–1935.