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Adherence to Antiseizure vs Other Medications Among US Medicare Beneficiaries With and Without Epilepsy

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Abstract

Objective: To 1) compare adherence to antiseizure medications (ASMs) versus non-ASMs among individuals with epilepsy, 2) assess the degree to which variation in adherence is due to differences between individuals versus between medication classes among individuals with epilepsy, and 3) compare adherence in individuals with versus without epilepsy.

Methods: This was a retrospective cohort study using Medicare. We included beneficiaries with epilepsy (≥1 ASM, plus *International Classification of Diseases, Ninth Revision, Clinical Modification* diagnostic codes), and a 20% random sample without epilepsy. Adherence for each medication class was measured by the proportion of days covered (PDC) in 2013-2015. We used Spearman correlation coefficients, Cohen's kappa statistics, and multilevel logistic regressions.

Results: There were 83,819 beneficiaries with epilepsy. Spearman correlation coefficients between ASM PDCs and each of the 5 non-ASM PDCs ranged 0.44-0.50, Cohen's kappa ranged 0.33-0.38, and within-person differences between each ASM's PDC minus each non-ASM's PDC were all statistically significant ($p<0.01$) though median differences were all very close to 0. Fifty-four percent of variation in adherence across medications was due to differences between individuals. Adjusted predicted probabilities of adherence were: ASMs 74% (95% confidence interval [CI] 73%-74%), proton pump inhibitors 74% (95% CI 74%-74%), antihypertensives 77% (95% CI 77%-78%), selective serotonin reuptake inhibitors 77% (95% CI 77%-78%), statins 78% (95% CI 78%-79%), and levothyroxine 82% (95% CI 81%-82%). Adjusted predicted probabilities of adherenc**e** to non-ASMs were 80% (95% CI 80%-81%) for beneficiaries with epilepsy versus 77% (77%-77%) for beneficiaries without epilepsy.

Conclusion: Among individuals with epilepsy, ASM and non-ASM adherence were moderately correlated, half of variation in adherence was due to between-person rather than between-medication differences, adjusted adherence was slightly lower for ASMs than several non-ASMs, and epilepsy was associated with a quite small increase in adherence to non-ASMs. Nonadherence to ASMs may provide an important cue to the clinician to inquire about adherence to other potentially life-prolonging medications as well. Although efforts should focus on improving ASM adherence, patient-level rather than purely medication-specific behaviors are also critical to consider when developing interventions to optimize adherence.

Introduction

Between 20-50% of individuals with epilepsy are classified as non-adherent to their antiseizure medications (ASMs).[1] Non-adherence to ASMs is associated with adverse consequences including increased seizures,[2] mortality,[3] healthcare costs,[4–6] and acute care visits.[4] However, because adults with epilepsy often have a wide variety of treatable chronic conditions[7] and most medications taken by individuals with epilepsy are taken for indications other than epilepsy,[8] optimizing adherence to non-ASMs in people with epilepsy would also reduce preventable adverse outcomes.

Whereas prior work has explored risk factors and prevalence of ASM non-adherence,[1,6,9–14] little is known about how adherence to ASMs compares to adherence to non-ASMs among individuals with epilepsy. Understanding if differences exist would inform whether interventions to improve adherence in adults with epilepsy should target ASMs specifically, or more global patient-level behaviors across medication classes. ASM non-adherence may correlate with general attitudes towards medications,[15] though it is plausible that the unique side effect profiles, monitoring regimens, and psychosocial

constructs[16] surrounding ASMs and the unique consequences of seizures may lead to different drivers and prevalence of non-adherence to ASMs versus non-ASMs.

Furthermore, it remains unknown whether individuals with epilepsy demonstrate different rates of adherence across medication classes, compared to individuals without epilepsy. Individuals with epilepsy have heightened risk for cognitive, psychiatric, and physical comorbidities[7] as well as disparities in healthcare access[17–19] which could all increase risk for non-adherence compared to individuals without epilepsy. Still, such barriers are common across individuals with chronic conditions. Determining whether adherence differs between people with versus without epilepsy could inform whether epilepsy-specific interventions are needed.

Using Medicare data, we 1) compared adherence to ASMs versus non-ASMs among individuals with epilepsy, 2) assessed the degree to which variation in adherence is due to differences between individuals versus between medication classes among individuals with epilepsy, and 3) compared adherence in individuals with versus without epilepsy. We hypothesized that ASM adherence would be partially correlated with non-ASM adherence, within-person correlation rather than between-medication differences may explain a substantive amount of variation in adherence, and individuals with epilepsy may have worse adherence compared with the general population.

Methods

Study Design and Dataset

We performed a retrospective cohort study of beneficiaries in fee-for-service Medicare across the entire US, incorporating data from 2011-2015.

Standard protocol approvals, registrations, and patient consents

This study was deemed exempt by the University of Michigan Institutional Review Board.

Patient Selection

Similar to prior work,[20] we included patients with epilepsy defined as filling ≥1 ASM, plus *International Classification of Disease, Ninth Revision, Clinical Modification* (ICD-9-CM) criteria for inpatient, outpatient, or emergency Evaluation and Management (E/M) or consultation codes: 1) ≥1 for epilepsy (ICD-9-CM 345.xx), or 2) ≥2 for convulsions (ICD-9-CM 780.3x) at least 30 days apart, in 2013. Recent work in Medicare[21] demonstrated good performance of combining ICD codes plus ASM to identify patients with epilepsy (area under the curve 0.93, sensitivity 88%, and specificity 98%). Because we required ICD codes to determine the diagnosis of epilepsy (2013) and refractory (2011-2013) or prevalent (2011-2012) epilepsy, we excluded beneficiaries without continuous enrollment in Medicare parts A and B, or with managed care plans (whose claims do not appear in Medicare carrier files) in 2011-2013. Because we required medication fill data to determine proportion of days covered (PDCs; 2013-2015), we also excluded beneficiaries without continuous enrollment in Medicare part D 2013-2015. We included all individuals qualifying for Medicare; Medicare criteria include age >65 years old, disability, and/or end-stage renal disease.

In addition to the cohort with epilepsy, we also included a 20% random Medicare sample of beneficiaries without epilepsy.

Variables

Adherence was measured using PDCs. The PDC represents the proportion of days (0%-100%) in an observation period during which an individual has medication

supply. It is a widely accepted measure for claims-based analysis of medication adherence[22,23] and is a standard measure in ASM adherence studies.[4,6,9,10,24] We also dichotomized <80% (non-adherent) versus ≥80% (adherent) as is typically performed in adherence literature for analysis.[4,6,9,10,22–24] We calculated one PDC for each medication class for each beneficiary. If a beneficiary took >1 unique medication in a given class, we summed the numerators and denominators for all medications within a class. Numerators were the number of days with medication supply (determined using the days supply field in the prescription claim) during the total observation period 7/2013-6/2015. We did not double count days if a fill occurred prior to the last day of the prior fill. Denominators were the total number of days summed across quarters, unless one of the following was true: If there was no supply of a medication 180 days before a given fill, we considered that a newly started medication and we started counting the denominator at the time of the first fill rather than 7/1/2013. If a prescription did not have enough days to last through the end of the observation period and there was no fill 180 days after the end of a given prescription, we stopped counting the denominator at the end of the last fill rather than stopping at the end of the period. Other investigators[4] have similarly used this methodology in order to acknowledge that a medication could lapse for valid medical reasons (i.e. intolerance, remission) rather than non-adherence. We only counted medications towards PDC calculations if there was >1 fill for each medication during the observation period, given it is not possible to calculate a valid PDC if a medication is filled just once; hence, sample sizes to calculate PDCs may be slightly smaller than the total population on at least 1 medication in a given class. An alternative to the PDC in administrative claims research is the medication possession ratio (MPR), which represents the summed days' supply of medication divided by the number of days in the observation window. However, we chose the PDC because the

MPR can overestimate adherence (e.g. if refilling a medication before the end of the previous fill, or if changing doses or switching agents) theoretically even producing values over 100%, and the PDC is the standard approach used by CMS.[25]

We recorded the PDC for ASMs, plus 5 non-ASM medication classes: antihypertensives, levothyroxine, proton pump inhibitors (PPIs), selective serotonin reuptake inhibitors (SSRIs), and statins. Non-ASM medication classes were chosen to represent a broad range of the most common medications for chronic conditions taken by individuals with epilepsy.[8] eTable 1,http://links.lww.com/WNL/B673 lists all ASMs and the most common considered non-ASMs.

We captured baseline variables including age, sex, race, Medicaid dual eligibility, rural ZIP code,[26] and reason for entitlement. We calculated the Charlson comorbidity index[27–29] in 2013 (a weighted sum of 22 comorbidities where higher numbers indicate greater comorbidity), refractory epilepsy (≥1 claim for refractory epilepsy[30]: ICD-9-CM 345.01, 345.11, 345.41, 345.51, 345.61, 345.71, 345.81, 345.91 in 2011-2013), prevalent epilepsy (≥1 claim for seizures or epilepsy in 2011-2012), and number of unique medications or unique ASMs and total out of pocket drug expenses in 2013.

Statistical Analysis

We described baseline variables using medians and interquartile ranges [IQR], and frequencies (%).

In the first part, we assessed the PDC for each medication class, among individuals with epilepsy. The distribution of each medication class's PDC was compared first using violin plots. Violin plots[31] are a modification of boxplots (which display quartiles) by superimposing plots of the estimated kernel density. We also repeated violin plots, except stratifying all classes further in terms of brand name versus

generic medications, and also stratifying ASMs in terms of older (carbamazepine, ethosuximide, phenytoin, phenobarbital, primidone, valproate) versus newer generation (all others). We then displayed a separate scatterplot comparing each individual's ASM PDC versus non-ASM PDC among each beneficiary who filled any of the 4 non-ASMs. We assessed correlations using Spearman's correlation coefficients because PDCs were monotonically but not linearly related. One thousand bootstrapped samples were used to calculate empiric confidence intervals around correlation coefficients. We subtracted the ASM PDC minus each non-ASM's PDC to further depict within-person differences and assessed the significance of each difference using Wilcoxon signed rank tests. We then performed Chi-squared tests assessing differences between adherence to ASMs versus non-ASM classes, and Cohen's kappa statistics to assess agreement beyond chance.

In the second part, we performed multilevel models to calculate intraclass correlation coefficients (ICCs) among beneficiaries with epilepsy. An ICC represents the percentage (0-100%) of variation in an outcome explained by between-person differences independent of other covariates.[32] Stated another way, an ICC represents the within-person correlation (ranging 0-1, equivalent to 0%-100%) for each medication's adherence outcome. If PDCs for each medication were identical within each individual but differed between individuals, the ICC would be 100%; that would imply adherence was totally determined by individual factors rather than differences between medications. In these models, each person could have between 1 to 6 rows (depending on whether they filled only ASMs, or filled any of the 5 other medication classes as well), and there was a person-level random intercept. The main outcome was binary adherence, PDC≥80%. We calculated an unadjusted ICC, then adjusted for medication class, then in the fully adjusted model adjusted for medication class in

addition to age, sex, race, dual eligibility, rural ZIP code, reason for Medicare entitlement, neurologist visit, refractory epilepsy, prevalent epilepsy, number of unique medications, number of unique ASMs, total part D out of pocket drug costs in 2013, maximal doses per day of chronic medications with ≥2 fills 30 days apart with ≥90 days supply in 2013, and Charlson comorbidity index. We displayed the predicted percent adherent to each medication class from this fully adjusted mixed effects logistic regression. We conducted sensitivity analyses where we 1) evaluated robustness of model discrimination when varying the PDC cutoff to ≥80%, ≥70%, or ≥60%, and then 2) considered brand name and generic medications within each class as a separate row of data.

In the third part, we compared non-ASM adherence in beneficiaries with epilepsy versus without epilepsy. We repeated a mixed effects logistic regression with a fixed effect for epilepsy and a random effect accounting for variability between individual beneficiaries. We performed an unadjusted model, and then adjusted for the same covariates as in the previous fully adjusted model except omitting variables for prevalent epilepsy, refractory epilepsy, and number of ASMs as these variables were perfectly collinear with epilepsy.

Data were analyzed using SAS 9.4 (Cary, NC) and Stata 16.0 (College Station, TX).

Data accessibility statement

All datasets are available to purchase at https://www.resdac.org/. Aggregated de-identified data may be shared upon request.

Results

Cohort description

The cohort included 83,819 eligible beneficiaries with epilepsy and 653,812 from our 20% sample without epilepsy (eFigure 1,http://links.lww.com/WNL/B673). There were 77,261 eligible beneficiaries with epilepsy who filled an ASM at least twice for whom we could calculate an ASM PDC. Among beneficiaries with epilepsy, median age was 62 years (IQR 49-75 years), 54% were female, 78% were white, 67% were dual eligible for Medicaid, and 43% qualified for Medicare due to age whereas 57% qualified due to disability (Table 1).

Comparing adherence to ASMs versus non-ASMs among beneficiaries with epilepsy

Median PDCs for each of the 6 classes ranged 0.90 to 0.93 (Figure 1A). Distributions appeared similar when stratifying according to older versus newer generation ASM, and brand name versus generic (Figure 1B).

Wilcoxon signed rank tests for the within-person differences between each ASM's PDC minus each non-ASM's PDC were all statistically significant ($p<0.01$). However, the median values for differences were all very close to 0 (-0.01 for each; Figure 1C, sample sizes are the same as in Figure 2).

Scatterplots demonstrated a positive relationship between ASM versus each non-ASM's PDC (Figure 2). Spearman correlation coefficients quantified this relationship from minimum 0.44 (PPIs) to maximum 0.53 (levothyroxine), which all represented moderate positive correlations between ASM and non-ASM PDCs.

Associations between ASM and non-ASM dichotomized adherence are presented in Table 2 (populations are the same as in the above Figures). Seventy-five percent of beneficiaries were adherent to ASMs. Beneficiaries who were adherent to ASMs were more likely to be adherent to non-ASMs (p-values all<0.01). For example,

among beneficiaries filling antihypertensives and ASMs, 6,488/12,740 (51%) of those who were not adherent to their ASM were adherent to their antihypertensives, whereas 28,337/32,716 (87%) of those who were adherent to their ASM were adherent to their antihypertensive. Cohen's kappa ranged 0.33 to 0.38 which represented fair agreement beyond chance between ASM and non-ASM adherence.

Assessing the degree to which variation in adherence is due to differences between beneficiaries versus between medication classes among beneficiaries with epilepsy

In mixed effects logistic models predicting adherence, ICCs were 57% (95% confidence interval [CI] 56%-57%; $N_{observations}$=230,939; $N_{beneficiaries}$=79,585) in an unadjusted model, 57% (95% CI 56%-58%; $N_{observations}$=230,939; $N_{beneficiaries}$=79,585) in a model adjusting for medication class, and 54% (95% CI 53%-55%; $N_{observations}$=230,374; $N_{beneficiaries}$=79,379; AUC 0.95, 95% CI 0.95-0.95) in the fully adjusted model.

Marginal predicted proportions for adherence rates from the fully adjusted mixed effects logistic model in ascending order were: ASMs 74% (95% CI 73%-74%), proton pump inhibitors 74% (95% CI: 74%-74%), antihypertensives 77% (95% CI 77%-78%), SSRIs 77% (95% CI: 77%-78%), statins 78% (95% CI: 78%-79%), and levothyroxine 82% (95% CI 81%-82%). Each non-ASM proportion was significantly different from the ASM proportion ($p<0.05$).

In sensitivity analyses, ICCs and AUCs were similar when changing the adherence cutoff to ≥70% (ICC 55%; AUC 0.96) or ≥60% (ICC 54%; AUC 0.98), or whether distinguishing between brand name versus generic medications (ICC 52%).

Comparing adherence to non-ASMs in beneficiaries with epilepsy versus without epilepsy

We repeated a mixed effects logistic model, except including beneficiaries both with and without epilepsy, and included only non-ASMs. Epilepsy had an unadjusted odds ratio for adherence of 1.00 (95% CI: 0.96-1.02; N_{obs}=1,342,456; $N_{beneficiaries}$=605,492). This odds ratio was 1.03 (95% CI 01.01-1.06; N_{obs}=1,342,456; $N_{beneficiaries}$=605,492) after adjusting for medication class, and 1.35 (95% CI 1.32-1.39; N_{obs}=1,331,642, $N_{beneficiaries}$=598,967) in the fully adjusted model. The adjusted marginal predicted probability of adherence was 0.80 (95% CI 0.80-0.81) for beneficiaries with epilepsy versus 0.77 (0.77-0.77) for beneficiaries without epilepsy ($p<0.01$).

In sensitivity analyses, ORs for epilepsy were similar when changing the adherence cutoff to ≥70% (OR 1.39, 95% CI 1.34-1.43) or ≥60% (OR 1.38, 95% CI 1.32-1.43), or whether distinguishing between brand name versus generic medications (OR 1.34, 95% CI 1.31-1.38). eTable 2,http://links.lww.com/WNL/B673 displays all odds ratios for the model including brand name as a variable (OR 0.85, 95% CI 0.84-0.87).

Discussion

In this large retrospective Medicare database study, ASM adherence and non-ASM adherence were moderately positively correlated with fair agreement, and individual patient-level factors accounted for slightly more than half of variation in adherence. While unadjusted median adherence was similar across medical classes and within-individual differences between ASM and non-ASM adherence were very close to 0, adjusted ASM adherence nonetheless was significantly lower than all non-ASMs but absolute differences were quite small. Finally, while individuals with epilepsy had similar unadjusted adherence across non-ASMs to individuals without epilepsy,

after adjusting for demographics and comorbidities, individuals with epilepsy demonstrated 40% increased odds of adherence though the absolute difference was small (4%).

Prior work has placed adherence within the context of the Necessity-Concerns Framework,[33,34] whereby adherence is a complex interplay between general or medication-specific beliefs regarding need for treatment and concern about potential adverse consequences of medications. For example, in one study[15] expressing concern about long-term ASM harms predicted ASM nonadherence (odds ratio 1.4). However, when respondents were asked about their attitudes towards medications in general, general concern about medications similarly predicted ASM nonadherence (odds ratio 1.6). In our study, 54% of variation in adherence was due to person-to-person differences, rather than medication-to-medication differences or other patient factors related to demographics or comorbidities. While Medicare lacks individual data about medication attitudes and beliefs, our findings are concordant with the concept that mechanisms underlying ASM adherence may not be totally unique to ASMs, seizures, or epilepsy. Rather, this result could reflect that adherence barriers unique to each individual (i.e. forgetting doses and cognitive function, difficulty swallowing, difficulty affording medications or getting to the pharmacy, health literacy, patient-provider relationship[35–37]) apply to all medication classes, and perceived importance of medications in general varies between individuals. Evidence-based interventions[36,38] targeting common features (i.e. calendar or text reminders) may prove useful for both ASM and non-ASM classes alike, and nonadherence to ASMs may provide an important cue to the clinician to inquire about adherence to other potentially life-prolonging medications. Non-adherence is a problem across chronic conditions,[39–41] generally lower for brand name drugs similar to our findings rather than unique to any

single medication class,[42] and individual, family, healthcare system, and community factors all may play a role in adherence behaviors compared to the single chronic condition alone.

Still, in our study ASM adherence was not perfectly correlated with non-ASM adherence; ~50 to 60% of beneficiaries who were not adherent to ASMs were still adherent to non-ASMs, and agreement beyond chance between ASM and non-ASM adherence was only fair. Even if common belief structures or individual-level barriers existed influencing adherence to all of a patient's medications, one would still not expect perfect correlation between ASM and non-ASM adherence given vastly different consequences of nonadherence to each studied medication class. For example, we studied both symptomatic medications (i.e. PPIs, SSRIs) and prevention medications (i.e. antihypertensives, statins). Increased side effects, monitoring, and psychosocial implications all could explain lower adjusted ASM adherence compared with other medication classes despite similar unadjusted PDCs, though are not captured in Medicare data. Thus, these data do not inform the mechanisms underlying differences.

We also found that while adherence to non-ASMs was higher in individuals with epilepsy compared to without epilepsy, the absolute magnitude of such differences was small. We initially hypothesized that patients with epilepsy may exhibit suboptimal adherence due to increased underlying memory dysfunction or more complex polypharmacy making adherence to any single medication more challenging. However, our data suggested the opposite. Prior work has shown that individuals with epilepsy are more likely to have a regular place of care and have more frequent health visits than patients without epilepsy,[43] which could lead to more rapid detection of non-adherence across medications.

Our adherence rates were somewhat higher than compared to previous literature. One comparable study in Medicare[13] found 68% were adherent to ASMs compared to our 74%. Differences could have emerged due to slightly different methodologies used to calculate PDCs in absence of a single gold-standard methodology: 1) Their study did not restrict to medications with >1 fill. While we acknowledge that this exclusion would not detect early non-persistence after a single fill, we applied this exclusion because counting medications filled only once could misclassify a poorly tolerated, discontinued medication as 'non-adherence' and pharmacy fills requires at least 2 fills to understand adherence over time. 2) That study counted all days towards the denominator between the first and end of their follow-up period. While Medicare data do not explicitly inform reasons for extended lapses in medications, we did not count days at the end of each quarter towards the denominator if there was no subsequent 180-day fill, similar to other literature,[4] to allow for the possibility that medications could be intentionally discontinued for valid medical reasons such as seizure remission[44] rather than nonadherence. 3) Their study counted the proportion of days with at least 1 ASM prescription. However, that method would not detect non-adherence for patients on polytherapy who were fully adherent to one but not their other ASMs, whereas our method summing the numerators and denominators across all medications within a class would do so. Other studies have found adherence rates ranging from 50%-79%, though it is difficult to directly compare across populations, study designs, and adherence measures (e.g. privately insured adults using retrospective claims and PDCs [61%][6,39]; or children at a single academic hospital, using longitudinal follow-up of electronic pill caps[79%][45]).

Our study has several limitations. Measuring adherence using PDCs from claims data could overestimate adherence; filling a medication does not guarantee ingestion. It

also could underestimate adherence; a beneficiary could obtain medications over the counter (PPIs) which would not appear as a Part D claim. Regardless, we calculated PDCs using the exact same methodology across all medication classes and thus it is unlikely that measurement error affected between-medication or between-person comparisons. Additionally, PDC represents an integral component of how the Centers for Medicare and Medicaid evaluate Medicare Advantage and Part D plan performance,[25] and thus comprises a clinically relevant accepted metric driving policy. Also, while Medicare is a large, diverse national database optimally suited to study older Americans in addition to those with disabilities (individuals with epilepsy demonstrate 3-fold increased rates of physical disability compared with the general population[46]), future studies may seek to reproduce our findings in younger, nondisabled, and less well-insured populations. While many studies using Medicare reduce heterogeneity by restricting to those eligible only due to age≥65, that strategy sacrifices generalizability. We included all ages which is a strength to make inferences about a wider population range, and we entered both age and reason for Medicare eligibility as covariates to account for this variation. It is also well-known that identifying epilepsy cases in administrative datasets using ICD codes risks some degree of misclassification,[47] patients could receive a diagnosis but not fill an ASM prescription[48] thus not enter into our case definition, and prior work determining the accuracy of identifying epilepsy based on different numbers of ASM fills is limited. Still, recent work has suggested good sensitivity (up to 88%) and specificity (98%) of Medicare data compared with chart review epilepsy diagnoses,[21] and it is also known that positive predictive value of identifying epilepsy cases improves when requiring ≥1 ASM fill.[49] Furthermore, while 2013-2015 prescription data may not reflect contemporary advances, the medications studied here remain in widespread use.

Conclusions

These results suggest that while unique features of seizures and ASMs may drive a small portion of ASM nonadherence, a substantive portion of adherence is not ASM- or epilepsy-specific, but rather person-specific. While adjusted ASM adherence was slightly lower than non-ASMs and people with epilepsy demonstrated significantly higher adherence to non-ASMs compared to those without epilepsy, these absolute differences were quite small. Nonadherence to ASMs may provide an important cue to the clinician to inquire about adherence to other potentially life-prolonging medications as well. Acknowledging that many medications and chronic conditions likely share common adherence barriers, future interventions aimed at improving adherence in patients with epilepsy may more broadly target underlying patient-level barriers beyond ASM-specific concerns. This work could be addressed in the context of Epilepsy Learning Health Systems focusing on ensuring providers assess medication barriers which may or may not be unique to ASMs in order to improve outcomes.

Supplement - http://links.lww.com/WNL/B673

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Table 1: Population description. ESRD = end-stage renal disease; ASM = antiseizure medication.

		Median (interquartile range) or No. (%)			
		Epilepsy (N=83,819)		No epilepsy (N=653,812)	
Age		62	49-75	74	68-81
Female sex		45,053	54%	388,292	59%
Race	White	65,300	78%	543,930	83%
	Black	13,222	16%	66,524	10%
	Hispanic	2,505	3%	9,336	2%
	Asian	805	1%	13,220	2%
Dual eligible for Medicaid		56,383	67%	211,634	32%
Rural ZIP code		24,014	29%	204,318	31%
Reason for entitlement	Age	36,022	43%	519,911	80%
	Disability	47,377	57%	132,201	20%
	ESRD	1,217	1%	4,351	1%
Neurology visit, 2013		37,358	45%	38,246	6%
Refractory epilepsy, 2011-2013		11,335	14%	N/A	N/A
Prevalent epilepsy, 2011-2012		51,415	61%	N/A	N/A
Unique medications, 2013 (No.)		12	8-18	8	5-13
Unique ASMs, 2013 (No.)		2	1-2	0	0-0
Older generation ASM, 2013		46,995	56%	N/A	N/A
Total Part D out of pocket cost, 2013		$70	$0-$279	$168	$38-$506
Max doses of chronic medications per day	0	2,213	3%	48,529	8%
	>0, ≤1	2,029	2%	161,016	26%
	>1, ≤2	13,244	16%	171,070	28%
	>2	66,333	79%	236,313	38%
Charlson comorbidity index, 2013	0	31,500	38%	299,287	46%
	1-3	34,632	41%	274,512	42%
	4-6	12,015	14%	59,846	9%
	7+	5,672	7%	20,167	3%

Table 2: Among beneficiaries with epilepsy, dichotomous adherence to non-ASMs and ASMs. Numerators are the number adherent to each non-ASM. Denominators are the number either not adherent to ASMs ("No"), adherent to ASMs ("Yes"), or total among those filling each row's listed non-ASM. ASM = antiseizure medication; HTN = antihypertensive; Levo. = levothyroxine; PPI = proton pump inhibitor; SSRI = selective serotonin reuptake inhibitor.

		Adherent to ASM							
		No		Yes		Total		p	κ
Non-ASM	HTN	6,488/12,740	51%	28,337/32,716	87%	34,825/45,456	77%	<0.01	0.38
	Levo	2,382/4,173	57%	12,277/13,456	91%	14,659/17,638	83%	<0.01	0.38
	PPI	3,992/8,017	50%	16,987/20,628	82%	20,979/28,645	73%	<0.01	0.33
	SSRI	3,375/6,677	51%	15,704/18,061	87%	19,079/24,738	77%	<0.01	0.38
	Statin	4,535/8,420	54%	20,986/23,889	88%	25,521/32,309	79%	<0.01	0.36
ASM		19,170		56,610		56,610/75,780	75%		

κ: Cohens' kappa represents agreement beyond what would be expected due to chance. Common interpretations are: slight agreement 0-0.2, fair agreement 0.21-0.40, moderate agreement 0.41-0.60), substantial agreement 0.61-0.80, almost perfect agreement >0.81.[50]

Figure legends

Figure 1:
Title: Distribution of proportion of days covered by medication class.
Legend: Among beneficiaries with epilepsy, violin plots of PDCs for (A) each medication class (ASMs and 4 non-ASMs) summed across all quarters, (B) each medication class stratified by older versus newer generation for ASMs and brand name versus generic for all classes, and (C) within-individual ASM minus non-ASM PDCs. PDC = proportion days covered. ASM = antiseizure medication; HTN = antihypertensive; Levo. = levothyroxine; PPI = proton pump inhibitor.

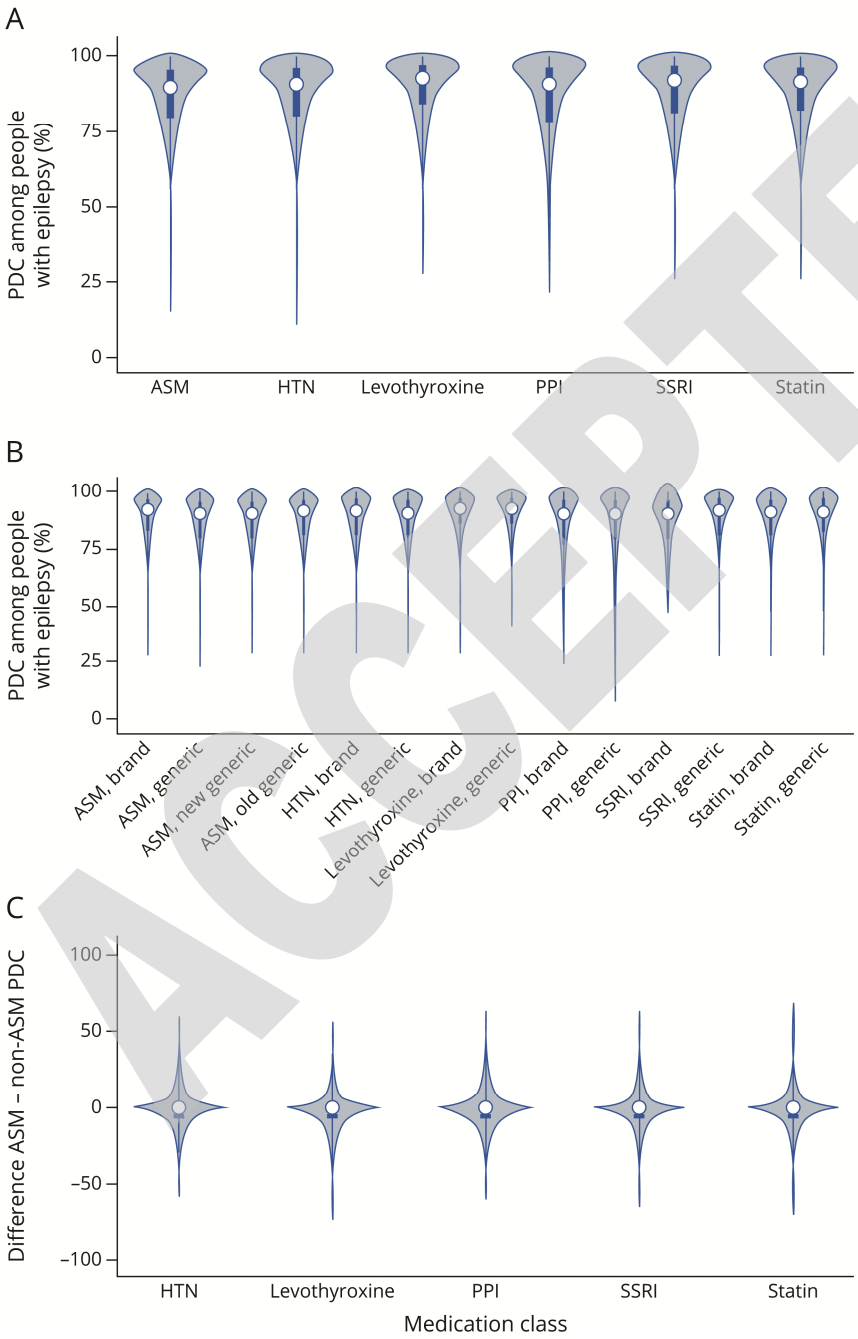
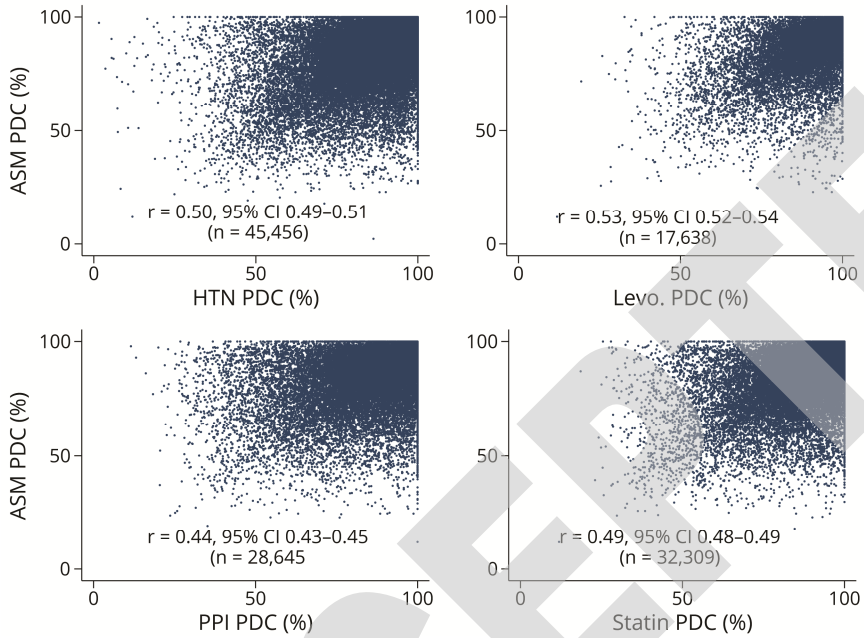


Figure 2:
Title: Antiseizure medication (ASM) versus non-ASM proportion of days covered (PDC).
Legend: Among beneficiaries with epilepsy, separate scatterplots of ASM PDC (x-axis) versus each non-ASM PDC (y-axis). Each plot contains a Spearman's correlation coefficient (r), sample size (N), and a superimposed regression line with 95% confidence interval and regression equation. Note SSRIs are not included due to space constraints, but results are similar to displayed panels (r=0.50, 95% CI 0.49-0.51, N=24,738). PDC = proportion days covered. ASM = antiseizure medication; HTN = antihypertensive; Levo. = levothyroxine; PPI = proton pump inhibitor.



Appendix 1: Authors

Name	Location	Contribution
Samuel W Terman, MD MS	University of Michigan	Data acquisition, study design, statistical analysis, manuscript preparation
Wesley T Kerr, MD PhD	UCLA	Statistical analysis, contribution of important intellectual content, manuscript preparation
Carole E Aubert, MD	University of Bern	Study design, contribution of important intellectual content, manuscript preparation
Chloe E Hill, MD MS	University of Michigan	Study design, contribution of important intellectual content, manuscript preparation
Zachary A Marcum, PharmD PhD	University of Washington	Study design, contribution of important intellectual content, manuscript preparation
James F Burke, MD MSc	University of Michigan	Study design, contribution of important intellectual content, manuscript preparation

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