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Polypharmacy composition and patient- and provider-related variation in patients with epilepsy

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ABSTRACT

Objective: To describe polypharmacy composition, and the degree to which patients versus providers contribute to variation in medication fills, in people with epilepsy.
Methods: We performed a retrospective study of Medicare beneficiaries with epilepsy (antiseizure medication plus diagnostic codes) in 2014 (N = 78,048). We described total number of medications and prescribers, and specific medications. Multilevel models evaluated the percentage of variation in two outcomes (1. number of medications per patient-provider dyad, and 2. whether a medication was filled within thirty days of a visit) due to patient-to-patient differences versus provider-to-provider differences.
Results: Patients filled a median of 12 (interquartile range [IQR] 8–17) medications, from median of 5 (IQR 3–7) prescribers. Twenty-two percent filled an opioid, and 61% filled at least three central nervous system medications. Levetiracetam was the most common medication (40%), followed by hydrocodone/acetaminophen (27%). The strongest predictor of medications per patient was Charlson comorbidity index (7.5 [95% confidence interval (CI) 7.2–7.8] additional medications for index 8+ versus 0). Provider-to-provider variation explained 36% of variation in number of medications per patient, whereas patient-to-patient variation explained only 2% of variation. Provider-to-provider variation explained 57% of variation in whether a patient filled a medication within 30 days of a visit, whereas patient-to-patient variation explained only 30% of variation.
Conclusion: Patients with epilepsy fill a large number of medications from a large number of providers, including high-risk medications. Variation in medication fills was substantially more related to provider-to-provider rather than patient-to-patient variation. The better understanding of drivers of high-prescribing practices may reduce avoidable medication-related harms.

1. Introduction

Approximately fifty percent of patients with epilepsy take at least five medications (polypharmacy) [1], which is three times higher than in the general population [2]. While such prescribing may be clinically appropriate, more medications also risk inappropriate prescribing [3], which is associated with adverse outcomes such as hospitalization and death [4,5]. Medication side effects may explain up to one-quarter of variation in quality of life in people with epilepsy [6], and central nervous-system (CNS) polypharmacy may be particularly harmful in an aging multimorbid population such as those with epilepsy exposed to cumulative CNS toxicity [7,8].

Little work has investigated overall medication regimen complexity in people with epilepsy. Prior cross-sectional work in the National Health and Nutrition Examination Study contained a relatively small sample size with only a limited number of older adults [1], and only limited additional data have described the composition of polypharmacy or CNS-active medications taken by patients with epilepsy outside of the US [9,10] or in selected

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privately insured US populations [11,12] without an existing large national study of polypharmacy in epilepsy in the US. Another key knowledge gap exists because only scarce prior work has explored drivers of polypharmacy, specifically the extent to which polypharmacy is driven by patient comorbidities as opposed to prescriber practice differences. Disentangling sources of variation would critically inform whether future interventions attempting to reduce polypharmacy-related harms should focus on high-risk patients versus high-prescribing providers.

In this study, we used a large national cohort enriched in older adults with robust prescribing provider information. We first described polypharmacy composition. We then calculated the percentage of variation in pharmacy fills due to patient-to-patient differences versus provider-to-provider differences.

2. Methods

2.1. Study design and dataset

This was a retrospective cohort study of people with epilepsy in fee-for-service Medicare in 2014. Medicare is the US's federal health insurance program for people age 65 and older in addition to younger people with disabilities or end-stage renal disease which covers inpatient and outpatient care as well as prescription drugs [13]. We obtained physician information from the 2013 American Medical Association (AMA) Masterfile which contains demographics and training information regarding 1,001,536 physicians.

2.2. Standard protocol approvals, registrations, and patient consents

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

2.3. Patient selection

Similar to prior work [14], we included patients with epilepsy, defined as filling at least one antiseizure medication (ASM), plus either of the following *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) at least one for epilepsy (345.xx), or 2) at least two for convulsions (780.3x) at least thirty days apart, in 2014. Recent work in Medicare [15] demonstrated good performance of combining ICD-9 codes plus ASM to identify patients with epilepsy (c-statistic 0.93, sensitivity 88%, and specificity 98%), and other recent investigations have used 2014 data given ICD-10 codes beginning in 2015 are less well validated [16,17]. 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 2012–2014 to allow a two-year lookback period (2012–2013) for baseline data. For our main analyses, we excluded those who died in 2014 because competing risk of death could underestimate prescribing patterns in the most ill patients. There was no age cutoff.

2.4. Variables

We described baseline variables related to polypharmacy [1,18]. Demographics included age, sex, race, rural ZIP code, reason for entitlement, and Medicaid dual eligibility. From 2013 claims, we calculated Charlson comorbidity index [19] and refractory epilepsy ($\geq$1 claim for refractory epilepsy: 345.01, 345.11, 345.41, 345.51, 345.61, 345.71, 345.81, 345.91). We determined established versus incident epilepsy according to whether an epilepsy or convulsion claim was present in 2012–2013. As the Masterfile does not contain a reliable field for epilepsy specialty, we counted whether a provider saw at least 25% of their E/M visits for a primary diagnosis of epilepsy.

We described medication fills using 2014 Part D data. We determined the number of unique medications per patient, defined polypharmacy according to commonly used thresholds of at least five or ten medications filled in 2014 [20,21], and displayed the most common medications. We described the most common ASMs, and specific categories (older generation: phenytoin, phenobarbital, valproic acid, carbamazepine; enzyme-inducing: phenytoin, phenobarbital, primidone, and carbamazepine). We determined whether patients filled: at least one opioid; medications known to lower the seizure threshold (tramadol [22,23] and bupropion [24,25]); or several drug–drug combinations with black box warnings from the US Food and Drug Administration (opioid-benzodiazepine [26]; opioid-gabapentinoid [27]). We defined CNS polypharmacy as at least three CNS-active medications, according to updated Beers criteria [28,29]. We summed the total number of days dispensed for all medications and for ASMs in particular, and assessed which specialties conducted the most E/M visits for patients with epilepsy compared with which specialties dispensed the greatest number of pill days to provide a broad understanding of prescribing in epilepsy.

Because there is no single accepted measure of prescribing variation, we used several complementary outcomes: (1) the number of unique medications a patient filled in 2014; (2) the number of unique medications each patient filled from each provider with whom they had at least one E/M visit in 2014; and (3) whether a patient filled a medication within thirty days of a visit, prescribed by that visit's provider.

2.5. Statistical analysis

We used three main models, which we refer to as: (1) the Patient Model, (2) the Patient-Provider Model, and (3) the Patient-Visit Model.

In the Patient Model, we determined the correlation between patient predictors with number of unique medications filled in 2014. This was a linear regression with a single row per patient. Patient predictors included the patient's age, race, sex, rural versus urban ZIP code, Medicaid dual eligibility, Charlson comorbidity index, number of ER visits in 2013, number of inpatient admissions in 2013, and reason for Medicare entitlement. There was no 'provider' information in this model.

In the Patient-Provider Model, we determined the correlation between patient and provider predictors with the number of medications filled per patient-provider dyad in 2014. This was a linear regression with a single row for each patient-provider dyad. Patient predictors were the same as in the Patient Model. Provider predictors included the provider's specialty (neurology, epilepsy, primary care physician [PCP], psychiatry), sex, decades since medical school graduation, rural practice location, D.O. versus M.D., whether they attended a top ten medical school per the 2014 US News and World Report rankings, whether their residency institution was a top ten medical school, whether they were trained in the US versus internationally, region of the US, and number of E/M visits for each patient-provider combination in 2014. In our primary analyses of the Patient-Provider Model and also the Patient-Visit Model (described next), we included only physician providers because only physicians are represented in the Masterfile.

In the Patient-Visit Model, we determined the correlation between the above predictors with whether a medication was filled from that provider within 30 days of a visit. This was a logistic regression with a single row per patient-visit.

We used the Patient-Provider Model and Patient-Visit Model to calculate the percentage of variation (the intraclass correlation coefficient [ICC]) in each outcome occurring at different levels [30]. One level was 'patients.' The 'patient ICC' should be interpreted as the percentage in each outcome attributable to patient-to-patient variation. Another level was 'providers.' The 'provider ICC' should be interpreted as the percentage in each outcome attributable to provider-to-provider variation. Formally,

$$\mathrm{ICC} = \frac{Between - group\ variance}{(Between - group\ variance) + (Within - group\ variance)}$$

where observations were 'grouped' by either patients ('patient ICC') or providers ('provider ICC') depending on the model. In other words, a high patient ICC would argue that variation in the outcome is primarily driven by some patients filling more medications than others from all of their providers, whereas a high provider ICC would instead argue that variation in the outcome is primarily driven by some providers filling more prescriptions than others for all of their patients. We first performed unadjusted analyses at the patient and then provider levels, then also adjusted for patient and then patient plus provider predictors (fully adjusted). We conducted various sensitivity analyses modifying the population (e.g. expanding to all providers including physician extenders, including those who died in 2014, restricting to only neurologists or PCPs) or the outcome (e.g., new medications not prescribed in 2013, or ASMs).

We then used the fully adjusted Patient-Provider Model and Patient-Visit Model to visually display patient-to-patient and provider-to-provider differences using 'caterpillar plots.' On the X-axis, patients or providers (depending on the plot) were ordered from lowest (left) to highest (right) for each predicted outcome (either average medications per dyad or probability of a medication fill within 30 days of visits depending on the plot). We generated four caterpillar plots – 1. Patient-Provider Model 'patients' 2. Patient-Provider Model 'providers,' 3. Patient-Visit Model 'providers', and 4. Patient-Visit Model 'patients.'

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

2.6. Data accessibility statement

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

3. Results

Our sample included 78,048 out of 11,550,386 (0.7%) Medicare beneficiaries (Supplemental Fig. 1). Table 1 describes our cohort.

Over the course of 2014, patients filled a median of 12 (interquartile range [IQR] 8–17) unique medications which included 4 (2–8) medications they had not been prescribed in the prior year, with a median of 33 (IQR 20–50) unique fill dates, from a median of 5 (IQR 3–7) unique prescribers. Table 2 lists additional characteristics regarding polypharmacy prevalence (90%) and composition. For example, after levetiracetam (40%), hydrocodone/acetaminophen was the second most common medication (27%), and 61% of the sample demonstrated CNS polypharmacy. Table 3 displays the most common specialties who conducted visits, and the percentage of all pill days dispensed from each specialty. For example, primary care conducted four times as many visits with patients with epilepsy compared with neurologists, yet dispensed a fairly similar amount of medications including ASMs (and even

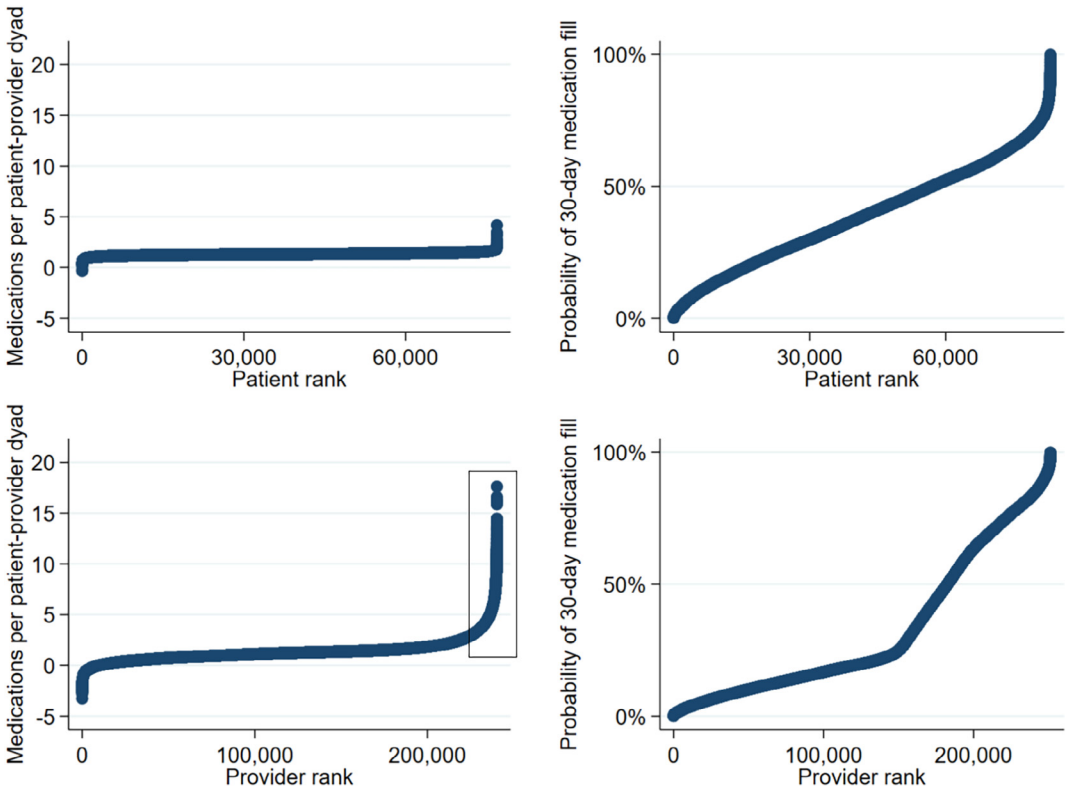

Fig. 1. Caterpillar plots for fully adjusted Patient-Provider Models (left) and Patient-Visit Models (right), by either patient (top) or provider (bottom). This ranks the predicted outcome for each group from lowest to highest to facilitate visual display of between-group variation. The box in the lower left plot is included in order to draw attention to a relatively small number of providers filling a relatively high number of medications across all of their patients. Note that while observed number of medications cannot be negative, predicted medications in a linear model could be negative as was the case for a small number of providers and patients in our models.

Table 1
Population description. $N = 78{,}048$.

		Median (Interquartile range) or No. (%)
Age		62 (50–75)
Female sex		41,971 (54%)
Race	White	61,447 (79%)
	Black	11,874 (15%)
	Hispanic	829 (1%)
	Other/Unknown	1,085 (1%)
	Asian	739 (1%)
	North American Native	662 (1%)
Dual eligible		51,114 (65%)
Rural ZIP code		22,638 (29%)
Reason for Medicare entitlement	Disability	40,709 (52%)
	Old age	36,383 (47%)
	Disability + ESRD[a]	662 (1%)
	ESRD[a]	294 (<1%)
Established epilepsy, 2012–2013		56,252 (72%)
Refractory epilepsy code, 2013		5,255 (7%)
Charlson comorbidity index, 2013	0	32,973 (42%)
	1–3	32,419 (42%)
	4–7	10,186 (13%)
	8+	2,470 (3%)
# ER[a] visits without inpatient admission, 2013		0 (0–2)
# inpatient admissions, 2013		0 (0–1)
# E/M[a] visits, 2014		13 (7–24)
Saw a neurologist, 2014		48,122 (62%)
Saw an epilepsy specialist, 2014		12,344 (16%)

[a] ESRD: end-stage renal disease; ER: Emergency Room; E/M: Evaluation and Management.

Table 2
Composition of polypharmacy.

		No. (%)
≥5 unique medications		70,339 (90%)
≥10 unique medications		49,437 (63%)
# ASMs[a]	1	36,779 (47%)
	2	24,888 (32%)
	3	11,339 (15%)
	4	3,738 (5%)
	5+	1,304 (2%)
Older generation ASM[a]		40,626 (52%)
Enzyme-inducing ASM[a]		30,675 (39%)
Opioid		16,865 (22%)
Benzodiazepine		28,260 (36%)
Opioid + benzodiazepine		9,126 (12%)
Opioid + (benzodiazepine or gabapentinoid)		11,946 (15%)
Bupropion		1,799 (2%)
Tramadol		9,265 (12%)
Gabapentinoid		17,484 (22%)
CNS polypharmacy[b]		47,940 (61%)
Top prescribed ASMs	Levetiracetam	31,321 (40%)
	Phenytoin	18,776 (24%)
	Valproate	15,723 (20%)
	Gabapentin	14,703 (19%)
	Lamotrigine	11,760 (15%)
	Carbamazepine	10,522 (13%)
	Clonazepam	9,685 (12%)
	Topiramate	7,599 (10%)
Top 10 medications	Levetiracetam	31,321 (40%)
	Hydrocodone/Acetaminophen	21,337 (27%)
	Phenytoin	18,776 (24%)
	Levothyroxine Sodium	17,107 (22%)
	Omeprazole	16,958 (22%)
	Valproate	15,723 (20%)
	Gabapentin	14,703 (19%)
	Lisinopril	13,782 (18%)
	Furosemide	13,072 (17%)
	Ciprofloxacin	12,743 (16%)

[a] ASM: antiseizure medication. Older generation included phenytoin, phenobarbital, valproic acid, and carbamazepine. Enzyme-inducing included phenytoin, phenobarbital, primidone, and carbamazepine.
[b] CNS: Central Nervous System. CNS polypharmacy: At least three CNS-active medications including ASMs, antipsychotic, benzodiazepine, non-benzodiazepine benzodiazepine receptor agonist, tricyclic antidepressant, selective serotonin reuptake inhibitor, selective serotonin-norepinephrine reuptake inhibitor, and opioids, as defined in Beers criteria [28].

more newly started ASMs) compared with neurologists. Twenty-three percent of all pill days dispensed were for ASMs. Supplemental Table 1 lists the percent of all E/M visits attributed to each specialty according to Medicare (not the Masterfile).

Table 4 presents associations from our three main models. All values are adjusted for all other predictors with values in that column.

In the Patient Model ($N = 77{,}607$), the strongest predictor of number of medications per patient was Charlson comorbidity index (7.5 (95% confidence interval [CI] 7.2–7.8) additional unique medications for a Charlson comorbidity index of 8+ compared with a Charlson comorbidity index of 0), and age had a quadratic relationship (predicted ~ 10.5 at age extremes, peaking at 13.8 at age ~ 50). Including those who died in 2014 ($N_{total} = 83{,}795$) lead to nearly identical coefficients.

In the Patient-Provider Model ($N = 576{,}224$ patient-physician dyads including 76,951 patients and 240,248 physicians), the strongest adjusted predictor was the number of visits per dyad (6.1 (95% CI 6.0–6.2) additional medications for 20 + visits compared with only 1 visit).

In the Patient-Visit Model ($N = 1{,}241{,}678$ visits including 76,951 patients and 240,248 physicians), again total number of visits per patient-provider dyad was the strongest adjusted predictor of a 30-day prescription (OR 11.9, 95% CI 11.2–12.7 for 20 + visits versus 1 visit), and visit with a psychiatrist was the next strongest predictor (OR 5.4, 95% CI 5.1–5.7).

Table 5 presents ICCs for each multilevel model (Patient-Provider Model, and Patient-Visit Model) at each level (patient, or provider). For the Patient-Provider Model, patient ICCs were 1% in an unadjusted model, 1% after adjusting for patient characteristics, and 2% after adjusting for patient plus provider characteristics. Provider ICCs were 48% in the unadjusted model, 48% after adjusting for patient characteristics, and 36% after adjusting for patient plus provider characteristics. In sensitivity analyses (Supplemental Table 2a), the only meaningful difference occurred when restricting to only neurologist visits; patient and provider ICCs became more similar (11 and 12%, respectively).

For the Patient-Visit Model, patient ICCs were 35% in the unadjusted model, 28% after adjusting for patient characteristics, and 30% after adjusting for patient plus provider characteristics. Provider ICCs were 69% in the unadjusted model, 66% after adjusting for patient characteristics, and 57% after adjusting for patient plus provider characteristics. In sensitivity analyses (Supplemental Table 2b), meaningful difference occurred when modifying the outcome to new ASM fills (provider ICC 69%, patient ICC 62%) or when restricting to neurologist visits and ASM fills (provider ICC 23%, patient ICC 65%).

Caterpillar plots (Fig. 1) illustrated patient-to-patient and provider-to-provider variation, for either adjusted predicted number of medications per dyad (Patient-Provider Model) or probability of a 30-day medication fill (Patient-Visit Model). Notably, the bottom left plot (Patient-Provider Model, providers ranked from lowest to highest number of average number of medications they prescribe for their patients) demonstrated a small number of relatively high outlying providers (denoted by the box). Note a small number of providers with negative predictions in this plot, due

Table 3
Visits and fills by specialty.

	% of all E/M[a] visits (*N* = 1,628,907)	% of all E/M visits for primary diagnosis of epilepsy (*N* = 155,352)	% of all medication day supply	% of all ASM[a] day supply	% of all new ASM day supply[b]
PCP[c]	43%	28%	67%	47%	47%
Neurologist	10%	60%	13%	43%	39%
Epilepsy specialist	2%	17%	4%	15%	10%
Psychiatrist	6%	1%	8%	7%	7%

[a] E/M: Evaluation/Management. ASM: Antiseizure medication.
[b] Did not fill an ASM in 2013 but did in 2014. Note all columns do not add up to exactly 100% because these are only the most common but not all specialties who patients with epilepsy, and it could be possible that a physician is attributed to more than one specialty in the Masterfile.
[c] PCP: Primary care physician. PCP was defined according to the Masterfile as family medicine, general practice, internal medicine, or geriatrics.

Table 4
Regression results. All numbers are adjusted for all variables listed in the column.

		Patient Model[a]	Patient-Provider Model[a]	Patient-Visit Model[a]
Patient predictors (95% confidence interval)				
Age		See text	See text	See text
Race	White	reference	reference	reference
	Black	**−1.7 (−1.8 to −1.6)**	**−0.1 (−0.1 to −0.1)**	**0.8 (0.8–0.8)**
	Asian	**−0.9 (−1.4 to −0.5)**	0.0 (0.0 to 0.1)	**1.1 (1.0–1.2)**
	Hispanic	**−0.7 (−1.0 to −0.5)**	0.0 (−0.0 to 0.1)	**1.1 (1.0–1.1)**
Female		**2.0 (1.9 to 2.1)**	**0.1 (0.1 to 0.1)**	**1.2 (1.2–1.2)**
Rural		**0.6 (0.5 to 0.7)**	**−0.0 (−0.1 to −0.0)**	**1.0 (0.9–1.0)**
Dual		**1.8 (1.7 to 1.9)**	0.0 (0.0 to 0.0)	**0.8 (0.7–0.8)**
Established epilepsy, 2012–2013		**−0.9 (−1.0 to −0.8)**	**0.0 (0.0 to 0.1)**	**1.1 (1.1–1.1)**
Refractory epilepsy, 2013		**−0.5 (−0.7 to −0.3)**	**−0.0 (−0.0 to −0.0)**	**1.0 (1.0 to 1.1)**
Charlson category, 2013	0	reference	Reference	reference
	1–3	**4.1 (4.0 to 4.2)**	**0.1 (0.1 to 0.1)**	**0.9 (0.9–0.9)**
	4–7	**7.1 (7.0 to 7.3)**	**0.1 (0.1 to 0.1)**	**0.8 (0.8–0.8)**
	8+	**7.5 (7.2 to 7.8)**	**0.1 (0.1 to 0.1)**	**0.8 (0.7–0.8)**
# ER[b] visits, 2013		**0.3 (0.3 to 0.3)**	**0.0 (0.0 to 0.0)**	**1.0 (1.0–1.0)**
# admissions, 2013		**1.7 (1.7 to 1.7)**	**−0.1 (−0.1 to −0.1)**	**0.8 (0.8–0.8)**
Entitlement reason	Age	reference	Reference	reference
	Disability	**0.2 (0.1 to 0.4)**	**0.0 (0.0 to 0.1)**	**1.1 (1.0–1.1)**
	ESRD[b]	**−1.5 (−2.3 to −0.8)**	−0.0 (−0.1 to 0.0)	**0.9 (0.8–1.0)**
	Disability +ESRD[b]	**−1.3 (−1.8 to −0.7)**	**−0.2 (−0.2 to −0.1)**	**0.8 (0.8–0.9)**
Visit for principal diagnosis of epilepsy		–	–	**1.1 (1.1–1.2)**
Provider predictors (95% confidence interval)				
Neurologist		**−0.1 (−0.2 to −0.0)**	**0.2 (0.2 to 0.3)**	**2.9 (2.8–3.1)**
Epilepsy specialist		**−0.0 (−0.6 to 0.6)**	**0.4 (0.3 to 0.5)**	**1.7 (1.5–2.0)**
Primary care provider		-	**1.4 (1.4 to 1.4)**	**3.7 (3.6–3.8)**
Psychiatrist		-	**0.7 (0.6 to 0.7)**	**5.4 (5.1–5.7)**
Female		-	**0.1 (0.1 to 0.2)**	**1.2 (1.2–1.3)**
Decades since medical school graduation		-	**0.1 (0.1 to 0.1)**	**1.2 (1.2–1.2)**
Rural		-	**0.7 (0.6 to 0.7)**	**1.9 (1.8–1.9)**
D.O. [b]		-	**0.2 (0.2 to 0.2)**	**1.3 (1.3–1.4)**
Top 10 medical school		–	**−0.2 (−0.2 to −0.1)**	**0.8 (0.7–0.8)**
Top 10 medical school for residency		–	**−0.1 (−0.2 to −0.1)**	**0.8 (0.7–0.8)**
US trained		–	**0.2 (0.2 to 0.2)**	**1.3 (1.3–1.3)**
Region	Northeast	–	reference	reference
	Midwest	–	**0.3 (0.3 to 0.3)**	**1.4 (1.4–1.5)**
	South	–	**0.3 (0.3 to 0.3)**	**1.5 (1.5–1.6)**
	West	–	**0.2 (0.1 to 0.2)**	**1.3 (1.3–1.4)**
Number E/M[b] visits this patient-provider combo	1	–	reference	reference
	2–4	–	**1.0 (1.0–1.0)**	**3.0 (2.9–3.0)**
	5–19	–	**3.7 (3.7–3.7)**	**8.3 (8.1–8.4)**
	20+	–	**6.1 (6.0–6.2)**	**11.9 (11.2–12.7)**

[a]Patient Model: Single level linear model with one row per patient, the linear outcome is number of unique prescriptions per patient in 2014, and no random intercept. *N* = 77,607 patients. Interpretation of each number: the absolute increase in number of unique medications per patient, for each 1-unit increase in predictor (or compared to reference category), adjusted for all other variables listed in the column. Note 'neurologist' and 'epilepsy specialist' refer to whether a patient saw at least one such provider for an E/M visit in the year. In contrast, in Models 2 and 3 these variables refer to the particular provider in a dyad or visit.
[a]Patient-Provider Model: Multilevel linear model with one row per patient-provider combination, and the outcome is number of unique prescriptions per patient filled from that provider in 2014. *N* = 576,224 patient-provider combinations, including 76,951 patients and 240,248 providers. Interpretation of each number: the absolute increase in number of unique medications per patient-provider dyad, for each 1-unit increase in predictor (or compared to reference category), adjusted for all other variables listed in the column.
[a]Patient-Visit Model: Multilevel logistic model with one row per patient-visit, the outcome is whether a script was filled from that provider for that patient within 30 days of a visit, and random intercept for provider. *N* = 1,241,678 patient-visits, including 76,951 patients and 240,248 providers. Interpretation of each number: the odds ratio of a 30-day medication fill from that provider for that patient, for each 1-unit increase in predictor (or compared to reference category), adjusted for all other variables listed in the column.
[b]ER: Emergency Room; ESRD: end-stage renal disease; D.O: Doctor of Osteopathy; E/M: Evaluation/Management

Table 5
Intraclass correlation coefficients (ICC) from multilevel models. For example, this suggests that 36% of adjusted variation in medications per patient-provider dyad was explained by provider-to-provider differences, whereas only 2% of adjusted variation in medications per patient-provider dyad was explained by patient-to-patient differences.

Level	Covariates	Intraclass correlation coefficient[a]	
		Patient-Provider Model	Patient-Visit Model
Patient	Unadjusted	1%	35%
	Patient characteristics only	1%	28%
	Patient and provider characteristics	2%	30%
Provider	Unadjusted	48%	69%
	Patient characteristics only	48%	66%
	Patient and provider characteristics	36%	57%

[a]An intraclass correlation coefficient (ICC) represents the percentage of total variation in the outcome explained by variation at a particular level, remaining after adjusting for covariates.

to the fact that in a linear model it is possible to have negative predictions.

4. Discussion

In this study, we described the composition of polypharmacy in Medicare beneficiaries with epilepsy, in addition to the degree to which variation in medication fills is related to patient versus provider sources of variation. We found that 90% met criteria for polypharmacy (at least five unique medications), of which ASMs themselves represented only about one-quarter of all pill days. CNS polypharmacy was common (61%) including the striking finding that the second most common medication contained an opioid. Neurologists provided only 10% of E/M visits and prescribed only 13% of all days dispensed, and in fact non-neurologists dispensed more than half of all ASM supply. Whereas patient factors did predict medication fills (e.g. age, comorbidities), we found that provider differences explained 57% of total variation whereas patient differences explained only 35% of variation in whether a post-visit prescription fill occurred, and provider differences explained 36% of total variation whereas patient differences explained only 2% of variation in medications per patient-provider dyad. This was even after adjusting for a large number of elements related to patient demographics and comorbidities and physician demographics and training. These results suggest that a large degree of prescribing variation is driven by an individual physician's practice, rather than clearly defined differences in measured patient severity or physician specialty or training background.

While these data do not inform the degree to which any single medication is appropriate, literature in general documents that 20% of prescriptions to older patients may be inappropriate [3], most Medicare beneficiaries would like to reduce their number of medications if possible [31], and 100,000 ER visits occur each year in the US in adults >65 years due to adverse drug effect [32]. Our finding that 90% demonstrated polypharmacy is considerably higher than the overall Medicare population where about half demonstrate polypharmacy [33]. Our findings therefore underscore the likelihood that deprescribing may improve health outcomes.

Our finding that hydrocodone/acetaminophen was the second most common medication is particularly concerning. Patients with epilepsy demonstrate three to five times increased medication self-poisoning especially opioids and psychotropic medications compared with populations without epilepsy [34], and there isa physician's role in increasing opioid dependence beyond patient characteristics [35]. We found an even higher proportion of patients filling opioids (22%) and having CNS polypharmacy (61%) in Medicare compared with our prior work (16% and 34% respectively) in a nationally representative population including more younger patients [1], which is problematic given older patients are particularly prone to adverse effects from accumulating CNS polypharmacy. Similarly, the high prevalence of older generation or enzyme-inducing ASMs elevates potential risk of a host of potential outcomes such as cognitive dysfunction [36], drug–drug interactions, and hyperlipidemia [37,38]. Within the context of a patient population with heightened physical, psychosocial, and cognitive disability [39], a median of 12 (90th percentile 24) unique medications from a median of 5 (90th percentile 10) different prescribers underscores the serious burden of pharmacotherapy.

We did find that certain provider factors were associated with increased number or chance of medication fills. For example, seeing a psychiatrist resulted in a 5.4-fold increased odds of a post-visit prescription fill whereas seeing a neurologist resulted in only a 2.9-fold increased odds, and the number of visits with a given provider was the strongest predictor of medication fills. These provider factors far outweighed the magnitude of associations between medication fills per dyad and patient characteristics (e.g. race, sex, comorbidities, etc.).

Still, adjusting for extensive patient and physician factors explained away only a small amount of variation. This could suggest that we omitted certain important patient characteristics. However, no study can capture all possible conditions for which medications might be prescribed, and Medicare data do not contain seizure characteristics like semiology or frequency which could influence ASM prescribing. Our data nonetheless suggest the presence of "high versus low prescribing" providers; the Patient-Provider caterpillar plot especially identifies a small number of providers filling a substantially larger number of medications than all others (Fig. 1, box), which was not explained away by adjusting for factors like physician training, physician specialty, or both physician and patient demographics. It is known that patients fall into certain categories including "medical maximizers" whereas others are "medical minimizers" [40] which critically influences the degree of healthcare over- versus under-use. Likewise, we provide hypothesis-generating exploratory data here that physicians may fall into a similar continuum, where the belief structure of each prescribing physician influences different prescribing thresholds independent of all other variables or demographics/training characteristics per se. High outlier prescribing practices have key implications regarding practices such as audit-feedback mechanisms which can reduce extreme prescribing [41].

In interpreting our results, we considered that high within-provider clustering could simply be due to the fact that some specialties tend to treat with medications whereas others (i.e. surgeons) tend to treat with non-medication routes. However, this was not actually the predominant explanation for our findings. Table 3 and Supplemental Table 1 demonstrate that the majority of visits in this sample were for medical specialties, and ICCs remained largely unchanged when restricting to PCPs.

While most sensitivity analyses modifying the outcome or population made little substantive difference, restricting analysis to neurologists or ASMs did reduce the amount of variation attributable to the provider level. There may be more patient-to-patient variation in epilepsy severity for those who see neurologists given they may have either mild or severe epilepsy, whereas there might be less patient-to-patient variation in epilepsy severity if those with milder disease tend to not seek ongoing expert services. More patient-to-patient variation would decrease the provider ICC when restricting to neurologist visits. Regardless, identifying outlier prescribing patterns was not as simple as stratifying by specialty, as provider-to-provider differences still explained 36% (Patient-

Provider Model) to 57% (Patient-Visit Model) of variation in medication fills after adjusting for specialty. Furthermore, neurologists accounted for only 10% of all visits, only 43% of all ASM day supply, and only 13% of all medication supply, which all emphasizes the importance of engaging non-neurologist stakeholders when addressing determinants of polypharmacy in patients with epilepsy. Interestingly, sensitivity analyses restricting to PCPs did not meaningfully reduce provider ICCs which suggests there remain large PCP-to-PCP differences in number of medication fills per patient even after accounting for patient comorbidities.

The most similar study to our own that we are aware of [33] included all Medicare beneficiaries and found a large influence of patient comorbidity count on the maximal number of medications in a year, but also small absolute effects (all <0.4) of a limited number of primary care provider characteristics (sex, years since medical school, patient volume, primary care specialty). Their study was unique in that they, like us, attempted to disentangle the effect of patient comorbidities versus provider practices on medication count within nested models. Our study had advantages though – we addressed likely otherwise extensive confounding by restricting our population to those with epilepsy rather than the entirety of Medicare, we included more robust physician data via the Masterfile rather than the more limited Medicare Data on Provider Practice and Specialty, we assessed variation both at the patient and physician levels of clustering (not just the physician level), and we explicitly modeled ICCs to quantify within-cluster variation rather than simply using multilevel modeling as a mechanism to correct standard errors to calculate coefficients.

Our work has several limitations. First, residual confounding likely exists given it is not possible to account for all possible comorbidities for which medications are prescribed which may explain a portion of remaining provider-to-provider variation. Further variation could also occur at levels not considered here, such as different degrees of pharmacist involvement which is relevant given pharmacists likely play a key role in combating polypharmacy [42–44]. Still, we adjusted for several key patient factors such as refractory epilepsy, Charlson comorbidity index, and age, which likely explains a large amount of patient-to-patient variation in comorbidities and medication indications. Specifically, the Charlson comorbidity index spans a wide range of organ systems including cardiovascular, pulmonary, rheumatologic, endocrine, infectious, malignant, gastric, hepatic, renal, and neurologic disease. Second, misclassification may exist. We cannot be certain regarding how much of a filled prescription a patient actually took, Medicare captures medications only after they are filled (not just prescribed), and does not capture aspects of medication regimen complexity such as frequency or route of dosing [45]. Third, there are important remaining outcomes which our study did not address. For example, drug–drug interactions are common in people with epilepsy [9,46] though were beyond the scope of the current study, and detailed description of drug–drug interactions in people with epilepsy in Medicare could be the focus of future investigation. Fourth, results from the older and disabled Medicare population in 2014 may not completely generalize to non-Medicare or more recent populations. Though, this is a quite relevant population given patients with epilepsy have three-fold increased disability compared to people without epilepsy [39], epilepsy incidence is highest in older age [47], and our studied medications remain in widespread clinical use in more recent years [1,48].

5. Conclusions

Patients with epilepsy experience intense medication burden in terms of number and type of medications including opioids and central nervous system polypharmacy. Only a minority of visits and prescriptions were prescribed by neurologists, and more ASM (and even new ASM) pills were prescribed by PCPs than by neurologists, thus neurologist and non-neurologist stakeholders are both key to understanding drivers of polypharmacy in patients with epilepsy. Variation in prescribing was substantially more so related to prescriber-to-prescriber rather than patient-to-patient variation even after accounting for a large array of patient and provider covariates. This may have key implications regarding mechanisms such as audit-feedback which can reduce extreme prescribing, or at least encourages future work exploring drivers of differences in physician prescribing patterns as a potential major lever toward maximizing prescribing appropriateness for people with epilepsy.

Author contributions

Dr Terman contributed to hypothesis generation, study design, data collection, statistical analysis, and manuscript preparation. All other authors contributed to study design and manuscript preparation and editing.

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Declaration of competing interests

The authors have no competing interest to disclose.

Declaration of interests

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2021.108428.

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