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ORIGINAL RESEARCH

Impact of Formulary Restrictions on Antiepileptic Drug Dispensation Outcomes

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ABSTRACT

Introduction: The aim of this analysis was to assess the relationship between formulary restrictions and antiepileptic drug (AED) dispensation in patients with focal seizure (FS).
Study Design: A retrospective cohort analysis was conducted using data from Symphony Health's Integrated Dataverse® (1 April 2015–30 June 2018).
Methods: This study included two patient populations: the overall patient population (N = 54,097) and a pediatric population (< 18 years) (N = 12,610). Cohorts were defined based on approval or rejection of the index AED claim. Study outcomes were prescription life cycle analysis, proportion of patients with dispensation, time to dispensation, and likelihood of successful dispensation. A multivariable Cox proportional hazards model was estimated to study the association between formulary restriction and likelihood of successful AED dispensation.
Results: Among patients in the overall population with a rejected claim (n = 9133), 8.0% did not receive any AED and 77.6% received approval for the index AED following an appeal. Among the pediatric patients with a rejected claim (n = 3081), 6.0% did not receive any AED and 81.7% received approval for the index AED after an appeal. In both populations, formulary restrictions were associated with significant delays in index AED dispensation (6.9 and 5.3 days, respectively; $P < 0.0001$ for each population), compared to approved AED claims. In the overall and pediatric populations, formulary-related rejections of AEDs were associated with a 35% (hazard ratio [HR] 0.65; 95% confidence interval [CI] 0.64–0.66; $P < 0.0001$) and 27% (HR 0.73; 95% CI 0.69–0.76; $P < 0.0001$) lower likelihood of successful dispensation of the index AED, respectively.
Conclusions: Formulary restrictions of AEDs were associated with significant delays in treatment and significantly lower likelihood of successful AED dispensation in patients with FS.

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PLAIN LANGUAGE SUMMARY

Formulary restrictions on antiepileptic drugs (AEDs) are adopted by payers in the USA to

guide the use of therapies and contain the costs of care. However, formulary restrictions on AEDs are inconsistent with the American Epilepsy Society position statement that indicates patients with epilepsy must have unrestricted access to all AEDs. This retrospective cohort analysis of open-source claims data assessed the effects of formulary restrictions on AED dispensation in patients with focal seizure (FS). Findings showed that formulary-related rejections of AED claims were associated with significant delays in treatment initiation and a significantly lower likelihood of successful AED dispensation. The treatment delays associated with formulary restrictions on AEDs may have a negative clinical and economic impact on patients with epilepsy and the healthcare system. Approximately 80% of rejected initial claims were reversed after an appeal. Claim denials and appeals represent an unnecessary administrative burden on physicians' practices. Further studies are required to identify the patient, physician, or payer factors that drive the delay in access to AEDs among patients with FS.

Keywords: Antiepileptic drug; Dispensation; Focal seizure; Formulary restriction; Treatment delay

Key Summary Points

Why carry out this study?

Healthcare payers in the USA have instituted restrictive formulary access to antiepileptic drugs (AEDs) to contain costs of care.

Formulary restrictions may be associated with negative patient outcomes and additional burden to the healthcare system.

How do formulary restrictions impact dispensation outcomes for AEDs?

What was learned from the study?

Formulary restrictions were associated with significant delays in treatment initiation and a significantly lower likelihood of successful AED dispensation among patients with focal seizures.

The results from the study suggest formulary restrictions on AEDs may represent a burden to patients and healthcare systems due to delays in treatment initiation, missed doses, and medication abandonment.

INTRODUCTION

Epilepsy is one of the most common neurological disorders in the USA, affecting an estimated 3.4 million people, including 470,000 children [1–3]. Epilepsy is characterized by spontaneous, recurrent seizures, with focal seizure (FS) comprising approximately 60% of all epilepsy cases [4–7]. Antiepileptic drugs (AEDs) are the mainstay of epilepsy treatment.

Healthcare payers in the USA, both commercial and government, have instituted restrictive formulary access across many drug classes, including AEDs, to contain costs of care [8, 9]. These restrictions are implemented through prior authorization (PA; including step therapy, sometimes known as fail first policy), cost sharing, quantity limits, and preferred drug lists (PDLs) [9]. Formulary restrictions have reduced medication expenditures in the therapies they target; however, prior studies suggest that these restrictions are associated with negative patient outcomes and additional burden to the healthcare system, in part due to delays in treatment initiation, missed doses, and medication abandonment [10–12]. These unintended consequences of formulary restrictions may be of particular concern for patients with refractory FS who have increased mortality, experience greater rates of neuropsychiatric

comorbidities, and have a reduced health-related quality of life compared to patients who have achieved seizure control [13–15]. Limiting access to AEDs has been shown to result in more frequent and potentially injurious or even fatal seizures and increased healthcare utilization among patients with epilepsy [16, 17].

Epilepsy is a heterogeneous disease that necessitates access to a variety of rational therapy options to tailor treatment according to seizure type, adverse-effect profile, patient-specific features, and comorbidities [18]. Restricting access to AEDs conflicts with the need for an open formulary with numerous therapeutic options that allow the treating physician to consider individual patient characteristics when selecting an AED [8]. Limiting the availability of AEDs is also inconsistent with the American Epilepsy Society (AES) position statement on access to epilepsy care [19]. The AES emphasizes that all AEDs must be available to patients with epilepsy without formulary restrictions [19].

Although some reports have documented negative consequences of formulary restrictions in epilepsy, little is known about the association between formulary restrictions and dispensation-related outcomes for AEDs [16, 17]. This retrospective study of data from a unique database allowed access to a large patient population, as compared to other studies of formulary restrictions of AEDs, permitting an examination of the entire AED prescription life cycle. The objective of the analysis was to assess the relationship between formulary restrictions of AEDs in patients with FS and: (1) AED prescription life cycle; (2) proportion of patients with successful dispensation and time to AED dispensation; and (3) likelihood of successful AED dispensation.

METHODS

Study Design and Data Source

This was a retrospective cohort analysis of open-source claims data assessing formulary access restrictions at the individual patient level (Fig. 1). The study utilized Symphony Health's Integrated Dataverse (IDV®) database, a longitudinal patient data source that tracks 274 million active patients in the USA. The Symphony Health IDV® database captures the full life cycle of a pharmacy claim, from initial prescription submission to final dispensation, and covers all payment types, including commercial plans, Medicare Part D, cash, assistance programs, and Medicaid. At total of 39 months of open source claims data from 1 April 2015 through to 30 June 2018 were licensed from Symphony Health Solutions (Phoenix, AZ, USA). The data were de-identified in compliance with the US Health Insurance Portability and Accountability Act; therefore, review by an institutional review board was not required for this study. The study period was from 1 April 2015 through to 30 June 2018.

Study Population

The study included two populations: the overall population (patients of all ages) and the pediatric population (patients among the overall population aged < 18 years). Patients were included in the analyses if they met the following criteria: (1) residence in the USA; (2) diagnosis of FS (International Classification of Diseases, 9th Revision [ICD-9], Clinical Modification codes 345.4× or 345.5× or ICD-10 codes G40.1× or G40.2×); (3) ≥ 1 pharmacy claim for any AED approved in the USA [20]; (4) first AED pharmacy claim approved or rejected for a formulary-related reason and coded as a new prescription; (5) no diagnosis of active pregnancy in the 6 months prior to the first AED pharmacy claim; and (6) ≥ 6 months of pharmacy data prior to and following the index date.

Eligible patients in the overall and pediatric populations were each assigned to study cohorts based on the approval or rejection status of their index AED claim. Patients were classified into the 'approved' cohort if their index AED claim was approved. The 'rejected' cohort consisted of patients who had a rejected claim for an index AED attributable to a formulary restriction. Pharmacy claim approval status (i.e., approved, rejected, reversed) and rejection justification were extracted from the dataset. The index date was defined as the earliest AED pharmacy claim

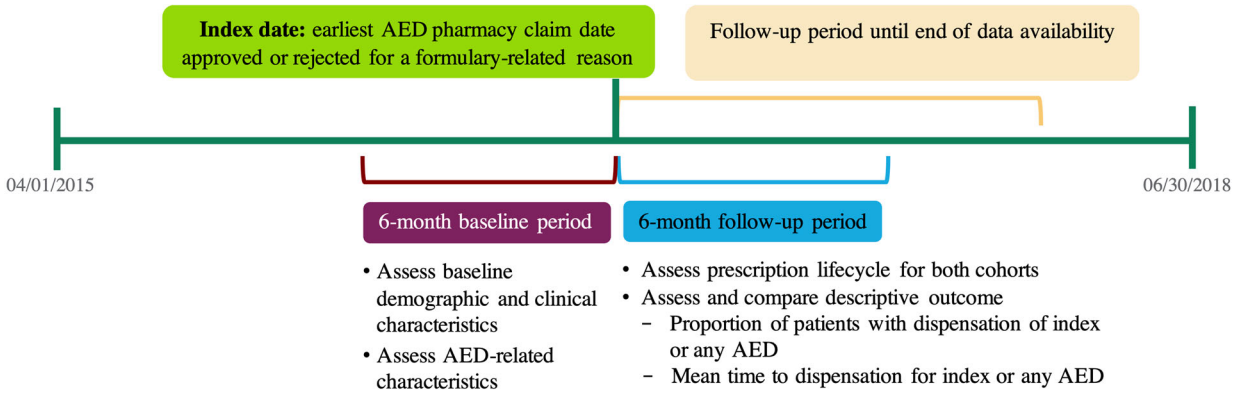

Fig. 1 Flow diagram of study design. *AED* Antiepileptic drug

date that was approved or rejected for a formulary-related reason. For patients in the approved claim cohort, the index date was the date the prescription was filled at the pharmacy by the patient. For the subset of patients in the approved cohort who abandoned their prescription, the index date was defined as the date the pharmacy reversed the claim (i.e., return-to-stock). For patients in the rejected claim cohort, the index date was the date their pharmacy claim was rejected by the payer. The study included a 6-month baseline period prior to the index date and a 6-month follow-up period after the index date.

Study Measures and Statistical Analyses

Baseline Characteristics

During the 6-month baseline period, patient demographic and clinical characteristics were measured, including gender, age, payer type, Charlson Comorbidity Index (CCI), and baseline total charges. AED-related characteristics were recorded on the index date, and included the number of index AED claims (1 or multiple), AED type (branded and/or generic), and expected patient copay.

Study Outcomes

Three outcomes were studied for the index AED, and a sensitivity analysis was conducted for any AED.

AED prescription life cycle During the 6-month follow-up period, claims were tracked from initial AED prescription to final dispensation or abandonment. Abandonment, defined as a reversal of the initial approved claim with no subsequent dispensation during the follow-up period, was studied for patients in both cohorts. In the rejected claim cohort, rates of appeal of initial rejections and appeals for new AEDs were assessed. Rates of appeal approvals, appeal rejections, and subsequent reversals of appeal rejections of AED prescription claims were also evaluated (see Electronic Supplementary Material [ESM] Table Sl for an overview of processing of prescriptions in the USA).

Proportions of patients with successful AED dispensation and time to first AED dispensation The proportions of patients with dispensation of their index AED or any AED were calculated and compared across the cohorts using Chi-square tests. Mean times to first dispensation of index AED or any AED were analyzed and compared across the cohorts using *t* tests.

Likelihood of successful AED dispensation A multivariable Cox proportional hazards model was estimated to study the association between formulary restriction and the likelihood of successful AED dispensation from the index date until the end of data availability. Time to dispensation of the index AED and any AED were assessed as outcomes in two separate models. Patients were censored at the end of data

availability. Covariates in the model included: baseline demographics (age, gender, payer), clinical characteristics (comorbidities), patient expected copay, AED characteristics (generic vs. branded AEDs; single vs. multiple AEDs), and baseline healthcare costs. Hazard ratios (HRs) were estimated for successful AED dispensation. Dollar values of charges were inflated to 2018 US dollars using the US gross domestic product price index [21, 22].

Statistical Analyses

Statistical analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC, USA). Two-sided statistical tests were used, and $P < 0.05$ was considered significant.

RESULTS

Baseline Characteristics

The overall population included 54,097 patients, with 44,964 patients in the approved claim cohort and 9133 patients in the rejected claim cohort (ESM Fig. S1). Compared to patients in the approved claim cohort, those in the rejected claim cohort were younger (34.0 vs. 44.3 years; $P < 0.0001$) and more likely to be enrolled in a Medicaid plan (45.1% vs. 24.0%; $P < 0.0001$), and had a lower comorbidity burden (63.7% vs. 52.7% with zero CCI conditions; $P < 0.0001$). Patients in the rejected claim cohort were prescribed multiple AEDs on the index date more frequently (19.1% vs. 6.5%; $P < 0.0001$) and had more claims for branded AEDs (14.1% vs. 5.4%; $P < 0.0001$) compared to the approved claim cohort (Table 1).

The pediatric population included 12,610 patients, with 9529 in the approved claim cohort and 3081 patients in the rejected claim cohort (ESM Fig. S1). Patients in the rejected claim cohort were younger (7.5% vs. 8.2 years; $P < 0.0001$) and more likely to be enrolled in a Medicaid plan (64.4% vs. 50.3%; $P < 0.0001$) than patients in the approved claim cohort. Compared to patients in the approved claim cohort, those in the rejected claim cohort were prescribed multiple AEDs on the index date more frequently (16.0% vs. 3.5%; $P < 0.0001$), had more claims for branded AEDs (6.7% vs. 3.0%; $P < 0.0001$), and had higher baseline total charges (all $P < 0.0001$) (Table 1).

AED Prescription Life Cycle

Among the 44,964 patients in the overall population's approved claim cohort, the rates of prescription abandonment for index AED and any AED were 8.3% and 4.0%, respectively. Of the 9133 patients in the rejected claim cohort, 7087 (77.6%) received approval for the index AED after one formulary-related rejection, 955 (10.5%) received approval for a new AED, and 359 (3.9%) received approval of an AED after multiple formulary-related rejections (Fig. 2a). Appeals were never reversed for 262 patients (2.9%), and 470 patients (5.1%) never appealed the rejection. Of all patients, 732 (8.0%) did not receive their index or any AED due to formulary-related restrictions.

Among the 9529 patients in the pediatric population's approved claim cohort, the rates of prescription abandonment for index and any AED were 7.2% and 2.8%, respectively. Of the 3081 patients in the rejected claim cohort, 2516 (81.7%) received approval for the index AED after one formulary-related rejection, 284 (9.2%) received approval for a new AED, and 97 (3.1%) received approval of an AED after multiple formulary-related rejections (Fig. 2b). Appeals were never reversed for 67 patients (2.2%), and 117 patients (3.8%) never appealed the rejection. 184 (6.0%) patients did not receive their index or any AED due to formulary-related restrictions.

Proportions of Patients with Successful AED Dispensation and Time to First AED Dispensation

In the overall population, a significantly greater proportion of patients in the approved claim cohort compared to those in the rejected claim cohort had a successful dispensation of an index AED (91.7% vs. 70.1%; $P < 0.0001$) (Fig. 3a) or any AED (96.0% vs. 87.8%; $P < 0.0001$) (ESM Fig. S2a) at 6 months from the initial prescription date. Mean (standard deviation [SD]) time

Table 1 Baseline demographics and clinical characteristics of the patient populations

Characteristic	Overall patient population (N = 54,097)			Pediatric patient population (N = 12,610)		
	Approved (n = 44,964)	Rejected (n = 9133)	P value	Approved (n = 9529)	Rejected (n = 3081)	P value
Male, n (%)[a]	21,567 (48.0)	4432 (48.5)	0.33	5314 (55.8)	1707 (55.4)	0.7247
Age (years)						
Mean (SD)[b]	44.3 (24.8)	34.0 (23.8)	< 0.0001	8.2 (5.1)	7.5 (5.0)	<0.0001
0–3, n (%)				2478 (26.0)	943 (30.6)	<0.0001
4–7, n (%)				2403 (25.2)	861 (28.0)	0.0027
8–11, n (%)				2153 (22.6)	609 (19.8)	0.0010
12–17, n (%)				2495 (26.2)	668 (21.7)	<0.0001
0–17, n (%)	9529 (21.2)	3081 (33.7)	< 0.0001			
18–39, n (%)	9080 (20.2)	2273 (24.9)	< 0.0001			
40–64, n (%)	14,473 (32.2)	2713 (29.7)	< 0.0001			
65+, n (%)	11,882 (26.4)	1066 (11.7)	< 0.0001			
Index AED claims, n (%)						
1 AED claim	42,023 (93.5)	7385 (80.9)	< 0.0001	9194 (96.5)	2587 (84.0)	<0.0001
≥ 2 AED claims	2941 (6.5)	1748 (19.1)	< 0.0001	335 (3.5)	494 (16.0)	<0.0001
Generic vs. branded index AED claims, n (%)						
Claims for generic AED(s) only	41,808 (93.0)	7204 (78.9)	< 0.0001	9136 (95.9)	2739 (88.9)	<0.0001
Claims for branded AED(s) only	2418 (5.4)	1288 (14.1)	< 0.0001	288 (3.0)	205 (6.7)	<0.0001
Claims for generic and branded AEDs	738 (1.6)	641 (7.0)	< 0.0001	105 (1.1)	137 (4.5)	<0.0001
Payer, n (%)[c]						
Commercial	18,091 (40.2)	3773 (41.3)	0.056	3941 (41.4)	1062 (34.5)	<0.0001
Medicaid	10,785 (24.0)	4121 (45.1)	< 0.0001	4790 (50.3)	1983 (64.4)	<0.0001
Medicare	12,290 (27.3)	1057 (11.6)	< 0.0001	46 (0.5)	14 (0.5)	0.8425

Table 1 continued

Characteristic	Overall patient population (N = 54,097)			Pediatric patient population (N = 12,610)		
	Approved (n = 44,964)	Rejected (n = 9133)	P value	Approved (n = 9529)	Rejected (n = 3081)	P value
Cash	2237 (5.0)	13 (0.1)	< 0.0001	536 (5.6)	2 (0.1)	<0.0001
Assistance programs	1561 (3.5)	169 (1.9)	< 0.0001	216 (2.3)	20 (0.7)	<0.0001
Expected patient copay amount, $, mean (SD)	22.10 (108.9)	–	–	14.55 (73.6)	–	–
Expected patient copay amount for branded AEDs, $, mean (SD)[c, d]	128.52 (356.7)	–	–	87.35 (308.2)	–	–
Expected patient copay amount for generic AEDs, $, mean (SD)[c, d]	15.12 (59.2)	–	–	11.86 (43.6)	–	–
CCI						
Mean (SD)	1.40 (2.3)	0.96 (1.9)	< 0.0001	0.34 (0.8)	0.36 (0.9)	0.6779
0 CCI conditions, n (%)	23,700 (52.7)	5814 (63.7)	< 0.0001	7594 (79.7)	2450 (79.5)	0.8349
1 CCI condition, n (%)	10,054 (22.4)	1832 (20.1)	< 0.0001	1601 (16.8)	510 (16.6)	0.7483
2 CCI conditions, n (%)	5348 (11.9)	766 (8.4)	< 0.0001	267 (2.8)	98 (3.2)	0.2756
≥3 CCI conditions, n (%)	5862 (13.0)	721 (7.9)	< 0.0001	67 (0.7)	23 (0.8)	0.8036
Baseline total charges, $, mean (SD)[d]	15,316 (37,788)	15,088 (39,427)	0.0002	12,126 (26,508)	14,133 (31,920)	<0.0001

Patient demographics were assessed as of the index date. Comorbidities and baseline resource use were assessed in the 6 months prior to the index date
AED Antiepileptic drug, *CCI* Charlson Comorbidity Index, *SD* standard deviation

[a] Remaining percentage were female

[b] Only patient birth year was available; therefore, all patients were assigned a birthdate of 1 July for the purpose of calculating age

[c] For patients with an approved initial claim, the value was taken from the first approved index AED claim. For patients with a rejected initial claim, the value was taken from the first index AED claim rejected for formulary-related reasons

[d] Dollar values of charges were inflated to 2018 US dollars using the US gross domestic product price index [22]

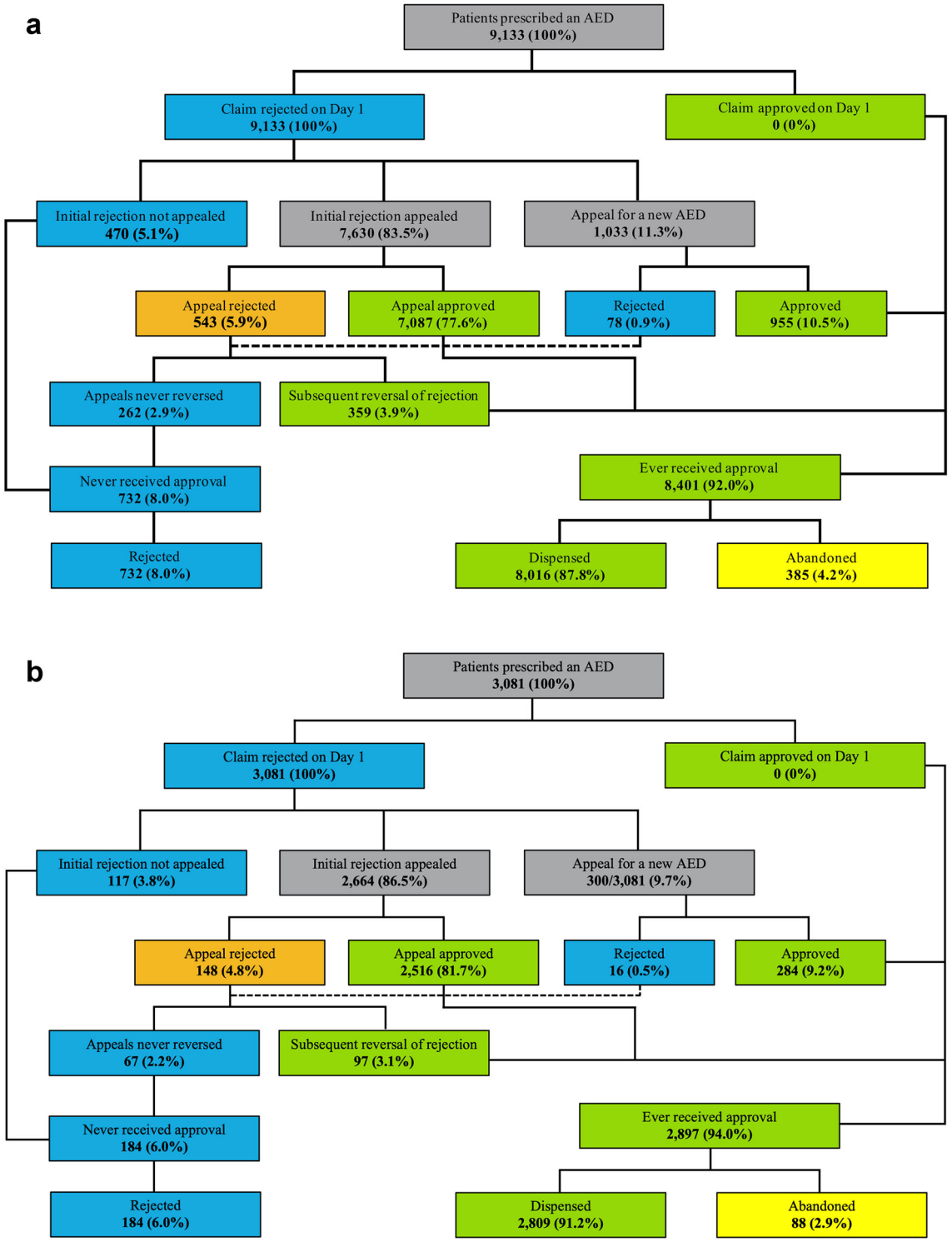

Fig. 2 Prescription life cycle for patient in rejected cohort during 6-month follow-up period. **a** Overall patient population. **b** Pediatric patient population. *AED* antiepileptic drug

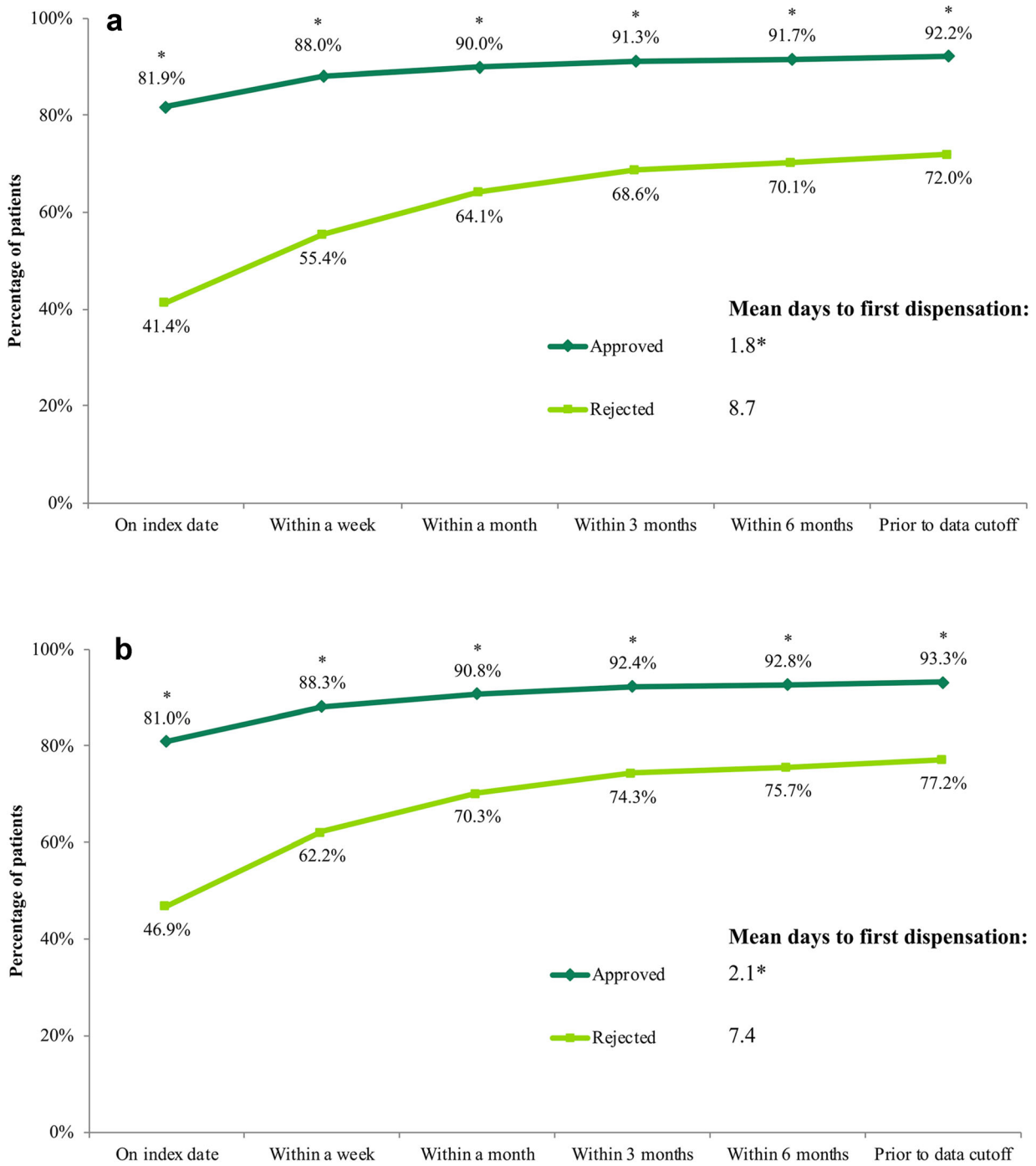

Fig. 3 Distribution by time to first dispensation of index AED. **a** Overall patient population. **b** Pediatric patient population. Asterisk indicates significant difference at $P < 0.0001$. *AED* antiepileptic drug

to first dispensation of an index AED was 1.8 (± 11.1) days for the approved claim cohort and 8.7 (± 23.5) days for the rejected claim cohort, resulting in a mean delay of 6.9 days for the latter ($P < 0.0001$) (Fig. 3a). Mean (± SD) time to first dispensation of any AED was 2.6 (± 13.5) days for the approved claim cohort and 8.8 (± 23.5) days for the rejected cohort, resulting

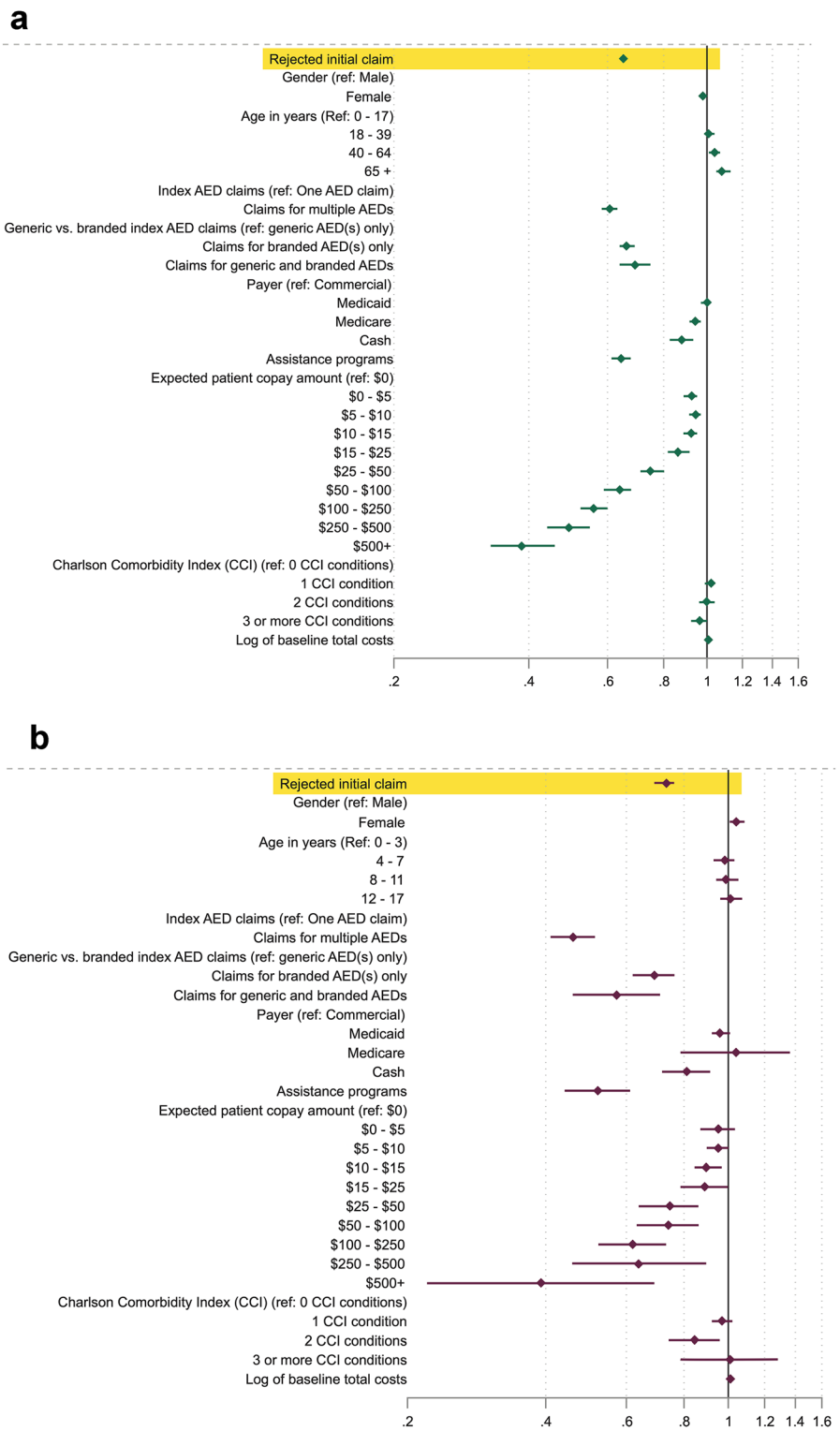

Fig. 4 Hazard ratios of successful dispensation of prescribed index AED. **a** Overall patient population. **b** Pediatric patient population. Horizontal lines indicate 95% confidence intervals plotted on a logarithmic scale. Dollar values of charges were inflated to 2018 United States (US) dollars using the US gross domestic product price index [22]. *AED* antiepileptic drug, *CCI* Charlson Comorbidity Index, *ref* reference

in a mean delay of 6.2 days for the latter ($P < 0.0001$) (ESM Fig. S2a).

In the pediatric population, a greater proportion of patients in the approved claim cohort compared to those in the rejected claim cohort had a successful dispensation of an index AED (92.8% vs. 75.7%; $P < 0.0001$) (Fig. 3b) or any AED (97.2% vs. 91.2%; $P < 0.0001$) (ESM Fig. S2b) at 6 months from the initial prescription date. Mean (SD) time to first dispensation of an index AED was 2.1 (± 11.9) days for the approved claim cohort and 7.4 (± 21.5) days for the rejected claim cohort, resulting in a mean delay of 5.3 days for the latter ($P < 0.0001$) (Fig. 3b). Mean (SD) time to first dispensation of any AED was 2.5 (± 12.6) days for the approved claim cohort and 6.2 (± 18.5) days for the rejected cohort, resulting in a mean delay of 3.7 days for the latter ($P < 0.0001$).

Likelihood of Successful AED Dispensation

In the overall population, after adjusting for baseline characteristics, formulary-related rejections of a prescribed AED were associated with a 35% lower likelihood of successful dispensation of an index AED (HR 0.65; 95% confidence interval [CI] 0.64–0.66; $P < 0.0001$) (Fig. 4a) and a 30% lower likelihood of successful dispensation of any AED (HR 0.70; 95% CI 0.69–0.71; $P < 0.0001$), relative to no formulary restrictions (ESM Fig. S3a).

In the pediatric population, adjusting for baseline characteristics, formulary-related rejections of a prescribed AED were associated with a 27% lower likelihood of successful dispensation of an index AED (HR 0.73; 95% CI 0.69–0.76; $P < 0.0001$) (Fig. 4b) and a 24% lower likelihood of successful dispensation of any AED (HR 0.76; 95% CI 0.72–0.79; $P < 0.0001$), relative to no formulary restrictions (ESM Fig. S3b).

Across both populations, additional factors statistically significantly associated with a lower likelihood of successful AED dispensation included higher patient copay, claims for multiple and/or branded AEDs, and payer type (ESM Table S2).

DISCUSSION

The results from this retrospective study of real-world national claims data suggest that formulary restrictions of AED claims were associated with significant delays in treatment initiation among patients with FS. For an index AED, mean delays of 6.9 and 5.3 days were observed in the overall and pediatric populations, respectively, if a claim was rejected for a formulary-related reason, compared to an approved claim. Formulary restrictions were associated with a significantly lower likelihood of successful AED dispensation. For an index AED, 35 and 27% lower likelihoods of successful dispensation were observed for the overall and pediatric populations, respectively, relative to no formulary restrictions.

Factors other than formulary restriction that were statistically significantly associated with a lower likelihood of successful dispensation of an AED included higher patient copay, claims for multiple and/or branded AEDs, and Medicare coverage. The cost of medication is an important factor in patients' compliance, especially for those with chronic diseases, as treatment could be life-long [23]. Higher patient copay represents a burden to chronically ill patients and has been associated with lower use of prescribed medicines and higher rates of medication abandonment [24]. It may therefore drive a lower likelihood of AED dispensation among patients in this study [25–27]. Increased treatment complexity, defined as the number of pills taken and frequency of administration, has been associated with reduced medication adherence across therapeutic classes, including epilepsy, and may explain the lower likelihood of successful AED dispensation among the patients in this study with claims for multiple different AEDs [23, 28]. Results from the present study are in accordance with existing reports of patients with Medicare coverage in various therapeutic areas showing that restricted access is associated with lower drug use [29, 30].

Previous studies found that formulary restrictions of AEDs resulting in delays in the initiation of therapy had negative impacts on seizure control and were associated with higher

healthcare costs [16, 17]. A retrospective analysis of treatment patterns, healthcare costs, and resource utilization among 1926 patients with epilepsy who had an index date-linked AED restriction showed that more restrictions to newer AEDs led to increased odds of emergency room visits without reducing all-cause or epilepsy-specific healthcare costs [16]. In a survey of parents of 164 children with epilepsy, 38% reported a requirement for a PA each year, and most patients for whom a PA was required had refractory epilepsy [17]. Among the patients with a missed dose of an AED resulting from a PA, 64% had a worsening of seizures, with some requiring hospitalization [17].

Restrictions on formulary medications are primarily adopted to control drug expenditures, but they can also serve to guide the use of therapies to improve patient outcomes and prevent adverse events [9, 31, 32]. In certain therapeutic classes, formulary restrictions have been effective at reducing pharmacy costs and drug utilization while positively impacting clinical outcomes [33–35]. However, considering that nearly 80% of rejected initial claims in the current study were reversed after an appeal, formulary restrictions may represent a burden to physicians and the healthcare system. A survey by the American Medical Association about the impact of PAs on clinical practice revealed that treating physicians and their staff spend nearly 2 days each week completing PAs, which represents time not reimbursed by payers that could be devoted to patient care [36, 37]. The vast majority of physicians reported wait times of 1–3 business days for PA responses, 28% reported that PAs led to a serious adverse event, and 36% reported having a staff member dedicated to working on PAs [36, 37]. The annual costs of PDLs, including prescriptions not covered (thus requiring PAs and appeals), fixed costs, PDL training, and PDL tracking, vary between physicians and across states [38]. In 2005, cost estimates associated with PDLs for certain therapeutic specialties exceeded US$53 million in nine states, representing considerable healthcare expenditures [38]. The greatest PA costs were incurred by physicians who practiced in lower-income areas or those with a higher share of minorities. These physicians more frequently prescribed drugs they viewed as inferior, or no medication was provided as a result of PDLs [39].

Limitations

This study has several limitations. Defining study cohorts by claims rejection status provides an accurate representation of life cycle outcomes for a particular prescription; however, it is not a complete measure of the drug formulary a patient is subject to and may lead to potential misclassification of patients. The Symphony Health IDV® is an open-source database and may not capture all claims for a patient, resulting in incomplete data. There may be measurement limitations due to unobservable factors, including patient drug use prior to data start date, as well as missing claims data, and lack of medical charts or electronic records. Pharmacy claims capture commercial, Medicare, and Medicaid as the primary payer for the majority of patients. For these patients, reliance on any other financial assistance (e.g., discount cards, financial assistance program) was not reported. Among patients with missing primary payer information, reliance on other financial assistance programs was reported as primary payers. Therefore, the association between financial assistance programs and dispensation outcomes was not fully ascertained. Patient copay reported in the data may not be an accurate representation of the actual burden incurred by the patient (e.g., it may not fully capture copay assistance received by patients). The study's patient selection criteria limit generalizability to other patient populations (e.g., patients diagnosed with other conditions). Finally, the study could not assess whether patient, physician, or payer factors drove the delay in access to AEDs.

CONCLUSIONS

Formulary restrictions of AEDs were associated with significant delays in access to treatment and a significantly lower likelihood of successful AED dispensation in patients with FS. Future studies are needed to examine the impact of

these treatment delays on clinical and economic outcomes.

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