

METHODOLOGICAL ISSUES IN CLASSIFYING ADJUNCT ANTI EPILEPTIC DRUG (AED) TREATMENT IN CLAIMS DATA: ANALYSIS OF THE EFFECT OF THE MINIMUM AED CO-ADMINISTRATION PERIOD

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BACKGROUND

- Epilepsy is a chronic neurological disorder characterized by recurrent seizures. Approximately 2.2 to 3 million people in the United States have epilepsy and about 150,000 new cases are diagnosed each year.¹
- One in 26 people will develop recurring seizures in their lifetime.²
- Epilepsy results in an estimated annual cost of \$15.5 billion in combined direct and indirect costs.³
- There are two fundamental types of epilepsy:
 - primary generalized epilepsy and
 - localization-related epilepsy.
- Localization-related epilepsy accounts for 60-75% of all epilepsy cases and has one of three types of partial-onset seizures (POS):⁴
 - simple partial,
 - complex partial, and
 - partial onset with secondary generalization.
- Appropriate drug selection is multi-faceted and special consideration must be given to tolerability, the potential for drug interactions, and the numerous pharmacokinetic and pharmacodynamic challenges.⁵
- Initial antiepileptic drug (AED) therapy is in large part selected based on the patient's seizure/epilepsy type.
 - Monotherapy has been the gold standard for several decades based on studies showing equal efficacy, increased tolerability and lower toxicity when compared to therapy with multiple agents.^{6,6}
 - If the first monotherapy agent is ineffective, the patient should be switched to another monotherapy agent using the transitional polytherapy method by which the new agent is initiated and titrated up slowly towards the target dose, while the dose of the baseline drug is reduced over time.
 - Unless the patient is experiencing a life-threatening reaction, conversion from one monotherapy to another uses coordinated up- and down-titration.⁷
- About 35% of patients with epilepsy are considered to be refractory and do not respond to monotherapy.^{7,8} After two failed sequential monotherapy trials, adding an adjunctive agent with a different mechanism of action is recommended.⁹
- Approximately 1/3 of patients with partial-onset seizures (POS) are drug resistant and frequently require adjunctive treatment.⁹
- Although adjunctively-treated patients are identified in claims data by the concurrent administration of two or more antiepileptic drugs (AEDs), the minimum AED co-administration period has not been established.
- In order to avoid confounding in claims data analyses, the titration time to maintenance dose of AEDs used in adjunctive therapy needs to be carefully weighed in the classification of adjunctively-treated patients.

OBJECTIVE

- To identify the impact of different co-administration periods on the proportion of patients identified as receiving adjunctive therapy within claims data.

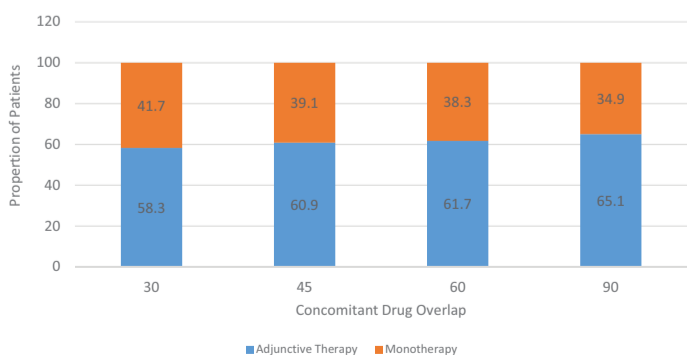
METHODS

- Retrospective study using the Human Capital Management Systems (HCMS) database of commercially-insured subjects:
 - Represents multiple geographically diverse, US-based employers in the retail, service, manufacturing, and financial industries and includes information on more than 2 million employees plus spouses.
 - Extracted from claims between January 2001 to June 30, 2014.
 - The HCMS database has been used in prior epilepsy research.¹⁰
 - The data were de-identified to comply with the Health Insurance Portability and Accountability Act and the contractual obligations between HCMS and its employer-contributors.
- Inclusion criteria:
 - Patients with partial-onset seizures were required to be spouses of employees and were identified by any primary, secondary or tertiary claims containing International Classification of Diseases 9th revision Clinical Modification (ICD-9-CM) codes for localization-related (focal) (partial) epilepsy and epileptic syndromes with:
 - complex partial seizures (ICD-9=345.4x) or
 - simple partial seizures (ICD-9=345.5x).
- Patients were:
 - assigned an index date based on their initial AED use.
 - required to have > 365 days of continuous eligibility following their index date.
- Using data through March 30, 2014:
 - Patients were classified as having adjunctive therapy on the basis of having at least 30, 45, 60, or 90 days of concomitant AED use in the period following their index date.
 - The different overlap periods were compared with the literature to yield the correct representation.
- Once the cohorts were identified the database was updated to add information through June 30, 2014. Using the updated database, the following information was generated:
 - Descriptive information comparing the monotherapy and adjunctive therapy cohorts on:
 - Age and Gender [employees and patients]
 - Charlson Comorbidity Index scores [employees and patients]
 - Region of the country
 - For the employees only:
 - Self-reported racial information and
 - Job-related information (Salary, full/part-time status, and exempt status).
 - The time from the partial-onset seizures (POS) diagnosis until the initiation of:
 - monotherapy
 - adjunctive therapy from
 - no therapy
 - monotherapy.

RESULTS

- 350 eligible patients married to employees were identified from the initial dataset (through March 30, 2014).
- Based on the length of the overlap period, various scenarios were evaluated for eligibility by direct and indirect components (Table 1)
- Using medical and prescription eligibility, the percent classified as receiving adjunctive therapy:
 - At 30, 45, 60, and 90-days were 41.7%, 39.1%, 38.3% and 34.9%, respectively (Figure 1).
 - The 90 day overlap period was selected as the appropriate overlap period (Figure 2).

Figure 1. Classification of Partial-Onset Seizure (POS) Patients as using Monotherapy or Adjunctive Therapy Based on Concomitant Drug Overlap*



* N=350

RESULTS (CONTINUED)

Figure 2. Proportion of Partial-Onset Seizure (POS) Patients Classified as Using Monotherapy or Adjunctive Therapy

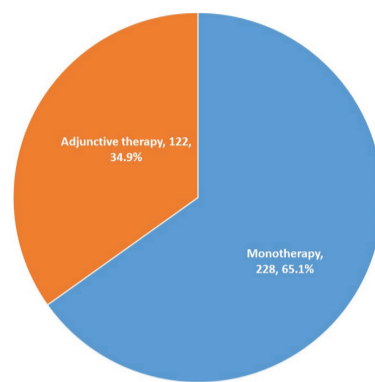


Table 1. Comparison of sample sizes for 350 patients with partial onset seizures and their employee spouses

Minimum Number of Overlap Days	Type of therapy	Spouses with condition married to "Employees" with at least 1 year Medical and Drug Eligibility		Employees with 1 year Medical and Drug Eligibility and 1 year eligibility for:							
		N	%	Sick Leave		Short-term Disability		Long-term Disability		Workers' Compensation	
				N	%	N	%	N	%	N	%
30 Days	Monotherapy	204	58.3%	102	52.6%	172	57.3%	154	57.2%	189	57.4%
	Adjunctive therapy	146	41.7%	92	47.4%	128	42.7%	115	42.8%	140	42.6%
	Total	350		194		300		269		329	
45 Days	Monotherapy	213	60.9%	110	56.7%	180	60.0%	164	61.0%	199	60.5%
	Adjunctive therapy	137	39.1%	84	43.3%	120	40.0%	105	39.0%	130	39.5%
	Total	350		194		300		269		329	
60 Days	Monotherapy	216	61.7%	110	56.7%	183	61.0%	164	61.0%	201	61.1%
	Adjunctive therapy	134	38.3%	84	43.3%	117	39.0%	105	39.0%	128	38.9%
	Total	350		194		300		269		329	
90 Days	Monotherapy	228	65.1%	117	60.3%	193	64.3%	175	65.1%	213	64.7%
	Adjunctive therapy	122	34.9%	77	39.7%	107	35.7%	94	34.9%	116	35.3%
	Total	350		194		300		269		329	

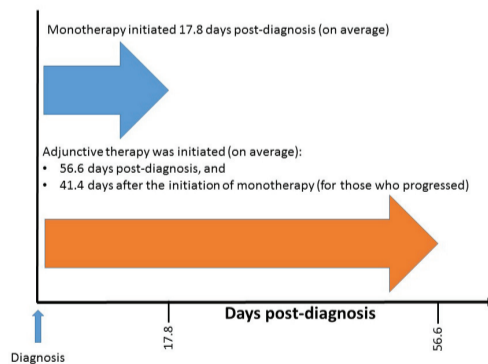
- After the addition of data through June 30, 2014:
 - Descriptive statistics were generated for the two cohorts (Table 2) and found the cohorts to be similar.
 - The average time to (Figure 3):
 - initiate monotherapy was 17.8 days from the first POS diagnosis,
 - initiate adjunctive therapy was 56.6 days from the POS diagnosis; and
 - progress to adjunctive therapy from monotherapy was 41.4 days.

Table 2. Descriptive Statistics for Study Cohorts

Variable	Monotherapy	Adjunctive therapy
N (employee-spouse pairs)	238	129
Employee:		
Age, in years (at index date), mean [SE]	45.15 [0.67]	44.14 [0.87]
Tenure, in years (at index date), mean [SE]	9.86 [0.59]	10.24 [0.80]
Female, %	31.5%	27.9%
Self-reported race:		
White, %	38.2%	37.2%
Black, %	38.2%	37.2%
Hispanic, %	5.5%	5.4%
Other race, %	5.5%	7.8%
Race missing, %	2.1%	2.3%
Exempt, %	48.7%	47.3%
Annual salary (in US \$), mean [SE] *	47.9%	37.2%
Full-time status, %	\$73,549	\$63,758
Charlson Comorbidity Index Score, mean [SE]	98.7%	98.4%
	0.37	0.31
Patients with Partial Onset Epilepsy (Spouses)		
Age, in years (at index date), mean [SE]	44.65 [0.68]	43.38 [0.90]
Female, %	68.1%	72.1%
Charlson Comorbidity Index Score, mean [SE]	0.96 [0.11]	1.05 [0.17]

* P=0.0341

Figure 3. Time from Partial-Onset Seizure (POS) Diagnosis to Mono or Adjunctive Therapy



CONCLUSIONS

- Using a 90-day co-administration period, approximately 1 in 3 patients with partial-onset seizures were classified as using adjunctive therapy.
- Researchers may find this consideration of different overlap periods useful for studies of anti-epileptic drugs requiring short vs. long titration periods.

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