

Prevalence and Cost Impact of Nonadherence with Antiepilepsy Drugs Among Adults in a Managed Care Population

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BACKGROUND

Medication nonadherence is widespread in chronic disease and is a significant problem faced by medical practice.¹ Nonadherence results in reduced treatment benefits and therefore may lead to an increased financial burden on patients, payers, and society.² This burden has been estimated to be \$100 billion per year across all chronic diseases in the United States (US).³ The issue of nonadherence in epilepsy and its cost implications, particularly for third-party payers, has not been widely investigated.

OBJECTIVES AND PURPOSE

In this study, we estimate the prevalence and cost impact of nonadherence with antiepilepsy drugs (AEDs) among adults with epilepsy in a US managed care population.

METHODS

Study Design

The study is a retrospective database analysis.

Data Source

Data were pulled from the PharMetrics database, which comprises longitudinal insurance claims from 75 health plans, covering diverse geographic regions and more than 40 million patients in the US.

Inclusion Criteria

Subjects included in the study met the following inclusion criteria:

- Age 21 or older,
- At least one diagnosis of epilepsy (ICD-9 345.xx) or nonfebrile convulsions (ICD-9 780.3 or 780.39) between 1/1/2000 and 12/31/2005,
- At least two AED prescriptions between 1/1/2000 and 12/31/2005,
- At least one neurologist visit with a diagnosis of epilepsy or nonfebrile convulsions, and
- Continuous plan enrollment for at least 6 months pre-AED initiation and at least 12 months post-AED initiation.

Primary Outcomes

- AED adherence was assessed via the medication possession ratio (MPR), which was defined as follows:
 - Overall MPR: Total AED days supplied divided by days between AED initiation and expiration of last AED refill,
 - AED-specific MPR: Total days supplied for AED of interest divided by days between first prescription and expiration of last refill for that AED,
- Adherence status:
 - MPR ≥ 0.8 = Adherent,
 - MPR < 0.8 = Non-adherent,
- Health care utilization and costs were evaluated over the maximum follow-up time available (≥ 12 months) and annualized for reporting.

Other Outcomes

- Incidence of accident or injury, as defined by relevant ICD-9 codes,^{4,5} including the following:
 - Motor vehicle accident (MVA),
 - Injury due to fall, and
 - Traumatic brain injury (TBI),
- Adherence, utilization, and cost outcomes for elderly subcohort.

Statistical Analyses

- Descriptive statistics are presented for patient characteristics and all outcome variables.
- Regression models were estimated to formally assess the impact of overall AED nonadherence and continuous MPR on utilization and costs.
 - Utilization and cost outcomes were estimated as a function of alternative adherence measures, including the following:
 - Dichotomous indicator for nonadherence (1 = MPR < 0.8 , 0 = MPR ≥ 0.8),
 - Continuous MPR,
 - Additional covariates include age, gender, the Charlson Comorbidity Index (CCI), and follow-up duration.
 - The continuous MPR specification includes a squared MPR term to capture a possible nonlinear relationship between MPR and outcomes.

RESULTS

Patient Characteristics

- Overall, 10,892 patients qualified for study inclusion. The mean age was 44 years, and 58% of patients were female. The mean CCI was 0.93, and the mean follow-up exceeded 27 months (Table 1).

Antiepilepsy Drug Adherence

- Results indicate that 39.3% of subjects were nonadherent with overall AED therapy (Table 2, Figure 1).
- Nonadherence rates were lowest for phenytoin (31.9%), levetiracetam (32.1%), and lamotrigine (32.3%) and highest for gabapentin (52.7%) (Table 2).
- Mean MPR was highest for lamotrigine (MPR = 0.83), levetiracetam (MPR = 0.82), and phenytoin (MPR = 0.82) (Figure 2).

Table 1. Patient Characteristics

	All Patients	
	N	%
All patients	10,892	100.00
Mean age in years	43.83	
Age category		
21-39	4,147	38.07
40-64	6,254	57.42
≥ 65	491	4.51
Gender		
Male	4,537	41.65
Female	6,355	58.35
Mean CCI	0.928	
Mean follow-up duration in months	27.41	

CCI = Charlson Comorbidity Index.

Table 2. AED Adherence Rates

AED Generic Name	N*	Adherent (MPR ≥ 0.8)		Nonadherent (MPR < 0.8)	
		N	% (Row)	N	% (Row)
All AEDs	10,892	6,614	60.72	4,278	39.28
Newer agents					
Lamotrigine	1,193	808	67.73	385	32.27
Tiagabine	130	71	54.62	59	45.38
Levetiracetam	1,309	889	67.91	420	32.09
Pregabalin	0	---	---	---	---
Gabapentin	1,960	928	47.35	1,032	52.65
Topiramate	1,275	710	55.69	565	44.31
Oxcarbazepine	970	605	62.37	365	37.63
Zonisamide	351	204	58.12	147	41.88
Newer AEDs (Overall)	5,623	3,117	55.43	2,506	44.57
Older agents					
Valproate	2,299	1,335	58.07	964	41.93
Phenytoin	4,029	2,743	68.08	1,286	31.92
Phenobarbital	454	275	60.57	179	39.43
Carbamazepine	2,169	1,361	62.75	808	37.25
Older AEDs (Overall)	7,832	4,967	63.42	2,865	36.58

*For each AED, MPR calculation includes patients with ≥ 2 prescriptions (initial Rx + ≥ 1 subsequent refill) for the AED of interest. Because patients may have used multiple AEDs during follow-up, samples are not mutually exclusive. MPR = medication possession ratio; AED = antiepilepsy drug.

Figure 1. MPR Distribution for Overall AED Therapy

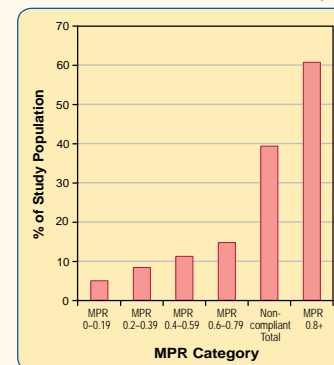
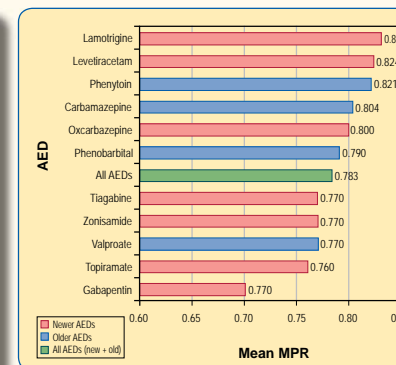


Figure 2. Mean MPR by AED



Health Care Utilization and Costs

- Nonadherence to AED therapy was associated with an 11% increased likelihood of hospitalization (odds ratio [OR] = 1.110, $P = 0.013$), number of inpatient admissions (+0.080 admissions, $P < 0.001$), inpatient days (+0.579 days, $P < 0.001$), and inpatient costs (+\$1,799, $P = 0.001$) per patient per year (Table 3).
- AED nonadherence was associated with a 48% increased likelihood of emergency room (ER) admission (OR = 1.479, $P < 0.001$), number of ER admissions (+0.436 admissions, $P < 0.001$), and costs (+\$260, $P < 0.001$) per patient per year (Table 3).
- Large net effect of AED nonadherence on total health care costs remained (+\$1,466, $P = 0.034$) despite expected offset from reduced prescription drug costs (Table 3).
- Inpatient, ER, and total health care costs decrease significantly for every 1 percentage point increase in MPR (Table 3).
- Squared MPR coefficient in all models was negative and significant, indicating a diminishing effect as MPR increases (e.g., MPR improvement from 0.10 to 0.20 leads to a greater reduction in costs than improvement from 0.70 to 0.80).

Table 3. Cost Impact of AED Nonadherence on Annual Per Patient Health Care Utilization and Costs

Dependent Variable	Mean Value of Dependent Variable	Regression Specification			
		Dichotomous Indicator for Nonadherence		Continuous MPR	
		Coefficient/Odds Ratio	P Value	Coefficient/Odds Ratio	P Value
Inpatient					
Had ≥ 1 admission	42.76%	1.110	0.013	0.983	<0.001
Number of admissions	0.52	0.080	<0.001	-0.006	0.001
Number of days in hospital	2.39	0.579	<0.001	-0.032	0.013
Costs	\$7,639	\$1,799	0.001	-\$119.29	0.016
Emergency room					
Had ≥ 1 admission	57.38%	1.479	<0.001	0.981	<0.001
Number of admissions	0.98	0.436	<0.001	-0.019	<0.001
Costs	\$597	\$260	<0.001	-\$6.53	0.033
Physician office visits					
Had ≥ 1 visit	99.54%	0.455	0.007	1.020	0.504
Number of visits	14.11	-0.047	0.865	-0.043	0.098
Costs	\$1,431	-\$37	0.603	\$4.27	0.529
Other ancillary care					
Had ≥ 1 visit	98.73%	0.723	0.066	1.004	0.794
Number of visits	13.06	-0.662	0.021	-0.067	0.013
Costs	\$4,866	\$163	0.394	-\$30.08	0.094
Prescription drugs					
AED costs	\$897	-\$701	<0.001	\$8.35	<0.001
Other drug costs	\$2,671	-\$358	0.003	\$10.06	0.376
Total costs for all services	\$18,101	\$1,466	0.034	-\$169.68	0.009

Note: Coefficient estimate reported for linear regressions estimated for continuous outcomes (e.g., costs, number of hospital admissions). Odds ratios reported for logistic regressions estimated for dichotomous outcomes (e.g., had ≥ 1 hospital admission). AED = antiepilepsy drug.

Other Outcomes

- AED nonadherence was associated with a 44% increased likelihood of an MVA (OR = 1.439, $P = 0.038$) (Table 4).
- MPR was inversely related to the probability of an MVA and injury due to fall (Table 4).
- In the elderly subcohort, AED nonadherence prevalence was 43%, and the increase in total health care costs due to nonadherence was substantially larger (+\$5,705, $P = 0.042$) than in the general population.

Table 4. Logistic Regression Results for Likelihood of Accident or Injury

Dependent Variable	Mean Value of Dependent Variable	Regression Specification			
		Dichotomous Indicator for Nonadherence		Continuous MPR	
		Odds Ratio	P Value	Odds Ratio	P Value
Had MVA	1.26%	1.439	0.038	0.992	0.004
Had injury due to fall	3.63%	1.187	0.105	0.996	0.038
Had TBI	6.21%	1.047	0.577	0.998	0.234

TBI = traumatic brain injury; MVA = motor vehicle accident.

LIMITATIONS

- The MPR measure assumes complete medication ingestion, causing possible overestimation of actual adherence.
- Therapy may be interrupted for clinically appropriate reasons, causing MPR to possibly underestimate actual adherence.
- It is difficult to measure the cost impact of recurrent (i.e., "breakthrough") seizures as these events generally do not result in direct resource utilization unless the patient is seriously injured.
- Our study does not address costs paid by noncommercial payers (e.g., Medicare or Medicaid). Direct total health care costs are therefore underestimated.
- Our study does not address costs incurred by the patient and employers due to lost wages from disability or missed work time.

CONCLUSIONS

- We estimated an AED nonadherence prevalence of 39%, which is consistent with previous studies of self-reported data that suggest a nonadherence rate between 30% and 60%.^{6, 7, 8}
- Adherence with AEDs is suboptimal.
- AED nonadherence appears to be associated with increased health care utilization and costs, as well as an increased likelihood of having an MVA.
- Efforts to promote AED adherence may lead to cost savings for managed care payers.

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