

SUPPLEMENTARY MATERIALS

Title: Impact of Antiepileptic Drug Treatment Burden on Healthcare Resource Utilization and Costs

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Supplementary materials

Table S1. All-Cause and Epilepsy-Related^a Unadjusted Healthcare Resource Utilization and Costs per Patient During the 12-Month Follow-up Period, by Index AED Pill Burden

All-Cause Healthcare Resource Utilization and Costs					
	All Patients	>0-1 Pill per Day	>1-2 Pills per Day	>2-3 Pills per Day	>3 Pills per Day
	(N = 53,338)	(n = 7027)	(n = 20,068)	(n = 11,071)	(n = 15,172)
Patients with inpatient services, n (%)	11,700 (21.9)	1512 (21.5)	4535 (22.6)	2618 (23.6)	3035 (20.0)
Number of inpatient admissions, mean (SD)	0.4 (1.1)	0.4 (1.0)	0.4 (1.1)	0.4 (1.2)	0.4 (1.0)
Length of stay (in days), mean (SD)	6.3 (12.2)	6.6 (11.6)	6.2 (12.3)	6.2 (12.5)	6.4 (12.1)
Cost of inpatient services (2017 USD), mean (SD)	\$8403 (\$37,258)	\$8220 (\$40,257)	\$8383 (\$34,093)	\$9061 (\$39,776)	\$8034 (\$37,914)
Patients with outpatient pharmacy services, n (%)	53,338 (100.0)	7027 (100.0)	20,068 (100.0)	11,071 (100.0)	15,172 (100.0)
Number of outpatient prescriptions, mean (SD)	26.7 (18.8)	28.5 (19.5)	26.1 (18.0)	27.7 (19.5)	25.9 (18.8)
Cost of outpatient prescriptions (2017 USD), mean (SD)	\$5285 (\$9509)	\$4782 (\$9027)	\$5404 (\$9932)	\$4,921 (\$8728)	\$5627 (\$9682)
Patients with emergency room services, n (%)	20,502 (38.4)	2778 (39.5)	7757 (38.7)	4497 (40.6)	5470 (36.1)

Number of emergency room visits, mean (SD)	1.0 (2.7)	1.1 (2.8)	1.0 (2.8)	1.1 (2.8)	0.9 (2.5)
Cost of emergency room visits (2017 USD), mean (SD)	\$894 (\$4287)	\$1109 (\$5448)	\$883 (\$5044)	\$936 (\$3339)	\$779 (\$3007)
Patients with physician office services, n (%)	51,813 (97.1)	6871 (97.8)	19,574 (97.5)	10,736 (97.0)	14,632 (96.4)
Number of physician office visits, mean (SD)	14.5 (15.3)	16.4 (16.2)	14.7 (15.3)	14.8 (15.4)	13.1 (14.4)
Cost of physician office visits (2017 USD), mean (SD)	\$3180 (\$10,336)	\$3048 (\$7311)	\$3481 (\$11,702)	\$3117 (\$9709)	\$2888 (\$10,035)
Patients with other outpatient services, n (%)	46,913 (88.0)	6274 (89.3)	17,670 (88.1)	9810 (88.6)	13,159 (86.7)
Number of other outpatient visits, mean (SD)	10.1 (18.0)	10.1 (18.1)	10.3 (18.2)	10.2 (16.8)	9.7 (18.3)
Cost of other outpatient visits (2017 USD), mean (SD)	\$8253 (\$28,359)	\$7623 (\$27,958)	\$9039 (\$32,252)	\$8157 (\$24,197)	\$7575 (\$25,708)
Total costs (2017 USD)					
Mean (SD)	\$26,015 (\$59,880)	\$24,781 (\$60,518)	\$27,190 (\$61,577)	\$26,193 (\$59,059)	\$24,903 (\$57,842)
Median	\$8720	\$8896	\$8919	\$8761	\$8349
(Q1, Q3)	(\$3415, \$22,633)	(\$3488, \$22,598)	(\$3662, \$22,846)	(\$3264, \$23,549)	(\$3112, \$21,567)
Epilepsy-Related^a Healthcare Resource Utilization and Costs					
Patients with inpatient services, n (%)	5949 (11.2)	636 (9.1)	2480 (12.4)	1217 (11.0)	1616 (10.7)

Number of inpatient admissions, mean (SD)	0.1 (0.5)	0.1 (0.4)	0.2 (0.6)	0.1 (0.5)	0.1 (0.5)
Length of stay (in days), mean (SD)	5.8 (14.9)	6.0 (14.6)	5.8 (15.5)	5.7 (14.3)	5.8 (14.7)
Cost of inpatient services (2017 USD), mean (SD)	\$2867 (\$16,770)	\$2141 (\$10,177)	\$3218 (\$15,221)	\$2656 (\$16,001)	\$2892 (\$21,145)
Patients with outpatient pharmacy services, n (%)	53,338 (100.0)	7027 (100.0)	20,068 (100.0)	11,071 (100.0)	15,172 (100.0)
Number of outpatient prescriptions, mean (SD)	6.8 (4.3)	6.6 (4.4)	6.8 (4.3)	6.5 (4.2)	7.1 (4.4)
Cost of outpatient prescriptions (2017 USD), mean (SD)	\$1075 (\$1741)	\$691 (\$1234)	\$1144 (\$1483)	\$751 (\$1372)	\$1398 (\$2327)
Patients with emergency room services, n (%)	8500 (15.9)	965 (13.7)	3450 (17.2)	1775 (16.0)	2310 (15.2)
Number of emergency room visits, mean (SD)	0.3 (0.9)	0.2 (0.8)	0.3 (1.0)	0.3 (0.8)	0.2 (0.8)
Cost of emergency room visits (2017 USD), mean (SD)	\$239 (\$1215)	\$235 (\$1224)	\$261 (\$1365)	\$235 (\$1115)	\$215 (\$1061)
Patients with physician office services, n (%)	35,090 (65.8)	4054 (57.7)	13,966 (69.6)	6729 (60.8)	10,341 (68.2)

Number of physician office visits, mean (SD)	2.0 (2.6)	1.8 (2.6)	2.2 (2.6)	1.8 (2.6)	2.0 (2.5)
Cost of physician office visits (2017 USD), mean (SD)	\$334 (\$849)	\$323 (\$785)	\$380 (\$974)	\$284 (\$725)	\$316 (\$779)
Patients with other outpatient services, n (%)	25,006 (46.9)	2838 (40.4)	9725 (48.5)	4941 (44.6)	7502 (49.4)
Number of other outpatient visits, mean (SD)	1.4 (4.5)	1.1 (3.4)	1.4 (4.1)	1.2 (2.9)	1.6 (6.2)
Cost of other outpatient visits (2017 USD), mean (SD)	\$1042 (\$5995)	\$772 (\$3492)	\$1131 (\$6464)	\$976 (\$6196)	\$1095 (\$6115)
Total costs: (2017 USD)					
Mean (SD)	\$5557 (\$19,190)	\$4161 (\$12,011)	\$6134 (\$18,149)	\$4903 (\$18,370)	\$5917 (\$23,327)
Median	\$1219	\$773	\$1599	\$812	\$1320
(Q1, Q3)	(\$362, \$3917)	(\$201, \$2685)	(\$507, \$304)	(\$234, \$3289)	(\$428, \$4430)

^aServices are considered epilepsy-related if claims contain either an epilepsy diagnosis, nonfebrile convulsions diagnosis, or an AED prescription.

AED = anti-epileptic drug; Q = quartile; SD = standard deviation; USD = US dollars.

Table S2. Poisson Regression Models Evaluating Significant Effects on Healthcare Resource Utilization per Patient During the 12-Month Follow-up Period, by Index AED Pill Burden

	All Patients (N= 53, 338)		
	Incidence Rate Ratio	95% Confidence Interval	P Value
All-Cause Healthcare Resource Utilization			
Inpatient			
Index AED pill burden (ref = >0-1 pill/day)			
>1-2 pills/day	1.026	(0.980-1.075)	0.2644
>2-3 pills/day	1.046	(0.997-1.097)	0.0681
>3 pills/day	0.990	(0.944-1.037)	0.6665
Outpatient pharmacy			
Index AED pill burden (ref = >0-1 pill/day)			
>1-2 pills/day	0.963	(0.958-0.969)	<0.0001
>2-3 pills/day	0.960	(0.955-0.966)	<0.0001
>3 pills/day	0.982	(0.977-0.988)	<0.0001
Emergency room			
Index AED pill burden (ref = >0-1 pill/day)			
>1-2 pills/day	1.019	(0.991-1.048)	0.1800
>2-3 pills/day	1.033	(1.003-1.064)	0.0318
>3 pills/day	0.971	(0.944-1.000)	0.0500
Physician office			
Index AED pill burden (ref = >0-1 pill/day)			
>1-2 pills/day	0.949	(0.942-0.955)	<0.0001
>2-3 pills/day	0.906	(0.899-0.913)	<0.0001
>3 pills/day	0.880	(0.874-0.887)	<0.0001
Other outpatient			
Index AED pill burden (ref = >0-1 pill/day)			
>1-2 pills/day	0.968	(0.959-0.977)	<0.0001
>2-3 pills/day	0.973	(0.963-0.982)	<0.0001
>3 pills/day	1.010	(1.001-1.020)	0.0273
Epilepsy-Related Healthcare Resource Utilization			
Inpatient			
Index AED pill burden (ref = >0-1 pill/day)			
>1-2 pills/day	1.125	(1.039-1.218)	0.0036
>2-3 pills/day	1.231	(1.129-1.342)	<0.0001
>3 pills/day	1.194	(1.101-1.296)	<0.0001
Outpatient pharmacy			
Index AED pill burden (ref = >0-1 pill/day)			
>1-2 pills/day	1.010	(0.999-1.021)	0.0814

>2-3 pills/day	1.010	(0.998-1.022)	0.1102
>3 pills/day	1.071	(1.059-1.083)	<0.0001
Emergency room			
Index AED pill burden (ref = >0-1 pill/day)			
>1-2 pills/day	1.155	(1.089-1.224)	<0.0001
>2-3 pills/day	1.252	(1.174-1.334)	<0.0001
>3 pills/day	1.151	(1.083-1.222)	<0.0001
Physician office			
Index AED pill burden (ref = >0-1 pill/day)			
>1-2 pills/day	1.084	(1.062-1.107)	<0.0001
>2-3 pills/day	1.147	(1.121-1.174)	<0.0001
>3 pills/day	1.125	(1.101-1.149)	<0.0001
Other outpatient			
Index AED pill burden (ref = >0-1 pill/day)			
>1-2 pills/day	1.056	(1.029-1.083)	<0.0001
>2-3 pills/day	1.162	(1.130-1.196)	<0.0001
>3 pills/day	1.316	(1.283-1.351)	<0.0001

Note: Each setting represents model results from separate Poisson regressions. The following candidate covariates were removed due to collinearity or insufficient sample sizes: index AED type and diagnoses observed during data period. AED = anti-epileptic drug.

Table S3. All-Cause and Epilepsy-Related^a Healthcare Resource Utilization and Costs per Patient During the 12-Month Follow-up Period, by Index AED Dosing Frequency

All-Cause Healthcare Resource Utilization and Costs					
	All Patients	Once Daily	Twice Daily	Thrice Daily	Four Times Daily
	(N = 53,338)	(n = 5974)	(n = 31,218)	(n = 16,102)	(n = 44)
Patients with inpatient services, n (%)	11,700 (21.9)	1025 (17.2)	6512 (20.9)	4155 (25.8)	8 (18.2)
Number of inpatient admissions, mean (SD)	0.4 (1.1)	0.3 (0.9)	0.4 (1.0)	0.5 (1.3)	0.4 (1.2)
Length of stay (in days), mean (SD)	6.3 (12.2)	7.2 (16.9)	6.2 (12.4)	6.3 (10.3)	10.4 (8.1)
Cost of inpatient services (2017 USD), mean (SD)	\$8403 (\$37,258)	\$5841 (\$27,100)	\$7559 (\$35,055)	\$10,988 (\$43,945)	\$8954 (\$26,528)
Patients with outpatient pharmacy services, n (%)	53,338 (100.0)	5974 (100.0)	31,218 (100.0)	16,102 (100.0)	44 (100.0)
Number of outpatient prescriptions, mean (SD)	26.7 (18.8)	25.0 (17.9)	25.6 (17.6)	29.4 (20.8)	34.2 (28.2)
Cost of outpatient prescriptions (2017 USD), mean (SD)	\$5285 (\$9509)	\$4091 (\$6687)	\$5779 (\$10,074)	\$4772 (\$9211)	\$5142 (\$5921)
Patients with emergency room services, n (%)	20,502 (38.4)	2067 (34.6)	11,670 (37.4)	6749 (41.9)	16 (36.4)
Number of emergency room visits, mean (SD)	1.0 (2.7)	0.9 (2.4)	0.9 (2.6)	1.2 (3.1)	1.0 (2.5)
Cost of emergency room visits (2017 USD), mean (SD)	\$894 (\$4287)	\$695 (\$2514)	\$839 (\$4437)	\$1075 (\$4506)	\$580 (\$1474)
Patients with physician office services, n (%)	51,813 (97.1)	5787 (96.9)	30,433 (97.5)	15,553 (96.6)	40 (90.9)
Number of physician office visits, mean (SD)	14.5 (15.3)	12.7 (14.0)	14.2 (14.9)	15.7 (16.3)	11.2 (12.1)
Cost of physician office visits (2017 USD), mean (SD)	\$3180 (\$10,336)	\$2177 (\$5585)	\$3171 (\$10,527)	\$3573 (\$11,267)	\$1644 (\$2197)

Patients with other outpatient services, n (%)	46,913 (88.0)	5135 (86.0)	27,393 (87.7)	14,343 (89.1)	42 (95.5)
Number of other outpatient visits, mean (SD)	10.1 (18.0)	8.0 (14.8)	9.6 (17.6)	11.7 (19.5)	23.9 (28.3)
Cost of other outpatient visits (2017 USD), mean (SD)	\$8253 (\$28,359)	\$5245 (\$21,063)	\$8107 (\$29,203)	\$9617 (\$28,878)	\$21,010 (\$49,124)
Total costs (2017 USD)					
Mean (SD)	\$26,015 (\$59,880)	\$18,049 (\$42,440)	\$25,455 (\$58,894)	\$30,026 (\$66,565)	\$37,331 (\$71,184)
Median	\$8720	\$6461	\$8973	\$9207	\$14,766
(Q1, Q3)	(\$3415, \$22,633)	(\$2461, \$15,921)	(\$3888, \$21,781)	(\$2839, \$27,853)	(\$3687, \$35,973)
Epilepsy-Related^a Healthcare Resource Utilization and Costs					
Patients with inpatient services, n (%)	5949 (11.2)	537 (9.0)	3743 (12.0)	1666 (10.3)	3 (6.8)
Number of inpatient admissions, mean (SD)	0.1 (0.5)	0.1 (0.5)	0.2 (0.6)	0.1 (0.5)	0.2 (0.8)
Length of stay (in days), mean (SD)	5.8 (14.9)	6.8 (20.5)	5.8 (14.0)	5.6 (14.9)	7.9 (7.8)
Cost of inpatient services (2017 USD), mean (SD)	\$2867 (\$16,770)	\$2213 (\$13,968)	\$3172 (\$17,714)	\$2516 (\$15,799)	\$3447 (\$17,581)
Patients with outpatient pharmacy services, n (%)	53,338 (100.0)	5974 (100.0)	31,218 (100.0)	16,102 (100.0)	44 (100.0)
Number of outpatient prescriptions, mean (SD)	6.8 (4.3)	6.9 (4.5)	7.0 (4.4)	6.4 (4.2)	8.5 (5.4)
Cost of outpatient prescriptions (2017 USD), mean (SD)	\$1075 (\$1741)	\$757 (\$1133)	\$1526 (\$2055)	\$320 (\$608)	\$638 (\$733)
Patients with emergency room services, n (%)	8500 (15.9)	866 (14.5)	5319 (17.0)	2311 (14.4)	4 (9.1)
Number of emergency room visits, mean (SD)	0.3 (0.9)	0.2 (0.8)	0.3 (0.9)	0.2 (0.8)	0.1 (0.4)
Cost of emergency room visits (2017 USD), mean (SD)	\$239 (\$1215)	\$201 (\$999)	\$257 (\$1306)	\$220 (\$1100)	\$88 (\$461)

Patients with physician office services, n (%)	35,090 (65.8)	4004 (67.0)	22,420 (71.8)	8639 (53.7)	27 (61.4)
Number of physician office visits, mean (SD)	2.0 (2.6)	1.9 (2.5)	2.3 (2.7)	1.5 (2.4)	1.8 (1.9)
Cost of physician office visits (2017 USD), mean (SD)	\$334 (\$849)	\$298 (\$721)	\$395 (\$953)	\$230 (\$644)	\$220 (\$313)
Patients with other outpatient services, n (%)	25,006 (46.9)	2880 (48.2)	15,431 (49.4)	6666 (41.4)	29 (65.9)
Number of other outpatient visits, mean (SD)	1.4 (4.5)	1.3 (3.8)	1.5 (4.7)	1.2 (4.4)	3.5 (7.2)
Cost of other outpatient visits (2017 USD), mean (SD)	\$1042 (\$5995)	\$860 (\$5227)	\$1168 (\$6374)	\$862 (\$5481)	\$1510 (\$3273)
Total costs (2017 USD)					
Mean (SD)	\$5557 (\$19,190)	\$4330 (\$16,223)	\$6517 (\$20,412)	\$4149 (\$17,581)	\$5903 (\$19,565)
Median	\$1219	\$970	\$1954	\$467	\$1175
(Q1, Q3)	(\$362, \$3917)	(\$408, \$2509)	(\$653, \$5069)	(\$168, \$1764)	(\$496, \$2578)

^aServices are considered disease related if claims contain either an epilepsy diagnosis, nonfebrile convulsions diagnosis, or an AED prescription.

AED = anti-epileptic drug; Q = quartile; SD = standard deviation; USD = US dollars.

Table S4. Poisson Regression Models Evaluating Significant Effects on Healthcare Resource Utilization per Patient During the 12-Month Follow-up Period, by Index AED Dosing Frequency

	All Patients (N = 53, 338)		
	Incidence Rate Ratio	95% Confidence Interval	P Value
All-Cause Healthcare Resource Utilization			
Inpatient			
Index AED dosing frequency (ref = once daily)			
Twice daily	1.000	(0.951-1.052)	0.9986
Thrice daily	1.362	(1.294-1.434)	<0.0001
Four times daily	0.939	(0.597-1.476)	0.7851
Outpatient pharmacy			
Index AED dosing frequency (ref = once daily)			
Twice daily	0.965	(0.959-0.970)	<0.0001
Thrice daily	1.064	(1.058-1.070)	<0.0001
Four times daily	1.219	(1.159-1.283)	<0.0001
Emergency room			
Index AED dosing frequency (ref = once daily)			
Twice daily	0.987	(0.957-1.017)	0.3868
Thrice daily	1.403	(1.360-1.448)	<0.0001
Four times daily	0.779	(0.575-1.056)	0.1075
Physician office			
Index AED dosing frequency (ref = once daily)			
Twice daily	1.028	(1.020-1.037)	<0.0001
Thrice daily	1.112	(1.103-1.122)	<0.0001
Four times daily	0.741	(0.678, 0.809)	<0.0001
Other outpatient			
Index AED dosing frequency (ref = once daily)			
Twice daily	0.973	(0.964-0.983)	<0.0001
Thrice daily	1.183	(1.171-1.195)	<0.0001
Four times daily	2.024	(1.904-2.151)	<0.0001
Epilepsy-Related Healthcare Resource Utilization			
Inpatient			
Index AED dosing frequency (ref = once daily)			
Twice daily	1.068	(0.987-1.156)	0.1026
Thrice daily	1.005	(0.924-1.093)	0.9007
Four times daily	1.200	(0.598-2.410)	0.6075
Outpatient pharmacy			
Index AED dosing frequency (ref = once daily)			
Twice daily	1.002	(0.991-1.012)	0.7781
Thrice daily	0.929	(0.918-0.940)	<0.0001
Four times daily	1.251	(1.130-1.386)	<0.0001
Emergency room			
Index AED dosing frequency (ref = once daily)			
Twice daily	1.092	(1.031-1.157)	0.0029
Thrice daily	1.151	(1.082-1.225)	<0.0001

Four times daily	0.401	(0.167-0.966)	0.0416
Physician office			
Index AED dosing frequency (ref = once daily)			
Twice daily	1.059	(1.037-1.080)	<0.0001
Thrice daily	0.834	(0.816-0.853)	<0.0001
Four times daily	0.941	(0.752-1.177)	0.5949
Other outpatient			
Index AED dosing frequency (ref = once daily)			
Twice daily	0.960	(0.937-0.984)	0.0011
Thrice daily	0.950	(0.925-0.975)	0.0001
Four times daily	2.298	(1.957-2.698)	<0.0001

Note: Each setting represents model results from separate Poisson regressions. The following candidate covariates were removed due to collinearity or insufficient sample sizes: index AED type, index AED mechanism class, and diagnoses observed during data period. AED = anti-epileptic drug.