

Anticonvulsant Use After Formulary Status Change for Brand-Name Second-Generation Anticonvulsants

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Anticonvulsants belong to a group of drugs that control or prevent convulsions.¹ Newer second-generation anticonvulsant agents have a well-documented beneficial effect as adjunctive treatment for those who suffer from seizure disorders. Besides being approved by the US Food and Drug Administration (FDA) to treat epilepsy, topiramate is approved for migraine prophylaxis, gabapentin for postherpetic neuralgia, and lamotrigine for the treatment of bipolar disorder. First-generation anticonvulsants such as valproic acid, carbamazepine, and phenytoin are effective, but require closer monitoring, are dosed more frequently, and have a more serious side-effect profile than second-generation drugs such as gabapentin, lamotrigine, and levetiracetam. After review of a pooled analysis of placebo-controlled clinical studies in which these drugs were used to treat epilepsy as well as psychiatric disorders and other conditions, the FDA required manufacturers to include warnings about suicide risk with the use of these anticonvulsants.²

The approved FDA labeling summarizes safety and efficacy data obtained from clinical trials. Neurontin is the brand-name version of gabapentin; generic gabapentin was made available in the United States as of November 2004. Once a drug is approved by the FDA, physicians may prescribe the drug for any indication, without regard for the specific indication that was the basis for the FDA approval.³ Such off-label prescribing often raises questions regarding patient safety and healthcare costs. Managed care, however, can restrict utilization of medication to indicated uses only.

Stafford recently defined off-label prescribing as “the prescription of a medication in a manner different from that approved by the FDA.”⁴ A 2003 report showed that off-label use in the United States accounted for approximately 21% of prescriptions.⁵ An analysis of office-based physician prescribing showed that almost 1 of every 5 prescriptions in the United States in 2001 was prescribed for off-label use.⁶ Anticonvulsants account for the highest rates of off-label use (74%), followed by antipsychotics (60%) and antibiotics (41%).^{4,5} In the Georgia Medicaid population in 1999-2000, 71% of anticonvulsant use was for off-label purposes.⁷ In 2001, 83% of gabapentin use was off-label.⁶

Following the availability of generic gabapentin in November 2004, a managed care plan with 1,036,345 members implemented a formulary change in January 2005, assigning second-generation anticonvulsants to nonformulary status and making generic gabapentin the only preferred anticonvulsant

Background: Anticonvulsant medications are commonly used for off-label indications. However, managed care organizations can restrict utilization of medication to indicated uses only.

Objective: To evaluate the pattern of off-label use of second-generation anticonvulsants after implementing a formulary change.

Methods: We did a retrospective analysis of an administrative pharmacy claims database for a managed care plan with more than 1 million members continuously enrolled during 2004-2005. The study evaluated off-label use and explored pharmacy utilization patterns (by physician specialty, region, plan type, age, sex, copayment) across the study population following the formulary change.

Results: A total of 10,185 patients had at least 1 pharmacy claim (total of 137,638 claims) for a second-generation anticonvulsant during the study period. Most members were female (68%), and 4.9% were <18 years old. A total of 3986 of 4698 patients (84.8%) and 4600 of 5487 patients (83.8%) had anticonvulsants prescribed for off-label use in 2004 and 2005, respectively ($P = .162$). The off-label usage pattern varied for individual anticonvulsants in 2004 and 2005 ($P < .050$), which may have been because of the change to nonpreferred coverage. Primary care physicians accounted for 41.3% of the prescribing of second-generation anticonvulsants for off-label uses, followed by neurologists (9.4%), psychiatrists (2.8%), and other (46.5%). The coverage change resulted in cost savings for the plan of \$0.16 per member per month.

Conclusions: The off-label usage pattern varied for individual anticonvulsants in 2004 and 2005. Future considerations for controlling off-label use may include requiring prior authorization and provider education.

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Take-Away Points

A formulary change assigning brand-name second-generation anticonvulsants to non-formulary status and making generic gabapentin the only preferred anticonvulsant was implemented in January 2005 by a managed care plan.

- In 2004 and 2005, respectively, 84.8% and 83.8% of anticonvulsants had off-label use ($P = .162$).
- The off-label usage pattern varied for individual anticonvulsants in 2004 and 2005 ($P < .050$), which may have been because of the change to nonpreferred formulary status.
- The health plan reported savings of \$0.16 per member per month (PMPM); a decrease from \$0.78 PMPM in 2004 to \$0.62 PMPM in 2005.

drug (Figure 1). All members had a 3-tier benefit. Most typical copayments (\pm \$5) were \$10 (tier 1), \$25 (tier 2), and \$50 (tier 3). Copayments were not changed from 2004 to 2005 from a benefit perspective. The plan had a mandatory generic benefit design; therefore, members had to pay an ancillary charge to obtain Neurontin.

The primary objective of the present study was to evaluate the pattern of off-label use after the formulary change. To explore the variation in utilization after the change in pharmacy benefit design (a third-tier copayment for second-generation anticonvulsants, Figure 1), the secondary objective of this study was to explore the utilization pattern and costs of second-generation anticonvulsants after the formulary change.

METHODS

Study Design and Study Population

This study was a retrospective analysis using medical and pharmacy claims data from a large, national, managed care health plan of approximately 1 million commercially insured members with pharmacy benefits. The plan members were evenly distributed with a male to female ratio of 1:1. For the study, patients were selected who had at least 1 second-generation anticonvulsant pharmacy claim (topiramate, zonisamide, lamotrigine, gabapentin, tiagabine, or levetiracetam) during the study period (Figure 1). Pharmacy and medical claims were matched during the given year. Members with an anticonvulsant prescription were matched to their medical claims by *International Classification of Diseases, Ninth Revision (ICD-9)* codes and separated by labeled versus off-labeled indications. Those members who had an ICD-9 code for a labeled indication were grouped as “labeled” users. These patients had to be continuously enrolled from January 1, 2004, through December 31, 2005; there were no age criteria in patient selection.

Recruitment Strategy and Creation of Analytical Data Sets

Pharmacy claims data for this cohort were matched to medical claims data using unique member identification

numbers. The medical claims data contained ICD-9, diagnosis (primary, secondary, and tertiary) codes of predetermined indicated and off-labeled uses. Labeled indications were derived from the product prescribing information. Off-label uses were obtained from the Micromedex Healthcare series database and abstracts of the Cochrane Collaborative Systemic Review.^{8,9} Key words used in the Cochrane Review search included [second generation

anticonvulsants], [off-label use], [anti-epileptics], [gabapentin], [pain], [neuropathy], and [labeled indications]. These ICD-9 diagnosis codes for off-label uses were grouped into 7 categories, which included bipolar disorder, migraines, neuropathy, other mental disorders, other neurologic disorders, other pain, and miscellaneous. The Appendix lists all ICD-9 codes used to recognize off-label indications during the data extraction. Because topiramate has a migraine indication and lamotrigine has a bipolar disorder indication, those indications were not recorded as off-label uses. Physician specialty was identified as the primary description in the database of contracted providers with the plan. Noncontracted physicians whose information was not loaded into the database defaulted to the “other” category.

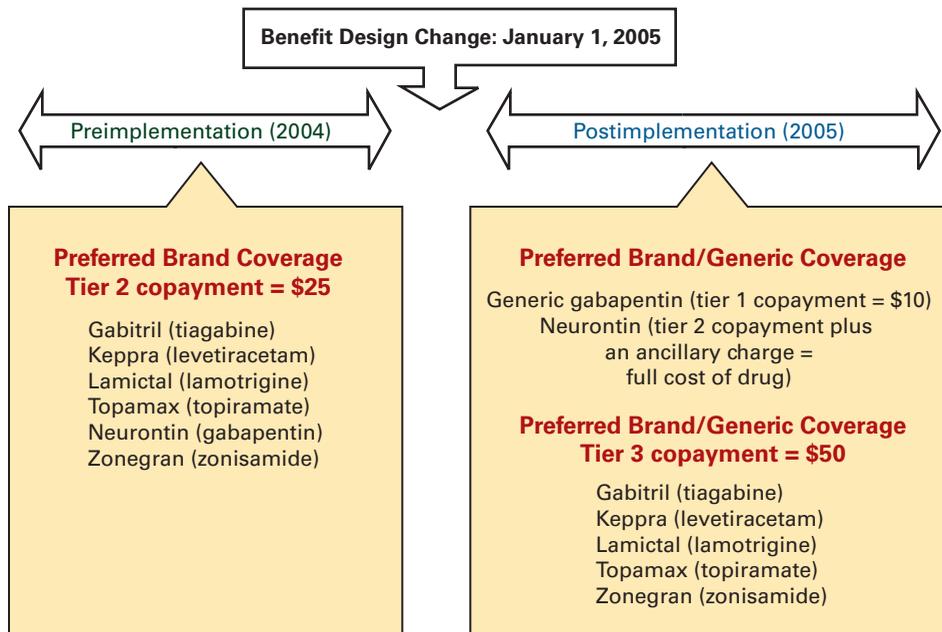
Statistical Analysis

Descriptive analyses for all variables were conducted for all study variables. The measured characteristics included age (at the beginning of the study), sex, and physician specialty. Patients’ baseline characteristics were identified from prescriptions filled during the year prior to implementing the benefit change (calendar year 2004). Bivariate comparisons of preimplementation versus postimplementation of the formulary change were conducted with *t* tests for continuous variables and χ^2 tests for categorical variables. All statistical tests were considered significant at $P < .05$. All analyses for this study were conducted using SPSS version 11.0 (SPSS, Chicago, IL). Drug costs were measured as average wholesale price obtained from First Data Bank in February 2006¹⁰; exact pharmacy claim costs were not used due to proprietary information held by the plan.

RESULTS

The final sample consisted of 10,185 patients with a total of 137,638 pharmacy claims. Table 1 shows patient characteristics, provider specialty, and patterns of anticonvulsant utilization in study population by year. Among those patients, 68.0% were female, whereas the health plan is evenly

■ **Figure 1.** Drug Formulary Changes in 2005 Versus 2004



distributed with a male to female ratio of 1:1. Mean (SD) patient age was 46.75 (14.53) years; 4.9% were younger than age 18 years, 13.9% were age 18 to 35 years, 39.3% were age 36 to 50 years, 35.0% were age 51 to 65 years, and 7.0% were age >65 years. We found that more than 80% of anticonvulsant prescriptions were for off-label uses during the study period. In 2004 and 2005, respectively, 3986 of 4698 (84.8%) and 4600 of 5487 (83.8%) anticonvulsants had an off-label use ($P = .162$). The distribution of the second-generation anticonvulsant utilization during the study period is shown in **Figure 2**. There was an increase in overall utilization of gabapentin (68% to 72%) and lamotrigine (6% to 9%), and a decrease in utilization of topiramate (16% to 13%), tiagabine (4% to 2%), and zonisamide (3% to 1%) (**Figure 2**) ($P < .05$).

Off-label use of individual anticonvulsants varied ($P < .050$) after the change in preferred-formulary coverage (**Table 2**). Generic gabapentin utilization increased (11.5% to 68.0%), whereas topiramate utilization decreased (16.2% to 12.5%). Detailed utilization rates for each anticonvulsants are given in **Table 2**. Primary care providers accounted for 41.3% of the pharmacy claims for generation anticonvulsants for off-label uses versus 9.4% for neurologists, 2.8% for psychiatrists, and 46.5% for other specialty (**Table 2**). Only psychiatrists' prescribing pattern changed with the formulary change during the study period ($P = .001$, **Table 2**). Most of these off-label uses were for pain other than neuropathy (22%) and for a miscellaneous category that included symptoms of involun-

tary movement, malnutrition, or injuries. Use of these agents to treat migraines decreased nonsignificantly between 2004 and 2005. Bipolar disorder-related off-label use decreased significantly from 2004 to 2005 (6.3% to 3.6%; $P < .001$). This study considered the use of topiramate for migraine prophylaxis, gabapentin for postherpetic neuralgia, and lamotrigine for bipolar disorder as labeled indications because these medications were FDA approved for those uses.

A noteworthy decrease in cost was noticed from the benefit change as the plan paid per member per month (PMPM) by \$0.16 (PMPM \$0.78 in 2004 to \$0.62 in 2005). The number of anticonvulsant claims per patient remained the same for both years (**Table 3**).

DISCUSSION

We found that more than 80% of anticonvulsant prescriptions were for off-label purposes. Most of these uses were for pain, neuropathic pain, and other mental and neurologic disorders, which is consistent with the study of off-label anticonvulsant use in the Georgia Medicaid population.⁸ Several studies reported that 71% to 74% of these anticonvulsants claims were being used for off-label indications.^{3,4,7,11} Since this study, there have been regulatory changes that allow off-label promotion to physicians. Allowing promotion of drugs for off-label uses without evidence to support their safety and efficacy for these purposes may lead to additional costs and unknown outcomes.¹²

■ **Table 1.** Patient Characteristics, Provider Specialty, and Patterns of Anticonvulsant Utilization in 2004 and 2005^a

Characteristic	Total Population (N = 10,185)	2004 (n = 4698)	2005 (n = 5487)	P ^b
Age, mean (SD), y^c	46.75 (14.53)	46.44 (14.31)	47.01 (14.69)	.496
Age group, y				
<18	496 (4.9)	238 (5.1)	258 (4.7)	.395
18-35	1414 (13.9)	638 (13.6)	778 (14.1)	.413
36-50	4004 (39.3)	1924 (40.9)	2080 (37.9)	.002
51-65	3561 (35.0)	1585 (33.7)	1976 (36.0)	.016
≥65	710 (7.0)	313 (6.7)	397 (7.2)	.258
Female	6931 (68.0)	3221 (68.5)	3710 (67.6)	.307
Physician specialty^d				
Neurologist	1373 (13.5)	644 (13.7)	729 (13.3)	.534
Psychiatrist	281 (2.8)	157 (3.3)	124 (2.2)	.001
Primary care provider	4067 (40.0)	1859 (39.6)	2208 (40.2)	.491
Other	4464 (43.8)	2038 (43.3)	2426 (44.2)	.398
Anticonvulsant use^e				
Gabapentin only	6058 (59.4)	2717 (57.8)	3341 (60.9)	.002
Other second-generation anticonvulsant	4127 (40.5)	1981 (42.2)	2146 (39.1)	.002
Labeled versus nonlabeled anticonvulsant use^f				
Labeled indications only	1599 (15.7)	712 (15.2)	887 (16.2)	.162
Nonlabeled indications only (off-label use)	8586 (84.3)	3986 (84.8)	4600 (83.8)	.162
Both labeled and nonlabeled indications	10,185 (100.0)	4698 (46.13)	5487 (53.87)	—

^aValues are number (percentage) unless indicated otherwise.
^bP value for comparison of 2004 with 2005 using the *t* test for age and cost and the Pearson χ^2 test for categorical variables. Boldface entries are significant ($P < .05$).
^cAll means are per patient per year; that is, per patient treated with anticonvulsants during the calendar year indicated.
^dPhysician specialty was identified as the primary description in the database of contracted providers with the plan. Noncontracted physicians whose information was not loaded into the database defaulted to the "other" category.
^eIndicates whether patient had at least 1 claim for the drug shown during the year. Other second-generation anticonvulsants include tiagabine, levetiracetam, lamotrigine, topiramate, and zonisamide.
^fIndicates pattern of utilization for patient during the year.

Changing the formulary by removing selected second-generation anticonvulsants, which resulted in a mean \$25 increase in member copayment, was not associated with a significant change in overall rates of off-label prescribing. However, the usage patterns for individual anticonvulsants changed among off-label users ($P < .050$), which may have been because of the change in the formulary plan. Utilization of individual anticonvulsants both decreased and increased. In this managed care plan only psychiatrists prescribed anticonvulsants at a significantly lower rate after the formulary change (3.3% vs 2.2%; $P = .001$).

In this study population, gabapentin was utilized most frequently for off-label purposes (70.1%) compared with levetiracetam (3.1%), tiagabine (2.5%), and zonisamide (2.0%) (Table 2). The 2005 change in gabapentin utilization was probably due to the availability of gabapentin at the lowest-tier copayment (standard generic copayment of \$10 per pre-

scription) in 2005. Gabapentin became available in a generic form in November 2004. More investigation is needed to examine the reason of this utilization pattern.

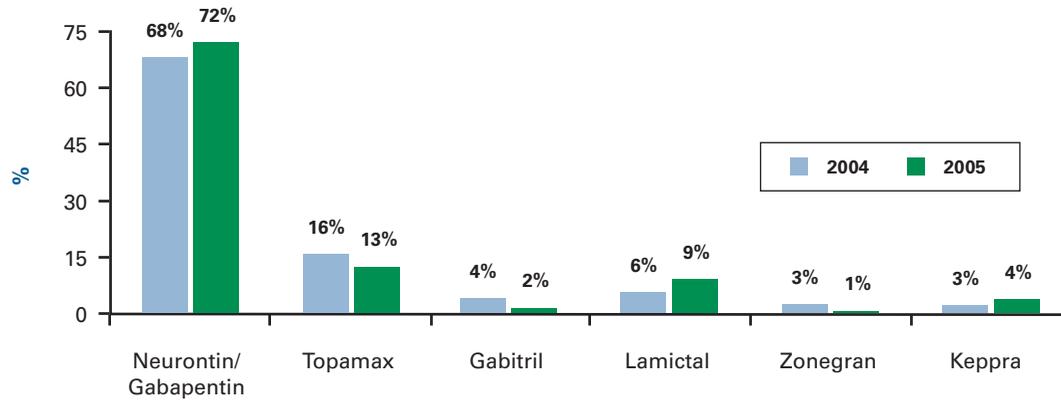
The study results show a significant decrease in the plan's PMPM cost from 2004 to 2005, which may be due to the change in the benefit structure (Table 3) for the second-generation anticonvulsants. The decrease in cost to the plan was attributable to the availability of generic gabapentin in late 2004, thereby saving the plan \$0.16 PMPM (Table 3).

Limitations

First, our study was a retrospective analysis without a control group, which prevents determination of a causal relationship between the change in benefit and the change in prescribing patterns. Second, the long-term impact of the formulary change on prescribing patterns may not be reflected in the short duration (1 year) of the study period. Third, this

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■ **Figure 2.** Distribution of Second-Generation Anticonvulsant Users in 2004 and 2005 (N = 10,185 Patients)^a



^a $P < .05$.

■ **Table 2.** Off-Label Anticonvulsant Utilization by Drug, Physician Specialty, and Diagnosis^a

Variable	No. (%)			P^b
	Total Off-Label Population (N = 8586)	2004 (n = 3986)	2005 (n = 4600)	
Brand-name gabapentin (Neurontin)	2434 (28.3)	2241 (56.2)	191 (4.1)	.001
Generic gabapentin	3592 (41.8)	461 (11.5)	3131 (68.0)	.001
All gabapentin	6024 (70.1)	2702 (67.7)	3322 (72.2)	.001
Topiramate	1224 (14.2)	648 (16.2)	576 (12.5)	.001
Tiagabine	217 (2.5)	149 (3.7)	68 (1.5)	.001
Lamotrigine	680 (7.9)	255 (6.3)	425 (9.2)	.001
Zonisamide	172 (2.0)	126 (3.1)	46 (1.0)	.001
Levetiracetam	269 (3.1)	106 (2.7)	163 (3.5)	.019
Physician specialty^c				
Neurologist	809 (9.4)	383 (9.6)	426 (9.3)	.582
Psychiatrist	238 (2.8)	135 (3.3)	103 (2.2)	.001
Primary care physician	3550 (41.3)	1643 (41.2)	1907 (41.4)	.824
Other	3989 (46.5)	1825 (45.7)	2164 (47.0)	2.44
Diagnosis				
Bipolar disease	418 (7.85)	251 (6.3)	165 (3.6)	.001
Migraine	1128 (13.14)	538 (13.5)	590 (12.8)	.359
Other mental disorders	1132 (13.18)	540 (13.5)	592 (12.9)	.335
Other neurologic disorders	569 (6.63)	255 (6.4)	314 (6.8)	.426
Neuropathy	709 (8.26)	312 (7.8)	397 (8.6)	.178
Other pain	1881 (21.91)	878 (22.0)	1003 (21.8)	.803
Miscellaneous	2751 (32.04)	1212 (30.4)	1539 (33.5)	.003

^aAn off-label claim was defined as use for a nonlabeled indication.

^b P for comparison of 2004 with 2005 using the Pearson χ^2 test for categorical variables. Boldface entries are significant ($P < .05$).

^cPhysician specialty was identified as the primary description in the database of contracted providers with the plan. Noncontracted physicians whose information was not loaded into the database defaulted to the "other" category.

study did not address several outcomes that could potentially have been affected by the change in copayment, including discontinuation, medication possession ratios, and use of anticonvulsants for labeled indications such as epilepsy. Fourth, felbamate (Felbatol) and oxcarbazepine (Trileptal) were not

included in this study. Fifth, although each member was counted only once as having anticonvulsants, they may or may not have had more than 1 anticonvulsant. Sixth, the exact pharmacy claim costs were not used in this study because of proprietary information held by the plan.

■ **Table 3.** Utilization and Cost of Second-Generation Anticonvulsants

Variable	2004	2005	Difference
Paid pharmacy claims	52,028	54,050	—
Total health plan membership	1,036,414	1,035,441	—
Rx PMPY (paid pharmacy claims/ total health plan membership)	0.0502	0.0522	0.002
Number of claims per anticonvulsant user	11.07	9.85	-1.22
Total anticonvulsant cost ^a	\$10.7 million	\$9.5 million	\$1.2 million
Average cost per Rx	\$206.20	\$175.81	-\$30.39
Drug cost PMPM	\$0.86	\$0.73	-\$0.13
Member paid PMPM	\$0.08	\$0.11	\$0.03
Plan paid PMPM	\$0.78	\$0.62	-\$0.16

PMPM indicates per member per month; PMPY, per member per year; Rx, prescription.

^aAnticonvulsant cost was defined as average wholesale price as an average of all second-generation anticonvulsant costs. Actual claim costs were not provided as proprietary confidential information was held by the plan.

CONCLUSIONS

A change in pharmacy drug formulary status to require a third-tier copayment for second-generation anticonvulsants appeared to have no effect on off-label use in this population overall; however, utilization patterns varied among individual anticonvulsants because of this formulary change. A cost saving of \$0.16 PMPM was attributable to the availability of generic gabapentin in late 2004. Future considerations for controlling off-label utilization in managed care organizations may include requiring prior authorizations, and provider education and guidance. This study addressed a need for the management of a medication class that has generally been left unmanaged. Further studies on the cost of adverse effects from the utilization of off-label medications should be done.

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Anticonvulsant Use After Formulary Status Change

■ Appendix. ICD-9 Diagnosis Codes^a Grouping for Labeled and Off-Label Uses

ICD-9 Code ^b	Neurontin/ Gabapentin	Topamax	Lamictal	Keppra	Zonegran	Gabitril	Description	Section
250	o	o	o	o	o	o	Diabetes with neuro- logic manifestations, type II or unspecified, not uncontrolled	Neuropathy
274	o	o	o	o	o	o	Gouty arthropathy	Other pain
053	●	o	o	o	o	o	Postherpetic neuralgia	Postherpetic neuralgia
290	o	o	o	o	o	o	Senile dementia, uncomplicated	Mental disorders
291	o	o	o	o	o	o	Alcohol-induced men- tal disorders	Mental disorders
292	o	o	o	o	o	o	Drug-induced mental disorders	Mental disorders
293	o	o	o	o	o	o	Transient mental disor- ders due to conditions classified elsewhere	Mental disorders
294	o	o	o	o	o	o	Other organic psychot- ic conditions (chronic)	Mental disorders
295	o	o	o	o	o	o	Schizophrenic disorders	Mental disorders
296	o	o	●	o	o	o	Episodic mood disor- ders/bipolar disorders	Bipolar disorder
297	o	o	o	o	o	o	Delusional disorders	Mental disorders
298	o	o	o	o	o	o	Other nonorganic psychoses	Mental disorders
299	o	o	o	o	o	o	Pervasive developmen- tal disorders	Mental disorders
300	o	o	o	o	o	o	Anxiety, dissocia- tive and somatoform disorders	Mental disorders
301	o	o	o	o	o	o	Personality disorders	Mental disorders
303	o	o	o	o	o	o	Alcohol dependence syndrome	Mental disorders
305	o	o	o	o	o	o	Nondependent antide- pressant-type abuse	Mental disorders
307	o	o	o	o	o	o	Special symptoms or syndromes, other	Mental disorders
309	o	o	o	o	o	o	Adjustment reaction	Mental disorders
315	o	o	o	o	o	o	Specific delays in development	Mental disorders
332	o	o	o	o	o	o	Parkinson's disease	Neurologic disorders
333	o	o	o	o	o	o	Other extrapyramidal disease and abnormal movement disorders	Neurologic disorders
337	o	o	o	o	o	o	Disorders of the auto- nomic nervous system	Neurologic disorders
340	o	o	o	o	o	o	Multiple sclerosis	Neurologic disorders
342	o	o	o	o	o	o	Hemiplegia and hemiparesis	Neurologic disorders
345	●	●	●	●	●	●	Epilepsy	Epilepsy

(Continued)

■ Appendix. ICD-9 Diagnosis Codes^a Grouping for Labeled and Off-Label Uses (Continued)

ICD-9 Code ^b	Neurontin/ Gabapentin	Topamax	Lamictal	Keppra	Zonegran	Gabitril	Description	Section
346	○	●	○	○	○	○	Migraine	Migraine
350	○	○	○	○	○	○	Trigeminal nerve disorders	Neurologic disorders
351	○	○	○	○	○	○	Facial nerve disorders	Neurologic disorders
352	○	○	○	○	○	○	Disorders of other cranial nerves	Neurologic disorders
356	○	○	○	○	○	○	Hereditary and idiopathic peripheral neuropathy	Neuropathy
357	○	○	○	○	○	○	Inflammatory and toxic neuropathy	Neuropathy
367	○	○	○	○	○	○	Spasm of accommodation	Other pain
379	○	○	○	○	○	○	Nystagmus and other irregular eye movements	Neurologic disorders
642	○	○	○	○	○	○	Mild or unspecified preeclampsia	Miscellaneous
728	○	○	○	○	○	○	Spasm of muscle	Other pain
780	○	○	○	○	○	○	General symptoms	Miscellaneous
781	○	○	○	○	○	○	Symptoms involving nervous and musculo-skeletal systems	Neurologic disorders
783	○	○	○	○	○	○	Symptoms concerning nutrition, metabolism, and development	Miscellaneous
784	○	●	○	○	○	○	Headache	Migraine
719	○	○	○	○	○	○	Pain in joint	Other pain
724	○	○	○	○	○	○	Pain in thoracic spine	Other pain
729	○	○	○	○	○	○	Pain in limb	Other pain
786	○	○	○	○	○	○	Chest pain	Other pain
789	○	○	○	○	○	○	Abdominal pain	Other pain
908	○	○	○	○	○	○	Late effect of certain complications of trauma	Miscellaneous
951	○	○	○	○	○	○	Injury to other cranial nerve(s)	Miscellaneous
952	○	○	○	○	○	○	Spinal cord injury without evidence of spinal bone injury	Miscellaneous
966	○	○	○	○	○	○	Poisoning—other unspecified anticonvulsants	Miscellaneous
969	○	○	○	○	○	○	Poisoning—antidepressants	Miscellaneous

ICD-9 indicates *International Classification of Diseases, Ninth Revision*; open circles, off-label use; solid circle, labeled indication.

^aBased on primary, secondary, and tertiary diagnosis codes. Three-digit ICD-9 code is inclusive of 4- and 5-digit subcodes.

^bICD-9 codes grouped as specific diagnosis codes are lengthy. Please refer to description to view diagnosis. For example, ICD-9 code 250 above refers only to ICD-9 codes 250.61, 250.62, and 250.63. ICD-9 code 784 here represents ICD-9 code 784.0 (headache) only. These ICD-9 codes were determined at data extraction.