



Modular Program Report

The following report(s) provides findings from an FDA-initiated query using its Mini-Sentinel pilot. While Mini-Sentinel queries may be undertaken to assess potential medical product safety risks, they may also be initiated for various other reasons. Some examples include determining a rate or count of an identified health outcome of interest, examining medical product use, exploring the feasibility of future, more detailed analyses within Mini-Sentinel, and seeking to better understand the capabilities of the Mini-Sentinel pilot.

Data obtained through Mini-Sentinel are intended to complement other types of evidence such as preclinical studies, clinical trials, postmarket studies, and adverse event reports, all of which are used by FDA to inform regulatory decisions regarding medical product safety. The information contained in this report is provided as part of FDA's commitment to place knowledge acquired from the Mini-Sentinel pilot in the public domain as soon as possible. Any public health actions taken by FDA regarding products involved in Mini-Sentinel queries will continue to be communicated through existing channels.

FDA wants to emphasize that the fact that FDA has initiated a query involving a medical product and is reporting findings related to that query does not mean that FDA is suggesting health care practitioners should change their prescribing practices for the medical product or that patients taking the medical product should stop using it. Patients who have questions about the use of an identified medical product should contact their health care practitioners.

The following report contains a description of the request, request specifications, and results from the modular program run(s).

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Overview	
<u>Request Description</u>	<p>FDA requested execution of Modular Program #3 (MP3), version 4.0, to investigate use of several anti-epileptic drug products (AEDs) and diagnosis of kidney stones (see Appendix A). Due to the large list of exposure codes, a code list for AEDs is not provided in this report. Please contact the Mini-Sentinel Operations Center (MSOC_Requests@harvardpilgrim.org) for a list of exposure codes. Each product was analyzed by two unique incidence definitions and two unique kidney stone definitions. Incidence was defined with respect to a specified list of AEDs (phenytoin, phenobarbital, carbamazepine, oxcarbazepine, gabapentin, pregabalin, lacosamide, valproic acid, lamotrigine, topiramate, zonisamide, levetiracetam, clonazepam, rufinamide, diazepam, thosuxamide, felbamate, primidone, tiagabine, lorazepam, ezogabine, vigabatrin, clobazam, and acetazolamide - Please contact MSOC for a list of exposure codes) as well as with respect to the drug of interest, acetazolamide, topiramate, and zonisamide only. Kidney stone events were defined with the list of codes in Appendix A: one definition including ICD-9-CM diagnosis code 788.0, the other excluding ICD-9-CM diagnosis code 788.0. The query was run against the Mini-Sentinel Distributed Database (MSDD) for the time period of January 1, 2004 to December 31, 2012. This request was distributed to 18 Mini-Sentinel Data Partners on May 13, 2013.</p> <p>This report presents results for gabapentin and phenytoin only. Separate reports present results for lamotrigine, levetiracetam, and topiramate (MSY4_MPR29_V1, Report 1 of 3) and carbamazepine, oxcarbazepine, and zonisamide (MSY4_MPR29_V1, Report 2 of 3).</p> <p>Results provide counts of new AED users, total dispensings, new episodes, days supplied, days at risk (days supplied + any episode gap days + any episode extension days), kidney stone events, eligible members, and member-days.</p>
<u>Request ID</u>	msy4_mpr29_v1 Report 3 of 3

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<u>Notes:</u>	Please contact the Mini-Sentinel Operations Center (MSOC_Requests@harvardpilgrim.org) for questions and to provide comments/suggestions for future enhancements to this document

Modular Program Specifications MSY4_MPR29_V1

Modular Program #3, version 4.0, was used to investigate exposure to antiepileptic drugs (AEDs) and kidney stone events. The query period was from January 1, 2004 to December 31, 2012. The enrollment gap was set at 45 days, and age groups were split as follows: 0-<2, 2-<5, 5-<10, 10-<17, 17-<40, 40-<65, 65+ years. In total, 8 different scenarios with differing exposures of interest, incidence definitions, and event definitions were examined in this report.

Drug/Exposure									Event/Outcome								
Incident exposure	Incident w/ respect to:	Washout (days)	Incidence Type	Episode Gap	Exposure Extension Period	Min. Episode Duration	Min. Days Supplied	Event/ Outcome	Care Setting	Principal Dx	Event incident w/ respect to:	Incident Only Care Setting	Washout (days)	Incidence Type	Incident Only Principal Dx	Blackout Period	
IVIG																	
1	gabapentin	All AEDs	183	Single	10	10	0	0	Kidney stones including 788.0	All	NO	Kidney stones including 788.0	All	183	Multiple	NO	0
2	gabapentin	All AEDs	183	Single	10	10	0	0	Kidney stones excluding 788.0	All	NO	Kidney stones excluding 788.0	All	183	Multiple	NO	0
3	gabapentin	gabapentin, topiramate, zonisamide, acetazolamide	183	Single	10	10	0	0	Kidney stones including 788.0	All	NO	Kidney stones including 788.0	All	183	Multiple	NO	0
4	gabapentin	gabapentin, topiramate, zonisamide, acetazolamide	183	Single	10	10	0	0	Kidney stones excluding 788.0	All	NO	Kidney stones excluding 788.0	All	183	Multiple	NO	0
5	phenytoin	All AEDs	183	Single	10	10	0	0	Kidney stones including 788.0	All	NO	Kidney stones including 788.0	All	183	Multiple	NO	0
6	phenytoin	All AEDs	183	Single	10	10	0	0	Kidney stones excluding 788.0	All	NO	Kidney stones excluding 788.0	All	183	Multiple	NO	0

Modular Program Specifications MSY4_MPR29_V1

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IVIG																	
7	phenytoin	phenytoin, topiramate, zonisamide, acetazolamide	183	Single	10	10	0	0	Kidney stones including 788.0	All	NO	Kidney stones including 788.0	All	183	Multiple	NO	0
8	phenytoin	phenytoin, topiramate, zonisamide, acetazolamide	183	Single	10	10	0	0	Kidney stones excluding 788.0	All	NO	Kidney stones excluding 788.0	All	183	Multiple	NO	0

NDC codes checked against First Data Bank's "National Drug Data File (NDDF®) Plus"
 ICD-9-CM diagnosis and procedure codes checked against "Ingenix 2012 ICD-9-CM Data File" provided by OptumInsight
 HCPCS codes checked against "Optum 2012 HCPCS Level II Data File" provided by OptumInsight
 CPT codes checked against "Optum 2012 Current Procedure Codes & Relative Values Data File" provided by OptumInsight

Glossary of Terms in Modular Program 3*

- Blackout Period** - number of days at the beginning of a treatment episode that events are to be ignored. If an event occurs during the blackout period, the episode is excluded.
- Care Setting** - type of medical encounter or facility where the exposure, event, or condition code was recorded. Possible care settings include: Inpatient Hospital Stay (IP), Non-Acute Institutional Stay (IS), Emergency Department (ED), Ambulatory Visit (AV), and Other Ambulatory Visit (OA).
- Days at Risk** - number of days supplied plus any episode gaps and exposure extension periods.
- Eligible Members** - Number of members eligible for an incident treatment episode (defined by the drug/exposure and event washout periods) with drug and medical coverage during the query period.
- Enrollment Gap** - number of days allowed between two consecutive enrollment periods without breaking a “continuously enrolled” sequence.
- Episode Gap** - number of days allowed between two (or more) consecutive exposures (dispensings/procedures) to be considered the same treatment episode.
- Exposure Extension Period** - number of days post treatment period in which the outcomes/events are counted for a treatment episode.
- Incidence Type (drug/exposure)**- *Minimum incidence type* will consider the first treatment episode in the query period as long as it is the first treatment episode in the user's entire available history. *Single* and *Multiple incidence types* will use the washout period to establish incidence, however *Single* will only consider the first treatment episode whereas *Multiple* will consider all qualifying incident treatment episodes.
- Incidence Type (event/outcome)**- *Minimum incidence type* considers the first event in a valid episode as long as it is the first event in the user's entire available history. *Multiple incidence type* uses the washout period to establish incidence and considers all qualifying incident treatment episodes. The program will only consider one event per episode, but the *Multiple incidence type* will consider more than one event per user if a user has more than one incident episode.
- Lookback Period (pre-existing condition)** - number of days wherein a member is required to have evidence of pre-existing condition (diagnosis/procedure/drug dispensing).
- Member-Days** - sum of all days of enrollment with medical and drug coverage** in the query period preceded by an exposure washout period.
- Minimum Days Supplied** - specifies a minimum number of days in length of the days supplied for the episode to be considered.
- Minimum Episode Duration** - specifies a minimum number of days in length of the episode for it to be considered.
- New Episodes** - new treatment episodes; length of episode is determined by days supplied in one dispensing (or consecutive dispensings bridged by the episode gap).
- New Users** - number of members with incident exposure during the query period. Member must have no evidence of exposure (s) of interest (defined by incidence criteria) in the prior washout period. A user may only be counted once in a query period.
- Principal Diagnosis** - diagnosis or condition established to be chiefly responsible for admission of the patient to the hospital. YES will only consider diagnoses flagged as Principal
- Query Period** - period in which the modular program looks for exposures and outcomes of interest.
- Total Days Supplied** - number of days supplied for all dispensings in qualifying treatment episodes.
- Washout Period (drug/exposure)**** - number of days a user is required to have no evidence of prior exposure (drug dispensing/procedure) and continuous drug and medical coverage prior to an incident treatment episode.
- Washout Period (event/outcome)**** - number of days a user is required to have no evidence of a prior event (procedure/diagnosis) and continuous drug and medical coverage prior to an incident treatment episode.

*all terms may not be used in this report

**incident treatment episodes must be incident to both the exposure and the event

Table 1: Summary of Incident AED Use and Kidney Stones in the MSDD between January 1, 2004 and December 31, 2012, by Drug, Exposure Incidence Definition, and Event Definition

	New Users	New Episodes	Dispensings	Total Days Supplied	Days at Risk	New Events	Eligible Members	Member-Days	New Users/ 1K Eligible Members	Days Supplied/ User	Dispensings/ User	Days Supplied/ Dispensing	Events/ 100K Days at Risk
Gabapentin													
Incident to all specified AEDs													
Events including code 788	1,250,526	1,250,526	2,705,969	95,753,486	103,382,227	7,352	91,828,109	75,452,363,610	13.62	76.57	2.16	35.39	7.11
Events excluding code 788	1,252,115	1,252,115	2,709,103	95,853,415	103,546,030	6,843	91,832,994	75,479,893,198	13.63	76.55	2.16	35.38	6.61
Incident to drug of interest, topiramate, zonisamide, acetazolamide only													
Events including code 788	1,585,505	1,585,505	3,735,000	132,369,291	143,684,946	10,359	93,231,880	78,110,749,195	17.01	83.49	2.36	35.44	7.21
Events excluding code 788	1,587,642	1,587,642	3,739,652	132,516,842	143,944,725	9,609	93,236,723	78,140,585,949	17.03	83.47	2.36	35.44	6.68
Phenytoin													
Incident to all specified AEDs													
Events including code 788	3,636	3,636	9,283	266,926	272,517	8	91,828,036	75,855,420,034	0.04	73.41	2.55	28.75	2.94
Events excluding code 788	3,637	3,637	9,289	267,064	272,695	7	91,832,921	75,883,731,772	0.04	73.43	2.55	28.75	2.57
Incident to drug of interest, topiramate, zonisamide, acetazolamide only													
Events including code 788	89,552	89,552	319,853	11,722,263	12,232,574	586	93,510,710	79,370,712,126	0.96	130.90	3.57	36.65	4.79
Events excluding code 788	89,638	89,638	320,202	11,732,768	12,250,442	536	93,515,504	79,402,628,196	0.96	130.89	3.57	36.64	4.38

Table 2: Summary of Incident AED Use and Kidney Stones in the MSDD between January 1, 2004 and December 31, 2012, by Drug, Exposure Incidence Definition, Kidney Stone (Events) Definition, and Age Group

	New Users	New Episodes	Dispensings	Total Days Supplied	Days at Risk	New Events	Eligible Members	Member-Days	New Users/ 1K Eligible Members	Days Supplied/ User	Dispensings/ User	Days Supplied/ Dispensing	Events/100K Days at Risk
Gabapentin													
Incident to all specified AEDs													
Events including code 788													
00 to 01 year	131	131	320	9,608	10,352	0	3,830,208	1,281,071,959	0.03	73.34	2.44	30.03	0.00
02 to 04 years	587	587	1,504	45,024	48,592	0	5,843,725	2,907,000,029	0.10	76.70	2.56	29.94	0.00
05 to 09 years	1,887	1,887	4,811	150,864	164,649	4	8,453,332	5,159,814,916	0.22	79.95	2.55	31.36	2.43
10 to 16 years	10,434	10,434	21,219	661,046	738,005	11	11,275,200	7,793,767,116	0.93	63.35	2.03	31.15	1.49
17 to 39 years	209,458	209,458	377,763	11,596,776	13,022,613	868	35,979,392	23,263,169,477	5.82	55.37	1.80	30.70	6.67
40 to 64 years	685,552	685,552	1,454,703	50,074,577	54,385,620	3,997	33,392,348	27,638,241,118	20.53	73.04	2.12	34.42	7.35
65+ years	342,477	342,477	845,649	33,215,591	35,012,396	2,472	8,013,295	7,333,115,215	42.74	96.99	2.47	39.28	7.06
Events excluding code 788													
00 to 01 year	131	131	320	9,608	10,352	0	3,830,292	1,281,166,018	0.03	73.34	2.44	30.03	0.00
02 to 04 years	587	587	1,504	45,024	48,592	0	5,843,778	2,907,260,763	0.10	76.70	2.56	29.94	0.00
05 to 09 years	1,889	1,889	4,814	151,014	164,846	3	8,453,425	5,160,181,150	0.22	79.94	2.55	31.37	1.82
10 to 16 years	10,445	10,445	21,240	661,674	738,803	8	11,275,354	7,794,436,112	0.93	63.35	2.03	31.15	1.08
17 to 39 years	209,792	209,792	378,481	11,618,813	13,051,553	796	35,981,918	23,272,519,630	5.83	55.38	1.80	30.70	6.10
40 to 64 years	686,422	686,422	1,456,129	50,119,176	54,465,327	3,722	33,394,488	27,651,298,702	20.55	73.02	2.12	34.42	6.83
65+ years	342,849	342,849	846,615	33,248,106	35,066,557	2,314	8,013,971	7,336,840,975	42.78	96.98	2.47	39.27	6.60

Table 2: Summary of Incident AED Use and Kidney Stones in the MSDD between January 1, 2004 and December 31, 2012, by Drug, Exposure Incidence Definition, Kidney Stone (Events) Definition, and Age Group

	New Users	New Episodes	Dispensings	Total Days Supplied	Days at Risk	New Events	Eligible Members	Member-Days	New Users/ 1K Eligible Members	Days Supplied/ User	Dispensings/ User	Days Supplied/ Dispensing	Events/100K Days at Risk
Gabapentin (continued)													
Incident to drug of interest, topiramate, zonisamide, acetazolamide only													
Events including code 788													
00 to 01 year	188	188	594	17,905	19,191	0	3,833,425	1,283,374,433	0.05	95.24	3.16	30.14	0.00
02 to 04 years	792	792	2,397	74,871	80,581	2	5,850,529	2,913,924,935	0.14	94.53	3.03	31.24	2.48
05 to 09 years	2,389	2,389	6,778	212,596	231,964	8	8,470,967	5,182,761,631	0.28	88.99	2.84	31.37	3.45
10 to 16 years	12,890	12,890	29,695	931,440	1,042,086	20	11,315,832	7,857,756,069	1.14	72.26	2.30	31.37	1.92
17 to 39 years	275,584	275,584	554,354	17,166,721	19,320,659	1,397	36,374,979	23,908,625,232	7.58	62.29	2.01	30.97	7.23
40 to 64 years	882,611	882,611	2,059,429	71,334,798	77,788,509	5,746	34,238,356	29,087,854,087	25.78	80.82	2.33	34.64	7.39
65+ years	411,051	411,051	1,081,753	42,630,960	45,201,956	3,186	8,281,284	7,800,137,287	49.64	103.71	2.63	39.41	7.05
Events excluding code 788													
00 to 01 year	188	188	594	17,905	19,191	0	3,833,510	1,283,469,170	0.05	95.24	3.16	30.14	0.00
02 to 04 years	792	792	2,397	74,871	80,581	2	5,850,582	2,914,186,850	0.14	94.53	3.03	31.24	2.48
05 to 09 years	2,392	2,392	6,783	212,774	232,199	7	8,471,061	5,183,132,494	0.28	88.95	2.84	31.37	3.01
10 to 16 years	12,903	12,903	29,723	932,238	1,044,307	14	11,315,983	7,858,443,425	1.14	72.25	2.30	31.36	1.34
17 to 39 years	276,069	276,069	555,455	17,200,280	19,370,685	1,279	36,377,498	23,918,638,653	7.59	62.30	2.01	30.97	6.60
40 to 64 years	883,783	883,783	2,061,679	71,404,536	77,920,765	5,331	34,240,472	29,102,153,534	25.81	80.79	2.33	34.63	6.84
65+ years	411,515	411,515	1,083,021	42,674,238	45,276,997	2,976	8,281,947	7,804,240,234	49.69	103.70	2.63	39.40	6.57

Table 2: Summary of Incident AED Use and Kidney Stones in the MSDD between January 1, 2004 and December 31, 2012, by Drug, Exposure Incidence Definition, Kidney Stone (Events) Definition, and Age Group

	New Users	New Episodes	Dispensings	Total Days Supplied	Days at Risk	New Events	Eligible Members	Member-Days	New Users/ 1K Eligible Members	Days Supplied/ User	Dispensings/ User	Days Supplied/ Dispensing	Events/100K Days at Risk
Phenytoin													
Incident to all specified AEDs													
Events including code 788													
00 to 01 year	169	169	344	10,486	10,957	0	3,830,208	1,281,068,022	0.04	62.05	2.04	30.48	0.00
02 to 04 years	295	295	609	19,745	19,913	0	5,843,695	2,907,006,130	0.05	66.93	2.06	32.42	0.00
05 to 09 years	411	411	1,035	32,672	33,584	1	8,453,417	5,160,110,500	0.05	79.49	2.52	31.57	2.98
10 to 16 years	388	388	738	21,707	22,925	0	11,275,847	7,796,252,619	0.03	55.95	1.90	29.41	0.00
17 to 39 years	396	396	1,112	31,936	32,599	1	35,983,481	23,319,497,912	0.01	80.65	2.81	28.72	3.07
40 to 64 years	672	672	1,449	38,994	39,985	0	33,417,825	27,859,793,323	0.02	58.03	2.16	26.91	0.00
65+ years	1,305	1,305	3,996	111,386	112,554	6	8,042,859	7,455,507,655	0.16	85.35	3.06	27.87	5.33
Events excluding code 788													
00 to 01 year	169	169	344	10,486	10,957	0	3,830,292	1,281,162,081	0.04	62.05	2.04	30.48	0.00
02 to 04 years	295	295	609	19,745	19,913	0	5,843,748	2,907,267,047	0.05	66.93	2.06	32.42	0.00
05 to 09 years	411	411	1,035	32,672	33,606	0	8,453,510	5,160,476,876	0.05	79.49	2.52	31.57	0.00
10 to 16 years	388	388	738	21,707	22,925	0	11,276,002	7,796,925,200	0.03	55.95	1.90	29.41	0.00
17 to 39 years	397	397	1,118	32,074	32,755	1	35,986,012	23,328,988,069	0.01	80.79	2.82	28.69	3.05
40 to 64 years	672	672	1,449	38,994	39,985	0	33,420,007	27,873,296,838	0.02	58.03	2.16	26.91	0.00
65+ years	1,305	1,305	3,996	111,386	112,554	6	8,043,573	7,459,425,720	0.16	85.35	3.06	27.87	5.33

Table 2: Summary of Incident AED Use and Kidney Stones in the MSDD between January 1, 2004 and December 31, 2012, by Drug, Exposure Incidence Definition, Kidney Stone (Events) Definition, and Age Group

	New Users	New Episodes	Dispensings	Total Days Supplied	Days at Risk	New Events	Eligible Members	Member-Days	New Users/ 1K Eligible Members	Days Supplied/ User	Dispensings/ User	Days Supplied/ Dispensing	Events/100K Days at Risk
Phenytoin (continued)													
Incident to drug of interest, topiramate, zonisamide, acetazolamide only													
Events including code 788													
00 to 01 year	270	270	629	19,635	21,724	0	3,833,394	1,283,335,204	0.07	72.72	2.33	31.22	0.00
02 to 04 years	468	468	1,406	44,609	48,338	0	5,850,532	2,913,969,726	0.08	95.32	3.00	31.73	0.00
05 to 09 years	724	724	2,225	71,970	77,906	2	8,471,372	5,183,620,531	0.09	99.41	3.07	32.35	2.57
10 to 16 years	2,255	2,255	6,692	219,391	238,575	3	11,318,189	7,864,079,570	0.20	97.29	2.97	32.78	1.26
17 to 39 years	20,238	20,238	62,305	2,083,559	2,229,218	95	36,411,494	24,064,140,348	0.56	102.95	3.08	33.44	4.26
40 to 64 years	40,734	40,734	146,964	5,256,254	5,502,812	278	34,451,459	29,800,266,439	1.18	129.04	3.61	35.77	5.05
65+ years	24,863	24,863	99,632	4,026,845	4,114,001	208	8,423,044	8,184,981,646	2.95	161.96	4.01	40.42	5.06
Events excluding code 788													
00 to 01 year	270	270	629	19,635	21,724	0	3,833,479	1,283,429,941	0.07	72.72	2.33	31.22	0.00
02 to 04 years	468	468	1,406	44,609	48,338	0	5,850,585	2,914,231,824	0.08	95.32	3.00	31.73	0.00
05 to 09 years	724	724	2,225	71,970	77,928	1	8,471,466	5,183,992,351	0.09	99.41	3.07	32.35	1.28
10 to 16 years	2,256	2,256	6,693	219,398	238,595	3	11,318,342	7,864,773,598	0.20	97.25	2.97	32.78	1.26
17 to 39 years	20,266	20,266	62,445	2,087,663	2,234,872	81	36,414,006	24,074,546,864	0.56	103.01	3.08	33.43	3.62
40 to 64 years	40,766	40,766	147,036	5,258,470	5,507,779	258	34,453,623	29,815,744,908	1.18	128.99	3.61	35.76	4.68
65+ years	24,888	24,888	99,768	4,031,023	4,121,206	193	8,423,741	8,189,583,980	2.95	161.97	4.01	40.40	4.68

Table 3: Summary of Incident AED Use and Kidney Stones in the MSDD between January 1, 2004 and December 31, 2012, by Drug, Exposure Incidence Definition, Kidney Stone (Events) Definition, and Sex

	New Users	New Episodes	Dispensings	Total Days Supplied	Days at Risk	New Events	Eligible Members	Member-Days	New Users/ 1K Eligible Members	Days Supplied/ User	Dispensings/ User	Days Supplied/ Dispensing	Events/100K Days at Risk
Gabapentin													
Incident to all specified AEDs													
Events including code 788													
Female	748,639	748,639	1,599,445	56,547,022	61,216,527	3,635	46,559,998	38,324,729,834	16.08	75.53	2.14	35.35	5.94
Male	501,084	501,084	1,104,954	39,156,708	42,110,039	3,714	45,159,221	37,018,092,639	11.10	78.14	2.21	35.44	8.82
Unknown	803	803	1,570	49,756	55,661	3	108,890	109,541,137	7.37	61.96	1.96	31.69	5.39
Events excluding code 788													
Female	749,600	749,600	1,601,400	56,609,466	61,316,379	3,330	46,562,842	38,339,802,775	16.10	75.52	2.14	35.35	5.43
Male	501,712	501,712	1,106,133	39,194,193	42,173,990	3,510	45,161,260	37,030,518,659	11.11	78.12	2.20	35.43	8.32
Unknown	803	803	1,570	49,756	55,661	3	108,892	109,571,764	7.37	61.96	1.96	31.69	5.39
Incident to drug of interest, topiramate, zonisamide, acetazolamide only													
Events including code 788													
Female	967,398	967,398	2,264,862	80,254,509	87,319,324	5,368	47,429,028	39,998,523,214	20.40	82.96	2.34	35.43	6.15
Male	617,096	617,096	1,468,006	52,045,965	56,288,405	4,985	45,693,420	38,000,646,527	13.51	84.34	2.38	35.45	8.86
Unknown	1,011	1,011	2,132	68,817	77,217	6	109,432	111,579,454	9.24	68.07	2.11	32.28	7.77
Events excluding code 788													
Female	968,724	968,724	2,267,823	80,348,563	87,484,721	4,884	47,431,850	40,015,117,142	20.42	82.94	2.34	35.43	5.58
Male	617,907	617,907	1,469,697	52,099,462	56,382,787	4,719	45,695,441	38,013,856,554	13.52	84.32	2.38	35.45	8.37
Unknown	1,011	1,011	2,132	68,817	77,217	6	109,432	111,612,253	9.24	68.07	2.11	32.28	7.77

Table 3: Summary of Incident AED Use and Kidney Stones in the MSDD between January 1, 2004 and December 31, 2012, by Drug, Exposure Incidence Definition, Kidney Stone (Events) Definition, and Sex

	New Users	New Episodes	Dispensings	Total Days Supplied	Days at Risk	New Events	Eligible Members	Member-Days	New Users/ 1K Eligible Members	Days Supplied/ User	Dispensings/ User	Days Supplied/ Dispensing	Events/100K Days at Risk
Phenytoin													
Incident to all specified AEDs													
Events including code 788													
Female	1,780	1,780	4,759	135,267	138,617	4	46,559,969	38,567,164,551	0.04	75.99	2.67	28.42	2.89
Male	1,852	1,852	4,519	131,555	133,814	4	45,159,177	37,178,412,316	0.04	71.03	2.44	29.11	2.99
Unknown	4	4	5	104	86	0	108,890	109,843,167	0.04	26.00	1.25	20.80	0.00
Events excluding code 788													
Female	1,780	1,780	4,759	135,267	138,617	4	46,562,813	38,582,715,656	0.04	75.99	2.67	28.42	2.89
Male	1,853	1,853	4,525	131,693	133,992	3	45,161,216	37,191,142,322	0.04	71.07	2.44	29.10	2.24
Unknown	4	4	5	104	86	0	108,892	109,873,794	0.04	26.00	1.25	20.80	0.00
Incident to drug of interest, topiramate, zonisamide, acetazolamide only													
Events including code 788													
Female	42,525	42,525	146,857	5,310,803	5,562,138	237	47,622,601	40,812,029,513	0.89	124.89	3.45	36.16	4.26
Male	46,955	46,955	172,540	6,395,799	6,654,359	349	45,778,598	38,446,359,857	1.03	136.21	3.67	37.07	5.24
Unknown	72	72	456	15,661	16,077	0	109,511	112,322,756	0.66	217.51	6.33	34.34	0.00
Events excluding code 788													
Female	42,575	42,575	147,057	5,317,039	5,571,389	209	47,625,415	40,829,986,060	0.89	124.89	3.45	36.16	3.75
Male	46,991	46,991	172,689	6,400,068	6,662,976	327	45,780,578	38,460,286,028	1.03	136.20	3.67	37.06	4.91
Unknown	72	72	456	15,661	16,077	0	109,511	112,356,108	0.66	217.51	6.33	34.34	0.00

Table 4: Summary of Incident AED Use and Kidney Stones in the MSDD between January 1, 2004 and December 31, 2012, by Drug, Exposure Incidence Definition, Kidney Stone (Events) Definition, and Year

	New Users	New Episodes	Dispensings	Total Days Supplied	Days at Risk	New Events	Eligible Members	Member-Days	New Users/ 1K Eligible Members	Days Supplied/ User	Dispensings/ User	Days Supplied/ Dispensing	Events/100K Days at Risk
Gabapentin													
Incident to all specified AEDs													
Events including code 788													
2004	59,541	59,541	156,171	5,360,720	5,795,979	335	18,956,681	4,110,724,626	3.14	90.03	2.62	34.33	5.78
2005	76,642	76,642	181,710	6,449,390	6,987,247	383	20,870,444	5,870,172,729	3.67	84.15	2.37	35.49	5.48
2006	76,696	76,696	185,471	6,977,420	7,500,647	396	22,283,083	6,148,457,225	3.44	90.98	2.42	37.62	5.28
2007	94,824	94,824	220,807	8,295,766	8,922,847	516	24,802,942	6,534,004,925	3.82	87.49	2.33	37.57	5.78
2008	164,060	164,060	372,422	13,211,615	14,368,929	943	45,291,762	10,051,338,645	3.62	80.53	2.27	35.47	6.56
2009	223,841	223,841	495,562	17,353,059	18,904,687	1,385	46,256,029	12,915,168,967	4.84	77.52	2.21	35.02	7.33
2010	225,536	225,536	492,343	17,087,308	18,634,626	1,440	44,386,301	12,447,975,003	5.08	75.76	2.18	34.71	7.73
2011	210,978	210,978	415,996	14,507,717	15,804,173	1,364	42,778,157	11,959,101,062	4.93	68.76	1.97	34.87	8.63
2012	118,408	118,408	185,487	6,510,491	6,463,092	590	25,366,905	5,415,420,428	4.67	54.98	1.57	35.10	9.13
Events excluding code 788													
2004	59,638	59,638	156,435	5,368,316	5,808,861	309	18,958,382	4,112,371,124	3.15	90.02	2.62	34.32	5.32
2005	76,749	76,749	181,912	6,456,022	7,002,092	349	20,871,945	5,872,441,430	3.68	84.12	2.37	35.49	4.98
2006	76,771	76,771	185,561	6,980,108	7,507,475	361	22,284,546	6,150,720,136	3.45	90.92	2.42	37.62	4.81
2007	94,954	94,954	221,097	8,305,046	8,936,586	472	24,805,386	6,536,332,150	3.83	87.46	2.33	37.56	5.28
2008	164,275	164,275	372,861	13,226,775	14,391,079	885	45,295,795	10,055,214,224	3.63	80.52	2.27	35.47	6.15
2009	224,135	224,135	496,166	17,372,085	18,936,676	1,293	46,258,899	12,920,090,054	4.85	77.51	2.21	35.01	6.83
2010	225,837	225,837	492,968	17,107,110	18,665,803	1,344	44,388,819	12,452,391,702	5.09	75.75	2.18	34.70	7.20
2011	211,225	211,225	416,428	14,521,242	15,826,898	1,270	42,780,183	11,963,049,509	4.94	68.75	1.97	34.87	8.02
2012	118,531	118,531	185,675	6,516,711	6,470,560	560	25,368,645	5,417,282,869	4.67	54.98	1.57	35.10	8.65

Table 4: Summary of Incident AED Use and Kidney Stones in the MSDD between January 1, 2004 and December 31, 2012, by Drug, Exposure Incidence Definition, Kidney Stone (Events) Definition, and Year

	New Users	New Episodes	Dispensings	Total Days Supplied	Days at Risk	New Events	Eligible Members	Member-Days	New Users/ 1K Eligible Members	Days Supplied/ User	Dispensings/ User	Days Supplied/ Dispensing	Events/100K Days at Risk
Gabapentin (continued)													
Incident to drug of interest, topiramate, zonisamide, acetazolamide only													
Events including code 788													
2004	81,245	81,245	241,683	8,316,489	8,983,382	536	19,372,957	4,265,705,223	4.19	102.36	2.97	34.41	5.97
2005	101,232	101,232	264,736	9,434,684	10,254,392	592	21,291,241	6,084,861,383	4.75	93.20	2.62	35.64	5.77
2006	98,065	98,065	262,963	9,973,774	10,773,950	583	22,670,475	6,353,621,555	4.33	101.71	2.68	37.93	5.41
2007	120,593	120,593	308,694	11,644,356	12,604,373	740	25,307,901	6,760,078,911	4.77	96.56	2.56	37.72	5.87
2008	211,270	211,270	528,372	18,803,396	20,526,034	1,418	46,279,952	10,418,136,247	4.57	89.00	2.50	35.59	6.91
2009	284,929	284,929	687,231	24,113,426	26,375,029	1,969	47,168,363	13,376,184,674	6.04	84.63	2.41	35.09	7.47
2010	281,650	281,650	660,891	22,941,167	25,140,268	1,990	45,250,339	12,879,257,025	6.22	81.45	2.35	34.71	7.92
2011	260,877	260,877	543,871	18,904,182	20,748,059	1,789	43,582,734	12,361,897,342	5.99	72.46	2.08	34.76	8.62
2012	145,644	145,644	236,559	8,237,817	8,279,459	742	25,938,038	5,611,006,835	5.62	56.56	1.62	34.82	8.96
Events excluding code 788													
2004	81,391	81,391	242,085	8,328,386	9,007,882	485	19,374,649	4,267,532,089	4.20	102.33	2.97	34.40	5.38
2005	101,382	101,382	265,051	9,444,830	10,277,702	542	21,292,676	6,087,348,930	4.76	93.16	2.61	35.63	5.27
2006	98,163	98,163	263,105	9,978,239	10,788,255	530	22,671,802	6,356,053,975	4.33	101.65	2.68	37.92	4.91
2007	120,767	120,767	309,104	11,657,799	12,626,894	683	25,310,354	6,762,582,584	4.77	96.53	2.56	37.71	5.41
2008	211,572	211,572	529,092	18,827,127	20,563,620	1,320	46,283,860	10,422,348,016	4.57	88.99	2.50	35.58	6.42
2009	285,340	285,340	688,103	24,141,277	26,425,293	1,826	47,171,064	13,381,532,502	6.05	84.61	2.41	35.08	6.91
2010	282,025	282,025	661,747	22,968,275	25,183,703	1,855	45,252,653	12,884,016,730	6.23	81.44	2.35	34.71	7.37
2011	261,191	261,191	544,513	18,923,900	20,780,738	1,670	43,584,564	12,366,148,507	5.99	72.45	2.08	34.75	8.04
2012	145,811	145,811	236,852	8,247,009	8,290,638	698	25,939,679	5,613,022,616	5.62	56.56	1.62	34.82	8.42

Table 4: Summary of Incident AED Use and Kidney Stones in the MSDD between January 1, 2004 and December 31, 2012, by Drug, Exposure Incidence Definition, Kidney Stone (Events) Definition, and Year

	New Users	New Episodes	Dispensings	Total Days Supplied	Days at Risk	New Events	Eligible Members	Member-Days	New Users/ 1K Eligible Members	Days Supplied/ User	Dispensings/ User	Days Supplied/ Dispensing	Events/100K Days at Risk
Phenytoin													
Incident to all specified AEDs													
Events including code 788													
2004	529	529	1,546	44,741	46,019	0	18,956,664	4,111,124,926	0.03	84.58	2.92	28.94	0.00
2005	535	535	1,485	40,952	41,885	1	20,904,319	5,877,665,121	0.03	76.55	2.78	27.58	2.39
2006	448	448	1,292	41,603	41,736	3	22,352,940	6,165,866,313	0.02	92.86	2.88	32.20	7.19
2007	384	384	821	25,136	25,784	1	24,909,245	6,561,965,328	0.02	65.46	2.14	30.62	3.88
2008	472	472	1,278	36,002	36,712	0	45,440,251	10,090,645,652	0.01	76.28	2.71	28.17	0.00
2009	486	486	1,150	31,674	33,236	2	46,482,593	12,975,120,711	0.01	65.17	2.37	27.54	6.02
2010	363	363	803	22,940	23,520	0	44,707,555	12,534,799,787	0.01	63.20	2.21	28.57	0.00
2011	285	285	687	17,421	17,783	1	43,184,468	12,068,129,412	0.01	61.13	2.41	25.36	5.62
2012	134	134	221	6,457	5,842	0	25,644,724	5,470,102,784	0.01	48.19	1.65	29.22	0.00
Events excluding code 788													
2004	530	530	1,552	44,879	46,175	0	18,958,365	4,112,772,475	0.03	84.68	2.93	28.92	0.00
2005	535	535	1,485	40,952	41,885	1	20,905,887	5,879,950,843	0.03	76.55	2.78	27.58	2.39
2006	448	448	1,292	41,603	41,758	2	22,354,518	6,168,170,805	0.02	92.86	2.88	32.20	4.79
2007	384	384	821	25,136	25,784	1	24,911,845	6,564,352,857	0.02	65.46	2.14	30.62	3.88
2008	472	472	1,278	36,002	36,712	0	45,444,506	10,094,599,086	0.01	76.28	2.71	28.17	0.00
2009	486	486	1,150	31,674	33,236	2	46,485,788	12,980,157,840	0.01	65.17	2.37	27.54	6.02
2010	363	363	803	22,940	23,520	0	44,710,527	12,539,387,473	0.01	63.20	2.21	28.57	0.00
2011	285	285	687	17,421	17,783	1	43,187,064	12,072,285,052	0.01	61.13	2.41	25.36	5.62
2012	134	134	221	6,457	5,842	0	25,646,813	5,472,055,341	0.01	48.19	1.65	29.22	0.00

Table 4: Summary of Incident AED Use and Kidney Stones in the MSDD between January 1, 2004 and December 31, 2012, by Drug, Exposure Incidence Definition, Kidney Stone (Events) Definition, and Year

	New Users	New Episodes	Dispensings	Total Days Supplied	Days at Risk	New Events	Eligible Members	Member-Days	New Users/ 1K Eligible Members	Days Supplied/ User	Dispensings/ User	Days Supplied/ Dispensing	Events/100K Days at Risk
Phenytoin (continued)													
Incident to drug of interest, topiramate, zonisamide, acetazolamide only													
Events including code 788													
2004	10,996	10,996	49,292	1,852,859	1,928,905	71	19,441,296	4,296,050,947	0.57	168.50	4.48	37.59	3.68
2005	11,771	11,771	45,327	1,687,794	1,763,225	77	21,404,007	6,136,316,676	0.55	143.39	3.85	37.24	4.37
2006	10,346	10,346	43,405	1,647,111	1,709,088	66	22,826,221	6,415,605,023	0.45	159.20	4.20	37.95	3.86
2007	9,210	9,210	33,825	1,257,763	1,314,844	51	25,548,985	6,845,592,514	0.36	136.56	3.67	37.18	3.88
2008	12,403	12,403	45,130	1,625,120	1,708,860	73	46,666,385	10,557,627,462	0.27	131.03	3.64	36.01	4.27
2009	12,941	12,941	42,630	1,494,216	1,569,334	104	47,666,775	13,577,686,680	0.27	115.46	3.29	35.05	6.63
2010	10,176	10,176	31,965	1,134,824	1,193,839	73	45,907,480	13,129,696,302	0.22	111.52	3.14	35.50	6.11
2011	8,074	8,074	21,359	768,580	802,436	59	44,370,723	12,650,556,992	0.18	95.19	2.65	35.98	7.35
2012	3,635	3,635	6,920	253,996	242,043	12	26,540,489	5,761,579,530	0.14	69.88	1.90	36.70	4.96
Events excluding code 788													
2004	11,011	11,011	49,336	1,854,078	1,932,075	60	19,442,947	4,297,930,604	0.57	168.38	4.48	37.58	3.11
2005	11,784	11,784	45,364	1,688,882	1,764,565	77	21,405,521	6,138,890,845	0.55	143.32	3.85	37.23	4.36
2006	10,358	10,358	43,442	1,648,487	1,711,140	60	22,827,715	6,418,152,431	0.45	159.15	4.19	37.95	3.51
2007	9,215	9,215	33,923	1,260,825	1,318,285	47	25,551,681	6,848,246,946	0.36	136.82	3.68	37.17	3.57
2008	12,414	12,414	45,167	1,626,230	1,712,326	64	46,670,559	10,562,078,582	0.27	131.00	3.64	36.00	3.74
2009	12,954	12,954	42,681	1,495,686	1,572,037	94	47,669,864	13,583,365,094	0.27	115.46	3.29	35.04	5.98
2010	10,184	10,184	31,975	1,135,069	1,194,413	67	45,910,322	13,134,877,511	0.22	111.46	3.14	35.50	5.61
2011	8,080	8,080	21,387	769,314	803,358	56	44,373,251	12,655,267,262	0.18	95.21	2.65	35.97	6.97
2012	3,638	3,638	6,927	254,197	242,243	11	26,542,571	5,763,818,921	0.14	69.87	1.90	36.70	4.54

Appendix A. Diagnosis and procedure codes used to define kidney stone events

ICD-9 diagnosis codes

592.0	Calculus of kidney (excludes uric acid stone)
592.1	Calculus of ureter
592.9	Urinary calculus, unspecified
274.11	Uric acid nephrolithiasis
788.0	Renal colic
594	Calculus of lower urinary tract

ICD-9 procedure codes

55.04	Percutaneous fragmentation with fragmentation
55.92	Repeat nephroscopic removal during current episode
56.2	Ureterotomy for removal of calculus or exploration
59.8	Transurethral ureteral stent placement for passage of calculus
59.95	Ultrasonic fragmentation of urinary stones
98.51	ESWL
55.04	percutaneous nephrostomy with fragmentation
98.51	Extracorporeal shockwave lithotripsy of the kidney, ureter, or bladder
59.95	ultrasonic fragmentation of urinary stones

CPT codes

50060	Nephrolithotomy; removal of calculus
50065	Secondary surgical operation for calculus
50070	Nephrolithotomy complicated by congenital kidney abnormality
50075	Removal of large staghorn calculus filling renal pelvis (includes anastrophic pyelolithotomy)
50080	Percutaneous nephrostolithotomy with or without lithotripsy, up to 2 cm
50081	PCNL, over 2 cm
50130	Pyelotomy, with removal of calculus
50590	ESWL
50610	Ureterolithotomy; upper one third of ureter
50620	Ureterolithotomy, middle one third of ureter
50630	Ureterolithotomy, lower one third of ureter
52320	Cysto, ureteral cath, removal of calculus

Appendix A. Diagnosis and procedure codes used to define kidney stone events

CPT codes (continued)

52325	With fragmentation of calculus (ultrasound or EHL)
52330	With manipulation, but not removal of stone
52336	With removal of stone
52337	With lithotripsy
50945	Laproscopy, surgical; ureterolithotomy
50561	Renal endoscopy through established nephrostomy or pyelostomy; with removal for foreign body or calculus
50580	Renal endoscopy through nephrotomy or pyelotomy, with or without irrigation, instillation or ureteropyelography, exclusive of radiologic service; with removal of foreign body or calculus
51060	transvesical ureterolithotomy
51065	Cystotomy, with calculus basket extraction and/or ultrasonic or electrohydraulic fragmentation of urethral calculus
50080	Percutaneous nephrostolithotomy or pyelostolithotomy, with or without dilation, endoscopy, lithotripsy, stenting: up to 2cm
50081	Percutaneous nephrostolithotomy or pyelostolithotomy, with or without dilation, endoscopy, lithotripsy, stenting: over 2cm
50060	Nephrolithotomy; removal of calculus
50070	Nephrolithotomy; complicated by congenital kidney abnormality
50075	Nephrolithotomy; removal of large staghorn calculus filling renal pelvis and calyces
50610	Ureterolithotomy; upper one-third of ureter
50620	Ureterolithotomy; middle one-third of ureter
50630	Ureterolithotomy; lower one-third of ureter
50590	Lithotripsy, extracorporeal shock wave
52320	Cystourethroscopy with removal of ureteral calculus
52325	cystourethroscopy with fragmentation of ureteral calculus
52352	Cystourethroscopy with ureteroscopy; with removal or manipulation of calculus
52353	Cystourethroscopy with ureteroscopy; with lithotripsy
