

Analysis of Anti-Epileptic Drugs in Fee-For-Service Wisconsin Medicaid

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ABSTRACT

Introduction: Off-label use of prescription drugs presents issues of patient safety and can significantly increase the overall prescription drug expenditure in providing health care services. As a class, the anti-epileptic drugs are provided for off-label use on a frequent basis. Because of the safety issues and increased cost with such prescribing practices, the Wisconsin Medicaid Drug Utilization Review Board (DUR board) reviewed the use of anti-epileptic agents in the fee-for-service Wisconsin Medicaid population.

Methods: Prescribers with the highest amount paid for drugs in this class, and for which there was no appropriate diagnosis (intervention group), were provided with a list of the patients for whom they prescribed the drug for an off-label clinical condition. A total of 488 prescribers were contacted and informed of the costs and hazards of off-label prescribing.

Results: Using a comparison group of patients who were prescribed anti-epileptic agents but who did not reach the amount paid threshold (non-intervention group), the study demonstrated a decrease of 6652 prescriptions in the intervention group and an increase of 4194 in the non-intervention group. In addition, expenditures for the intervention group dropped by \$752,232 and the non-intervention group rose by \$835,351. It is estimated that the overall financial impact of this inter-

vention was a savings of \$2,552,077 over the 5-month period of review.

INTRODUCTION

It has become accepted policy that physicians may prescribe FDA-approved prescription-only drugs for purposes other than those listed in the FDA-approved package insert. Guidelines published in OBRA'90 allow for the use of drugs for off-label indications if there is support in an authorized compendial source. This "off-label" use has been allowed provided the use is generally accepted in the scientific community and does not constitute experimentation.¹ In 2002, the American Academy of Pediatrics pointed out that the package insert is intended to provide all the information judged to be necessary for the safe usage of drugs. However, special groups, such as children and pregnant women, have commonly been excluded. Three fourths of the prescription drugs currently marketed in the United States lack pediatric use information and are labeled with disclaimers.²

In 1962, following the thalidomide experience, even though the drug was never approved for use in the United States, the Kefauver-Harris Amendments to the US Drug Laws made it mandatory for all new drugs to pass through stringent testing for toxicity, safety, and efficacy before they are permitted for use in clinical trials. In a study conducted by Knight Ridder, it was reported that approximately 8000 people became ill in 2001 after taking some of the most popular drugs for off-label use.³ Such statistics make off-label use of considerable interest to drug utilization review (DUR) programs. A study of drug-related morbidity and mortality in 2001 found that the cost of drug-related morbidity and mortality exceeds \$177.4 billion, more than doubling the estimated cost in 1995 of \$76.6 billion.⁴ Effective DUR should be able to demonstrate both cost reduction and avoidance of adverse events related to off-label drug use.

Prescription drug trends show a double-digit percentage increase in drug expenditures since 1995. These increases have been double or triple those of hospital

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care and physician services. Overall, prescription drugs are approximately 10% of the total national personal health care spending. The cost of newer, more expensive therapies and increasing use of those therapies—frequently for “off-label” indications—contributes to the increasing average retail price and expenditures.⁵

In a study using data from the 2001 IMS Health National Disease and Therapeutic Index (NDTI) to define prescribing patterns by diagnosis for 160 commonly prescribed drugs, Radley et al found an overall off-label use of 21%. Off-label use was most common for cardiac medications (46%) and anticonvulsants (46%). The highest off-label use was for gabapentin (83%) and amitriptyline hydrochloride (81%).⁶ Chen et al reviewed the off-label use of anticonvulsant drugs in the Georgia Medicaid population. Gabapentin was the anticonvulsant most widely used off-label (86%). Compared with other practitioners, neurologists were more likely to prescribe anticonvulsants off-label. In all, the anticonvulsant use off-label was 71%, with only a modest proportion of off-label uses supported by evidence from controlled trials.⁷

The Wisconsin Medicaid Drug Utilization Review Board is charged with the task of performing retrospective DUR. The Board is to “make recommendations on predetermined standards submitted to it by the Medicaid agency or the agency’s contractor, and to make recommendations to the Medicaid agency or the agency’s contractor concerning modification or elimination of existing predetermined standards or the addition of new ones.”⁸ As a function of DUR, the DUR Board elected to review the use of anti-epileptic drugs in the Wisconsin Medicaid population because of reported high volume off-label use of the drugs in this class.

METHODS

All claims for the newer anti-epileptic drugs (gabapentin, lamotrigine, felbamate, tiagabine, oxcarbazepine, topiramate, and levetiracetam) were extracted for the period June 2004 through May 2005. Prescribers’ specialties were extracted for all health care professionals and associated with the provider number attributed to the prescription. Data were aggregated by provider for preliminary analysis.

A query was run to gather any diagnosis for which these drugs are FDA-approved. They are post-herpetic neuralgia, diabetic neuropathy, or any seizure disorder since 2003 for all patients. If any diagnosis was found for these conditions, all prescriptions for the anti-epileptic were eliminated from the original extract. A similar aggregation was produced from the remaining claims.

Table 1. Total Expenditures, Anti-Epileptic Drugs, June 2004-May 2005, All Claims

Description	Amount Paid	% Total Costs
Gabapentin	\$12,824,937.08	32.3%
Lamotrigine	\$9,332,176.94	23.5%
Topiramate	\$8,194,263.08	20.6%
Levetiracetam	\$3,620,885.49	9.1%
Oxcarbazepine	\$2,995,423.40	7.5%
Zonisamide	\$1,426,056.73	3.6%
Tiagabine	\$697,710.41	1.8%
Felbamate	\$597,978.37	1.5%
Total	\$39,689,431.50	

Table 2. Off-Label Expenditures Claims with “Off-Label” Diagnosis, June 2004 to May 2005

Description	Amount Paid	% Claims with “Off-Label” Diagnosis
Gabapentin	\$10,120,079.42	78.9%
Topiramate	\$4,923,287.74	52.8%
Lamotrigine	\$4,226,915.60	51.6%
Oxcarbazepine	\$1,793,039.37	49.5%
Levetiracetam	\$834,471.05	27.9%
Tiagabine	\$478,171.62	33.5%
Zonisamide	\$458,028.42	65.6%
Felbamate	\$87,505.01	14.6%
Total	\$22,921,498.23	57.8%

Table 3. Prescriber Specialty, Anti-Epileptic Drugs, June 2004 to May 2005, Top 500 Prescribers, No “On-Label” Diagnosis

Specialty	Amount Paid	Count
Psychiatry	\$6,958,926.22	215
Neurology	\$1,895,900.83	69
Family Practice	\$1,226,323.54	63
Internal Medicine	\$1,092,991.39	52
None Specified	\$981,348.04	45
Anesthesiology	\$391,355.65	16
Physical Medicine/Rehab	\$269,556.07	14
Pediatrics	\$201,375.35	7
General Practice	\$149,693.17	5
Geriatrics	\$87,845.33	3
Pathology	\$52,013.16	1
Emergency Medicine	\$29,500.65	2
Radiology	\$13,337.81	1
Urgent Care	\$12,934.07	1
Cardiovascular Disease	\$10,360.86	1
Total	\$13,373,462.14	495

RESULTS

Total drug expenditures, and percent of total cost, for each drug is given in Table 1. The total expenditures for each drug having an “off-label” diagnosis are given in Table 2. A summary of the findings includes the following:

Table 4. Intervention Group Pre-Post Prescriptions and Change in Paid Amounts

Drug	Rxs Pre	Rxs Post	Decrease in Rxs	Decrease in Spending
Felbamate	94	93	1	-\$2,593.73
Gabapentin	11317	8674	2643	\$600,606.86
Lamotrigine	7446	6378	1068	\$91,458.71
Levetiracetam	1345	1117	228	\$20,383.51
Oxcarbazepine	3333	2613	720	\$83,991.11
Tiagabine	1136	663	473	\$32,545.22
Topiramate	6968	5450	1518	\$244,490.85
Zonisamide	810	593	217	\$21,251.04
Pregabalin	0	216	-216	-\$28,545.14
Total			6652	\$1,063,588.43
Adjusted for gabapentin price decrease				\$752,232.41

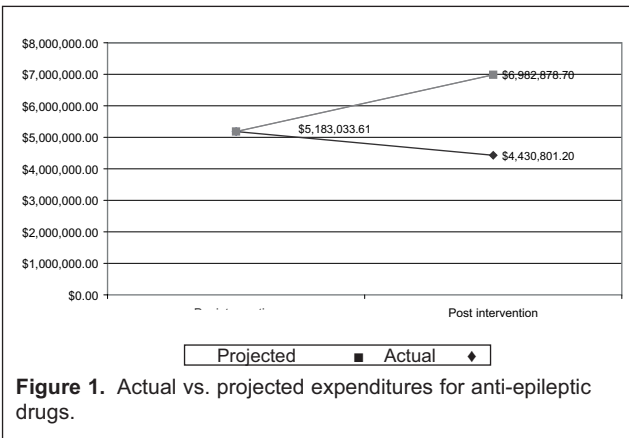


Table 5. Non-Intervention Group Pre-Post Prescriptions and Change in Paid Amounts

Drug	Rxs Pre	Rxs Post	Increase in Rxs	Increase in Spending
Felbamate	99	106	7	\$1,655.70
Gabapentin	20069	21343	1274	-\$389,174.20
Lamotrigine	2687	3654	967	\$258,702.09
Levetiracetam	1325	1720	395	\$92,520.58
Oxcarbazepine	1410	1806	396	\$83,635.96
Tiagabine	409	361	-48	\$13,003.79
Topiramate	3016	3756	740	\$218,380.36
Zonisamide	466	637	171	\$23,767.55
Pregabalin	0	292	292	\$39,339.70
Total				\$341,831.53
Adjusted for gabapentin price decrease				\$835,351.09

- Almost \$40 million was paid for these drugs in the 12 months analyzed. This represents 6.8% of the total FFS expenditures of \$591 million. A third of the payments was for gabapentin.
- No “on-label” diagnosis could be found for almost 60% of the prescriptions. Almost 80% of gabapentin prescriptions had an “off-label” diagnosis on file.

- Three drugs, levetiracetam (Keppra), felbamate (Felbatol), and tiagabine (Gabitril), had most of their use for “on-label” indications.

The top 500 prescribers, by amount paid, and broken down by specialty, are given in Table 3.

- The top 500 prescribers (less than 10%) account for almost 60% of the total expenditures for drugs for which no acceptable diagnosis was provided. Prescriber numbers identifying institutions were excluded from the intervention. Institutional prescribers numbers are often used by hospital staff in training and are needed for claims purposes but there is no easy method to trace this number back to a specific prescriber.
- Over 50% of the expenditures in the top 500 were for prescriptions written by psychiatrists.

Educational Intervention

The analysis suggests that there are a considerable number of prescriptions written for these drugs for off-label clinical diagnoses. The DUR Board recommended that an educational intervention be sent to the psychiatrists, family practitioners, general practitioners, and the unspecified specialty types to inform them of the Medicaid expenditures for anti-epileptic drugs, and asking them to review their use of these drugs. Based on subsequent Board input, the intervention was sent to all specialty types ranked in the top 500 by total amount paid for the prescriptions attributed to the prescriber. (Some of the top 500 prescribers were attributed to institutions and the default DEA number. As a result 495 intervention packets were prepared.) Seven prescriber addresses were not valid, leaving 488 prescribers who received an intervention packet.

The materials included in the intervention were a cover letter, a summary of the appropriate use of anti-epileptic drugs, a list of patients and their anti-epileptic drugs (including the amount paid) attributed to the prescriber, a physician profile, a response form, and a return envelope.

RESULTS

Pre/Post Evaluation

In order to compare the results of the intervention, the cumulative costs for the prescriber/patient combination sent in the intervention were extracted from the paid pharmacy claims. Five months post comparison data was compared with the 5 months of data preceding the intervention.

Intervention Group

Because the cost of gabapentin has been dropping, due to the availability of a generic version in this time period, an additional calculation was performed to adjust for cost savings due to price decrease. With the adjust-

ment, cost savings was calculated to be \$752,232. Table 4 and Figure 1 give the calculated and projected cost savings associated with the intervention.

Control Group – No Intervention

A similar cost analysis was performed for the cohort of prescriber/patient pairings that did not receive an intervention letter. The pharmacy claims data were extracted for this cohort for the same time periods used for the intervention comparisons. The summary of these results is shown in Table 5. In all cases the number of prescriptions increased in the control group. There was a substantial drop in the cost for gabapentin prescriptions as a result of the price decrease for generic gabapentin. Because of this, a similar adjustment was made for the gabapentin price. Table 5 gives the calculated number of prescriptions and cost associated with the non-intervention group.

The cost increases observed in the non-intervention group enables a projection of the increase in cost for the intervention group, had the intervention not taken place. This projection is displayed in Figure 1. For the intervention group, actual paid amounts decreased by \$752,232 in the post-intervention period. Based on the results of the non-intervention group, the post paid amount would have been expected to be \$6,982,878, an increase of \$1,799,845. Both the actual post-intervention and the projected post-intervention paid amounts were adjusted for the impact of gabapentin becoming available as a generic between the pre and post periods. Thus the likely overall financial effect of this intervention was \$2,552,077 in savings, which was achieved in 5 month comparison time.

Prescriber Response Forms

A prescriber response form was used to gather information from prescribers about their view of the usefulness of the material provided to them. Of 488 prescribers receiving the letter intervention, responses were obtained from 188, or 38.5% of prescribers. The results are as follows:

- I have reviewed the information provided and found it: (Number of respondents)
 - 33 very useful (5)
 - 68 useful (4)
 - 35 neutral (3)
 - 22 minimally useful (2)
 - 22 not useful (1)
- (Average of responses = 3.38)
- I have reviewed the information provided and:
 - 33% will review treatment regimens for my patients.
 - 50% have already explored other options before prescribing these drugs.
 - 2.7% changed how I am prescribing anti-epileptic drugs for non-approved indications.

37.8% did not modify the drug therapy because I believe treatment is appropriate.

5.3% have discussed an action with the patient.

0.5% referred the patient for additional evaluation.

(Percentages sum over 100% because a physician could check more than 1 option in keeping with having multiple patients profiled.)

CONCLUSIONS

Overall, fewer expenditures occurred in the intervention group after the intervention when compared to a similar time frame in the pre-intervention period. The opposite is true in the non-intervention group. This is despite the introduction of a new drug (pregabalin) in the anti-epileptic drug category in the post-intervention period.

While it is difficult to control for outside influences on the use of these drugs, the intervention seems to have contributed to the overall decrease in expenditures. Interventions of this type might be considered for other drug classes where clinical prescribing protocols have been developed.

One limitation of this study was the use of a comparison group that was different from the intervention group—lower use versus higher use of these drugs. However, it seems unlikely that this difference would negate the measured differences between the groups, given the magnitude of the difference.

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REFERENCES

1. Welcome to U.S. Pharmacist. Available at: www.uspharmacist.com/index.asp?show=article&page=8_1078.htm. Accessed September 5, 2006.
2. American Academy of Pediatrics, Policy Statement 2002; 110;1, July 2002:181-183.
3. PHARMABIZ.com. Friday March 10, 2006. Available at: www.pharmabiz.com/article/detnews.asp?articleid=24106§ionid=46&z=y. Accessed September 5, 2006.
4. Ernst FR, Grizzle AJ. Drug related morbidity and mortality: updating the cost of illness model. *J Amer Pharm Assoc*. 2001;41:192-199.
5. USP Public Policy Center Issue Brief: Prescription Drug Trends: Implications for State Drug Programs.
6. Radley DC, Findelstein SN, Stafford RS. Off-label prescribing among office-based physicians. *Arch Int Med*. 2006;166(9):1021-1026.
7. Chen H, Deshpande AD, Jiang R, Martin BC. An epidemiological investigation of off-label anticonvulsant drug use in the Wisconsin Medicaid Population. *Pharmacoepidemiol Drug Saf*. 2005;14(9):629-638.
8. Omnibus Budget Reconciliation Act (OBRA) 1990 § 456.716 DUR Board.

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