CONTEMPORARY SUBJECT

Examination of the Evidence for Off-Label Use of Gabapentin

ALICIA MACK, PharmD

ABSTRACT

OBJECTIVES: (1) Describe the relevance of off-label use of gabapentin to managed care pharmacy; (2) summarize recent FDA warnings and media reports related to off-label gabapentin use; (3) review medical information pertaining to the off-label use of gabapentin; (4) outline alternatives to off-label use of gabapentin in an evidence-based fashion, where literature exists to support such alternatives; and (5) encourage key clinicians and decision makers in managed care pharmacy to develop and support programs that restrict the use of gabapentin to specific evidence-based situations.

SUMMARY: Gabapentin is approved by the U.S. Food and Drug Administration (FDA) for adjunctive therapy in treatment of partial seizures and postherpetic neuralgia. Various off-label (unapproved) uses have been reported, and the use of gabapentin for off-label purposes has reportedly exceeded use for FDA-approved indications. Pharmaceutical marketing practices and physician dissatisfaction with currently available pharmacological treatment options may be key factors that contribute to this prescribing trend.

Recently, the media has focused on these issues, noting that many cases of reported safety and effectiveness of gabapentin for off-label use may have been fabricated. A thorough review of the medical and pharmacy literature related to off-label use of gabapentin was performed, and a summary of the literature for the following conditions is presented: bipolar disorder, peripheral neuropathy, diabetic neuropathy, complex regional pain syndrome, attention deficit disorder, restless legs syndrome, trigeminal neuralgia, periodic limb movement disorder of sleep, migraine headaches, and alcohol withdrawal syndrome. A common theme in the medical literature for gabapentin is the prevalence of open-label studies and a lack of randomized controlled clinical trials for all but a small number of indications.

CONCLUSIONS: In the majority of circumstances where it has reported potential for "off-label" use, gabapentin is not the optimal treatment. The off-label use of gabapentin for indications not approved by the FDA should be reserved for cases where there is solid research support (e.g., diabetic neuropathy and prophylaxis of frequent migraine headaches). Managed care pharmacists should develop programs to restrict the use of gabapentin to these specific evidence-based situations, and key decision makers in managed care practice should feel confident in supporting these use restrictions for gabapentin.

KEYWORDS: Neurontin, Gabapentin, Off-label, Comparison, Bipolar, Restless legs, Trigeminal neuralgia, Migraine, Peripheral neuropathy, Diabetic neuropathy, Complex regional pain syndrome, Attention deficit disorder, Periodic limb movement disorder of sleep, Alcohol withdrawal syndrome

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Gabapentin (Neurontin) was approved by the U.S. Food and Drug Administration (FDA) on December 30, 1993, for adjunctive therapy in the treatment of partial seizures, with and without secondary generalization, in patients above the age of 12 years. The FDA approved the indication for adjunctive therapy for partial seizures in children aged 3 to 12 years in October 2000 and the indication for postherpetic neuralgia in adults in May 2004.[1]

Gabapentin is an amino acid that is structurally related to the inhibitory neurotransmitter gamma-amino butyric acid (GABA); however, its antiepileptic activity appears unrelated to any direct effects on the GABAergic system.[2] The mechanism of action of the drug has led to tremendous scientific speculation as to the potential merits of the drug in other clinical conditions.

Since its introduction to the market in 1993, gabapentin has gained widespread use, and a significant portion of this use has been for non-FDA approved uses (Figure 1). A retrospective review of one managed Medicaid plan demonstrated that 95% of patients were using gabapentin for off-label diagnoses.[3] Gabapentin has also garnered unfavorable publicity because of accusations that the manufacturer illegally promoted the agent for at least 10 "off-label" medical conditions[4,5] (Figure 1). The FDA has issued various warning statements to the manufacturer as a result of these marketing practices.[6,7]

FIGURE 1 Reported Off-Label (Unapproved) Uses of Gabapentin

1. Bipolar disorder
2. Neuropathic pain
3. Diabetic neuropathy
4. Complex regional pain syndrome
5. Attention deficit disorder
6. Restless legs syndrome
7. Trigeminal neuralgia
8. Periodic limb movement disorder of sleep
9. Migraine
10. Drug and alcohol withdrawal seizures

While various summaries of these issues are accessible in the public domain, a more thorough evaluation of the issues from a clinical standpoint is warranted. The intent of this review is to tie the media concerns to clinical evidence obtained from a thorough literature review so that managed care pharmacists and physicians will be better prepared to address the subject of appropriate use of gabapentin.

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TABLE 1 Summary of Open-Label Trials and Case Reports With Gabapentin in Bipolar Illness

Study	Treatment	Population	Results	Reference
Ghaemi SN, Goodwin FK. Open, prospective chart review	8 patients received gabapentin monotherapy; 13 received adjunctive therapy	21 outpatients meeting DSM-IV criteria for bipolar spectrum disorder (type I, type II, NOS cyclothymia) who were treated with gabapentin	Alone, or as adjunct, gabapentin appeared moderately effective in treating depression. Using the CGI-BP, gabapentin was moderately to markedly effective in 43% of patients for overall bipolar illness, 38% for depressive symptoms, and 25% for manic symptoms.	*J Affect Disord.* 2001;65(2):167-71.
Altshuler LL, Keck PE, McElroy SL, et al. Open	Adjunctive therapy with gabapentin 600 mg-3,600 mg/day	28 bipolar patients, 5 experiencing manic symptoms, 5 experiencing depressive symptoms, and 5 experiencing rapidly cycling symptoms refractory to at least 1 mood stabilizer	As adjunctive therapy, gabapentin appears to have acute antimanic and antidepressant properties. Fourteen of the 18 (78%) mania or hypomania patients had a positive response. All of the patients treated for depression had positive response. (Positive response was a CGI response of much or very much improvement.)	*Bipolar Disord.* 1999;1(1):61-65.
Carta MG, Hardoy MC, Dessi I, et al. Open	Adjunctive therapy with gabapentin 300 mg-900 mg	10 patients with intellectual disability and demonstrable increases in symptomatology during significant life events that had interfered with or induced interruption of their rehabilitation programs	A positive response to therapy was observed with subsequent improvement of psychopathological conditions, particularly for anxiety and depressive symptoms.	*J Intellect Disabil Res.* 2001;45(pt 2):139-45.
Sokolski KN, Green C, Maris DE, et al. Open label	Adjunctive therapy for 1 month	10 bipolar patients with mixed symptoms who had previously demonstrated only partial treatment responses	Decreases in Hamilton depression ($P<0.05$) and Bech mania ratings ($P<0.01$) were evident in the first week of treatment and were sustained. Potent early improvements were noted in early, middle, and late insomnia.	*Ann Clin Psychiatry.* 1999; 11(4):217-22.
Young LT, Robb JC, Hasey GM, et al. Open	Adjunctive treatment for up to 6 months	37 patients with bipolar type I or II with or without rapid cycling course	Using HamD and YMS scales, mood symptoms were assessed and both depressive and manic symptoms were found to be significantly reduced with gabapentin.	*J Affect Disord.* 1999;55(1):73-77.
Hatzimanolis J, Lykouras, L, Oulis P, et al. Case report	Monotherapy for 2 weeks	2 patients with acute mania	After 2 weeks of treatment, a moderate improvement of both patients was observed.	*Eur. Neuropsychopharma.* 1999;9(3):257-9.
Erfurth A, Kammerer C, Grunze H, et al. Open label	6 add-on cases and 8 high-dose monotherapy cases; dose range of 1,200 mg-4,800 mg/day; treatment for up to 21 days	14 patients with acute mania	The study suggested that gabapentin monotherapy may be useful in treating modest but not severe manic states. In conjunction with other mood stabilizers such as lithium or depakote, it may be useful. Of note, there was not a comparison arm to the mood stabilizers alone, so any advantage of the combination over monotherapy with these agents remains unproven.	*J Psychiatr Res.* 1998;32(5):261-64.
Soutullo CA, Casuto LS, Keck PE. Case report	Add-on to carbamazepine	One boy, aged 13 years, with bipolar disorder, manic episode, and ADHD	Patient remained euthymic 7 months after gabapentin was added. Young Mania Rating Scale (YMRS) score was 27 when gabapentin was added, 9 after 1 month, 15 after 4 months, and 6 after 7 months.	*J Child Adolesc Psychopharmacol.* 1998;8(1):81-85.

label conditions; company medical science liaisons were also alleged to have been involved in this practice.[4] The authors of one news article noted that many reported cases of safety and effectiveness with unapproved use of the drug appeared to be fabricated by the manufacturer.

A follow-up story in January 2003 about a "whistle-blower" lawsuit related to allegedly illegal marketing practices included an explanation of some of the issues, with particular emphasis on the clinically inappropriate promotion of gabapentin for bipolar disorder.[4] The lawsuit involves charges made by a for-

TABLE 2 Summary of Selected Primary and Tertiary References Using Gabapentin in Management of Neuropathic Pain

Publication Type	Treatment or Method	Population	Results	Reference
Randomized, double-blind, placebo-controlled trial	Symptom-based, 8-week study design of patients receiving gabapentin in doses up to 2,400 mg/day or placebo	153 patients patients randomized to gabapentin and 152 patients randomized to placebo	Over the study, the average daily pain diary score improved by 1.5 (21%) in gabapentin-treated patients and by 1.0 (14%) in placebo-treated patients. (P=0.048, rank-based analysis of covariance). Significant differences were shown in favor of gabapentin (P<0.05) for the clinician and patient global impression of change and some domains of the Short-Form McGill Pain Questionnaire.	Serpell MG. *Pain.* 2002;99(3):557-66.
Pilot study	Gabapentin was administered orally in gradually increasing doses up to a maximum of 2,400 mg/day	18 patients with peripheral nerve injuries or central lesions	Gabapentin induced a moderate and statistically significant relief of ongoing or spontaneous pain and was particularly effective in reducing paroxysmal pain. A striking finding was the significant effect on brush-induced cold allodynia. In contrast, no effects were observed on detection of pain thresholds to static mechanical and hot stimuli.	Brasseur AN, Parker F, Chauvin M, et al. *Eur Neurol.* 1998;40(4): 191-200.
Retrospective chart review	Patients receiving gabapentin for at least 30 days were studied.	122 patients divided into 3 groups based on pain diagnosis of low back, myofascial, or neuropathic pain	Significant decrease in pain scores with gabapentin in the neuropathic pain group but not in the low-back-pain group. Patients with postherpetic neuralgia had the greatest decrease in pain scores. Patients who were taking opiates had significantly less benefit with gabapentin in terms of pain score.	Rosenberg JM, Harrell C, Ristic H, et al. *Clin J Pain.* 1997;13(3):351-55.
Meta-analysis	Extensive search of several electronic databases for controlled and uncontrolled studies. Efficacy was assessed through meta-analyses of randomized controlled trials (RCTs). Effectiveness of gabapentin in uncontrolled studies was assessed via a novel system of dichotomous classification of bad versus good results.	35 papers involving 727 patients with multiple neuropathic pain conditions met inclusion criteria	The meta-analysis of the 2 high-quality placebo-controlled randomized trials showed positive effect of gabapentin in diabetic neuropathy and postherpetic neuralgia. Addition of 2 low-quality PC, RCTs did not alter the magnitude or duration of the observed effect. The uncontrolled studies demonstrated positive effect on pain in different neuropathic syndromes as well as benefit for different types of neuropathic pain; highest dose administered and rate of dose escalation showed wide variability between prescribers. Fewer and less-severe side effects were reported in the uncontrolled studies.	Mellegers MA, Furlan AD, Mailis A. *Clin J Pain.* 2001;17(4):284-95.
Randomized controlled clinical trial	Gabapentin 3,600 mg/day (forced max) 67% achieved max dose	Uncontrolled diabetes (75% type 2) n=84 gabapentin, n=81 placebo	Gabapentin versus placebo: difference in mean pain score at endpoint = -1.2 (P<0.001); difference in mean sleep interference score = -1.47 P<0.001).	Backonja M, Beydoun A, Edwards K, et al. *JAMA.* 1998;280: 1831-36.
Randomized controlled clinical trial	Gabapentin 3,600 mg/day (65% achieved max dose) versus placebo	Postherpetic neuralgia n=113 gabapentin, n=112 placebo	Decrease in average daily pain score = 33% gabapentin, 7% placebo (P<0.001).	Rowbotham M, Harden N, Stacey B, et al. *Ann Pharmacother.* 2000;34:802-07.

TABLE 3 Price Comparisons for Gabapentin Versus Various Tricyclic Antidepressants Used in the Management of Neuropathic Pain

Drug	Dose for Management of Neuropathic Pain†*	FDA Approval	Cost per Unit†	Tablet or Capsules per Month	Maximum Average Cost per month
Gabapentin	300 mg/day up to 1,800 mg/day	No	100 mg cap ($0.51 ea)	up to 540	$275.40
			300 mg ($1.23 ea)	up to 180	$221.98
			400 mg ($1.47 ea)	up to 135	$199.48
			600 mg ($1.98 ea)	up to 90	$178.98
			800 mg ($2.38 ea)	up to 68	$162.44
Amitriptyline	10 mg-25 mg orally at bedtime, up to 150 mg-200 mg/day	No	10 mg tab ($0.09 ea)	up to 600	$54.00
			25 mg ($0.12 ea)	up to 240	$28.80
			50 mg ($0.09 ea)	up to 120	$10.80
			75 mg ($0.12 ea)	up to 90	$10.80
			100 mg ($0.13 ea)	up to 60	$7.80
Nortriptyline	10 mg/day orally, increase by 10 mg/day every 3 to 5 days as needed; doses up to 60 mg/day have been reported	No	10 mg cap ($0.14 ea)	up to 180	$25.20
			25 mg cap ($0.21 ea)	up to 60	$12.60
			50 mg cap ($0.25 ea)	up to 30	$7.50
			75 mg cap($0.28 ea)	up to 30	$8.40

† Gelman CR, Rumack BH, eds. DRUGDEX Information System. Denver, CO: Micromedex, Inc.; 1994.
‡ http://www.drugstore.com. Accessed September 7, 2003. Cost per unit based on 90 unit/month pricing.

mer salesman that the company used a systematic strategy to promote gabapentin for various off-label uses. The extension of potential uses of gabapentin contributed to the drug's tremendous financial success, essentially creating a "blockbuster" drug in terms of sales. In 2000 alone, gabapentin earned $1.3 billion in sales, and as much as 78% of these sales were for uses without clinical evidence of safety or effectiveness.[4]

Review of the Clinical Literature

Off-label use of gabapentin has been reported in bipolar disorder, peripheral neuropathy, diabetic neuropathy, complex regional pain syndrome, attention deficit disorder, restless legs syndrome, trigeminal neuralgia, periodic limb movement disorder of sleep, migraine headaches, and drug and alcohol withdrawal syndrome. A recurring theme in the literature, with the exception of neuropathic pain and migraine, is a prevalence of open-label studies with a lack of randomized controlled clinical trials. It is important to consider that an inherent problem with open-label trial design is the potential for introduction of bias because the treatment assignment is known.

Gabapentin in the Treatment of Bipolar Disorder

Extensive review confirms that current published literature on gabapentin is primarily based on open-label trials that evaluate small numbers of patients (Table 1).[8-15] The few randomized controlled trials designed to investigate the efficacy of gabapentin in treating bipolar disorder have concluded that there is no significant difference in the effects of the drug compared with placebo.[16,17] This supports the likelihood of bias in the various open-label studies since these results have not been confirmed in the randomized controlled trials. Various authors of medical reviews on this subject have concluded that gabapentin should not be recommended for treatment of bipolar disorder and that double-blind, randomized controlled trials are needed to confirm any true efficacy of the drug in management of this condition.[18-21]

Real-life practice involves instances of refractory bipolar disorder that exhaust the current treatment options. The Texas Medication Algorithm Project (TMAP) lists lamotrigine or gabapentin only as salvage therapy. Therefore, these 2 agents should be reserved for unstable patients at the seventh stage of treatment in hypomanic/manic episodes.[22] In all other forms of bipolar disorder, gabapentin is not recommended at any phase of therapy.

Although limited comparative data are available on the subject, results from a cross-over study suggest that lamotrigine may be superior to gabapentin as well as placebo for the management of refractory mood disorders.[23] The investigators studied 31 patients who had either bipolar I, bipolar II, or unipolar disorder and failures of other mood stabilizing agents. Lamotrigine was titrated to 300 mg–500 mg by weeks 5 and 6, and gabapentin was titrated to 4,800 mg daily by week 6. At week 6, based on the Clinical Global Impression Score, 52% of patients responded to lamotrigine, 26% responded to gabapentin, and 23% responded to placebo (P=0.011, lamotrigine versus gabapentin). The results of this study suggest that lamotrigine might be considered in cases of treatment refractory to first-line agents in bipolar disorder.

Gabapentin in the Treatment of Pain Syndromes, Peripheral Neuropathy, and Diabetic Neuropathy

The exact mechanism of action of gabapentin in managing neuropathic pain is unknown; however, it is speculated to work via

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