CONTEMPORARY SUBJECT

Examination of the Evidence for Off-Label Use of Gabapentin

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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.

Media Issues

The manufacturer of gabapentin has been accused of illegal promotion of the drug to prescribing physicians for at least 10 off-

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

TABLE 4 *Published Reports Related to Use of Gabapentin in Complex Regional Pain Syndrome I*

Study	Treatment	Population	Results	Reference
Case study	Gabapentin	1 child	Satisfactory pain relief was reported.	Wheeler DS, Vaux KK , Tam DA. Use of gabapentin in the treatment of childhood reflex sympathetic dystrophy. *Pediatr Neurol.* 2000; 22(3):2201-11.
Case study	Gabapentin	6 patients, aged 42-68 years, with severe, refractory RSD	Satisfactory pain relief was obtained in all patients.	Mellick GA, Mellick LB. Reflex sympathetic dystrophy treated with gabapentin. *Arch Phys Med Rehabil.* 1997;78(1):98-105.

voltage-activated calcium ion channels at the postsynaptic dorsal horn, thereby interrupting the series of events that leads to the sensation of neuropathic pain. Review of the various hypotheses concerning these pharmacologic theories is beyond the scope of this article but may be found elsewhere.[24-26]

While the clinical literature in support of gabapentin use for conditions of neuropathic pain is more favorable than that concerning its use in various other disease states, there remain issues concerning its merits in clinical practice. These involve variable doses, few direct comparisons to other agents, and, again, a number of open-label studies with the potential for bias. Nonetheless, gabapentin does have proven efficacy for the treatment of diabetic neuropathy and postherpetic neuralgia.[32,33] A summary of selected published studies on this subject appears in Table 2.[27-33]

Morello et al. demonstrated that there is no statistically significant difference between amitriptyline and gabapentin in the treatment of diabetics with peripheral neuropathic pain, as measured by pain scales and global pain scores.[34] In this study, 21 diabetic patients with stable glycemic control received either gabapentin or amitriptyline for 6 weeks and then crossed over to the other arm of therapy for 6 additional weeks, with a 1-week wash-out period between therapies. Dosage was adjusted based on the patient's response, with a mean gabapentin dose of 1,565 mg and a mean amitriptyline dose of 59 mg. Both medications were found to significantly decrease pain scores from baseline ($P<0.001$). Sixty-seven percent of amitriptyline patients reported moderate or greater pain relief, and 52% of gabapentin patients reported such relief ($P=0.26$).

Current treatment guidelines favor using amitriptyline, nortriptyline, or gabapentin for the management of painful neuropathic conditions. It is recognized that, in specific clinical circumstances, the adverse-effect profile of the tricyclics may prove unacceptable, thus warranting consideration of therapeutic alternatives. However, in cases without tricyclic contraindications, cost should also be considered when selecting an initial option for treatment.

In the Morello study,[34] the agents were proven comparable in clinical efficacy. In fact, these authors suggested a slight advantage to using amitriptyline over gabapentin, although the difference was not statistically significant. Comparing prices of the agents given in doses for the management of neuropathic pain, amitriptyline and nortriptyline cost only a small fraction of the significant direct drug cost associated with gabapentin (Table 3).[35] Therefore, the tricyclics appear to offer a lower-cost therapeutically equivalent alternative to gabapentin in many situations.

Gabapentin in the Treatment of Complex Regional Pain Syndrome

There are no reports that confirm efficacy of gabapentin in management of complex regional pain syndrome, also known as reflex sympathetic dystrophy (RSD). The literature is sparse and primarily anecdotal in nature, composed of 2 reports involving a total of 7 patients in addition to 2 letters (Table 4) that offer little scientific value.[36-40] From an evidence-based standpoint, the available information is insufficient to support use of gabapentin in this condition. Recognized medical treatments for RSD include adrenergic blockers, nonsteroidal anti-inflammatory drugs, calcium channel blockers, phenytoin, opioids, and calcitonin.[39]

Gabapentin in the Treatment of Attention Deficit Disorder

There are 3 published reports related to behavioral disturbances and the use of gabapentin, none of which were clinical trials. One case report is specific to the use of the drug in attention deficit hyperactivity disorder (ADHD). A second case report involved 7 patients who experienced behavioral side effects with gabapentin. The third citation was a letter (Table 5).[41-43] Thus, the evidence related to the use of gabapentin in ADHD is insufficient to warrant its use for this condition.

Stimulants have been the mainstay of ADHD therapy for decades, but there is a rising trend in pediatric polypsychopharmacy with little or no research to support this phenomenon.[44] Since there is no evidence to support the use of gabapentin in ADHD, alternative clinically appropriate and supportable treatment options should be given primary consideration when formulating treatment plans for cases refractory to stimulants in ADHD. Current treatment guidelines suggest a trial with a stimulant along with diet, behavior management, special education, and perhaps psychotherapy in ADHD disease management. [43]

TABLE 5 Published Reports of Gabapentin and Behavior in Children

Study type	Treatment	Population	Results	Reference
Case report	Gabapentin 200 mg/day added to methylphenidate 30 mg/day	1 boy, aged 12 years, with ADD, reading disorder, mixed receptive and expressive language disorder, encopresis, and bipolar disorder II	Within 3 weeks, mother, teacher, and clinician noted improvement and stabilization of mood symptoms as remarkable; it remained so for 6 months of follow-up.	Hamrin V, Bailey K. Gabapentin and methylphenidate treatment of a preadolescent with attention deficit hyperactivity disorder and bipolar disorder. *J Child Adolesc Psychopharmacol.* 2001;11(3):301-09.
Case report	Gabapentin as adjunct	7 children with baseline ADD and developmental delay	Children consequentially developed behavioral side effects, including tantrums, aggression toward others, hyperactivity, and defiance. All behavioral changes were reversible and were managed by dose reduction or discontinuation of gabapentin.	Lee DO, Steingard RJ, Casena M, et al. Behavioral side effects of gabapentin in children. *Epilepsia.* 1996;3(1):87-90.

Gabapentin in the Treatment of Restless Leg Syndrome

Restless leg syndrome (RLS) is an awake phenomenon characterized by an intense, irresistible urge to move the legs, usually associated with sensory complaints, motor restlessness, worsening of symptoms at rest and relief with motor activation, and increased severity in the evening or during the night. Sparse case reports have suggested potential use of gabapentin in RLS, but, again, there are no controlled clinical trials that assess its safety and effectiveness in treatment of this condition.[45-49]

The Standards of Practice Committee of the American Academy of Sleep Medicine (AASM), in conjunction with specialists and other interested parties, developed guidelines for managing RLS that were subsequently approved by the Board of Directors of AASM. The recommendations were identified as standards, guidelines, or options, based on the strength of evidence from published studies that meet criteria for inclusion (Table 6).

The AASM guideline classifies the following agents as having sufficient evidence to support their use in RLS treatment: (1) levodopa with decarboxylase inhibitor and pergolide, (2) oxycodone and propoxyphene, or (3) carbamazepine. AASM has reported that the dopaminergic agents are notably the best studied and most successful agents for the treatment of RLS.[50]

Alternatively, they have commented that gabapentin has limited "Level V" evidence (case-series reports only), consisting of only 2 case studies. For this reason, AASM has classified use of gabapentin in RLS as a patient-care strategy that reflects uncertain clinical use. The members of the panel felt that there is inconclusive data, conflicting evidence, or conflicting expert opinion on the use of gabapentin for managing RLS. [50]

Gabapentin in the Treatment of Trigeminal Neuralgia

Conclusive studies confirming the efficacy of gabapentin in the treatment of trigeminal neuralgia are lacking. To date, literature supporting the effectiveness of gabapentin in trigeminal neuralgia is limited to case studies in aggregate of less than 30 patients.[51-53] Carbamazepine remains the drug of first choice.[54] If paroxysms of pain still occur with therapeutic blood levels, phenytoin or baclofen should be added.[54] Lamotrigine was recently validated for use in refractory trigeminal neuralgia, especially due to multiple sclerosis.[51,52,55]

Gabapentin in the Treatment of Periodic Limb Movement Disorder of Sleep

Periodic limb movements of sleep occur as an asleep phenomenon and are characterized by periodic episodes of repetitive and highly stereotyped limb movements. These patients typically have complaints of insomnia or excessive sleepiness with no other disorder to explain the symptoms.

RLS and periodic limb movement disorder (PLMD) of sleep are distinct disorders by definition, but they have been reported to coexist in approximately 80% of cases. However, the treatment of the 2 conditions is not always the same. There is no reference to the use of gabapentin in PLMD, and there is no mention of gabapentin in recommendations of AASM.[50] There is no published evidence demonstrating efficacy of gabapentin in the management of PLMD. Experts have reported that symptoms may respond to correction of a coexisting iron deficiency anemia or to treatment with dopaminergic medication (such as levodopa or bromocriptine), benzodiazepines (diazepam or clonazepam), or opiates (codeine, propoxyphene, or oxycodone).[56]

Gabapentin in the Treatment of Migraine

Pharmacoeconomic analyses reveal that gabapentin is only cost effective for migraine prophylaxis in patients who experience very frequent migraine headaches. Adelman et al. studied the costs for acute migraine care following initiation of prophylactic medications. They reported that divalproex patients must have

TABLE 6A American Academy of Sleep Medicine Classification of Evidence

Recommendation Grade	Evidence Level	Study Design
A	I	Randomized, well-designed trials with low alpha and low beta errors*
B	II	Randomized trials with high beta errors*
C	III	Nonrandomized controlled or concurrent cohort studies
C	IV	Nonrandomized historical cohort studies
C	V	Case series

**Alpha error refers to the probability (generally set at 95% or greater) that a significant result (e.g., P<0.05) is the correct conclusion of the study or studies. Beta error refers to the probability (generally set at 80% or 90% or greater) that a nonsignificant result (e.g., P>0.05) is the correct conclusion of the study or studies. The estimation of beta error is generally the result of a power analysis. The power analysis includes a sample size analysis that projects the size of the study population necessary to ensure that significant differences will be observed if actually present.*

Source: *Chesson AL, Wise M, Davila D, et al. Practice parameters for the treatment of restless legs syndrome and periodic limb movement disorder. An American Academy of Sleep Medicine Report. Standards of Practice Committee of the American Academy of Sleep Medicine. Sleep. 1999;22(7):961-68.*

TABLE 6B American Academy of Sleep Medicine Recommendations for Restless Legs Syndrome or Periodic Limb Movement Disorder

Term	Definition
Standard	This is a generally accepted patient-care strategy that reflects a high degree of clinical certainty. The term "standard" generally implies the use of Level I evidence, which directly addresses the clinical issue or overwhelming Level II evidence.
Guideline	This is a patient-care strategy that reflects a moderate degree of clinical certainty. The term "guideline" implies the use of Level II evidence or a consensus of Level III evidence.
Option	This is a patient care strategy that reflects uncertain clinical use. The term "option" implies either inconclusive or conflicting evidence or conflicting expert opinion.

Source: *Chesson AL, Wise M, Davila D, et al. Practice parameters for the treatment of restless legs syndrome and periodic limb movement disorder. An American Academy of Sleep Medicine Report. Standards of Practice Committee of the American Academy of Sleep Medicine. Sleep. 1999;22(7):961-68.*

more than 10 migraine episodes per month while gabapentin patients must have more than 24 migraine episodes per month before these drugs can be considered cost effective.[57-60]

While there are clinical trials of gabapentin in migraine prophylaxis, outstanding questions remain regarding the drug's utility in clinical practice. One randomized, placebo-controlled study of 63 patients showed that gabapentin in daily prophylactic doses of 1,200 mg is well tolerated and reduces headache frequency and the use of drugs to produce symptomatic relief.[61] While gabapentin appeared to be effective in this particular trial, it is still unclear how gabapentin would compare to other more-established pharmacotherapy for migraine prophylaxis. Thus, gabapentin should be considered for use in migraine syndrome management only after failure of standard prophylaxis regimens (Table 7).

Gabapentin in the Treatment of Drug and Alcohol Withdrawal Seizures

Mayo-Smith published an evidence-based practice guideline for the pharmacological management of alcohol withdrawal.[62] He completed a meta-analysis of prospective controlled trials only, with methodologically sound endpoints (e.g., withdrawal severity, delirium, seizures, completion of withdrawal, entry into rehabilitation, adverse events) corresponding to the Diagnostic and Statistical Manual of Mental Disorders. Mayo-Smith concluded that benzodiazepines remain the gold standard for management of alcohol withdrawal and that dosage should be individualized based on withdrawal severity.

According to this analysis, the author notes that beta-blockers, clonidine, and carbamazepine may be considered as adjunctive therapy.[62] There was no mention of gabapentin in this guideline since published reports of gabapentin for these indications are limited to case reports, open-label studies, and anecdotal letters.[63-67] Thus, gabapentin cannot be recommended for use in any aspect of the management of alcohol withdrawal seizures, either as initial or add-on therapy.

Conclusions

In the majority of circumstances where it has reported potential for indications not approved by the FDA (i.e., off-label use), gabapentin is not the optimal treatment. The reader should remain cautious regarding claims that gabapentin offers any benefit in treating conditions other than those with FDA approval. Hamer et al. concluded, "While case reports and open-label trials are valuable for directing further research, they are generally not sufficient as the basis of treatment decisions."

Gabapentin is not recommended in the clinical guidelines or established treatment algorithms (e.g., American Academy of Neurology or AASM guidelines or TMAP algorithm) for any of the off-label indications. Considering the evidence, gabapentin should be used almost exclusively for the FDA-approved indications—treatment of seizures and postherpetic neuralgia.

Off-label use of gabapentin should be reserved for patients who have failed standard treatment options and in those cases where randomized controlled clinical trials have demonstrated gabapentin efficacy (i.e., diabetic neuropathy and migraine headaches). Cost-effectiveness ratios tend to be high (unfavorable) for the use of gabapentin in diabetic neuropathy and migraine syndrome except in those patients who experience a high frequency of acute episodes.

Pharmaceutical manufacturer marketing practices appear to

TABLE 7 *AAA Migraine Prophylaxis Guidelines: Assessment of the Relative Value of Preventive Therapies for Migraine Available in the United States*

Group I*		Group II†		Group III‡		Group IV§		Group V‖	
Drug	Efficacious Doses in Clinical Trials	Drug	Efficacious Doses in Clincial Trials	Drug	Efficacious Doses in Clinical Trials	Drug	Efficacious Doses in Clinical Trials	Drug	Efficacious Doses in Clinical Trials
Amitriptyline	30 mg-150 mg/day	Aspirin¶	1,300 mg/day	Cyproheptadine	Not established	Methysergide	6 mg/day	Acebutolol	Not established
Divalproex	500 mg-1,500 mg/day	Atenolol	100 mg/day	Buproprion	Not established			Carbamazepine	Not established
Propranolol	80 mg-240 mg/day	Fenoprofen	1,800 mg/day	Diltiazem	Not established			Comipramine	Not established
Timolol	20 mg-30 mg/day	Flurbiprofen	200 mg/day	Doxepin	Not established			Clonazepam	Not established
		Fluoxetine	20 mg every other day to 40 mg/day	Fluvoxamine	Not established			Indomethacin	Not established
		Gabapentin	900 mg-2,400 mg/day	Ibuprofen	Not established			Lamotrigine	Not established
		Guanfacine	1 mg/day	Imipramine	Not established			Nabumetone	Not established
		Ketoprofen	150 mg/day	Mirtazepine	Not established			Nicardipine	Not established
		Magnesium	400 mg-600 mg/day	Nortriptyline	Not established			Nifedipine	Not established
		Mefanamic acid	1,500 mg/day	Paroxetine	Not established			Pindolol	Not established
		Metoprolol	200 mg/day	Protriptyline	Not established				
		Nadolol	80 mg-240 mg/day	Sertraline	Not established				
		Naproxen sodium	1,100 mg/day	Tiagabine	Not established				
		Nimodipine	120 mg/day	Topiramate	Not established				
		Tolfenamic acid	300 mg/day	Trazadone	Not established				
		Verapamil	240 mg/day	Venlafaxine	Not established				
		Vitamin B2	400 mg/day	Methylergonovine	Not established				
				Phenelzine	Not established				

** Group I = Medium to high efficacy, good strength of evidence, and a range of severity (mild to moderate) and frequency (infrequent to frequent) of side effects.*
† Group II = Lower efficacy than those listed in the first column, or limited strength of evidence, and mild to moderate side effects.
‡ Group III = Clinically efficacious based on consensus and clinical experience, but no scientific evidence of efficacy.
§ Group IV = Medium to high efficacy, good strength of evidence, but with side concerns.
‖ Group V = Evidence indicating no efficacy over placebo
¶ Does not include combination products.

Adapted from Limroth V, Michel MC. The prevention of migraine: a critical review with special emphasis on beta adrenoreceptor blockers. Br J Clin Pharmacol. 2001;52(3):237-43; Adelman JU, Adelman RD. Current options for the prevention and treatment of migraine. Clin Ther. 2001;23(6):772-88; and Evidence-based Guidelines for Migraine Headache in the Primary Care Setting. Guidelines on Migraine Headache Prophylaxis: Pharmacological Management for the Prevention of Migraine (available at: http://www.aan.com/professionals/practice/pdfs/gl0090.pdf; accessed September 9, 2003).

be a key contributor to the use of gabapentin in excess of its scientifically proven value. One additional factor is the perceived need for treatment options among clinicians dissatisfied with currently available therapies. The financial success of gabapentin could be at least partially attributable to the placebo effect since the majority of the off-label conditions are associated with an underlying psychological component.

DISCLAIMER

Since various disease states are discussed in this review, it is essential to note that the references to treatment guidelines and algorithms are summary in nature and are in no way intended to replace the various expert consensus and more thorough reviews on the various subjects.

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