Examimation 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.

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. 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. Gabapentin has also garnered unfavorable publicity because of accusations that the manufacturer illegally promoted the agent for at least 10 “off-label” medical conditions 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-
Examination of the Evidence for Off-Label Use of Gabapentin

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. The lawsuit involves charges made by a for-

![Image of document page]

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Population</th>
<th>Results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Open, prospective chart review</td>
<td>therapy with gabapentin 600 mg-3,600 mg/day</td>
<td>5 experiencing manic symptoms, 5 experiencing depressive symptoms, and 5 experiencing rapidly cycling symptoms refractory to at least 1 mood stabilizer</td>
<td>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.)</td>
<td>Bipolar Disord 1999;1(1):61-65.</td>
</tr>
<tr>
<td>Alshuler LL, Keck PE, McElroy SL, et al.</td>
<td>Adjunctive</td>
<td>28 bipolar patients</td>
<td>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.)</td>
<td>J Affect Disord 2001;65(2):167-71.</td>
</tr>
<tr>
<td>Open</td>
<td>therapy with gabapentin 300 mg-900 mg</td>
<td>28 bipolar patients, 5 experiencing manic symptoms, 5 experiencing depressive symptoms, and 5 experiencing rapidly cycling symptoms refractory to at least 1 mood stabilizer</td>
<td>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.)</td>
<td>J Affect Disord 2001;65(2):167-71.</td>
</tr>
<tr>
<td>Carta MG, Hardoy MC, Dessi I, et al.</td>
<td>Adjunctive</td>
<td>10 patients</td>
<td>28 bipolar patients, 5 experiencing manic symptoms, 5 experiencing depressive symptoms, and 5 experiencing rapidly cycling symptoms refractory to at least 1 mood stabilizer</td>
<td>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.)</td>
</tr>
<tr>
<td>Open</td>
<td>therapy with gabapentin 300 mg-900 mg</td>
<td>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</td>
<td>A positive response to therapy was observed with subsequent improvement of psychopathological conditions, particularly for anxiety and depressive symptoms.</td>
<td>J Affect Disord 2001;65(2):167-71.</td>
</tr>
<tr>
<td>Sokolski KN, Green C, Maris DE, et al.</td>
<td>Adjunctive</td>
<td>10 bipolar patients</td>
<td>10 bipolar patients with mixed symptoms who had previously demonstrated only partial treatment responses</td>
<td>decreases in Hamilton depression (P&lt;0.05) and Bech mania ratings (P&lt;0.01) were evident in the first week of treatment and were sustained. Potent early improvements were noted in early, middle, and late insomnia.</td>
</tr>
<tr>
<td>Open label</td>
<td>therapy for 1 month</td>
<td>10 bipolar patients with mixed symptoms who had previously demonstrated only partial treatment responses</td>
<td>Decreases in Hamilton depression (P&lt;0.05) and Bech mania ratings (P&lt;0.01) were evident in the first week of treatment and were sustained. Potent early improvements were noted in early, middle, and late insomnia.</td>
<td>Ann Clin Psychiatry 1999;11(4):217-22.</td>
</tr>
<tr>
<td>Young LT, Robb JC, Hasey GM, et al.</td>
<td>Adjunctive</td>
<td>37 patients with bipolar type 1 or II with or without rapid cycling course</td>
<td>Using HamD and YMS scales, mood symptoms were assessed and both depressive and manic symptoms were found to be significantly reduced with gabapentin.</td>
<td>J Affect Disord 1999;55(1):73-77.</td>
</tr>
<tr>
<td>Open</td>
<td>treatment for up to 6 months</td>
<td>37 patients with bipolar type 1 or II with or without rapid cycling course</td>
<td>Using HamD and YMS scales, mood symptoms were assessed and both depressive and manic symptoms were found to be significantly reduced with gabapentin.</td>
<td>J Affect Disord 1999;55(1):73-77.</td>
</tr>
<tr>
<td>Case report</td>
<td>therapy for 2 weeks</td>
<td>2 patients with acute mania</td>
<td>After 2 weeks of treatment, a moderate improvement of both patients was observed.</td>
<td>Eur Neuropsychopharmac 1999;9(3):257-9.</td>
</tr>
<tr>
<td>Open label</td>
<td>treatment for up to 21 days</td>
<td>14 patients with acute mania</td>
<td>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.</td>
<td>J Psychiatr Res 1998;32(3):261-64.</td>
</tr>
<tr>
<td>Soutullo CA, Casuto LS, Keck PE.</td>
<td>Add-on to</td>
<td>One boy, aged 13 years</td>
<td>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.</td>
<td>J Child Adolesc Psychopharmac 1998;8(1):81-85.</td>
</tr>
<tr>
<td>Case report</td>
<td>carbamazepine</td>
<td>One boy, aged 13 years</td>
<td>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.</td>
<td>J Child Adolesc Psychopharmac 1998;8(1):81-85.</td>
</tr>
</tbody>
</table>

Label conditions; company medical science liaisons were also alleged to have been involved in this practice. 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.
**TABLE 2** Summary of Selected Primary and Tertiary References Using Gabapentin in Management of Neuropathic Pain

<table>
<thead>
<tr>
<th>Publication Type</th>
<th>Treatment or Method</th>
<th>Population</th>
<th>Results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized, double-blind, placebo-controlled trial</td>
<td>Symptom-based, 8-week study design of patients receiving gabapentin in doses up to 2,400 mg/day or placebo</td>
<td>153 patients patients randomized to gabapentin and 152 patients randomized to placebo</td>
<td>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 ($P&lt;0.05$) for the clinician and patient global impression of change and some domains of the Short-Form McGill Pain Questionnaire.</td>
<td>Serpell MG. Pain. 2002;99(3):557-66.</td>
</tr>
<tr>
<td>Pilot study</td>
<td>Gabapentin was administered orally in gradually increasing doses up to a maximum of 2,400 mg/day</td>
<td>18 patients with peripheral nerve injuries or central lesions</td>
<td>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.</td>
<td>Brasseur AN, Parker F, Chauvin M, et al. Eur Neurol. 1998;40(4):191-200.</td>
</tr>
<tr>
<td>Retrospective chart review</td>
<td>Patients receiving gabapentin for at least 30 days were studied</td>
<td>122 patients divided into 3 groups based on pain diagnosis of low back, myofascial, or neuropathic pain</td>
<td>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.</td>
<td>Rosenberg JM, Harrell C, Ristic H, et al. Clin J Pain. 1997;13(3):351-55.</td>
</tr>
<tr>
<td>Meta-analysis</td>
<td>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.</td>
<td>35 papers involving 727 patients with multiple neuropathic pain conditions met inclusion criteria</td>
<td>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.</td>
<td>Mellegers MA, Purlan AD, Mailis A. Clin J Pain. 2001;17(4):284-95.</td>
</tr>
<tr>
<td>Randomized controlled clinical trial</td>
<td>Gabapentin 3,600 mg/day (forced max) 67% achieved max dose</td>
<td>Uncontrolled diabetes (75% type 2) n=84 gabapentin, n=81 placebo</td>
<td>Gabapentin versus placebo: difference in mean pain score at endpoint = -1.2 ($P&lt;0.001$); difference in mean sleep interference score = -1.47 ($P&lt;0.001$).</td>
<td>Backonja M, Beydoun A, Edwards K, et al. JAMA. 1998;280:1831-36.</td>
</tr>
<tr>
<td>Randomized controlled clinical trial</td>
<td>Gabapentin 3,600 mg/day (65% achieved max dose) versus placebo</td>
<td>Postherpetic neuralgia n=113 gabapentin, n=112 placebo</td>
<td>Decrease in average daily pain score = 33% gabapentin, 7% placebo ($P&lt;0.001$).</td>
<td>Rowbotham M, Harden N, Stacey B, et al. Ann Pharmacother. 2000;34:802-07.</td>
</tr>
</tbody>
</table>
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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

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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose for Management of Neuropathic Pain†*</th>
<th>FDA Approval</th>
<th>Cost per Unit† per Month</th>
<th>Tablet or Capsules Maximum Average Cost per month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabapentin</td>
<td>300 mg/day up to 1,800 mg/day</td>
<td>No</td>
<td>100 mg cap ($0.51 ea) up to 540</td>
<td>$2,757.40</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>300 mg ($1.23 ea) up to 180</td>
<td>$2,219.98</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>400 mg ($1.47 ea) up to 135</td>
<td>$1,994.48</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>600 mg ($1.98 ea) up to 90</td>
<td>$1,787.98</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>800 mg ($2.38 ea) up to 68</td>
<td>$1,624.48</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>10 mg-25 mg orally at bedtime, up to 150 mg-200 mg/day</td>
<td>No</td>
<td>10 mg tab ($0.09 ea) up to 600</td>
<td>$54.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>25 mg ($0.12 ea) up to 240</td>
<td>$28.80</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>50 mg ($0.09 ea) up to 120</td>
<td>$10.80</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>75 mg ($0.12 ea) up to 90</td>
<td>$10.80</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>100 mg ($0.13 ea) up to 60</td>
<td>$7.80</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>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</td>
<td>No</td>
<td>10 mg cap ($0.14 ea) up to 180</td>
<td>$25.20</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>25 mg cap ($0.21 ea) up to 60</td>
<td>$12.60</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>50 mg cap ($0.25 ea) up to 30</td>
<td>$7.50</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>75 mg cap ($0.28 ea) up to 30</td>
<td>$8.40</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Population</th>
<th>Results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case study</td>
<td>Gabapentin</td>
<td>6 patients, aged 42-68 years, with severe, refractory RSD</td>
<td>Satisfactory pain relief was obtained in all patients.</td>
<td>Mellick GA, Mellick LB. Reflex sympathetic dystrophy treated with gabapentin. <em>Arch Phys Med Rehabil.</em> 1997, 78(1):98-103.</td>
</tr>
</tbody>
</table>

In the Morello study,\(^4^4\) 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).\(^5^3\) 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.\(^3^9-^4^2\) 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.\(^3^9\)

**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).\(^4^1-^4^3\) 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 polysynaptic pharmacology with little or no research to support this phenomenon.\(^4^4\) Since there is no evidence to support the use of gabapentin in ADHD, alternative clinically appropriate and supportive 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.\(^4^5\)

**TABLE 4**

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Population</th>
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<th>Reference</th>
</tr>
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</tr>
</tbody>
</table>

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.\(^2^4-^2^6\)

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.\(^3^2-^3^3\)

A summary of selected published studies on this subject appears in Table 2.\(^2^7-^3^3\)

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.\(^3^4\) 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.
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
Conclusions


TABLE 6A American Academy of Sleep Medicine Classification of Evidence

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

*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.


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

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard</td>
<td>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.</td>
</tr>
<tr>
<td>Guideline</td>
<td>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.</td>
</tr>
<tr>
<td>Option</td>
<td>This is a patient care strategy that reflects uncertain clinical use. The term “option” implies either inconclusive or conflicting evidence or conflicting expert opinion.</td>
</tr>
</tbody>
</table>


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.54-60

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.54-65 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
Examination of the Evidence for Off-Label Use of Gabapentin

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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REFERENCES


Examination of the Evidence for Off-Label Use of Gabapentin


**SUGGESTED READING**

