Guidance on the Use of Gabapentin

VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

These criteria are based on the best clinical evidence currently available. The recommendations in this document are dynamic, and will be revised as new clinical information becomes available. This guidance is intended to assist practitioners in providing consistent, high quality, cost effective drug therapy. These criteria are not intended to interfere with clinical judgment; the clinician must ultimately decide the course of therapy based on individual patient situations.

INTRODUCTION

Gabapentin is an antiepileptic drug (AED) with analgesic properties. It is approved by the Food and Drug Administration for adjunctive treatment of partial epilepsy and management of postherpetic neuralgia. Since its approval in 1993, the usage of gabapentin in the VHA has steadily increased, making expenditures for this drug the third highest of all drugs used in the VHA (as of fiscal year 2003 up to June 2003). VHA drug utilization evaluations for gabapentin suggest that much of the increase in use seems to be due to prescribing for off-label indications. Other problems are use of low doses that are unlikely to be beneficial (lack of titration) and continued use of gabapentin without adequate documentation of therapeutic response or despite documentation that it was not effective for the patient. This guidance was developed to identify the therapeutic indications and dosage regimens of gabapentin for which there are sufficient documentation of efficacy and safety and to define parameters for an adequate trial after which gabapentin should be discontinued if there has been no or little clinical benefit.

A review was performed of English language, double-blind randomized controlled trials (DB RCTs), long-term extension studies of DB RCTs, and quantitative systematic reviews or meta-analyses that involved gabapentin or alternative formulary agents and included primarily or solely adults (Medline/PubMed 1966 to November 2003). The quality of the evidence was rated using the U.S. Preventive Services Task Force method[1] modified to include only Level I studies (DB RCTs).

Various uses of gabapentin are summarized by grade of recommendation in Table 1 and explained in more detail in the remainder of this guidance.

Table 1 Summary of uses for gabapentin by grade of recommendation

Grade A **Strongly Recommend**	**Grade C** **Consider**[†]	**Grade D** **Ineffective**	**Grade I** **Insufficient Evidence**[†]
Indications always acceptable	*May be considered*	*May be considered ineffective*	
Postherpetic neuralgia Partial seizures Painful diabetic neuropathy	Social Phobia / Anxiety Acquired Pendular Nystagmus Essential tremor Generalized tonic-clonic seizures Migraine headaches, prophylaxis Parkinsonism Refractory spasticity, add-on therapy Restless leg syndrome Phantom limb pain Spinal cord injury-related pain Guillain-Barré–related pain Acute post-mastectomy pain Postmenopausal hot flashes	Bipolar mood disorders Panic disorder Cocaine dependence (Grade D/I)	Cocaine dependence (Grade D/I) Insomnia Posttraumatic stress disorder Irritable bowel syndrome Trigeminal neuralgia Other types of neuropathic pain Taxane-induced arthralgias and myalgias

[†] As a general rule, grade C and I indications are not routinely recommended uses, but they may be considered on an individual basis when other agents with evidence of efficacy are not effective, not tolerated, or contraindicated. Also see text below.

As a general rule, grade C and I indications are not routinely recommended uses, but they may be considered on an individual basis when other agents with evidence of efficacy are not effective, not tolerated, or contraindicated. The potential risks and benefits of using gabapentin for these indications should be discussed with the patient. The grade C and I indications and the gabapentin-related therapeutic goals should be clearly articulated and documented in the patient's medical records. Gabapentin use should be re-evaluated periodically against these goals, and discontinued if found ineffective.

RECOMMENDABLE INDICATIONS FOR USE OF GABAPENTIN

Indication for Gabapentin	Alternative formulary agents	Comments
Postherpetic neuralgia, monotherapy or add-on therapy (Grade A, Strongly Recommend)[2-7]	**Tricyclic antidepressant agents (TCAs)** (Grade A, Strongly Recommend)[3,6,7] **Capsaicin 0.075% cream** (Grade B, Recommend)[8,9] **Opioids** (Grade B, Recommend)[10] (see comments)	**Opioids** are efficacious and may be useful for the control of pain from postherpetic neuralgia in some patients. They are generally reserved for patients who have an unsatisfactory response to non-opioid therapy; see *Criteria for Use of Controlled-release Oxycodone* available at: http://www.vapbm.org and the VA/DoD Clinical Practice Guideline, *Management of Opioid Therapy for Chronic Pain* available at: http://www.oqp.med.va.gov/cpg/cpg.htm.
Partial seizures with or without secondary generalization, add-on therapy[11-18] *or monotherapy*[19-23] (Grade A, Strongly Recommend)	**Carbamazepine** (Grade A, Strongly Recommend)[24-26] **Phenytoin** (Grade A, Strongly Recommend)[25,27] **Valproate** (Grade A, Strongly Recommend)[24,28-31] **Topiramate** (Grade B, Recommend for monotherapy [32,33]; Grade A, Strongly Recommend for add-on therapy[34-48])	Gabapentin is FDA-approved as adjunctive therapy in the treatment of partial seizures with or without secondary generalization. Gabapentin monotherapy (off-label use) is effective for newly diagnosed partial seizures[19,20] and seems to be effective at higher doses for refractory partial epilepsy.[21-23] **Lamotrigine** is FDA-approved as adjunctive therapy in the treatment of partial seizures with or without secondary generalization (Grade A, Strongly Recommend[49-56]) and for conversion to monotherapy for partial seizures in patients being treated with a single enzyme-inducing AED (Grade B, Recommend[57]). It is also an alternative formulary agent; however, its use has been associated with potentially serious rashes.
Painful diabetic neuropathy, monotherapy or add-on therapy (Grade A, Strongly Recommend) [3,5,6,58-62]	**Tricyclic antidepressant agents (TCAs)** (Grade A, Strongly Recommend)[3,6,62] **Capsaicin** 0.075% cream (Grade B, Recommend)[6,63-65] **Tramadol** (Grade B, Recommend)[6,66] **Valproate** (Grade B, Recommend)[67,68] **Carbamazepine** (Grade C, Consider)[3,5,6] **Phenytoin** (Grade C, Consider)[5,6]	For painful diabetic neuropathy, optimize glucose control during trials of drug therapy.

AED = Antiepileptic drug; TCA = Tricyclic antidepressant

Postherpetic neuralgia. No alternative AEDs have been studied for postherpetic neuralgia in RCTs.[5] For gabapentin, number-needed-to-treat for at least 50% pain relief [NNT] is 3.2 (95% confidence interval [CI]: 2.4 to 5.0).[5] This NNT is comparable to that for TCAs (2.1; 1.7 to 3.0), suggesting the two agents are similar in efficacy. TCAs are less expensive than gabapentin (Table 6) and therefore, would be more cost-effective. However, TCAs are not as well tolerated as gabapentin, resulting in a more favorable benefit/harm ratio for gabapentin (TCAs 4 vs. gabapentin 8).[3] The benefit/harm ratio was calculated by dividing the absolute risk reduction (ARR) for benefit by ARR for major harm (drug withdrawal due to adverse event). A ratio of 8 means that for every 8 patients experiencing at least 50% pain relief as a result of taking the drug, one will experience an adverse event severe enough to discontinue treatment.

Partial epilepsy. There is a lack of good-quality evidence that gabapentin is more efficacious or better tolerated than traditional AEDs in patients with epilepsy. In one systematic review, gabapentin was similar in efficacy to divalproex.[69] A meta-analysis found no conclusive differences between gabapentin, lamotrigine, tiagabine, topiramate, vigabatrin, and zonisamide in terms of efficacy for partial seizures or discontinuations for any reason.[34]

Painful diabetic neuropathy. A systematic review indicates that TCAs (NNT 3.5; 95% CI: 2.5 to 5.6) and AEDs (carbamazepine, phenytoin, and gabapentin; NNT 2.7; 2.2 to 3.8) are similar in efficacy for diabetic neuropathy.[3] Antidepressants (number-needed-to-treat-for major harm [NNH, adverse event resulting in drug withdrawal] 17; 11 to 43) are less well tolerated than AEDs (no statistically significant difference versus placebo), with benefit/harm ratios of 6 for antidepressants, and 4 for TCAs as compared with 8 for AEDs, 6 for gabapentin, and 9 for phenytoin/carbamazepine.[3] Gabapentin is no better or safer than other antiepileptic agents for neuropathic pain, including diabetic neuropathy.[3,5] There is no clear evidence that gabapentin is better than carbamazepine; about 66% of patients (95% CI: 61% to 71%) who receive either drug will obtain good relief.[5] One small head-to-head trial comparing relatively low doses of gabapentin (900 to 1800 mg/d) and amitriptyline (25 to 75 mg/d) in 25 veterans with painful diabetic neuropathy found no difference in efficacy and similar safety and tolerability between the two agents.[62,70]

While there is evidence from a DB RCT of the efficacy of gabapentin in painful diabetic neuropathy,[58] there was also one unpublished DB RCT (N = 325) that did not show a statistically significant difference between gabapentin (600, 1200, and 2400 mg daily) and placebo for the same indication.[60] The improvements in pain scores seen in that study, however, could be considered *clinically* relevant (change from baseline of ≥ 2 on an 11-point Likert scale)[71] for the two higher doses of

gabapentin (change from baseline in mean daily pain score: –2.2 and –2.1 for 1200 and 2400 mg, respectively) but not for the lowest dose (–1.4) and placebo (–1.7). The negative statistical results were attributed to an unexplained high placebo response.

General comments. With the exception of a single small trial comparing gabapentin with amitriptyline for painful diabetic neuropathy, there is a lack of direct comparisons between gabapentin and other agents for any evaluated indication. There is also a lack of long-term trials of gabapentin for indications other than epilepsy.

It is uncertain whether gabapentin would be efficacious for all types of neuropathic pain if efficacy has been demonstrated for some neuropathic pain syndromes. There has been no evidence overall that gabapentin or other anti-neuralgic agents have a differential effect for certain types of neuropathic pain,[3,6,72,73] although different efficacies between pain conditions have been observed in individual studies for certain drugs (e.g., carbamazepine has demonstrated efficacy for diabetic peripheral neuropathy but is no better than placebo for central post-stroke pain.[6])

Although gabapentin has been studied in a patient population mostly refractory to previous drug therapies for postherpetic neuralgia, including other antiepileptic agents,[4] there are no clear data showing that patients with neuropathic pain refractory to other AEDs will respond to gabapentin.

Advantages and Disadvantages. Potential advantages of gabapentin include lack of cardiovascular or respiratory adverse effects, very good tolerability, lack of hepatic metabolism, lack of liver and enzyme-inducing or –inhibiting effects, less monitoring of laboratory tests, and absence of drug interactions with other AEDs. Gabapentin may have an advantage in patients taking medications (e.g., antiretroviral agents for HIV infection) that may result in clinically important interactions when taken concurrently with enzyme-inducing or –inhibiting drugs. In addition, acute oral overdoses of gabapentin tend to produce non–life-threatening symptoms (e.g., ataxia, diarrhea, diplopia, drowsiness, lethargy, and slurred speech).[74] A potential drawback to gabapentin is a delay in response due to need for dosage titration. Dosage adjustment is required in patients with renal impairment.

INDICATIONS FOR USE OF GABAPENTIN THAT MAY BE CONSIDERED (GRADE C, CONSIDER)

Condition	Comments on Available Evidence
MENTAL HEALTH	
Social Phobia / Anxiety	1 DB RCT (N = 69)[75], included in 1 meta-analysis[76]
NEUROLOGIC DISORDERS	
Acquired Pendular Nystagmus	1 small DB RCT (N = 21)[77]
Essential Tremor	Inconsistent evidence, 3 small DB RCTs (N = 25, 16, and 20)[78,79 80]
Generalized tonic-clonic seizures, newly diagnosed	In a multicenter DB RCT involving patients with newly diagnosed partial seizures with or without secondary generalization (n = 233) or primary generalized tonic-clonic seizures (n = 58), gabapentin was found to be statistically noninferior in seizure control and similar in tolerability to lamotrigine.[20] Among patients with primary generalized tonic-clonic seizures, 5 of 31 (16.1%) gabapentin and 0 of 27 (0.0%) lamotrigine patients incurred an exit event (lack of efficacy, status epilepticus, addition of another antiepileptic drug, or intolerable adverse event related to study medication). Further studies using larger study populations are required to validate the clinical relevance of these results.
Migraine headaches, preventive therapy	1 DB RCT[81] that met major criteria[82] for valid study of migraine prophylaxis (N = 145, 87 analyzed); 1 DB RCT[83] that did not meet the major criteria for valid study (N = 63)
Parkinsonism	1 small DB RCT (N = 19)[84]
Refractory spasticity associated with spinal cord injury or multiple sclerosis, add-on therapy	Small DB RCTs (N = 21, 15, 28, 6), 3 of 4 RCTs in veterans, limited to 2- to 6-day treatment.[85-89] Lacking good-quality evidence for long-term efficacy of gabapentin, although there are anecdotal reports of long-term effectiveness. Alternative FDA-approved treatments for spasticity have limited published evidence of either efficacy (**Dantrolene)** or improved patient function **(Baclofen, Diazepam,** and **Tizanidine)**.[87,90] No evidence that one agent is superior.[87,90]
Restless Leg Syndrome	2 small DB RCTs (N = 24 and 16)[91,92]
PAIN	
Phantom limb pain	1 DB RCT (N = 19)[93]
Spinal cord injury–related pain	1 DB RCT (N = 14)[94] and 1 crossover DB RCT (N = 20)[95]
Guillain-Barré–related pain	1 DB RCT (N = 18)[96]
Acute pain, with or without a neuropathic component, including abortive therapy of migraine headaches	No DB RCTs with gabapentin in Cochrane systematic review[5]; 2 DB RCTs (N = 75 and 70) in women with acute post-mastectomy pain[97,98]
WOMEN'S HEALTH	
Postmenopausal Hot Flashes	1 small DB RCT (N = 59)[99]

USES OF GABAPENTIN NOT SUPPORTED BY DOUBLE-BLIND RANDOMIZED CONTROLLED TRIALS (GRADE D, INEFFECTIVE OR GRADE I, INSUFFICIENT EVIDENCE)

Condition	Comments on Available Evidence
MENTAL HEALTH	
Bipolar mood disorders	Two DB RCTs (N = 117 and 38) have demonstrated that gabapentin is no better than placebo in refractory bipolar and unipolar mood disorders (Grade D, Ineffective).[100,101] The results of these trials failed to confirm positive findings previously reported in open-label studies.
Cocaine dependence / craving	Lack of evidence from published DB RCTs (Grade D, Ineffective / Grade I, Insufficient Evidence). A small published DB placebo-controlled non-randomized trial (N = 7) found that gabapentin did not reduce cocaine craving and actually increased choice to self-administer cocaine.[102] It did not reduce cocaine-positive urines, and either increased or decreased cocaine-related subjective effects. The abstract of an unpublished placebo-controlled DB RCT reported that gabapentin had poor treatment retention and was ineffective (and tiagabine was effective) for cocaine dependence.[103] The National Institute on Drug Abuse sponsored a Cocaine Rapid Efficacy Screening Trial (CREST), a phase II placebo-controlled open-label RCT comparing gabapentin, lamotrigine, and reserpine in cocaine dependence. According to the principal investigator and submitted manuscript, gabapentin was ineffective. Lamotrigine was also ineffective, while reserpine showed some benefit. [E. Somoza [somozae@email.uc.edu], e-mail, 24 June 2004) While there is insufficient evidence from well-designed, published clinical trials, limited lesser quality evidence does not support a role for gabapentin for cocaine dependence. Based on the lack of any well-done, published clinical trials demonstrating safety and efficacy for this indication, we do not recommend its use for this condition.
Insomnia	Lack of evidence from DB RCTs (Grade I, Insufficient Evidence)
Panic Disorder	Insufficient, negative evidence overall; possible positive evidence in subgroup (1 DB RCT, N = 103, poor quality)[104] (Grade D, Ineffective)
Posttraumatic Stress Disorder	Lack of evidence from DB RCTs (Grade I, Insufficient Evidence)
PAIN	
Irritable bowel syndrome	Lack of evidence from any trials (Grade I, Insufficient Evidence).
Neuropathic Pain: *Trigeminal Neuralgia*	Recommendable formulary agents: **Carbamazepine** (Grade A, Strongly Recommend)[5,6,105,106] and **Baclofen** (Grade C, Consider).[107] Carbamazepine has the best evidence of efficacy for trigeminal neuralgia (NNTs reported were 1.7 [95% CI: 1.3 to 2.2][105] and 3.4 [95% CI: 2.0 to 3.4]).[5] Although gabapentin is approved for postherpetic neuralgia and is efficacious for painful diabetic neuropathy, there is a lack of good-quality evidence of its efficacy specifically in trigeminal neuralgia (Grade I, Insufficient Evidence). **Lamotrigine** (Grade C, Consider),[108] **pimozide** (Grade C, Consider),[109] **tocainide** (Grade C, Consider),[110] and **tizanidine** (Grade C, Consider)[111] have been shown to be efficacious for trigeminal neuralgia, but these agents are associated with serious potentially irreversible or fatal toxicities. Many clinicians would consider trying gabapentin before these agents because of its efficacy in postherpetic neuralgia and painful diabetic neuropathy and good safety profile. There is a lack of evidence from DB RCTs for oxcarbazepine, phenytoin, valproate, clonazepam, and TCAs (Grade I, Insufficient Evidence).
Neuropathic Pain: *Other Types* *Central neuropathic pain* *Complex regional pain syndrome* *Disc injuries* *Neuropathy associated with low back pain* *Occipital neuralgia* *Peripheral nerve injury pain* *Polyneuropathy* *Polyneuropathy, HIV-related* *Post-stroke pain*	Lack of evidence from DB RCTs (Grade I, Insufficient Evidence).
Taxane-induced arthralgias and myalgias	Lack of evidence from DB RCTs (Grade I, Insufficient Evidence).

CONTRAINDICATIONS

Hypersensitivity to gabapentin or any of its product ingredients

DOSAGE AND ADMINISTRATION

The initiation dose and rate of titration of gabapentin should be based on the clinical situation and the patient's clinical response. Dosage regimens that were used for neuropathic pain and partial epilepsy in clinical trials are shown in Table 2 and Table 3, respectively.

Table 2 Gabapentin Dosage in Adults with Neuropathic pain

Dosing Phase	Timeframe	Daily oral dose (mg/d)	Comments
Initiation	Day 1 Day 2 Day 3	300 mg/d (single daily dose) 600 mg/d (divided b.i.d.) 900 mg/d (divided t.i.d.)	If doses lower than 1800 mg/d are ineffective, then a time-limited trial at higher doses up to 3600 mg per day may be attempted before discontinuing the drug. *No additional benefit has been demonstrated when fixed doses greater than 1800 mg/d were tested for postherpetic neuralgia[4,60] and greater than 1200 mg/d were used in diabetic neuropathy (unpublished trial reviewed by Backonja, 2003).[60] In titrated dosing trials, doses higher than these have been needed in some patients.[2,58]*
Titration	Days 4–14	900–1800 mg/d (divided t.i.d.)	
Maintenance	Days 14 and on	1800–3600 mg/d (divided t.i.d.)	

Sources: [60,74]

Table 3 Gabapentin Dosage in Adults with Partial Epilepsy, With or Without Secondary Generalization

Dosing Phase	Timeframe	Daily dose (mg/d)	Comments
Initiation	Days 1–3	900 mg/d (divided t.i.d.) or slower initiation (as in Table 2)	Slower initiation (i.e., increasing the dose from 300 to 900 mg/d over the first 3 days) may be associated with a lower frequency of dizziness.[112] In a subgroup of patients 60 years of age and older, rapid initiation (900 mg/d on day 1) and slow initiation (titration to 900 mg/d over 3 days) produced similar frequencies of fatigue, dizziness, somnolence, and ataxia.[112] Do not exceed 12 hours between doses.
Titration / Maintenance	Days 4 and on	900–3600 mg/d (divided t.i.d.) The maximum FDA-approved dose is 3600 mg/d. Doses titrated to 6400 mg/d have been well tolerated.[113]	

Sources: [22,74,112-114]

Generally, the dose of gabapentin may be initiated at 300 to 900 mg per day and increased by 300 mg per day every 1 to 7 days. A higher initiation dose (3600 mg per day) was well tolerated in a short-term study of hospitalized patients awaiting surgery for refractory partial epilepsy.[23] Titration should include interim assessments so that the lowest effective dose can be determined; upward titration should be halted once an effective dose is reached.

The highest dose of gabapentin demonstrated to be efficacious in clinical trials is 3600 mg daily in patients with neuropathic pain, 3600 mg daily as single-drug or adjunctive antiepileptic therapy, and 4800 mg daily when converting from antiepileptic polytherapy to high-dose monotherapy.[114] In a postmarketing study of patients with epilepsy, the highest dose reported to be effective and tolerated after one year of follow-up was 6400 mg daily.[113]

Adverse effects usually occur during initiation and titration and are often transient. Sufficient time should be allowed to determine the patient's tolerability of a new dose.

Dosing in special populations

Hepatic disease: No studies have been performed; gabapentin is not hepatically metabolized.

Renal disease: Gabapentin is renally eliminated as unchanged drug. Plasma and renal clearance of gabapentin are directly proportional to creatinine clearance (CrCl). Patients on gabapentin who have renal impairment (CrCl < 60 ml/min) or who undergo hemodialysis require dosage adjustment as shown in Table 4.

Table 4 Gabapentin Dosage in Adults Based on Renal Function

CrCl (ml/min)	Daily Dose Range (mg/d)	Maintenance Dosage Regimen (mg)				
≥ 60	900–3600	300 t.i.d.	400 t.i.d.	600 t.i.d.	800 t.i.d.	1200 t.i.d.
> 30–59	400–1400	200 b.i.d.	300 b.i.d.	400 b.i.d.	500 b.i.d.	700 b.i.d.
> 15–29	200–700	200 q.d.	300 q.d.	400 q.d.	500 q.d.	700 q.d.
15	100–300	100 q.d.	125 q.d.	150 q.d.	200 q.d.	300 q.d.
< 15	Based on CrCl	Reduce daily dose in proportion to CrCl (e.g., reduce dose by 50% if CrCl is decreased by 50%).				
Hemodialysis	Based on CrCl and frequency of dialysis	Reduce maintenance dose according to the schedule above and give supplemental post-hemodialysis dose after each 4 hours of hemodialysis, as follows:				
		Supplemental Post-hemodialysis Dose (mg)				
		125	150	200	250	350

CrCl = Creatinine clearance

Elderly: Doses of gabapentin should be decreased in patients with age-related reduction in renal function. In general, doses for elderly patients should usually start at the low end of the dosing range.

DISCONTINUING GABAPENTIN

Patients who do not respond to an adequate trial of gabapentin should be taken off the drug and reassessed.

Gabapentin should be tapered off gradually (e.g., over 1 week[74]) in patients with epilepsy. Tapering gabapentin should be considered even in patients without epilepsy, since abrupt discontinuation of gabapentin in such patients has been anecdotally associated with status epilepticus[115] and development of a syndrome resembling alcohol or benzodiazepine withdrawal.[116]

Duration and dose for adequate trials of gabapentin are suggested below:

Indication	Adequate Target Dose	Adequate Trial Duration at MTD†
Any type of neuropathic pain	3600 mg/d	6–8 wk
Partial epilepsy with or without secondary generalization[114]	3600 mg/d	4–8 wk

† MTD = Maximal tolerated dose

If no or little benefit is observed at doses titrated up to 3600 mg daily and maintained for 2 months, then gabapentin should be discontinued and alternative therapy considered.

MONITORING

The indication for use, particularly if it is off label, should be clearly documented and therapeutic outcome assessed and documented on a regular basis.

Periodic monitoring of effect in pain disorders is particularly important because there is a lack of long-term studies documenting the durability of benefit from gabapentin in these conditions.

Monitoring of gabapentin blood concentrations is not required.

DRUG INTERACTIONS

Gabapentin is involved in a small number of drug interactions (see selected interactions in Table 5). The clinical relevance of these interactions is uncertain. Gabapentin is not appreciably metabolized and, with the possible exception of phenytoin, does not interfere with the metabolism of commonly coadministered antiepileptic drugs.

Table 5 Selected Drug Interactions Involving Gabapentin

Object drug that may be affected by gabapentin	Mechanism	Potential effect of object drug
Felbamate	Possible competition for renal excretion sites; felbamate clearance decreased 37%; half-life increased 46%	↑
Hydrocodone	C_{max} and AUC values decreased by 21% to 22% after administration of gabapentin 500 mg	↓
Phenytoin	Unknown; case report of increased phenytoin serum concentrations, symptoms of toxicity after addition of gabapentin to polytherapy including phenytoin; effects recurred on re-challenge. A trend of increased phenytoin concentrations or no interaction noted in other reports	↑ / ↔
Drugs that may affect gabapentin	**Mechanism**	**Potential effect of gabapentin**
Antacid	Decreased gabapentin bioavailability by 20%	↓
Hydrocodone	Increased gabapentin AUC values by 14%	↑
Morphine	Increased gabapentin AUC by 44%	↑
Naproxen	Increased gabapentin absorption by 12% to 15%	↑

Source: Neurontin® (gabapentin) Package Insert[74]; DRUGDEX[117]; Drug Interaction Facts.[118] This list of drug interactions is not all-inclusive. Consult appropriate references for further information.

Co-administration of antacids may reduce the bioavailability of gabapentin by about 20%. Gabapentin should be taken at least 2 hours following antacid administration. No recommendations on management are given for other drug interactions shown in Table 5.

DRUG COSTS

For initial doses, gabapentin is at least 10 times more costly than carbamazepine, about 1.5 times more than phenytoin, and 1.3 times more than valproic acid. Gabapentin is 6 to 58 times more expensive than TCAs. At maximal doses, gabapentin is the most expensive antiepileptic drug of the seven agents listed in Table 6.

Table 6 Drug Acquisition Costs

	Total Daily Dose* (mg / d)	Cost ($ / mo)
TCAs		
Imipramine	25–200	0.32–1.33
Amitriptyline	10–150	0.46–2.48
Desipramine	25–300	0.75–12.70
Nortriptyline	25–150	3.02–12.05
AEDs		
Carbamazepine	200–1200	1.69–10.13
Phenytoin	300–600	12.53–25.05
Valproic acid	500–4000	14.50–116.02
Gabapentin	**300–3600**	**18.59–220.03**
Lamotrigine	12.5–500†	19.93–252.80
Divalproex	500–4000	24.43–195.45
Topiramate	25–400	26.52–142.27
Other		
Tramadol	50–400	1.49–11.93
Capsaicin Cream 0.075%	3–4 times/d (60 gm)	3.87
Baclofen	15–80	5.10–25.14

Lowest VA drug acquisition costs are shown. Drugs are listed in order of increasing initial cost by category.

* Total Daily Dose reflects a combination of doses evaluated in clinical trials, FDA-approved dose ranges spanning adults and elderly for any indication, and practical dosage sizes.

† Total daily dosage range for lamotrigine is 25 mg q.o.d. to 100 mg/d (in two divided doses; $19.93 to $43.05/mo.) in patients on concurrent valproate therapy; 25 to 200 mg/d ($39.86 to $86.10/mo.) in patients not on enzyme-inducing antiepileptic drugs or valproate; and 50 to 500 mg/d ($79.71 to $252.80/mo.) in patients on concurrent enzyme-inducing antiepileptic drugs without valproate.

CONCLUSION

The available evidence from DB RCTs supports the use of gabapentin for postherpetic neuralgia, partial seizures, and painful diabetic neuropathy, and suggests that it may be considered in a number of psychiatric, neurologic, and pain disorders. Most importantly, there is evidence indicating that it is *not* effective for bipolar mood disorders, panic disorder, and possibly for cocaine dependence. Its use for these disorders cannot be condoned when other proven therapies for these conditions are available.

For indications where there is insufficient evidence to recommend for or against its use, gabapentin may be considered after all other therapies with documented efficacy and safety and without contraindications have been given adequate trials and after weighing the potential benefits and risks of gabapentin.

During dosage titration, the patient should be assessed at regular intervals to determine the lowest effective dose. For neuropathic pain, no additional benefit could be demonstrated for doses greater than 1200 to 1800 mg per day; however, some individuals may require higher doses. In neuropathic pain and partial seizures, if maximally tolerated doses up to 3600 mg daily are of minimal or no benefit after a trial of 2 months, then gabapentin should be discontinued and other therapies considered. Adequate doses and durations of therapy cannot be recommended for other indications because of insufficient evidence.

To avoid confusion related to the use of an antiepileptic agent for non-seizure disorders, clinicians should communicate the intended use of gabapentin to the patient, pharmacists, and other health care providers and clearly document the indication and response to gabapentin therapy, particularly for off-label uses.

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