Impact of a Clinical Pharmacy Consult Service on Guideline Adherence and Management of Gabapentin for Neuropathic Pain

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ABSTRACT

OBJECTIVE: Our objectives were to (1) determine whether a computerized clinical pharmacy approval and follow-up consult process for ordering new prescriptions for gabapentin for the treatment of neuropathic pain decreased the number of patients without documented treatment benefit while increasing follow-up and documentation of effectiveness, and (2) describe gabapentin use patterns prior to gabapentin therapy for neuropathic pain.

METHODS: The clinical pharmacy intervention included review of (1) the indication for gabapentin; (2) the required use and failure or contraindication of 3 first-line therapies: nonsteroidal anti-inflammatory drugs (NSAIDs), tricyclic antidepressants (TCAs), and capsaicin cream; (3) the initial pain assessment; and (4) patient follow-up in 4 to 6 weeks, with repeat pain assessment. A retrospective chart review was performed for all patients who received a new prescription for gabapentin from October 2002 to April 2003 at the Portland VA Medical Center (PVAMC). The outcomes of interest for the provider group versus the clinical pharmacy managed group included follow-up at 6 weeks or less versus follow-up at more than 6 weeks, documentation of treatment benefit, how many of the 3 first-line therapies were tried before gabapentin, and whether the gabapentin therapy was discontinued.

RESULTS: There were 237 patients who received a new prescription for gabapentin between October 2002 and April 2003. Of these gabapentin prescriptions, 61% (n = 144) were prescribed for neuropathic pain. Of the new gabapentin prescriptions for neuropathic pain, 61% (n = 88) were made from approved clinical pharmacy consults, 38% (n = 54) were ordered without a clinical pharmacy consult, and 1% (n = 2) were not included because the patient received the drug despite denial by the clinical pharmacy consult. The rate of follow-up to assess documentation of benefit of therapy with gabapentin was 87% (n = 62) in the clinical pharmacy consult group compared with 51% (n = 27) in the provider-managed group (χ² = 18.07, P < 0.001). Of the patients who were assessed by follow-up, 89% (n = 55) of the clinical pharmacy consult group received follow-up within 6 weeks versus 52% (n = 14) of the provider-managed group (χ² = 12.63, P < 0.001). Compared with the patients managed by clinical pharmacists, 43% (n = 23) of the gabapentin patients in the provider-managed group had no evidence of prior use of any of the 3 agents required by the gabapentin neuropathic pain guideline, 55% (n = 29) had evidence of prior use of 1 or 2 first-line agents, and only 2% (n = 1) had evidence of prior use of all 3 required first-line agents, versus 100% (n = 71) of the patients managed by clinical pharmacy consult. There was no difference in the rate of continuation of gabapentin therapy in the group of patients who received clinical pharmacy consults (65%) compared with the provider-managed group (68%, χ² = 0.11, P = 0.718). Of the 148 pharmacy consults for new gabapentin prescriptions that were completed during the 7-month period from October 2002 through April 2003, 60 (40%) were denied, which resulted in the lack of gabapentin use in these 60 patients.

CONCLUSIONS: A clinical pharmacy intervention as part of the management of a treatment guideline for appropriate gabapentin use promotes documentation of drug therapy effectiveness in neuropathic pain and prevention of gabapentin use prior to a trial with alternative first-line therapies.

KEYWORDS: Gabapentin, Neuropathic pain, Clinical pharmacy, Formulary management

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When gabapentin (Neurontin) was introduced to the market in December 1993, its only approved indication was the adjunctive treatment of partial seizure disorders.1 The only other indication for gabapentin is for postherpetic neuralgia, which was approved by the U.S. Food and Drug Administration (FDA) in May 2002. Since market introduction, gabapentin has been used to treat a number of other conditions not approved by the FDA, including neuropathic pain. This outcome is not a new phenomenon since other antiepileptics have also been used to treat neuropathic pain.2-4

Gabapentin use continues to increase nationwide. In 2001, it was the 31st most prescribed drug, and in 2002, the 25th most prescribed drug.5 In May 2002, the manufacturer of gabapentin was accused of promoting non-FDA-approved uses of gabapentin.6,7 In June 2004, Pfizer, on behalf of the acquired company Warner-Lambert, pleaded guilty to criminal marketing of Neurontin. Pfizer agreed to pay $430 million in fines, including a criminal fine of $240 million and $190 million in economic damages to settle civil liability suits brought by 50 state attorney generals.8 The off-label uses promoted for gabapentin included bipolar mental disorder, various pain disorders, amyotrophic lateral sclerosis (ALS or Lou Gehrig’s disease), attention-deficit disorder, migraine, drug and alcohol withdrawal seizures, restless leg syndrome, and first-line monotherapy for epilepsy. It is not known how these marketing strategies may have affected the quality of patient care or the potential overutilization of gabapentin, but off-label use of gabapentin has been the subject of other evaluations.9-12

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At the Portland Veterans Affairs Medical Center (PVAMC), the use of gabapentin for non-FDA-approved indications increased from the time the drug appeared on the formulary, raising concerns regarding the ability to assess the effectiveness of gabapentin when used for neuropathic pain syndromes and the cost of the drug. In 1998, gabapentin appeared on the PVAMC list of highest expenditure drugs. Between 1999 and 2002, PVAMC experienced a 37% increase in the number of gabapentin prescriptions. In October 1999, there were 268 prescriptions of gabapentin and 1.6 fills per 100 primary care patients. In October 2002, there were 367 prescriptions of gabapentin and 1.3 fills per 100 primary care patients. While the proportion of primary care patients who received gabapentin did not increase between October 1999 and October 2002, the drug accounted for one third of the yearly financial allotment for care for the average VA patient.

Local prescribers participated in the development of the guideline for appropriate use of gabapentin. A literature review was conducted to assess the value of the evidence, including searches of PubMed and the Cochrane Collaboration. Search terms included neuropathic pain, nonsteroidal anti-inflammatory drugs, diabetic neuropathy, postherpetic neuralgia, and anti-inflammatory drugs; combinations of the terms were also used in the search. Emphasis was placed on the results of randomized controlled trials (RCT) and meta-analyses of RCTs.

The results of RCTs published since 1999 supported the use of gabapentin for painful diabetic neuropathy and Herpes Zoster. However, a search of the Cochrane Collaboration found gabapentin no better than older antiepileptics or tricyclic antidepressants (TCAs) for treatment of chronic pain, including neuropathic pain, and no benefit for treatment of acute pain. This latter finding stands today. The causes of neuropathic pain are many, yet the treatment with gabapentin is supported in the literature with the results of RCTs only for the 2 etiologies: diabetic neuropathy and Herpes Zoster. For the remainder of neuropathic pain patients, there is little published evidence of effectiveness of gabapentin compared with other therapies. In such cases, providers have a choice to use drugs for non-FDA-approved indications or use older medications, often with less evidence of effectiveness.

The PVAMC developed a guideline in 2000 for appropriate use of gabapentin for neuropathic pain. This was done to control costs of this expensive medication when its effectiveness could not be determined. The guideline defines neuropathic pain and diagnoses where neuropathic pain can exist. Prior to use of gabapentin, the guideline required that patients must have tried and failed, or have contraindications to, 3 first-line treatments: (1) an NSAID, (2) a TCA, and (3) capsaicin cream, prior to using gabapentin (Table 1). The NSAIDs and capsaicin cream of this protocol are not first-line treatment for neuropathic pain today. However, when this guideline was developed in 2000, the data were insufficient to support use of gabapentin in chronic pain.

**TABLE 1**

Gabapentin Neuropathic Pain Guideline—VA Medical Center*

| Definition: Pain with abnormal sensations, i.e., paresthesias (uncomfortable tingling) or dysesthesias (aching, burning, prickling, or shooting pain, either spontaneous or in response to normally painless stimuli like pulling sheets over feet) |
| Diagnosis: Peripheral neuropathy, radicular pain (not low back pain), postherpetic neuralgia, peripheral nerve injury, central (poststroke syndrome), etc. Remember to evaluate for etiology of concomitant pain prior to selection of pain therapy. |

Carefully designed treatment trials for neuropathic pain are few. Current medication regimens are based on a combination of observations from clinical studies, clinical anecdotes, and experimental findings. Treatment strategy is “trial and error” and yields clear improvement in only a minority of patients.

First-Line Therapy: (must be used on a scheduled basis for 1 month before failure is established)

1. Nonsteroidal anti-inflammatory drugs (NSAIDS): Patient must have failed therapy with at least 1 NSAID. Consider trial of different agents:
   a. Ibuprofen 600 mg QID
   b. Naproxen 500 mg BID
   Comments: Use with caution in patients with GI disease, cardiovascular disease, renal or hepatic impairment, and patients receiving anticoagulants

2. Tricyclic antidepressants (TCAs): Patient must have failed therapy with at least 1 TCA. Consider trial of 2 different agents:
   a. Nortriptyline 10-75 mg QHS
   b. Amitriptyline 10-100 mg QHS
   c. Imipramine 25-200 mg QHS
   d. Desipramine 10-100 mg QHS
   e. Doxepin 10-100 mg QHS
   Comments: Nortriptyline and desipramine have fewer incidences of anticholinergic side effects, sedation, and orthostatic hypotension than amitriptyline. Use with caution in those patients with cardiac conduction disturbances. An EKG prior to initiation of therapy is recommended. May titrate up to full antidepressant doses.

3. Capsaicin cream 0.025% or 0.075% QID scheduled: Patient must have failed capsaicin cream.
   a. In normal renal function, dose should be started at 300 mg QHS for 1 week, 300 mg BID for 1 week, then 300 mg TID for 1 month to increase tolerability. Initial prescriptions will be filled with 120 capsules with no refills. At 4 weeks, efficacy and tolerability will be evaluated by clinical pharmacist or designee and dose will be titrated to 3,200 mg per day if appropriate.
   b. In impaired renal function (serum Cr>1.3 mg/dL), dose should be started at 100 mg QHS for 1 week, 200 mg QHS for 1 week, then 300 mg QHS for 1 week. Titrate as above to maximum of 300 mg QHS if CrCl 15-30 mL/min, 300 mg BID if CrCl 30-60 mL/min, or 400 mg TID if CrCl >60 mL/min.
   c. Patient will be telephoned and evaluated by clinical pharmacist or other designee at 4 weeks.
   d. If gabapentin is ineffective or not tolerated, taper over 1 week and reassess pain level.

* Patient must have failed all 3 prerequisite therapies to receive approval of use of gabapentin by clinical pharmacy consult.

DID=twice a day; Cr=creatinine; CrCl=creatinine clearance; EKG=electrocardiogram; GI=gastrointestinal; QHS=every bedtime; QID=4 times a day; TID=3 times a day.
paine of nerve origin that was not diabetic neuropathic pain or postherpetic neuralgia. NSAIDs and capsaicin cream are recommended in guidelines for malignant pain, and nonmalignant chronic pain may be considered for individual neuropathic pain cases.

The drug choices of the PVAMC guideline for treating neuropathic pain (Table 1) reflect the standard of practice in the treatment for chronic nerve pain at the time of the review, excluding painful diabetic neuropathy or postherpetic neuralgia. Trials of these drug choices were required prior to use of gabapentin. There is ample evidence supporting TCA use for neuropathic pain. Capsaicin is FDA-approved for postherpetic neuralgia, diabetic neuropathy, and arthritis pain. While NSAIDs have not been shown consistently to treat neuropathic pain effectively, they are frequently used for chronic pain, pain of nerve entrapments, and pain with an inflammatory component. In 2002, neuropathic pain was treated by the medical community with therapies that worked on other forms of neuropathy and chronic pain.

Clinical assessment of gabapentin therapy was proposed to detect drug side effects and instances of ineffective use, and hence, to increase the safe use of gabapentin. In the fall of 2002, the PVAMC developed an electronic consult for gabapentin. Providers wishing to prescribe gabapentin for neuropathic pain, in accordance with the definition in the guideline, submitted a consult request to the clinical pharmacy department for assessment of adherence to the guideline, evaluation of treatment effect, and recommendation of titration or discontinuation of gabapentin when appropriate. Providers were educated about the process through conferences and e-mails.

The objectives of the present study were, through the conduct of a retrospective chart review of all new gabapentin prescriptions, to (1) evaluate the effectiveness of a computerized clinical pharmacy process to review gabapentin prescriptions for neuropathic pain and (2) describe the current pattern of use of gabapentin at the PVAMC.

**Methods**

**Clinical Pharmacy Intervention**

The consult requests that the clinical pharmacy department received for gabapentin were reviewed in accordance with the existing guideline for gabapentin use at the facility (Table 1). Patients had to have tried and failed, or have contraindications to, all 3 first-line agents of the guideline prior to consideration of gabapentin. Treatment failure with a first-line agent was defined as no treatment benefit or an adverse drug reaction. Providers at our institution include physicians, nurse practitioners, and physician assistants. On the consult, the prescribing provider was required to indicate (1) the patient's diagnosis of neuropathic pain in accordance with the definition in the treatment guideline, (2) the trial and failure of the 3 first-line therapies (or contraindications), and (3) the patient's current pain score. The pain score was based upon the patient's subjective assessment of pain on a scale from 0 (no pain) to 10 (the most excruciating pain). Pain is routinely assessed using this scale for all patients at PVAMC. If information was missing or unclear, the provider and patient were contacted for further information. Although consults were required for neuropathic pain, gabapentin prescriptions could be ordered without a consult. Those prescriptions were filled solely at the PVAMC outpatient pharmacist's discretion and did not require the treatment indication or the value from the pain scale.

Consult requests for use of gabapentin were managed by 3 clinical pharmacists. This became part of their regular formulary management duties, and no additional staff members were hired. One of the pharmacists reviewed each consult for appropriateness and either approved or denied gabapentin (Figure 1). The consult was denied and the prescription for gabapentin was not issued if the patient did not have a diagnosis of neuropathic pain or had not completed the appropriate trials of all 3 first-line

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**FIGURE 1 Clinical Pharmacy Intervention—Consult Review and Follow-up Process**

- **Consult Submission**
  - Required Information:
    1. Diagnosis of Neuropathic Pain
    2. Documented trials of 3 first-line therapies
    3. Pain Score (0-10 pain scale)

- **Clinical Pharmacist's Review**
  - Was consult documentation completed?
  - Yes or No

- **Consult approved**
  - Gabapentin initiated and patient counseling provided by pharmacist

- **Consult denied**
  - Alternative therapy recommended to physician

- **Patient contacted by clinical pharmacist within 5-6 weeks to assess treatment effectiveness and tolerability**

- **Inferable side effects?**
  - Yes or No

- **Treatment discontinued?**
  - Yes or No

- **Outcomes of assessment**
  - Yes / No

- **Intervention complete**
  - Yes / No

- **Dose increased**
  - Yes / No

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medications (Table 1). If approved, the patient was contacted by phone for counseling and the prescription was mailed. Patients with normal renal function were started on a standard titration of 300 mg at bedtime for 7 days, followed by 300 mg twice a day for 7 days, then 300 mg 3 times a day, in accordance with the prescribing information for gabapentin.21 Otherwise, dosing based on renal function was used.

A clinical pharmacist contacted the patient again after 4 to 6 weeks to evaluate the treatment effectiveness and tolerability. Pain was reassessed at the time of follow-up using the same 0 to 10 pain scale. The prescription for gabapentin was continued if there was improvement in the pain score, self-defined improvement in pain, or improvement in other signs or symptoms of neuropathy. The prescription was discontinued if the patient experienced self-defined side effects warranting discontinuation of the drug or had no improvement in pain. In some cases where treatment effect was unclear at the time of follow-up based on the patient’s impression or conflicting pain scale scores, the prescription was continued or the dose increased by the clinical pharmacist, and additional follow-up was scheduled.

Evaluation of the Intervention
A retrospective chart review was conducted from October 2002 through April 2003. By the time chart review began, there were 7 months of data available. At least 6 months of data were desired to assess the intervention. The sample consisted of all patients receiving new outpatient prescriptions for gabapentin that were documented in the PVAMC Veterans Health Information System and Technology Architecture (VistA) database. A new prescription was defined as a prescription filled between October 2002 and April 2003 for a patient who had not had a prior prescription for gabapentin filled since May 1997, when gabapentin first appeared in pharmacy records. The pharmacy data were extracted from VistA using VA Filemanager and then uploaded into Microsoft Excel. Data collected during the VA electronic medical chart review included (1) indication for the prescription, (2) whether a consult to the clinical pharmacy department was submitted, (3) the prescriber’s specialty, (4) whether and when treatment follow-up occurred, (5) documentation of treatment effectiveness, (6) continuation of the gabapentin prescription, and (7) whether the gabapentin prescription was initiated by a previous provider outside of the PVAMC. Information was also gathered on side effects and reasons for discontinuation. Prescriptions for neuropathic pain were then selected for further analysis. The number and status of all consults submitted were also collected for the same time frame using the VistA consult tracking reports. Data were analyzed using descriptive and chi-square statistics in Microsoft Excel and Vassar Stats statistical software.

Prescription data for TCAs, NSAIDS, and capsaicin were gathered for all patients on gabapentin to assess compliance with the gabapentin treatment guideline.

Results
The consults in the clinical pharmacy group that resulted in a prescription for gabapentin were examined. There were consults that were denied by a clinical pharmacist because of lack of first-line drug trials. There were also 2 patients who received the gabapentin from staff pharmacists even though the consults had been refused by a clinical pharmacy specialist. In the provider-managed group, no clinical pharmacy consults occurred.

Patient Selection
Figure 2 illustrates the method of patient selection for this study. Two hundred and thirty-seven patients had a new prescription for gabapentin initiated within the study period. Of the 144 prescriptions (61%) for neuropathic pain, 88 had clinical-pharmacy-approved consults, and these constitute the clinical-pharmacy-managed group. Unexpectedly, 54 patients had prescriptions resulting from the provider-prescriber’s bypassing the consult and ordering the drug directly. This finding led us to compare these 2 groups to help determine the effectiveness of the consult process. Two patients with denied consults received a gabapentin prescription through dispensing by staff pharmacists outside of the consult protocol, and these two patients were excluded. An additional 18 patients were excluded who had previous prescriptions of gabapentin for neuropathic pain prior to receiving care at the PVAMC and
already had demonstrated benefit with the drug (i.e., the efficacy of gabapentin had already been established in these patients).

Ninety-three patients (39%) had indications other than neuropathic pain for gabapentin and were therefore excluded from further analysis (Figure 2): 42 (18%) for migraine headaches; 18 (8%) for other pain syndromes; 15 (6%) for mental health usages; 15 (6%) for unknown indications; and 3 (1%) for seizure.

For the final analysis, 124 patients were included in the study: 71 (57%) of these patients received gabapentin prescriptions through the consult process (clinical-pharmacy-managed) and 53 (43%) received gabapentin prescriptions without a consult (provider-managed).

**Denied Consults**

A total of 148 consults were submitted to clinical pharmacy, and 60 (40%) of these were denied. The reasons for the 60 denials included the following: 2 (3%) patients chose not to start gabapentin; creatinine was elevated in 1 patient (2%); 9 (15%) consults had indications other than neuropathic pain (e.g., trigeminal neuralgia, nonanginal chest pain, restless leg syndrome, and chronic pain); and 48 (80%) consults did not document a trial of first-line medications as per protocol.

Overall, 61% (54) of the prescribers used the clinical pharmacy consult service. Surgical subspecialties used the clinical pharmacy consult according to the gabapentin treatment guideline 29% of the time, neurology 35% of the time, and medicine subspecialties 50% of the time. VA primary care providers and community (fee-based) providers used the clinical pharmacy consult according to the treatment guideline more often when ordering gabapentin than did other categories of prescribers, 76% and 82%, respectively. Fee-based providers are VA-authorized and are reimbursed as community providers; they are used by some patients who live a great distance from VA outpatient care. The pharmacy service department submitted consult requests to clinical pharmacists on behalf of the fee-based providers, which likely accounts for the high compliance rate with the gabapentin treatment guideline that was seen with this category of provider.

Table 2 summarizes the follow-up of all patients, the timing of follow-up, the documentation of treatment benefit in the time frame of the study, the number of required therapies tried according to the treatment guideline, and whether the gabapentin therapy was continued or not. Of the 124 patients eligible for follow-up, 89 (72%) patients had documentation in the medical record of follow-up. Patients in the clinical-pharmacy-managed group were significantly more likely to have follow-up documentation (89/124) than those not followed up (35/124). The table also shows the number of required therapies tried according to the treatment guideline. Overall, 61% (54) of the prescribers used the clinical pharmacy consult service. Surgical subspecialties used the clinical pharmacy consult according to the gabapentin treatment guideline 29% of the time, neurology 35% of the time, and medicine subspecialties 50% of the time. VA primary care providers and community (fee-based) providers used the clinical pharmacy consult according to the treatment guideline more often when ordering gabapentin than did other categories of prescribers, 76% and 82%, respectively. Fee-based providers are VA-authorized and are reimbursed as community providers; they are used by some patients who live a great distance from VA outpatient care. The pharmacy service department submitted consult requests to clinical pharmacists on behalf of the fee-based providers, which likely accounts for the high compliance rate with the gabapentin treatment guideline that was seen with this category of provider.

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pharmacy-managed group were more likely to receive documented follow-up after starting gabapentin than patients managed by the provider (usual care) group, 87% (n = 62) of patients compared with 51% (n = 27) of patients, respectively ($\chi^2=18.07, P<0.001$). Of the patients who received follow-up, a greater percentage of clinical-pharmacy-managed patients received follow-up within 6 weeks compared with the provider-managed group.

Of the 89 patients with follow-up in the 2 groups, 64% (n = 57) experienced clinical improvement, and 24% (n = 21) had no improvement. Of the 21 patients with follow-up who had no improvement, 15 (71%) were in the clinical pharmacy group (1 patient died and 14 patients had their gabapentin therapy discontinued), and 6 (29%) were in the provider-managed group (1 patient died and 5 patients had their gabapentin therapy discontinued). The outcomes were unknown for 12% (n = 11) of the patients who received follow-up. This occurred if documentation could not be found or if the treatment benefit was unclear at the time of the first follow-up. For several of the patients followed up by clinical pharmacy, their date of evaluation had not yet come due at the time of data collection for the present study.

Forty-two (68%) of 62 patients managed by the clinical pharmacy group experienced benefits with the use of gabapentin versus 15 (56%) of 27 patients managed by providers (68% vs. 56%, $\chi^2 = 0.74, P = 0.390$). The effect of treatment was unknown for 6 (22%) of the 27 patients followed up on by providers versus 5 (8%) of the 62 patients followed up on by clinical pharmacists ($\chi^2 = 2.3, P = 0.129$).

Similar percentages of prescriptions for gabapentin were continued and discontinued by the clinical pharmacists and providers. However, of the 53 patients followed by providers, 29 (55%) had tried 1 or 2 of the first-line therapies prior to the gabapentin trial. Only 1 patient (2%) had tried all 3 therapies, and 23 (43%) had no record of trying any of the 3 first-line therapies. Gabapentin prescriptions were continued in 46 (65%) of the 71 patients in the clinical pharmacy group versus 36 (68%) of the 53 patients in the provider group ($\chi^2 = 0.11, P = 0.718$). There were 5 deaths in the group followed by clinical pharmacy and 1 death in the group followed by providers. The cause of death for the 6 patients was reviewed by a physician, and the deaths were determined to be related to comorbid conditions and not attributable to the use of gabapentin.

**Discussion**

Through participation of stakeholders, a clinical pharmacy consult process was developed at the PVAMC to review and follow up on gabapentin efficacy for neuropathic pain. The goals of this project were (1) to evaluate the effectiveness of this process and (2) to describe the current pattern of use of gabapentin at our institution. Patients with a provider-given diagnosis of neuropathic pain were referred to clinical pharmacists for assessment, titration, and evaluation of treatment effect. The use of gabapentin by providers who bypassed this process and their assessment and management of neuropathic pain were compared with the use of gabapentin by the clinical pharmacy group and their assessment and management of neuropathic pain.

Of the 124 patients who received gabapentin prescriptions for the indication of neuropathic pain included in our review during the 7-month period, 57% of the patients went through the consult process and 43% did not. Although a similar percentage of patients in both groups ultimately continued gabapentin (65% and 68%), patients who did not have clinical pharmacy consults were less likely to receive follow-up within 6 weeks. A more coordinated pharmacy review process could have redirected some of this usage to the consult process.

The consult process allowed for a monitored trial of gabapentin, documentation of its efficacy, and denial of the prescription if guidelines for trial of other medications had not been followed or if the indication was inappropriate. In this study, 40% of consults were denied and thus 60 unnecessary prescriptions were avoided. This process contributed to increased documented effectiveness and quality for patients, education of providers on treatment criteria prior to use of gabapentin for neuropathic pain, and assistance with the management of neuropathic pain for providers and patients. The prompt assessment of efficacy and discontinuation and trial of other medications prior to trial of gabapentin promote efficient use of resources.

In theory, patients who had failed trials of NSAIDs, capsaicin, and TCAs and who had then received titrated gabapentin trials might be more refractory to treatment or more difficult to treat. However, when compared with the patients receiving gabapentin initially for neuropathic pain, a similar percentage of gabapentin prescriptions were continued for the groups of patients managed by providers versus clinical pharmacists. This suggests that the response to gabapentin is independent of response to trials of alternate, first-line therapies for neuropathic pain. Since nearly the same percentage of patients in the clinical-pharmacy-managed and provider-managed groups discontinued gabapentin therapy, 30% and 28%, respectively, a tiered trial of lower-cost therapeutic options seems particularly reasonable.

The pattern of gabapentin use at PVAMC showed that 39% of patients received the drug for non-FDA indications. Very few patients were on the drug for seizure or herpetic neuralgia. The primary care providers of the VA were most likely to use the consult process for the use of gabapentin for neuropathic pain. They had a formal training on the consult that was well attended. The pharmacy had a clinical pharmacist reviewing fee-basis prescriptions for formulary adherence, and thus the consult was completed for these patients.

Our attempt at standardizing the use of gabapentin for
neuropathic pain was based on the studies available in 2002 with the thought that this process would save this resource for patients failing the other standard therapies at the time. Unfortunately, some providers did not follow the procedure for neuropathic pain consults, resulting in 53 gabapentin prescriptions outside the consultation process. Had these prescriptions gone through the consult process, some would have received a trial of other therapies and most would have received more prompt follow-up and discontinuation if the drug was not effective. Provider desire for autonomy and the desire to please patients may have contributed to disregard of the clinical pharmacy consult protocol for gabapentin prescription. However, lack of knowledge of the process was another possible factor.

At PVAMC, consult in-services and discussions about needed documentation of efficacy and cost information occur for several drug classes, and providers have begun to change prescribing behavior. Educational processes have been changed to identify target opportunities (e.g., rotating resident provider-prescribers) and respond with more in-service presentations.

The PVAMC has found the clinical pharmacy consult process helpful in documenting and assessing the effectiveness of expensive therapies and has adapted this model for other treatments. The success of this process depends on support of leadership; buy-in of providers, pharmacists, patients, and informatics staff; and reassessment of work required versus savings as prices change. Since patient follow-up occurs outside of a provider visit and is handled by a pharmacist, it does not increase the need for additional clinic appointments with the patient's provider.

In addition, the evaluation process in the present study brought attention to the documentation of clinical benefit and trial of other medications prior to use of an expensive drug for a non-FDA-approved indication. As providers become more familiar with the protocol, the need for consults might decline. On the other hand, when another new, expensive agent for neuropathic pain is placed on formulary, this approach could be adapted to require step therapy trials with first-line agents.

At the time our guideline was created, there were few RCTs of gabapentin use for neuropathic pain syndromes other than nonherpetic neuralgia or diabetic neuropathy. Since that time, RCTs have been conducted, resulting in the recommendation of gabapentin as a first-line agent by the Agency for Healthcare Research and Quality’s National Guideline Clearinghouse on the topic. This guideline is for neuropathic pain, including peripheral neuropathic pain and central neuropathic pain of many etiologies. We have found patient literature of one other large managed care system that discusses similar therapies during 2002.

In 2003, Dworkin et al. published a review of the literature that is commonly cited as a reference for the treatment of neuropathic pain and is the basis for the guideline for the diagnosis and treatment of neuropathic pain from the National Guideline Clearinghouse; it was first released in November 2003. The section recommending use of gabapentin for neuropathic pain is based on 8 double-blind, placebo-controlled, randomized clinical trials. Three of these studies looked at the treatment of postherpetic neuralgia, 2 studies looked at diabetic neuropathy, 1 study looked at phantom limb pain, 1 study looked at Guillain Barre, and 1 study looked at spinal cord injury. These studies might be used to support treatment of these conditions compared with placebo.

Neuropathic pain is the end stage of many disease states, most of which are not well studied. The drugs recommended as first-line agents by Dworkin et al. in their review published in 2003 included 5% lidocaine patch, opioid analgesics, tramadol, and TCAs. The second-line agents listed are lamotrigine, carbamazepine, paroxetine, citalopram, sustained-release bupropion hydrochloride, venlafaxine, and imipramine hydrochloride. Treatments beyond second-line medications included capsaicin, clonidine, dextromethorphan, and mefoxaline. Most of the cited studies are placebo-controlled without comparison of therapies. Dworkin et al. acknowledged variable responses to drugs within a class and hypothesized that variable pain mechanisms are responsible. The review states that there are empiric and theoretical reasons for trying different agents in a class and in various classes for a patient not finding relief of neuropathic pain.

One appealing aspect of the use of gabapentin is its relatively benign side effects compared with other therapies such as TCAs. The side-effect profile of gabapentin is thought to be less severe, including dizziness, somnolence, gastrointestinal symptoms, ataxia, fatigue, nystagmus, viral infection, and mild peripheral edema. These are the side effects occurring in more than 8% of users as listed in Lexi-Comp for gabapentin. Gabapentin can cause gait, balance, and cognitive problems in the elderly but is thought to have excellent tolerability and safety.

The factors that are evaluated for use in a tiered approach to the use of medications include effectiveness, effectiveness over other therapies, costs, safety, and availability. While gabapentin appears to be relatively safe, available, and effective in many patients, it is expensive in the customary dose range of 900 mg to 1800 mg, yielding a price range off $117 to $219 per month according to data from drugstore.com as of December 2005. In 2002, with no generic gabapentin available, these prices were higher. Dworkin et al. also considered the cost to patients when they selected the first-line agents for neuropathic pain.

There is a large body of literature on the subject of physician adherence to medical practice and drug therapy guidelines. An algorithm designed to encourage physicians in an integrated health system to use over-the-counter NSAIDs as first-line therapy in musculoskeletal pain and arthritis was associated with a decrease in the number of prescription NSAID claims per member per month (PMPM). Use of a risk-scoring tool in a large group-model HMO was associated with a more-than-5-fold lower ratio.
of the use of COX-2 selective NSAIDs for arthritis patients in the lowest decile of risk (1.5% of these patients) compared with patients in the highest decile of risk for serious gastrointestinal complications (8.3%). However, poor prescriber adherence to FDA-approved guidelines for drug therapy has emphasized the need for managed care interventions.

Interventions such as physician profiles used in conjunction with academic (prescriber) detailing have been associated with savings in PMPM spending on antidepressants despite increased utilization due to use of lower-cost therapeutic alternatives. Use of electronic clinical decision support systems based upon evidence from the medical literature has similarly been associated with drug cost savings from the use of lower-cost therapeutic alternatives despite increased drug utilization in primary care medical groups. Previous research in the VA health system found that simple dissemination of national criteria for the appropriate use of tamsulosin had no measurable effects on prescribing and that a formal education process was probably necessary to reduce inappropriate prescribing of the nonformulary drug.

The PVAMC receives funding per patient, and there is no incentive pay for PVAMC providers to either conserve or use resources. In 2002, if a patient was on gabapentin, more than one third of their allotment for care was spent on this drug therapy alone. To place this in context, most VA patients receive therapy alone. To place this in context, most VA patients receive more patients.

**Limitations**

There were several methodological limitations in the present study, including the retrospective evaluation of a clinical process. When the process started, some prescriptions for gabapentin were being written and accepted that did not go through the protocol of the clinical pharmacy consult. This loop has since been closed by eliminating all other computer ordering routes of gabapentin except through the clinical pharmacy consult. We did not investigate the potential bias that might have been introduced had more difficult pain cases been referred to the clinical pharmacist since consults were only approved when the patients had failed the 3 first-line therapies for neuropathic pain. This study also did not measure service outcomes, such as patient dissatisfaction with care, or cost outcomes, including the administrative costs of this intervention or the possible offsetting cost reduction in expenditure for gabapentin. The follow-up period for a patient in this study could have been as short as 6 months.

**Conclusions**

Implementation of a clinical pharmacy consult for neuropathic pain resulted in 100% of patients using 3 first-line therapies prior to gabapentin compared with 2% for physician-managed patients. The clinical-pharmacy-managed patients also had a higher rate of follow-up to document response to gabapentin therapy and had more timely follow-up compared with physician-managed patients.

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**DISCLAIMER**

The views expressed in this article are those of the authors and do not necessarily represent the views of the Department of Veterans Affairs.

**REFERENCES**


