Conversion from thrice- to twice-daily pregabalin dosing for pain: Economic and clinical outcomes in a veteran population

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Pain is one of the most common ailments encountered in the American healthcare system. The management of pain and pain-related disorders exacts an enormous financial toll due to the combination of frequent outpatient physician visits, multiple hospitalizations, and lost workdays. According to a recent Institute of Medicine Report, Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research, pain is a significant public health problem that costs society at least $560–$635 billion annually. Pain also results in decreases of functional status and quality of life for afflicted patients.

There are several types of pain, and the choice of an appropriate therapeutic agent is essential for the correct management of the chronic pain syndrome. Neuropathic pain arises from damage within the nervous system due to medical conditions such as diabetes mellitus, stroke, and postherpetic neuralgia. In contrast, nociceptive pain results from actual tissue damage due to musculoskeletal conditions or inflammatory mediators.

The uses of pregabalin include the treatment of diabetic neuropathy, neuropathic pain, epilepsy, postherpetic neuralgia, fibromyalgia, and generalized anxiety disorder (GAD). Pregabalin is an analog of the neurotransmitter γ-aminobutyric acid and exerts analgesic, anxiolytic, and anticonvulsant properties through inhibition of the α2-δ subunit of voltage-gated calcium channels. The end products of this inhibition are the reduction of calcium influx and the prevention of the release of numerous transmitters such as norepinephrine, glutamate,

Purpose. Results of a study analyzing economic and clinical outcomes one year after conversion from thrice- to twice-daily pregabalin dosing for pain are presented.

Methods. A retrospective chart review was conducted at two Veterans Affairs facilities. The analyzed population included all patients receiving pregabalin for pain whose dosing was converted from thrice- to twice-daily pregabalin dosing during a one-year period. The primary endpoint was the economic impact of the conversion. Secondary endpoints included reversion to thrice-daily pregabalin dosing, pregabalin discontinuation, addition of medications for pain, and unscheduled neuropathy-related visits.

Results. Among the 57 patients included in the data analysis, 41 continued to take pregabalin twice daily, 10 had pregabalin discontinued, and 6 had dosing reverted to thrice daily. The mean age of patients and the distribution of add-on pain medications did not differ significantly between patients whose pregabalin dosing frequency remained at twice daily and patients whose frequency reverted to thrice daily. The costs associated with pregabalin therapy differed significantly between the preconversion and postconversion periods. A savings of $115,867 was realized from this conversion for both facilities combined over the course of one year.

Conclusion. In patients receiving pregabalin for pain, conversion from thrice- to twice-daily pregabalin dosing—while maintaining the same daily dose—resulted in substantial cost savings while having little effect on clinical outcomes.

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and substance P. The half-life of pregabalin is 6.3 hours in patients with normal renal function.

The Veterans Health Administration (VHA) uses a nationally defined formulary and local adjudication of nonformulary medications to ensure clinical appropriateness and fiscal stewardship. Pregabalin is a nonformulary drug within VHA and is dispensed only if evidence-based criteria established by VHA are met.7 Prior authorization for pregabalin use requires trial and failure with at least two of the following: tricyclic antidepressants, gabapentin, venlafaxine, tramadol, carbamazepine, capsaicin, and lidocaine. Pregabalin is a flat-priced medication (i.e., all capsules, irrespective of strength, cost the same). The average wholesale price of each capsule of pregabalin was $4.81; this price was used in all calculations.

Food and Drug Administration–approved dosing of pregabalin is thrice daily for diabetic neuropathy, twice or thrice daily for postherpetic neuralgia, and twice daily for fibromyalgia or neuropathic pain following spinal cord injury. Some studies have suggested equivalent efficacy between twice- and thrice-daily dosing. In 2008, Baron et al.3 examined the efficacy and safety of pregabalin given twice daily in patients with diabetic peripheral neuropathy or postherpetic neuralgia for 4 weeks. Patients (n = 217) were evaluated in 53 centers. The rate of twice-daily dosing continuation observed in this study was 92%. The authors concluded that twice-daily pregabalin dosing was efficacious and well tolerated for the aforementioned indications. Arnold et al.4 analyzed the safety and efficacy of twice-daily pregabalin dosing for 12–52 weeks in patients with fibromyalgia. Patients (n = 1206) were identified in 214 centers. The rate of twice-daily dosing continuation attained in this study was 81%. The authors concluded that twice-daily pregabalin dosing was safe and efficacious for fibromyalgia treatment for up to one year. In 2005, a double-blind, placebo-controlled trial compared twice- with thrice-daily dosing in patients (n = 341) with GAD for 6 weeks.5 The rate of twice-daily dosing continuation in this study was 72%.

The conversion from thrice- to twice-daily pregabalin administration for all indications began in August 2012 at the Veterans Affairs Palo Alto Health Care System (VAPAHS) and in January 2013 at the Veterans Affairs Northern California Health Care System (VANCHCS), after the pharmacy and therapeutics committees at both facilities approved the change.

This study evaluated economic and clinical outcomes at the two VHA facilities after the conversion. The results of this analysis could help determine the feasibility of twice-daily pregabalin dosing in the Veterans Affairs Health Care System.

Methods

VAPAHS and VANCHCS are part of closed healthcare systems in which patients see primary care providers and specialists in the ambulatory care setting with prescriptions filled within the same system. This allows for accurate documentation of all therapies and provider visits provided they occur within the system.

Prior to this analysis, approval was sought from the institutional review board (IRB) and research committee at VANCHCS, but the study was deemed to be a quality-improvement project and as such was deemed to be exempt. IRB exemption was extended to VAPAHS patients.

Study design. The study used retrospective review of medical records with the primary objective of assessing the financial impact of the dosing-frequency conversion; the secondary objective was to assess changes in therapeutic effectiveness associated with the change. Pharmacists converted thrice- to twice-daily dosing without changing the total daily pregabalin dose as long as the patient was not exempt from the conversion. For instance, if a patient had been treated with pregabalin 50 mg thrice daily, the regimen was converted to 75 mg twice daily.

The study included all patients for whom the pregabalin dosing frequency was changed from thrice- to twice-daily dosing during a one-year period starting in August 2012 and January 2013 for VAPAHS and VANCHCS, respectively. No follow-up data were collected after the one-year study time.

Patients were included if they received an outpatient prescription for thrice-daily pregabalin dosing prior to the conversion dates at each facility. Patients must have received at least two pregabalin prescriptions filled at either location at the same daily dose prior to conversion. The justification behind this specific requirement was to ensure that the patient had been on the current

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medication dose for enough time to accurately assess drug effectiveness at stable dosing.

Patients were excluded if VHA records indicated that they received pregabalin from a pharmacy outside of the VHA system, had pregabalin prescribed for the primary indication of seizures or anxiety, had previous adverse reactions to pregabalin, or, in response to their provider’s request, conversion to twice-daily dosing was not performed.

**Endpoint measures.** The costs of unscheduled neuropathy-related visits, dosage conversion (pharmacist labor and postage), pregabalin drug acquisition, and add-on therapies were calculated and used to assess the economic endpoint. Pricing information and costs utilized for this endpoint were in effect as of August 2012. Effectiveness was evaluated by examining the frequencies at which (1) twice-daily pregabalin dosing was converted back to thrice-daily dosing, (2) pregabalin was discontinued, (3) new pain medications were added to the existing regimen, and (4) patients had unscheduled neuropathy-related visits.

**Statistical analysis.** The primary endpoint was analyzed using the Wilcoxon signed-rank test. To achieve a power of 0.8 and a p value of <0.05, 66 patients were needed to detect a difference of $400, 53 patients were needed to detect a difference of $450, and 43 patients were needed to detect a difference of $500.

Chi-square analysis was used to analyze secondary endpoints as appropriate. For 80% power and a p value of <0.05, 241 patients were needed.

Assumptions made in the power analysis involved random sampling and independence between the two patient groups: reverted and nonreverted. Further postconversion analysis was conducted by comparing patients who remained on twice-daily dosing with those whose dosing reverted back to thrice daily. SQL Server and Excel (Microsoft Corporation) were used for the retrieval and analysis of data. The SigmaPlot 12.5 statistics program (Systat Software, Inc.) was used to compare and analyze differences between reverted and nonreverted patients. Statistical tests also utilized in this analysis included Fisher’s exact test to analyze frequencies and the Mann–Whitney rank-sum test to analyze continuous variables such as age and cost. This analysis was adequately powered for economic outcomes but inadequately powered for clinical outcomes.

**Results**

Eighty-six patients with outpatient pregabalin prescriptions were reviewed. Twenty-nine of these patients were excluded from the analysis—23 because no conversion was performed, 4 because they had received fewer than two preconversion refills of thrice-daily pregabalin, and 2 because their provider requested that the conversion not occur. After exclusions, 57 patients met inclusion criteria and were converted to twice-daily dosing.

The sex, age, and race of study patients were recorded (the mean age was 57.2 years; there were 48 men and 9 women, with 26 Caucasians, 3 Hispanics, 1 African American, and 27 patients of unknown race/ethnicity), but the most recent National Survey of Veterans (2010) states that 84.7% of veterans are Caucasian, while 91.9% are male. In contrast, the 2010 U.S. census shows the populace is 72.4% Caucasian and 49.2% male.

Indications for gabapentin among included patients were diabetic neuropathy (n = 15), neuropathic pain (n = 14), low back pain (n = 13), fibromyalgia (n = 8), cervical radiculopathy (n = 2), degenerative disk disease (n = 1), headache (n = 1), limb pain (n = 1), postherpetic neuralgia (n = 1), and neck or shoulder pain (n = 1).

At the end of the one-year study period, 41 (72%) of the 57 patients remained on twice-daily pregabalin dosing. One of these patients required a dosage increase from 150 to 200 mg twice daily to attain effective pain control. Among the remaining 16 patients, pregabalin was discontinued in 10 (6 for unspecified reasons, 2 because they developed confusion, 1 because of leg edema, and 1 because of headaches, weight gain, and blurry vision) and reverted back to thrice-daily dosing in 6 (5 because of inadequate pain control and 1 because of vision difficulties). The mean age did not differ significantly between patients whose dosing frequency remained twice daily and those whose dosing frequency reverted back to thrice daily (p = 0.286).

For the six reverted patients, opioids and lidocaine ointment were the pain medications most commonly added to existing therapy (Table 1). Three of the patients whose dosing frequency reverted to thrice daily had two add-on pain medications, while two of the patients in this category had only one add-on medication for pain control. Patients in this group had no unscheduled neuropathy-related clinic visits.

Among the nonreverted patients, opioids were the pain medications most commonly added to existing therapy, while tricyclic antidepressants and capsaicin cream were the least commonly added for pain. Eight patients in this category had three add-on medications for pain, five patients had two add-on pain medications, seven patients had one add-on pain medication, and three patients in this category had dosage increases to prior pain therapy. Interestingly, every patient in this category with more than one add-on pain medication was being treated with a nonsteroidal antiinflammatory drug. The distribution of add-on medication types did not differ significantly between patients whose dosing frequency remained twice daily and those whose frequency reverted to thrice daily. There were six unsched-
uled neuropathy-related clinic visits for patients in this category.

There was a mean monthly cost savings of $144 when changing from thrice- to twice-daily dosing; this figure does not include the one-time conversion cost of $3.36 per patient. The actual durations of thrice-daily therapy during the year before conversion accounted for a drug cost of $272,649. For the one year after conversion to twice-daily dosing, the pregabalin cost for all study patients was $147,698.

When the costs of conversion, add-on pain medications, and unscheduled neuropathy-related visits were added to twice-daily drug costs, there was still a substantial cost savings realized from this conversion. The combined one-year cost before and after conversion for all 57 participants was $272,649 (mean, $4,783; median, $5,196) and $156,782 (mean, $2,752; median, $3,471), respectively; the differences in mean and median were significant (p < 0.001). Add-on pain therapy accounted for $7,428 of the total postconversion costs, while neuropathy-related unscheduled visits cost $1,464.

Discussion

The results of this analysis suggest several benefits associated with this conversion. In addition to significant cost savings, the conversion reduced dosing frequency, an intervention that has been associated with increased adherence with other medications, as observed in numerous studies.10-13

Limitations included those inherent in a retrospective chart review. The analysis was not powered for evaluation of clinical outcomes. Because the sample was small and had a demographic composition that was disproportionately Caucasian and male, the findings have limited applicability to the general population.

Another limiting factor is that renal function was not assessed. It is possible that reducing pregabalin’s dosing frequency may have been clinically indicated in patients with certain degrees of renal impairment, which may have affected the results.

Incomplete chart documentation was also an issue during this analysis. Indications for additional pain medications were not always discernible, and it was difficult to determine if they were used for neuropathy or another reason. There were also difficulties in ascertaining patient visits to non-VHA providers as well as costs of some unscheduled VHA neuropathy-related visits. This led to uncertainty in assessing the differences in economic and clinical outcomes.

Adherence was assumed to be 100% in both groups because of limitations in data extraction. It is unknown if the high rates of additional pain medications resulted from the change to twice-daily dosing or were a consequence of natural disease progression. However, it is probable that at the very least, there was a beneficial impact from add-on therapies on continued twice-daily dosing.

The high frequency with which conversion was not performed (in 23 of 86 patients) is understandable, given the numerous conversions and other tasks that pharmacists are asked to perform when they process medication orders. It would be beneficial to have a lead pharmacist go through the list of pregabalin patients once a quarter to identify patients for whom conversion was not performed so that the change could be implemented if appropriate.

The conversion from thrice-to twice-daily pregabalin was safe and acceptable for a majority of the observed patients, with over 70% continuing on the new dosing schedule. The observed twice-daily continuation rate was comparable to that in prior clinical trials showing the efficacy of twice-daily dosing.1-5 Our analysis showed minimal negative outcomes with the realization of significant cost savings. The obser-

### Table 1.

<table>
<thead>
<tr>
<th>Added Pain Medication</th>
<th>No. (%) Pts Receiving Added Pain Medication&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pregabalin Dosing Reverted to Thrice Daily (n = 6)</td>
</tr>
<tr>
<td>Opioid</td>
<td>3 (50)</td>
</tr>
<tr>
<td>Lidocaine ointment</td>
<td>2 (33)</td>
</tr>
<tr>
<td>Tricyclic antidepressant</td>
<td>1 (17)</td>
</tr>
<tr>
<td>Capsaicin cream</td>
<td>1 (17)</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>1 (17)</td>
</tr>
<tr>
<td>Nonsteroidal antiinflammatory</td>
<td>0</td>
</tr>
<tr>
<td>Any</td>
<td>5 (83)</td>
</tr>
</tbody>
</table>

<sup>a</sup>p = 0.102 for between-group comparison of distribution of added pain medications (Fisher’s exact test).

<sup>b</sup>Includes 10 patients whose pregabalin therapy was discontinued before the end of the one-year study period.
vations from this analysis further provide an important potential for continued investigation into the safety and effectiveness of the pregabalin conversion in larger and more diverse patient populations.

**Conclusion**

In patients receiving pregabalin for pain, conversion from thrice- to twice-daily pregabalin dosing—while maintaining the same daily dose—resulted in substantial cost savings while having little effect on clinical outcomes.

**References**