ORIGINAL ARTICLE

Clinical Characteristics, Pharmacotherapy and Healthcare Resource Use among Patients with Fibromyalgia Newly Prescribed Gabapentin or Pregabalin

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■ **Abstract**

Objective: To characterize comorbidities, pain-related pharmacotherapy, and healthcare resource use among patients with fibromyalgia (FM) newly prescribed pregabalin or gabapentin in clinical practice.

Methods and design: Using the PharMetrics® Database, FM patients (International Classification of Diseases, Ninth Revision, Clinical Modification code 729.1X) newly prescribed pregabalin (n = 1,606; mean age 49.9 ± 9.6 years; 87.9% female) and gabapentin (n = 930; mean age 49.5 ± 9.6 years; 86.6% female) on/after July 1, 2007 were identified. Prevalence of comorbidities, pharmacotherapy, and healthcare resource use/costs (pharmacy, outpatient, inpatient, total) were examined during the 6 months preceding (preindex) and following (postindex) the date of their first pregabalin or gabapentin (index) prescription.

Results: Patients in both cohorts had a variety of comorbidities and used multiple medications. There were significant decreases (P values < 0.05) in the use of nonsteroidal anti-inflammatory drugs (32.1% vs. 29.5%), anticonvulsants (27.0% vs. 22.0%), and combination therapies in the pregabalin cohort in the postindex period. There were significant increases (all P values < 0.05) in use of short-acting opioids (58.8% vs. 63.7%), any opioids (61.5% vs. 65.6%), serotonin–norepinephrine reuptake inhibitors (22.5% vs. 24.5%), anticonvulsants (16.3% vs. 26.2%), benzodiazepines (33.2% vs. 36.6%), topical agents (6.6% vs. 9.0%), and combination therapies in the gabapentin cohort. Although there were no changes in units of healthcare resources used, there were increases in the postindex period in hospitalization, medications, and total costs for pregabalin, and office visits and medication costs for gabapentin (all P values < 0.05).

Conclusions: Results suggest a high comorbidity and medication use burden in FM patients in this study. Further evaluation is warranted to clarify differences in resource utilization/costs observed with these two anticonvulsants. ■

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INTRODUCTION

Fibromyalgia (FM) is a chronic condition characterized by widespread musculoskeletal pain, tenderness, and fatigue, often accompanied by sleep disruption, depression, and anxiety.[1] There is currently no definitive diagnostic test for FM; it is generally diagnosed symptomatically, with guidelines published by the American College of Rheumatology emphasizing the presence of both pain (widespread pain, including in the axial plus upper and lower body segments plus left- and right-sided pain) and tenderness (tenderness at 11 or more of the 18 specific tender point sites).[2]

It is estimated that 2% to 4% of the U.S. population is afflicted with FM, with a prevalence among women six- to ninefold higher than men.[1,3] FM is often difficult to differentiate from other pain syndromes, causing patients to spend long periods of time in the healthcare system until appropriately diagnosed.[4] One study of an incident FM population in the U.S.A. identified high resource use both before and after FM diagnosis.[5] High resource use prior to diagnosis is not surprising, given the absence of a definitive diagnosis and an attempt by patients to determine and treat the source of their complaints.[5] Studies in a different healthcare system (U.K.) and with longer follow-up of 4 years have suggested an initial decrease in some healthcare resource utilization following the period of diagnosis, primarily because of a decrease in diagnostic testing and visits to subspecialty physicians.[6,7] However, within 2 to 3 years after diagnosis, resource utilization increased in some cases, such as clinical visits, to levels higher than observed at diagnosis.[6,7]

Given the relatively young mean age of diagnosed subjects of 45 to 50 years,[6,8,9] FM has been documented to have a serious impact on productivity and employment status.[10,11] The disease burden and symptomatic nature of FM results in substantial morbidity and disability, which can be prolonged and debilitating. Studies have shown that patients with FM are characterized by an increased prevalence of comorbid disorders, including those of the musculoskeletal, cardiovascular, and neuropsychiatric systems relative to a non-FM population.[9,11–13] Furthermore, in a study of employees having either FM or osteoarthritis, the prevalence of comorbid conditions, excluding musculoskeletal pain, was significantly higher among individuals with FM compared with individuals with osteoarthritis.[11]

Information on pain-related treatment patterns and healthcare resource utilization in patients with FM is limited. A recent Internet study reported a high medication burden in individuals with FM, arising from the need to treat FM along with other comorbid conditions.[8] Similarly, polypharmacy, including the receipt of multiple pain-related pharmacotherapies in approximately 40% to 50% of patients, has contributed to this burden.[9,12]

Although the pathophysiology of FM has not been fully elucidated, evidence suggests that augmentation of pain and sensory processing pathways within the central nervous system at least partially contribute to the symptoms associated with FM.[14,15] Pharmacologic management has typically been targeted toward the major symptom, pain, although recommendations published by the American Pain Society (APS) in 2005 focus on both pain and sleep disturbance.[16] These recommendations suggest the use of low-dose tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), benzodiazepines, dopa-replenishing agents, and tramadol, limiting strong opioid use to when other pharmacologic and nonpharmacologic therapies have failed. However, these guidelines were developed prior to the many more recent studies of pharmacological therapies, including the specific approval of three drugs for use in FM by the U.S. Food and Drug Administration (FDA). More recent evidence-based guidelines developed by the European League Against Rheumatism (EULAR), recommend the anticonvulsant pregabalin in the pharmacologic management of patients with FM, as well as many of the drugs previously suggested for this condition (tramadol, antidepressants, including TCAs, the SSRI tropisetron, and the dopamine agonist pramipexole).[17]

Subsequent to the APS recommendations, pregabalin was the first drug to receive approval for the treatment of FM by the FDA, and duloxetine and milnacipran have also recently been approved.[18–20] Although not included in the APS or EULAR recommendations, gabapentin has been shown to be used in the clinical setting.[8,11,12] The generic status of gabapentin makes it a preferred choice for step edit to pregabalin by managed care organizations and pharmacy benefits managers concerned with rising pharmacy costs. This step edit is often required based on a single randomized clinical trial suggesting the efficacy of gabapentin for the treatment of FM.[21] Both pregabalin and gabapentin are alpha-2-delta ligands that are effective in the treatment of neuropathic pain, and are recommended as first-line therapy for neuropathic pain.[22]

Although there are theoretical pharmacological advantages to pregabalin over gabapentin (eg, linear

pharmacokinetics, a steeper dose/response curve relative to gabapentin and low inter-subject pharmacokinetic variability[23]), no trials have directly compared the efficacy or effectiveness of these two compounds.

Our objective in the present study was to characterize the use of pregabalin and gabapentin for the management of FM, more specifically to describe the clinical comorbidities, patterns of pain-related pharmacotherapy, and healthcare resource use in patients with FM newly prescribed pregabalin and gabapentin in actual practice.

METHODS

Data Source

Data were obtained from the PharMetrics® Patient-Centric Database (PharMetrics Inc, Watertown, MA, U.S.A.). This database is comprised of adjudicated medical and pharmaceutical claims data from a systematic sample of over 95 commercial managed care health plans throughout the U.S.A. (midwest 34%, northeast 22%, south 29%, west 15%), covering more than 57 million lives. The database includes information on patient demographics and enrollment, inpatient and outpatient diagnoses (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] format), and retail and mail-order prescription records. Available data on prescriptions include the National Drug Code numbers, days supply, and quantity dispensed. Medical records for each patient can be linked using a unique encrypted patient identifier (thereby maintaining patient confidentiality) to create a longitudinal record of an individual's healthcare claims during a specified time period. The database is in compliance with the Health Insurance Portability and Accountability Act.

Sample Selection

Patients who had 1 or more healthcare encounters with an associated diagnosis of FM (ICD-9-CM code 729.1X) during each of the years 2006 and 2007 were selected, and cohorts of patients who were newly prescribed pregabalin (which has been available for the treatment of FM in the U.S.A. since July 2007) or gabapentin (index event) on or after July 1, 2007 were identified. Patients in each cohort had to be naïve to that medication during the 6-month preindex period, and were excluded if they had missing data for age or gender, were less than 18 years old, were ≥65 years old and not enrolled in Medicare Risk plans, or were not continuously enrolled for a period of 6 months prior to (preindex) and 6 months following (postindex) the date of their first prescription for pregabalin or gabapentin. The continuous enrollment requirement was imposed to ensure that all healthcare claims for the study patients during the entire study period were represented in the analyses.

Measures and Analyses

Basic demographic and clinical characteristics of patients prescribed pregabalin or gabapentin for FM were determined, including average age, gender distribution, and coprevalence of selected chronic conditions, including mental disorders, sleep disorders, digestive disorders, musculoskeletal pain conditions (eg, arthritis and arthropathies, lumbago, low back pain, osteoarthritis), and neuropathic pain conditions. Comorbidities examined were those considered to have significant coprevalence in patients with rheumatic diseases, such as cardiovascular-related disorders,[24] or to be associated with FM or pain (eg, anxiety, depression, and sleep disorders).[25,26] Prevalence of comorbidities was determined based on the presence of two or more healthcare encounters, with an associated diagnosis code for the comorbidity during the 6-month preindex period. ICD-9-CM diagnoses codes used to define comorbidities examined in this study are described in Table 1.

Pain-related medication exposure was determined in terms of the proportion of patients who received one or more prescriptions during the pre- and postindex periods for the various medications and medication classes recommended and/or used for the treatment of FM or pain in clinical practice.[9,12,27–31,32–35] These medications included short-acting opioids (SAOs [eg, oxycodone, hydrocodone, morphine sulfate]), long-acting opioids (LAOs [eg, controlled release oxycodone, transdermal fentanyl]), anticonvulsants other than pregabalin and gabapentin (eg, lamotrigine), TCAs (eg, amitriptyline, desipramine), SSRIs (eg, citalopram, paroxetine), selective serotonin–norepinephrine reuptake inhibitors (SNRIs [eg, duloxetine, venlafaxine]), cyclooxygenase-2 specific and nonspecific nonsteroidal anti-inflammatory drugs (NSAIDs), tramadol, tetracyclic, and miscellaneous antidepressants (eg, bupropion, trazodone), topical agents approved for neuropathic pain (eg, capsaicin, Lidoderm), topical corticosteroids (eg, betamethasone, desoximetasone), injectables (eg, bupivacaine, lidocaine), triptans, and other antimigraines, and attention deficit hyperactivity disorder drugs. Additionally, exposure to benzodiazepines, sedatives/hypnotics, and muscle relaxants was evaluated, since these may be used adjunctively to treat pain-related

Table 1. Diagnostic Codes Used to Identify Relevant Comorbidities

Comorbidity	International Classification of Diseases, Ninth Revision, Clinical Modification Diagnosis Codes
Mental disorders	
Depression	296.2X, 296.3X, 300.4, 311
Anxiety	300.00, 300.5, 300.09, 300.20, 300.22, 300.23, 300.29, 300.3, 308.3
Bipolar disorder	296.4X, 296.5X, 296.6X, 296.7
Generalized anxiety disorder	300.02
Panic disorder	300.01, 300.21
Post-traumatic stress disorder	309.81
Migraine and tension headache	346.XX, 307.81
Sleep disorders	
Insomnia/sleep disorders	780.5X, 307.4X, 347.0X, 347.1X, V69.4
Sleep apnea	780.51, 780.53, 780.57
Fatigue-related conditions	
Chronic fatigue syndrome	780.71
Other malaise and fatigue	780.79
Cardiovascular disorders	
Hypertension	401.X
Hyperlipidemia	272.0, 272.1, 272.2, 272.4
Coronary heart disease	410.XX–414.XX
Congestive heart failure	428.0
Peripheral vascular disease	440.2X, 440.3X, 443.89, 443.9
Musculoskeletal pain conditions	
Rheumatism, excluding the back	725–728.9, 729.3–729.9
Arthritis and other arthropathies	711.XX, 712.XX, 713.X, 714.4X, 714.8X. 714.9X, 716.XX, 717.XX, 718.XX, 719.XX
Back and neck pain, excluding low back pain	720.81, 720.89, 720.9, 721.0, 721.2, 721.5, 721.6, 721.7, 721.8, 721.90, 722.11, 722.30, 722.31, 722.39, 722.4, 722.51, 722.6, 722.80, 722.81, 722.82, 722.90, 722.91, 722.92, 723.X (except 723.4), 724.01, 724.1, 724.5, 724.8, 724.9
Lumbago	724.2
Low back pain	720.0, 720.1, 720.2, 721.3, 722.10, 722.32, 722.52, 722.83, 722.93, 724.02, 724.6, 724.7X
Osteoarthritis	715.XX
Rheumatoid arthritis	714.0, 714.1, 714.2
Gastrointestinal conditions	
Irritable bowel syndrome	564.1
Gastroesophageal reflux disease	530.11, 530.81
Gastritis	535.00–535.5X
Other	520.5–530.10, 530.19–530.7, 530.82–534.91,535.60–537.X, 540.0–543.X, 550.00–553.XX, 555.0–558.X, 560.XX, 562.XX, 564.2–579.X
Neuropathic pain conditions	053.1, 250.6, 337.1, 337.2X, 337.9, 344.6, 350.1, 350.2, 353.0, 353.1, 353.6, 353.8, 353.9, 354.0, 354.1, 354.2, 354.3, 354.4, 354.5, 354.8, 354.9, 355.0, 355.1, 355.2, 355.3, 355.4, 355.5, 355.6, 355.71, 355.79, 355.8, 355.9, 357.1, 357.2, 357.3, 357.4, 357.5, 357.6, 357.7, 357.8, 357.9, 721.1, 721.41, 721.42, 721.91, 722.7X, 723.4, 724.3, 724.4, 729.2, Malignant neoplasms (140.XX–172.XX, 174.XX–208.XX) in conjunction with neuropathy 337.2X, 353.0, 353.1, 353.2, 353.3, 353.4, 353.8, 353.9, 354.0, 354.1, 354.2, 354.3, 354.4, 354.5, 354.8, 354.9, 355.0, 355.1, 355.2, 355.3, 355.4, 355.5, 355.6, 355.7X, 355.8, 355.9, 357.3, 357.8, 357.9, 729.2
Signs, symptoms, and ill-defined conditions	
Headache not otherwise specified	784.0X
Chest pain	786.5X
Abdominal pain	789.0X
Anxiety-related symptoms	780.4, 785.0, 785.1, 786.01, 786.05, 786.09
Gastric-related symptoms	787.0, 787.01–787.03, 787.1–787.3, 787.9, 787.91, 787.99
Other	780.02–780.39, 780.6, 780.8–783.9, 784.1–784.9, 785.2–786.00, 786.02–786.04, 786.06, 786.07, 786.1–786.4, 786.6–786.9, 787.4–787.7, 788.0–788.9, 789.1–796.9, 799.X

mood and sleep disorders, which are frequently reported in patients with FM. Because opioid analgesics are often prescribed and used as rescue pain medications or on an "as needed" basis, evaluation of opioid use was stratified by patients who received ≥1, only 1, or ≥2 opioid prescriptions in the pre- and postindex periods, respectively.

Resource utilization and direct medical costs of healthcare resources, including physician office visits, emergency room visits, hospitalizations, and other outpatient services (eg, labs, radiology, imaging), were examined in the pre- and postindex periods among users of these services for patients in both cohorts. The average number of prescriptions, days of therapy, and the time (days) to the first physician office visit after initiating therapy with each of the index medications were determined. The average daily dose was calculated as strength in milligrams multiplied by the quantity

prescribed divided by days supply. Several methods were used to evaluate average daily dose. First, average daily doses were determined across all prescriptions for the two index medications during the postindex period. Second, proportions of patients who received a dose within the therapeutic range (300 to ≥450 mg for pregabalin in FM, and ≥1,800 mg for gabapentin in neuropathic pain) were evaluated among patients who received one, two, and three or more consecutive prescriptions, respectively, in the postindex period. A consecutive prescription was defined as a prescription whose "start date" was no later than 15 days after the "end date" of the previous prescription. Additionally, the medication possession ratio (MPR) for the index drugs was considered as a proxy for determining patient adherence to therapy. The MPR was calculated as the total days supply (excluding day supply of last prescription) divided by the total number of days between the first and last prescriptions.

Statistics

All analyses were conducted using the SAS software system, PC version 8.0 (SAS Institute Inc., Cary, NC, U.S.A.). Chi-square tests, Cochran–Mantel–Haenszel tests, and Student's *t*-tests (for continuous data) were used to assess the statistical significance of the differences in demographic and clinical characteristics between the cohorts. Wilcoxon signed-rank tests were used to assess the changes in resource use and costs in the pre-index and postindex periods. McNemar tests were used to assess the statistical significance of changes in medication use between the two time periods, since the same subjects were included in the before and after measurements (ie, matched pairs). Student's *t*-tests were used to evaluate differences in total number of prescriptions, days of therapy, time to office visits, and MPRs between the two cohorts. Comparison tests did not utilize adjustments for bias. For all analyses, an alpha value of <0.05 was considered statistically significant.

RESULTS

Demographic and Clinical Characteristics

The demographic and clinical characteristics were similar among the patients newly prescribed pregabalin ($n = 1{,}606$) and gabapentin ($n = 930$), with women comprising more than 85% of the population and no significant difference in gender between treatments. The mean age was 49.9 ± 9.6 years for pregabalin and 49.5 ± 9.6 years for gabapentin. The proportion of patients in each age range was similar between treatments; the majority of patients were in the age range of 45 to 54 years (38.9% and 37.3% for pregabalin and gabapentin, respectively), followed closely by 55 to 64 years (34.6% and 33.0% for pregabalin and gabapentin, respectively), with few patients being 65 years of age or older (0.9% pregabalin, 1.1% gabapentin).

The prevalence of specific comorbid conditions in patients prescribed either pregabalin or gabapentin are presented in Table 2. Both cohorts were characterized by the presence of a wide range of comorbidities, and in general, the frequency of comorbid conditions was similar between the cohorts. Each cohort had a variety of comorbid musculoskeletal conditions, with back and neck pain (other than low back pain) being the most common musculoskeletal condition. Except for osteoarthritis, which was significantly more prevalent in the pregabalin cohort (12.5% vs. 9.5%, $P = 0.0197$), there were no differences in musculoskeletal pain conditions between the two cohorts. Slightly less than a quarter of the patients had a neuropathic pain condition. Except for post-traumatic stress disorder, which was more prevalent in the gabapentin cohort (0.7% vs. 1.6%, $P = 0.0254$), there were no significant differences in the prevalence of neuropsychiatric disorders between the groups, and depression was the most common neuropsychiatric disorder, occurring in 16.9% and 17.1% of the patients in the pregabalin and gabapentin cohorts, respectively. Anxiety was reported with a frequency of 3.7% and 5.0% in the pregabalin and gabapentin cohorts, respectively, and hypertension was the most frequently reported cardiovascular comorbidity, occurring in 16.1% of pregabalin patients, and 17.5% of gabapentin patients. Insomnia/sleep disorders were reported by 7.9% and 7.1% of patients prescribed pregabalin and gabapentin, respectively.

Concurrent comorbidities occurred in a high proportion of patients. At least one comorbidity was reported in 88.4% and 87.3% of patients in the pregabalin and gabapentin cohorts, respectively, and at least one-third of patients in each cohort had ≥5 comorbid conditions.

Medication Prescriptions

Patients prescribed pregabalin and gabapentin were characterized in the preindex period by a high burden of medications that are generally prescribed for the treatment of different types of pain (Table 3). These medications included traditional analgesics, such as NSAIDs and cyclo-oxygenase-2 inhibitors, short- and long-acting opioids, antidepressants, and anticonvulsants.

Table 2. Prevalence of Specific Chronic Comorbidities in Patients with Fibromyalgia Prescribed Pregabalin or Gabapentin

	Prevalence, %		
Comorbid Diagnosis*	Pregabalin (n = 1,606)	Gabapentin (n = 930)	$P^{\dagger}$
Musculoskeletal pain conditions			
Back and neck pain, other than low back pain	32.9	30.7	0.2331
Rheumatism, excluding the back	27.2	29.1	0.2966
Arthritis and other arthropathies	24.9	23.8	0.5188
Other	19.9	20.8	0.5907
Lumbago	19.7	22.3	0.1310
Low back pain	17.8	18.0	0.9249
Osteoarthritis	12.5	9.5	0.0197
Rheumatoid arthritis	3.1	2.8	0.6512
Neuropathic pain conditions	22.9	23.1	0.9281
Neuropsychiatric disorders			
Depression	16.9	17.1	0.8856
Anxiety	3.7	5.0	0.1422
Generalized anxiety disorder	2.6	2.8	0.7134
Bipolar disorder	1.7	1.7	0.9412
Panic disorder	1.0	1.5	0.2531
Post-traumatic stress disorder	0.7	1.6	0.0254
Psychosis	0.6	0.7	0.9450
Cardiovascular conditions			
Hypertension	16.1	17.5	0.3617
Hyperlipidemia	12.8	13.9	0.4272
Coronary heart disease	2.9	3.0	0.8327
Congestive heart failure	0.6	1.1	0.1473
Peripheral vascular disease	0.4	1.0	0.1031
Fatigue-related conditions			
Other malaise and fatigue	8.7	8.3	0.7441
Chronic fatigue syndrome	1.1	1.2	0.8875
Sleep disorders			
Insomnia/sleep disorders	7.9	7.1	0.4921
Sleep apnea	2.7	3.6	0.2527
Headaches			
Migraines	5.4	5.8	0.6801
Tension headache	0.3	1.2	0.0031
Diseases of the digestive system			
Gastroesophageal reflux disease	4.2	5.4	0.1882
Irritable bowel syndrome	1.1	1.5	0.4031
Gastritis	1.1	1.8	0.1413
Other	8.9	11.5	0.0342
Symptoms, signs, and ill-defined conditions			
Headaches not otherwise specified	8.8	9.6	0.5392
Anxiety-related symptoms	7.5	7.3	0.8821
Abdominal pain	7.0	9.5	0.0250
Gastric-related symptoms	6.0	6.8	0.4252
Chest pain	5.6	6.7	0.2773
Other	30.7	30.7	0.9781

* Comorbidities defined as ≥2 claims for each comorbid condition in the preindex period.
† Chi-square tests were used to calculate the statistical significance of differences between pregabalin and gabapentin for proportions.

Additionally, many patients (25% to 44%) were prescribed "adjunctive" medications, such as benzodiazepines, muscle relaxants, and sedatives/hypnotics, often used to treat conditions associated with pain such as depression, anxiety, and insomnia.

While a substantial medication burden was observed in the postindex period in both cohorts, there were some statistically significant differences in the proportions of patients prescribed specific medications relative to the preindex period (Table 3). In nearly all cases of a statistically significant change, the change was for an increase in medication use among those prescribed gabapentin, and a decrease among those prescribed pregabalin. For pregabalin, significant decreases were observed from preindex to postindex for the proportion of patients who received nonselective NSAIDs (32.1% vs. 29.5%, $P = 0.0299$) and anticonvulsants (27.0% vs. 22.0%, $P < 0.0001$). The sole exception was a significant increase in LAOs in the pregabalin group from preindex to follow-up (15.9% vs. 17.5%, $P = 0.0197$).

Table 3. Proportions (Percent) of Patients Prescribed Pregabalin and Gabapentin Who Had ≥1 Claim for Pain-Related Medications in the Pre- and Postindex Periods

	Pregabalin (n = 1,606)			Gabapentin (n = 930)		
Medications	Preindex	Postindex	P*	Preindex	Postindex	P*
Short-acting opioids	62.4	62.8	0.7532	58.8	63.7	0.0021
Long-acting opioids	15.9	17.5	0.0197	13.6	14.2	0.4855
Any opioids	65.0	66.1	0.3530	61.5	65.6	0.0066
Cyclo-oxygenase-2 inhibitors	9.5	10.2	0.2812	5.8	6.7	0.2382
Nonselective NSAIDs	32.1	29.5	0.0299	30.8	31.8	0.5002
Any NSAIDs	39.6	37.6	0.1002	35.7	37.0	0.4227
SSRIs	30.5	30.3	0.8795	27.9	29.3	0.2334
SNRIs	30.6	30.3	0.7243	22.5	24.5	0.0416
Tricyclic antidepressants	18.4	16.9	0.0502	15.6	15.9	0.7758
Anticonvulsants	27.0	22.0	0.0000	16.3	26.2	0.0000
Muscle relaxants	44.4	44.3	0.9167	41.2	41.6	0.7937
Benzodiazepines	38.7	40.7	0.0513	33.2	36.6	0.0178
Sedative/hypnotics	33.4	33.5	0.8864	25.4	26.8	0.2667
Tramadol	24.8	24.2	0.4768	17.6	19.3	0.1797
Miscellaneous agents	5.5	4.8	0.2640	5.3	5.3	1.0000
Tetracyclic and miscellaneous antidepressants	23.8	23.5	0.7548	22.9	24.6	0.1408
Topical agents approved for NeP	8.5	8.8	0.6737	6.6	9.0	0.0097
Topical corticosteroids	7.9	8.0	0.8096	8.8	9.4	0.6439
Injectables	0.1	0.1	0.3173	—	—	—
Attention deficit hyperactivity disorder drugs	7.0	7.4	0.4142	4.5	4.8	0.4913
Triptans	9.0	9.1	0.9115	8.6	7.9	0.2743
Other antimigraines	2.6	2.0	0.0956	2.3	1.8	0.4142
Corticosteroids	20.6	21.0	0.7247	19.1	19.8	0.6774

* McNemar test for difference between pre- and postindex values.
NSAIDs, nonspecific nonsteroidal anti-inflammatory drugs; SSRIs, selective serotonin reuptake inhibitors; SNRIs, selective serotonin–norepinephrine reuptake inhibitors.

However, when LAO use was stratified by the number of pregabalin prescriptions, the increase in proportions of patients who received LAOs was restricted to those patients who received only one pregabalin prescription in the postindex period (14.3% vs. 17.2%, $P = 0.0236$); with persistent pregabalin use (≥2 pregabalin prescriptions), the change in LAO use was not statistically significant (16.6% vs. 17.6%, $P = 0.1851$).

In the gabapentin group, observed increases included the use of SAOs (58.8% vs. 63.7%, $P = 0.0021$), any opioids (61.5% vs. 65.6%, $P = 0.0066$), SNRIs (22.5% vs. 24.5%, $P = 0.0416$), anticonvulsants (16.3% vs. 26.2%, $P < 0.0001$), benzodiazepines (33.2% vs. 36.6%, $P = 0.0178$), and topical agents approved for neuropathic pain (6.6% vs. 9.0%, $P = 0.0097$). When opioid use was stratified by the number of gabapentin prescriptions, there was an increase in proportions of patients who received SAOs regardless of the number of gabapentin prescriptions. Moreover, among patients who received ≥2 gabapentin prescriptions, there was also an increase in the proportions of patients who received any opioids in the postindex period (62.9% vs. 67.4%, $P = 0.0221$). Also among those patients who received ≥2 gabapentin prescriptions, there was an increase in the proportions of patients who received ≥2 prescriptions for SAOs (48.1% vs. 53.4%, $P = 0.0071$) or any opioids (51.1% vs. 56.5%, $P = 0.0026$). The increase in use of anticonvulsants in the gabapentin cohort was largely driven by the concomitant use of pregabalin; 16.7% of patients received pregabalin in the postindex period compared with 6.7% in the preindex period.

Combination therapy was common in the pre- and postindex periods among patients in both cohorts (Table 4). In the postindex period, nearly 70% of patients in the pregabalin group and greater than 60% of patients in the gabapentin group received one or more combinations of medications used to treat pain, anxiety, depression, or sleep disturbance. However, several significant changes in the patterns of combination therapy were observed. In the pregabalin group, there was a decrease in the proportions of patients who received four or more combinations from the preindex to the postindex period from 24.0% to 19.4% ($P = 0.0432$), whereas there was an increase in this proportion among those taking gabapentin, from 12.4% to 18.0% ($P < 0.0001$). For specific combinations, the pregabalin group was characterized by significant decreases in the postindex period (all P values ≤ 0.05) in the proportion of patients who received anticonvulsants and antide-

Table 4. Proportions (Percent) of Patients Prescribed Pregabalin and Gabapentin Who Received Combination Therapy in the Pre- and Postindex Periods

	Pregabalin (n = 1,606)			Gabapentin (n = 930)		
Combinations	Preindex (%)	Postindex (%)	P*	Preindex (%)	Postindex (%)	P*
Number of combinations						
No combinations	31.0	31.1		37.5	35.6	
One combination	22.3	23.2		27.1	24.7	
Two combinations	11.5	13.1		12.2	10.8	
Three combinations	10.3	12.6		8.6	10.8	
Four combinations	7.6	6.2		4.4	6.1	
Five combinations	5.4	5.0		2.0	4.0	
≥ 6 combinations	11.0	8.2		6.0	7.9	
Types of combinations						
Anticonvulsants and antidepressants	22.3	17.5	0.0000	11.6	18.7	0.0000
TCAs and sedatives/hypnotics	6.3	5.6	0.2383	4.5	5.1	0.4658
TCAs and SSRIs	6.2	5.7	0.3588	4.6	5.4	0.3072
TCAs and NSAIDs	8.4	7.6	0.2214	6.3	6.7	0.7255
Benzodiazepines and sedatives/hypnotics	16.7	17.2	0.5465	10.9	12.3	0.1869
Anticonvulsants and sedatives/hypnotics	11.5	8.7	0.0004	6.2	9.7	0.0004
Antidepressants and opioids	48.8	49.0	0.8686	42.6	47.2	0.0019
Muscle relaxants and sedatives/hypnotics	17.9	17.5	0.6215	12.2	13.2	0.3573
Benzodiazepines and NSAIDs	15.7	15.5	0.8468	11.4	13.4	0.0790
Anticonvulsants and antidepressants and opioids	17.4	13.6	0.0000	8.9	14.4	0.0000
Sedatives/hypnotics and opioids	24.8	25.5	0.4982	17.6	20.0	0.0574
Corticosteroids and anticonvulsants	6.1	4.7	0.0668	3.4	5.6	0.0153
Miscellaneous and anticonvulsants	2.2	1.7	0.2059	0.8	1.7	0.0389
Miscellaneous and TCAs	1.5	0.9	0.0499	1.0	1.2	0.5930
Miscellaneous and opioids	4.4	3.9	0.3827	4.2	4.0	0.7681
Antimigraine and Anticonvulsants	1.1	0.8	0.2513	0.5	1.2	0.0578
Antimigraine and TCAs	0.4	0.3	0.5271	0.7	0.3	0.2568
Antimigraine and opioids	2.1	1.4	0.0411	1.7	1.4	0.4669
Sedatives/hypnotics and anticonvulsants and TCAs	2.4	1.7	0.1048	1.2	2.0	0.1306

* McNemar test for difference between pre- and postindex values.
TCAs, tricyclic antidepressants; SSRIs, selective serotonin reuptake inhibitors; NSAIDs, nonspecific nonsteroidal anti-inflammatory drugs.

pressants (22.3% vs. 17.5%), anticonvulsants and sedative hypnotics (11.5% vs. 8.7%), anticonvulsants, antidepressants, and opioids (17.4% vs. 13.6%), miscellaneous agents and TCAs (1.5% vs. 0.9%), and antimigraines and opioids (2.1% vs. 1.4%).

In contrast, after initiation of gabapentin, significant increases (all P values ≤ 0.05) were observed in the proportions of patients using the specific combinations of anticonvulsants and antidepressants (11.6% vs. 18.7%), anticonvulsants and sedative hypnotics (6.2% vs. 9.7%), antidepressants and opioids (42.6% vs. 47.2%), anticonvulsants, antidepressants, and opioids (8.9% vs. 14.4%), corticosteroids and anticonvulsants (3.4% vs. 5.6%), and miscellaneous agents and anticonvulsants (0.8% vs. 1.7%).

Units of healthcare resource utilization did not change between the two time periods within the pregabalin cohort (Table 5), whereas for gabapentin, there was a significant decrease (P = 0.0076) in the number of emergency room visits in the follow-up period. In contrast to units of resource use, small but significant changes in healthcare costs were observed between the treatment periods. In the pregabalin group, there were no changes in costs for physician office visits, emergency room visits, and total outpatient visits, and significant ($P < 0.05$) increases in costs (median [interquartile range, IQR]) were observed for hospitalization, from $12,181.70 ($6,271.52 to $26,402.82) to $12,346.79 (IQR $5,291.43 to $26,396.71), medications, from $1,829.35 (IQR $764.07 to $3,740.51) to $1,955.93 (IQR $947.65 to $3,926.52), and total health care utilization, from $5,416.14 (IQR $2,737.58 to $10,538) to $5,864.33 (IQR $2,940.53 to $11,477.23). Significant increases in costs (median [IQR]) were also observed among patients prescribed gabapentin for medications, from $1,437.95 (IQR $563.00 to $2,787.15) to $1,558.55 (IQR $707.84 to $3,146.73), and for physician office visits, from $790.10 (IQR $413.00- to $1,394.21) to $836.32 (IQR $445.00 to $1,513.80), but there were no changes in costs of emergency room visits, total outpatient visits, hospitalizations, and total healthcare utilization.

Table 5. Medication and Healthcare Service Utilization in the Pre- and Postindex Periods among Patients Prescribed Pregabalin and Gabapentin

	Pregabalin (n = 1,606)					Gabapentin (n = 930)				
	Preindex		Postindex			Preindex		Postindex		
Resource Use Category	Mean	Median (IQR)	Mean	Median (IQR)	*P**	Mean	Median (IQR)	Mean	Median (IQR)	*P**
Outpatient visits (days)										
Physician office visits	11.4	9 (5–15)	11.5	9 (5–14)	0.5103	11.9	9 (5–16)	12.0	9 (5–16)	0.9410
Emergency room visits	1.8	1 (1–2)	1.7	1 (1–2)	0.1894	2.3	1 (1–2)	2.2	1 (1–2)	0.0076
Other outpatient visits	7.7	6 (3–10)	8.0	6 (3–10)	0.0528	8.3	6 (4–11)	8.6	6 (4–11)	0.1002
Total outpatient visits	15.4	12 (7–21)	15.7	13 (8–21)	0.4163	16.6	14 (8–22)	16.8	14 (8–23)	0.7695
Hospitalizations (inpatient days)	10.3	5 (3–9)	8.1	4 (3–8)	0.1228	8.1	4 (3–8)	9.0	5 (3–7.5)	0.5928

* Wilcoxon rank-sign tests for difference between pre- and postindex value.
IQR, interquartile range.

Index Drug Dosage and Adherence

The proportion of patients who received only a single prescription of their index drug in the postindex period was 27.5% for pregabalin and 42.4% for gabapentin. The mean number of total prescriptions for pregabalin was significantly higher than for gabapentin (3.5 ± 2.4 versus 2.7 ± 2.1; $P < 0.0001$), and the mean number of days of therapy was also significantly higher with pregabalin (112.8 ± 85.7 vs. 87.9 ± 69.6; $P < 0.0001$). The time to the first physician office visit after filling the index prescription was similar: 24.1 ± 27.9 days for pregabalin and 23.4 ± 27.8 days for gabapentin.

The average daily dose across all prescriptions was 211.1 ± 146.9 mg for pregabalin and 994.5 ± 764.2 mg for gabapentin. The proportions of patients prescribed pregabalin or gabapentin who received 2 and ≥3 consecutive prescriptions were 9.0% and 28.3% vs. 9.1% and 18.7%, respectively. Among pregabalin- or gabapentin-prescribed patients who received only one prescription, 15.6% of pregabalin-prescribed patients and 9.6% of gabapentin-prescribed patients received a dose within the therapeutic range (300 to ≥450 mg for pregabalin in FM, and ≥1,800 mg for gabapentin in neuropathic pain). Among patients who received two consecutive prescriptions, 13.1% and 24.8% of pregabalin, and 14.1% and 21.2% of gabapentin-prescribed patients, received a dose within the therapeutic range on their first and second prescription, respectively. Among patients who received three or more consecutive prescriptions, 15.2, 24.8, and 31.0% of patients prescribed pregabalin, and 6.3, 12.1, and 16.1% of patients prescribed gabapentin received a dose within the therapeutic range on their first, second, and third prescriptions, respectively.

Patient adherence to therapy was slightly better among the pregabalin cohort. While more than half the patients in each group achieved an MPR in excess of 80% (59.6% for pregabalin and 53.5% for gabapentin), the average MPR was significantly higher with pregabalin than with gabapentin (79.1% ± 24.4% vs. 75.8% ± 24.9%; $P = 0.0109$).

DISCUSSION

The data presented here demonstrate that patients with FM who are prescribed pregabalin and gabapentin have a high prevalence of comorbid conditions, and are characterized by a substantial medication burden. This burden was manifested by the use of a variety of medications for pain and pain-related symptoms, and by the high rate of combination therapies.

The comorbidity burden observed here is higher (suggesting that patients in this study were sicker) than what has previously been described in a cohort of 33,176 patients with FM relative to a comparison group without FM.[9] In that study, a variety of conditions affecting different body systems were reported to be present at a higher prevalence in patients with FM. Although the presence of comorbid conditions is not surprising, given that FM is multidimensional and patients frequently complain of a variety of symptoms and comorbidities,[8] the presence of these conditions is not necessarily suggestive of an etiologic link with FM. However, these comorbidities can confound medication use patterns, especially pain-related medications that might be prescribed for concurrent musculoskeletal pain conditions.

Consistent with previous studies,[9,12] a variety of cardiovascular comorbidities and musculoskeletal pain conditions were observed in this study, with the latter being especially prevalent; approximately two-thirds of patients reported some form of musculoskeletal pain condition. The presence of some form of neuropathic

pain condition was also substantial, occurring in approximately 23% of patients in each cohort, and was the same as the 23% reported in a previous study.[9]

The high medication burden in patients with FM, resulting from polypharmacy for the comorbid conditions and the use of multiple pain-related medications, has been routinely observed among patients with FM in clinical practice.[9,11–13,36] In this study, 60% to 70% of patients received combination therapies. Among the highest users of combination therapy, ie, those prescribed ≥4 concomitant medications, there was a significant decrease in the proportion of these patients after initiation of pregabalin, whereas this proportion increased with gabapentin.

Pain-related treatment patterns in the preindex period suggested a trend toward a greater proportion of patients in the pregabalin group being prescribed these medications relative to patients in the gabapentin group. That these proportions were also higher than reported in recent retrospective database studies in the general FM population[9,12] suggests the presence of channeling, in which patients with greater pain severity are being initiated on pregabalin. Channeling of patients with more severe disease is common after introduction of a new medication, and the launch of the first approved treatment for any indication may result in an evolution in prescribing patterns for that condition, particularly in the period immediately following its availability. The 6-month follow-up period corresponded with the period immediately following the availability of pregabalin for FM in the U.S.A. Thus, the potential for a channeling bias may have been particularly acute during our study period. It is possible that with a longer observation period, alternate trends in the prescription of pain-related medications or resource use would be observed.

Comparison of the pre- and postindex periods suggested that the changes in the proportion of patients receiving prescriptions for specific medication classes were generally consistent within patients prescribed pregabalin and gabapentin. Among pregabalin patients, significantly lower proportions of patients were prescribed anticonvulsants and nonselective NSAIDs. For gabapentin, there was a 62% increase in use of anticonvulsants (from 16.3% to 26.2%), predominantly driven by the concomitant use of pregabalin, as well as increases in SNRIs, benzodiazepines, topical preparations, short-acting opioids, and any opioids. These increases among patients prescribed gabapentin highlight the fact that although gabapentin is often used in the clinical setting, its efficacy in this patient population has been inadequately demonstrated. Although a significant increase in LAOs was observed in the pregabalin group, this was primarily driven by patients who received only one pregabalin prescription in the postindex period. Opioid analgesics are often prescribed and used as rescue pain medications or on an "as needed" basis; with persistent use of pregabalin, there was no observed increase in opioid use. Conversely, the increase in opioid use after initiation of gabapentin was not restricted to what could be defined as "rescue" use.

While no differences in the rate of outpatient or inpatient resource utilization was observed between the two periods for pregabalin, the costs of total healthcare utilization increased during the postindex period. Similar findings were noted in a recent study that evaluated healthcare resource utilization and costs among patients with FM across three stages (prediagnosis, postdiagnosis, and established FM), where medication use, resource utilization, and costs all increased with each subsequent stage.[5]

The difference in pain medication utilization between pregabalin and gabapentin is noteworthy, since both of these medications are alpha-2-delta ligands. Despite these drugs having a similar mechanism of action, their pharmacokinetic/pharmacodynamic (PK/PD) properties are different, with pregabalin displaying nonsaturable absorption at clinically relevant doses, resulting in linear pharmacokinetics, a steeper dose-response curve, and low intersubject pharmacokinetic variability.[18] The starting dose of pregabalin (150 mg/day) is a therapeutic dose. Whereas gabapentin requires at least a 4-step titration to reach the dose of 1,800 mg/day, which is considered effective for neuropathic pain.[37] Although no trials have directly compared the efficacy or effectiveness of these two compounds, it may be postulated that the trends observed in this study may be accounted for in part by these differences in pharmacokinetics and dosing.

The mean daily dose of pregabalin was lower than the dose recommended for the treatment of FM,[18] and similarly, the dose of gabapentin was lower than reported to be effective in a randomized clinical trial[21] and generally required for the effective management of neuropathic pain.[22] However, not only were the mean number of prescriptions and the mean number of days of treatment for pregabalin significantly higher than for gabapentin, but adherence was better with pregabalin, as shown by the significantly higher average MPR.

It is tempting to speculate on other possible reasons for the changes reported in this study, including

ascribing the continued use of multiple pain medications to suboptimal doses of pharmacotherapy. Suboptimal dosing may account for why few reductions in pain-related medication prescribing were observed, especially in the pregabalin cohort. Since this is a short-term study, the time frame may not have been adequate to observe upward titration to more effective dose levels and consequently potentially more effective pain management. Dosing analysis among patients who received consecutive prescriptions pointed toward an increase in dosage with each consecutive prescription. Longer-term evaluation (1 year to 18 months) would be needed to investigate pain-related treatment patterns among patients who are managed with optimal doses.

As with all studies that rely on retrospective database analysis, there are several limitations to be considered. These limitations include errors in coding and recording, potentially resulting in misdiagnosis in a proportion of patients and the difficulty in diagnosing FM, as there is no simple diagnostic test for FM. Additional items include the inability to link the condition of interest, FM, with the prescribing of a particular pain medication, including pregabalin and gabapentin. This is relevant to populations such as the one described here, characterized by multiple comorbidities that may be associated with intermittent or chronic pain, such as migraine and various inflammatory arthritic conditions. The prescribing of pregabalin, as well as gabapentin or any of the adjunctive medications often prescribed for pain-related sequelae (ie, depression/anxiety and sleep disorders), may in fact have been for indications other than pain related to FM. A similar limitation is that since patient compliance cannot be ascertained in retrospective database studies, the prescribing of a particular medication does not necessarily imply that the patient filled the prescription or used the medication.

The information contained in the database on medications was limited only to prescription medications. Consequently, it is not known to what extent these patients may have been taking over-the-counter medications for their FM. Finally, information on pain severity levels is not available in the database, and it is not possible to know what effects, if any, prescription of pregabalin or gabapentin may have had on pain-related outcomes. For these reasons, the results reported here should be interpreted with the appropriate caveats in mind.

In conclusion, our observations suggest substantial comorbidity and pain-related medication prescribing in patients with FM who are prescribed the alpha-2-delta ligands pregabalin and gabapentin. While decreases in prescriptions of specific classes of medications and combination therapies were observed among patients prescribed pregabalin, there was an increase in pain-related medication prescriptions among patients prescribed gabapentin. Further investigation is warranted to evaluate long-term prescribing patterns of other pain medications and the causal relationships among medication use and clinical outcomes in patients with FM.

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REFERENCES

1. Wolfe F, Ross K, Anderson J, Russell IJ, Hebert L. The prevalence and characteristics of fibromyalgia in the general population. *Arthritis Rheum*. 1995;38:19–28.

2. Wolfe F, Smythe HA, Yunus MB, et al. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia. Report of the Multicenter Criteria Committee. *Arthritis Rheum*. 1990;33:160–172.

3. Wolfe F. The epidemiology of fibromyalgia. J Musculoskeletal. *Pain*. 1993;1:137–148.

4. Arnold LM, Crofford LJ, Mease PJ, et al. Patient perspectives on the impact of fibromyalgia. *Patient Educ Couns*. 2008;73:114–120.

5. White L, Birnbaum H, Kaltenboeck A, Samuels S, Mallett D, Robinson R. Medical care and APS guideline-related prescription drug use in newly diagnosed and established fibromyalgia patients [Abstract]. *J Pain*. 2008;9:16.

6. Hughes G, Martinez C, Myon E, Taieb C, Wessely S. The impact of a diagnosis of fibromyalgia on health care resource use by primary care patients in the UK. An observational study based on clinical practice. *Arthritis Rheum*. 2006;54:177–183.

7. Annemans L, Wessely S, Spaepen E, et al. Health economic consequences related to the diagnosis of fibromyalgia syndrome. *Arthritis Rheum*. 2008;58:895–902.

8. Bennett RM, Jones J, Turk DC, Matallana L. An Internet survey of 2,596 people with fibromyalgia. *BMC Musculoskelet Disord*. 2007;8:27.

9. Berger A, Dukes E, Martin S, Edelsberg J, Oster G. Characteristics and healthcare costs of patients with fibromyalgia syndrome. *Int J Clin Pract*. 2007;61:1498–1508.

10. White KP, Speechley M, Harth M, Ostbye T. Comparing self-reported function and work disability in 100 community cases of fibromyalgia syndrome versus controls in London, Ontario. The London Fibromyalgia Epidemiology Study. *Arthritis Rheum*. 1999;42:76–83.

11. White LA, Birnbaum HG, Kaltenboeck A, Tang J, Mallett D, Robinson RL. Employees with fibromyalgia: medical comorbidity, healthcare costs, and work loss. *J Occup Environ Med*. 2008;50:13–24.

12. Berger A, Martin S, Dukes E, Edelsberg J, Oster G. Patterns of pain-related pharmacotherapy in patients with fibromyalgia. *Manag Care Interface*. 2008;20:30–38.

13. Berger A, Sadosky A, Dukes E, Martin S, Edelsberg J, Oster G. Characteristics and patterns of healthcare utilization of patients with fibromyalgia in general practitioner settings in Germany. *Curr Med Res Opin*. 2008;24:2489–2499.

14. Bennett RM. Emerging concepts in the neurobiology of chronic pain: evidence of abnormal sensory processing in fibromyalgia. *Mayo Clinic Proc*. 1999;74:385–398.

15. Staud R. Evidence of involvement of central neural mechanisms in generating fibromyalgia pain. *Curr Rheumatol Rep*. 2002;4:299–305.

16. Burckhardt C, Goldenberg D, Crofford L, et al. *Guideline for the Management of Fibromyalgia Syndrome Pain in Adults and Children*. Glenview, IL: American Pain Society; 2005.

17. Carville SF, Arendt-Nielsen S, Bliddal H, et al. EULAR evidence based recommendations for the management of fibromyalgia syndrome. *Ann Rheum Dis*. 2008;67:536–541.

18. *Lyrica (Pregabalin) Capsules Prescribing Information*. June. New York: Pfizer, Inc.; 2007.

19. *Cymbalta (Duloxetine Hydrochloride) Delayed Release Capsules Prescribing Information*. August. Indianapolis, IN: Eli Lilly and Company; 2008.

20. *Savella (Milnacipran Hydrochloride) Prescribing Information*. January. St. Louis, MO: Forest Pharmaceuticals; 2009.

21. Arnold LM, Goldenberg D, Stanford SB, et al. Gabapentin in the treatment of fibromyalgia. A randomized, double-blind, placebo-controlled, multicenter trial. *Arthritis Rheum*. 2007;56:1336–1344.

22. Dworkin RH, O'Connor PW, Backonja M, et al. Pharmacologic management of neuropathic pain: evidence-based recommendations. *Pain*. 2007;132:237–251.

23. Wesche D, Bockbrader H. A pharmacokinetic comparison of pregabalin and gabapentin [Abstract]. *J Pain*. 2005;6(suppl 3):S29.

24. Turesson C, Jacobsson LT, Matteson EL. Cardiovascular co-morbidity in rheumatic diseases. *Vasc Health Risk Manag*. 2008;4:605–614.

25. Haythornthwaite JA, Benrud-Larson LM. Psychological aspects of neuropathic pain. Clin. *J Pain*. 2000;2 (suppl 16):S101–105.

26. Berger A, Dukes EM, Oster G. Clinical characteristics and economic costs of patients with painful neuropathic disorders. *J Pain*. 2004;5:143–149.

27. Dworkin RH, Backonja M, Rowbotham MC, et al. Advances in neuropathic pain. Diagnosis, mechanisms, and treatment recommendations. *Arch Neurol*. 2003;60:

28. Dubinsky RM, Kabbani H, El-Chami Z, Boutwell C, Ali H. Practice parameter: treatment of postherpetic neuralgia. An evidence-based report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2004;63:959–965.

29. Argoff CE, Backonja MM, Belgrade MJ, et al. Consensus guidelines: treatment planning and options. *Mayo Clinic Proc*. 2006;81:S12–S25.

30. Attal N, Cruccu G, Haanpaa M, et al. EFNS guidelines on pharmacological treatment of neuropathic pain. *Eur J Neurol*. 2006;13:1153–1169.

31. Moulin DE, Clark AJ, Gilron I, et al. Pharmacological management of chronic neuropathic pain—consensus statement and guidelines from the Canadian Pain Society. *Pain Res Manag*. 2007;12:13–21.

32. Finnerup N, Otto M, McQuay HJ, Jensen TS, Sindrup SH. Algorithm for neuropathic pain treatment: An evidence based proposal. *Pain*. 2005;118:289–305.

33. World Health Organization. *Cancer Pain Relief*. Geneva, Switzerland: Health Organization; 1996.

34. Crofford LJ, Rowbotham MC, Mease PJ, et al. Pregabalin for the treatment of fibromyalgia syndrome: results of a randomized, double-blind, placebo-controlled trial. *Arthritis Rheum*. 2005;52:1264–1273.

35. Arnold L, Pritchett YL, D'Souza DN, Goldstein DJ, Iyengar S, Wernicke JF. A randomized, double-blind, placebo-controlled trial of duloxetine in the treatment of women with fibromyalgia with or without major depressive disorder. *Pain*. 2005;119:5–15.

36. Wolfe F, Anderson J, Harkness D, et al. A prospective, longitudinal, multicenter study of service utilization and costs in fibromyalgia. *Arthritis Rheum*. 1997;40:1560–1570.

37. *Neurontin (Gabapentin) Prescribing Information*. January. New York: Pfizer, Inc.; 2007.