Abstract

Objective: To compare comorbidities, drug use, benefit costs, absences, medication persistence/adherence between employees with fibromyalgia initiating treatment with pregabalin (PGB) vs. antidepressant Standard of Care (SOC) amitriptyline, duloxetine, or venlafaxine).

Methods: Retrospective study of 240 adults initiating PGB or SOC after 7/1/2007. Multivariate regression models on propensity-score-matched cohorts compared postindex costs, absences, and adherence between cohorts.

Results: Pregabalin users had significantly more preindex muscle pain and dizziness and less depression than SOC (each \( P < 0.05 \)). Use of some non-PBG/SOC drugs differed. No differences were found in total medical, drug, or absenteeism cost. PGB had more sick leave (9.8 vs. 6.8 days, \( P = 0.04 \)), but other absence types were similar. All adherence metrics were nonsignificantly greater for PGB vs. SOC.

Conclusion: Despite several comorbidity and drug use differences, most employee benefit outcomes and adherence did not differ between the cohorts.

Key Words: fibromyalgia, employees, pregabalin, Standard of Care, health benefit costs, compliance

INTRODUCTION

Background

Fibromyalgia (FM), a common nonarticular rheumatic syndrome of unknown origination, is characterized by widespread pain and multiple points of focal muscle tenderness to palpation (trigger points). FM affects 2% to 4% of the general population,\(^1\) with the majority of those inflicted with FM being female.\(^2\) Diagnosis is typically established in working-age adults between the ages of 20 and 55 years and incidence of FM increases with age, rising to more than 7% of those 70 to 79 years of age.\(^2\)

The American College of Rheumatology’s (ACR) 1990 criteria for diagnosing FM is defined as excessive tenderness at 11 or more of 18 specific tender points and widespread pain.\(^7\) These criteria reach a sensitivity and specificity of approximately 85 percent in
differentiating FM from other types of chronic musculoskeletal pain. In addition to pain, FM is associated with a number of other coexisting symptoms and conditions such as fatigue, insomnia, depression, difficulty thinking, nervousness, muscle weakness, and irritable bowel syndrome. To better address some of these symptoms, new diagnostic criteria have recently been endorsed by the ACR. These criteria require either a widespread pain index of at least 7 and a summed symptom severity index of at least 5, or a widespread pain index of 3 to 6 and a summed symptom severity index of at least 9.

Fibromyalgia has been shown to be a costly condition both in general populations and in employed populations. Incremental health care costs stem from FM patients’ high utilization of health care services, including emergency department and inpatient services, additional comorbidity, and increased use of pain-related medications. Patients with FM have also been reported to have significantly higher lifetime appendectomy, tonsillectomy, carpal tunnel, gynecologic and back/neck surgery rates than patients with other rheumatic disorders (controlling for age and gender). In one longitudinal study, Al-Allaf reported that between the time of an initial outpatient visit and the time of the survey (6 to 7 years later on average), only 19.4% of FM patients continued in the same job, compared with 57.6% of outpatients without FM (P < 0.0001), and 46.8% of patients with FM reported losing their job because of their condition, compared with only 14.1% of other outpatients (P < 0.0001).

Additionally, FM has a significant impact on productivity and functionality. Objectively measured annual work output in employees with FM was 19.5% lower than in employees without FM (P = 0.003). In a study by Waylonis et al., employees with FM reported having difficulty in performing repetitive motor tasks, sitting or standing for long periods, and dealing with stress. Bernard et al. found that patients with FM reported that FM had a negative impact on not only their mental health and personal relationships, but also on their career. Even coping with a spouse’s FM has been shown to have an association with poorer health, depression, loneliness, stress, and psychological difficulty in caregivers.

Fibromyalgia Treatment

A wide variety of pharmacological and nonpharmacological FM treatment options have been studied. The American Pain Society (APS) and the European League Against Rheumatism (EULAR) both recommend that pharmacological and nonpharmacological therapies be used together to treat FM. Medications recommended by the APS include tricyclic antidepressants (such as amitriptyline), selective serotonin reuptake inhibitors (SSRIs), tramadol, and sleep/anti-anxiety medications. EULAR recommends the use of amitriptyline, duloxetine and other antidepressants, tramadol, tropsioner, pramipexole, or pregabalin. Nonpharmacological therapies recommended by APS and EULAR include patient education, aerobic exercise, strength training, cognitive-behavioral therapy, and particularly heated pool therapy.

A number of controlled trial studies of amitriptyline use in the treatment of FM have been performed. Most showed significant short-term reductions in pain and disability and improvements in sleep, but evidence of significant improvement after 12 weeks is sparse. Duloxetine, a serotonin norepinephrine reuptake inhibitor (SNRI), has been shown in several controlled trials to have beneficial short-term effects (up to 6 months) on pain, fatigue, perception of physical and mental health, and physical functioning. One study of FM patients found improvements in pain with duloxetine for up to 52 weeks. Though venlafaxine was the first newer-generation antidepressant to be classified as both a serotonin and a norepinephrine reuptake inhibitor, few studies exist that describe its effectiveness in the treatment of FM. Two small open-label studies found significant pain improvement at 8 to 12 weeks of therapy.

Pregabalin, an alpha-2-delta ligand antiepileptic drug, was the first medication approved by the United States Food and Drug Administration (FDA) for the treatment of FM (duloxetine and the recent SNRI milnacipran are the only other approved medications). The results of a meta-analysis and four randomized, placebo-controlled clinical trials of pregabalin for the treatment of FM (8 to 26 weeks) have been published. Each of them found significant improvements in pain and sleep compared with placebo. Self-reported social functioning, vitality, and general health also improved.

Two studies were found that compared actual health care resource utilization of pharmaceutical
therapies for FM. Gore et al. compared prevalence of comorbidities, pharmacotherapy, and health care resource use and costs before and after initializing pregabalin or gabapentin therapy; however, this study only examined pre–post comparisons of pregabalin and gabapentin; ie, no comparisons between drugs were conducted.52 Zhao et al. compared adherence and direct health care costs between pregabalin and duloxetine.53 No studies were found that compared employee-related outcomes such as total health-related employee benefit costs, absence costs or absence time between users of different pharmaceutical therapies in FM patients. In addition, no studies were found examining the impact of copay on adherence or the impact of adherence on employee-related outcomes.

**Current Study Objectives**

The main objective of this research is to quantify differences in outcomes between employees with FM taking pregabalin vs. those taking any of the standard of care (SOC) antidepressants (amitriptyline, duloxetine, or venlafaxine). The current study compares preindex comorbidity prevalence, pre and postindex prescription medication use, employee benefit costs, absences from work (sick leave and short- and long-term disability), adherence to medication therapy, impact of employees’ copay on adherence, and the association of adherence with cost and absence outcomes.

**METHODOLOGY**

**Database**

The analytic database used in this research project was produced from the Human Capital Management Services Research Reference Database (RRDb). The RRDb contains de-identified, integrated information for approximately 800,000 employees from various large self-insured employers throughout the United States (U.S.) during 2001 to 2010. The database contains employee-specific information on demographics, salary and payroll, company type, job type, employment status, health plan, disability claims, workers’ compensation claims, and sick leave.

The database is organized in a person-centric manner to allow the data for separate benefits to be linked by person and studied using integrated analysis. In addition, because the database contains health care and pharmaceutical utilization as well as work absence information at the claim level, it is possible to measure the association of FM treatment with costs, absences, and adherence.

**Description of Study Cohorts**

Employees who met the study criteria were grouped into one of two cohorts, those initiating pregabalin treatment (PGB cohort) and those initiating treatment with one of three SOC antidepressants: duloxetine, venlafaxine, or amitriptyline (SOC cohort). All employees with at least two diagnoses of FM (ICD-9 729.1x) in any of the first three diagnosis positions at least 90 days apart and who were prescribed PGB or SOC after July 1, 2007 were eligible for inclusion. The first prescription for PGB or SOC on or after July 1, 2007 was considered the index date. Further inclusion criteria included employees with no PGB or SOC prescriptions in the 6-month period preceding the index date and those with at least 6 months of continuous health plan enrollment immediately before and after the index date.

**Patient Matching**

Because randomization is not possible in retrospective observational studies, propensity-score matching was used to control known biases while matching the SOC population (one-to-one) to the PGB population. Matching covariates included age, tenure (years with current employer), salary, gender, marital status, race, exempt/nonexempt status, full-time/part-time status, zip code region, and index year (year of the first PGB or SOC treatment). Logistic regression, controlling for the matching covariates, was used to create the propensity score (probability of being in the PGB cohort vs. the SOC cohort). Subsequently, a nearest-neighbor greedy matching algorithm without replacement was used on the propensity score and covariates such that the resulting PGB and SOC cohorts had no significant differences in the matching covariates.

**Baseline and Outcomes Measures**

**Baseline Characteristics.** The demographic and clinical characteristics were determined for the two cohorts and included age, gender, marital status, race, salary, tenure, exempt/nonexempt status, full-time/part-time status, zip code region, and year of index date.
Comparisons of Preindex Comorbidities among Employees. Several types of comorbidities and comorbidity scores were compared between the cohorts in the 6-month preindex period, including FM-related conditions of interest (the top 19 conditions in table 1 of Silverman, et al.9), 17 Major Diagnostic Categories (MDC) of all conditions (as defined by the Agency for Healthcare Research and Quality)55 and the Charlson Comorbidity Index score.56

Descriptive Analysis of Prescription Medication Use. Use of FM-related medications (as defined by Silverman, et al.9) was compared across the 6-month pre and postindex time periods within each cohort as well as between the 2 matched cohorts for each time period. For specific medication types, usage was defined based on whether an employee filled at least one prescription for this type of medication in the time period of interest. The compared medication classes are shown in Table 1.

Comparing the Cost to Employers of Employees Initiating PGB Treatment vs. SOC Treatment. In this section of the study, postindex comparisons are made between the matched PGB and SOC employee cohorts for the following outcomes:

- All-cause medical costs paid by employer.
- Fibromyalgia-specific medical costs paid by employer (from claims with a primary ICD-9 code of 729.1x).
- Fibromyalgia-related medical costs paid by employer (from claims with primary ICD-9 codes defining the top 19 conditions in table 1 of Silverman, et al.9).
- Medical costs by place of service category (doctor’s office, inpatient hospital, outpatient hospital or clinic, emergency department, laboratory, and other).
- Prescription drug costs paid by employer.
- Sick leave payments and days absent.
- Short-term disability payments and days absent.
- Long-term disability payments and days absent.
- Likelihood of emergency department visit or inpatient hospital stay.

Costs are adjusted for inflation to 2009 dollars based on the date of the claim. Only employees eligible for the given health benefit were included in the regression models for that benefit.

Sick leave is typically provided for short illnesses lasting < 1 or 2 weeks. While on sick leave, employees generally receive 100% of their salary. The number of days of sick leave offered per year varies by employer. Short-term disability is provided generally for illnesses that last between 1 or 2 weeks and 6 months, during which time employees usually receive 60% to 100% of their salary. If an employee is unable to work for an extended period (usually longer than 6 months), the employee begins long-term disability and typically receives 50% to 70% of salary.

Persistence, Discontinuance, and Adherence. In this section of the study, medication persistence, discontinuance, and adherence are compared between the two (matched) cohorts during the postindex period. Persistence is defined as the number of days from the index prescription to the beginning of the first 30 day gap in supply with or without evidence of resumption.

<table>
<thead>
<tr>
<th>Table 1. Fibromyalgia-related Prescription Medication Treatment Types</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregabalin</td>
</tr>
<tr>
<td>Gabapentin</td>
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<tr>
<td>Other antiepileptic drugs (AEDs)</td>
</tr>
<tr>
<td>Corticosteroids (oral or injectable)</td>
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<tr>
<td>COX-2 inhibitors</td>
</tr>
<tr>
<td>Other NSAIDs</td>
</tr>
<tr>
<td>Muscle relaxants</td>
</tr>
<tr>
<td>Short-acting opioids</td>
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<tr>
<td>Long-acting opioids</td>
</tr>
<tr>
<td>Other opioids</td>
</tr>
<tr>
<td>Anesthetics</td>
</tr>
<tr>
<td>Topical steroids</td>
</tr>
<tr>
<td>Other topical</td>
</tr>
<tr>
<td>Triptans</td>
</tr>
<tr>
<td>Other antimigraine medicines</td>
</tr>
<tr>
<td>5-Hydroxytryptamine receptors</td>
</tr>
<tr>
<td>Drugs</td>
</tr>
<tr>
<td>5-Aminosalicylic acids</td>
</tr>
<tr>
<td>Disease-modifying</td>
</tr>
<tr>
<td>anti-rheumatic</td>
</tr>
<tr>
<td>drugs</td>
</tr>
<tr>
<td>Antispasmodics</td>
</tr>
<tr>
<td>Bulk-forming agents</td>
</tr>
<tr>
<td>Softeners</td>
</tr>
<tr>
<td>Saline</td>
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<tr>
<td>Stimulants</td>
</tr>
<tr>
<td>Emollients</td>
</tr>
<tr>
<td>Hyperosmotics</td>
</tr>
<tr>
<td>Other constipation</td>
</tr>
<tr>
<td>Antimotility</td>
</tr>
<tr>
<td>Anticholinesterase muscle stimulants</td>
</tr>
</tbody>
</table>

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before the end of the 6-month postindex study period. Discontinuance is defined as the number of days from the index prescription to discontinuation, or the complete cessation of the PGB/SOC therapy (for at least 30 days) with no resumption of treatment during the 6-month study period. Adherence as measured by proportion of days covered (PDC), was calculated by dividing the total days supply of PGB or SOC by 180. The impact of medication (either PGB or SOC) copay on PDC is also modeled.

**Association of Adherence with Outcomes.** This section of the study measured the impact of adherence (PDC) on postindex all-cause medical costs, FM-specific medical costs, FM-related medical costs, prescription drug costs, sick leave costs and absence days, and short- and long-term disability costs and absence days.

**Statistical Methods**

Employee characteristics of the two cohorts were compared (and P values provided) using t-tests for continuous variables and chi-square tests for binary variables. Significance between cohort comorbidity prevalence values was tested using chi-square tests.

Two-part regression modeling was used for cost and absence comparisons. The first part of the modeling employed logistic regression to model those employees with more than zero costs or absence days during the period. The second part used generalized linear regression (with gamma distribution and log link) to model the cost and absence days of those persons who have more than zero costs or absence days. The results of the two parts were then combined to produce average cost estimates for all persons in the study for the given period.\(^5\) Logistic regression was used to model the likelihood of an emergency room visit and a hospital admission.

The regression modeling controlled for differences between the two cohorts in the following factors: age, gender, marital status, race, prior comorbidity differences, log of weekly salary, preperiod Charlson Index, preindex benefit costs, and the year of the index prescription. A stepwise selection process was used to determine which of these variables would remain in the final regression models used to calculate the estimated outcomes.

Parametric duration regression models (with Weibull distribution) were used to model persistence and time to discontinuance.\(^5\) Gamma generalized linear models were used to model PDC.\(^5\) In addition to the control variables used in models described above, the persistence, discontinuance, and PDC models also controlled for the employee’s average PGB or SOC prescription copay.

In the two-part regression models measuring the association of postindex adherence with cost and absence outcomes, a binary variable indicating whether the employee’s PDC was 0% to 80% vs. 80% to 100% was included along with a variable representing the interaction between the cohort indicator variable (PGB or SOC) and the binary PDC indicator variable.

**RESULTS**

The study found 315 employees who met the inclusion and exclusion criteria: 120 initiating treatment with PGB and 195 initiating treatment with SOC medications. After propensity-score matching, 120 employees remained in each cohort.

**Employee Characteristics**

Patient characteristics between the two groups were similar (Table 2). Study employees were 45.2 to 46.1 years old and 77.5% female. Annual salary averages were $56,809 to $58,935, and average tenure (time) with their current employer was 10.2 years. Most employees (96.7%) worked full-time. No significant differences in age, gender, marital status, race, salary, tenure, exempt/nonexempt status, full-time/part-time status, zip code region, or year of index date existed between the matched PGB and SOC cohorts.

**Preindex Comorbidities**

Comparisons were made between these matched cohorts using two different sets of comorbid condition categories as well as the Charlson Comorbidity Index. Table 3 shows preindex prevalence differences in 19 specific conditions that have been shown to be related to FM. Prior to initiating PGB or SOC therapy, PGB employees were significantly more likely than SOC employees to have muscle pain or dizziness, while the SOC employees had a significantly higher prevalence of depression.

Table 4 shows preindex prevalence differences in the 17 MDC defined by the Agency for Healthcare Research and Quality. These MDCs span all
conditions. Of the 17 MDCs, only one was significantly more prevalent among PGB employees than among SOC employees (musculoskeletal/connective tissue). Similarly, only one MDC was significantly more prevalent among SOC employees (skin & subcutaneous tissue).

**Prescription Medication Use**

Pre and postindex percentages of employees from the PGB and SOC cohorts using the drug classes specified in Table 1 were compared. Significant differences in short-acting opioids (PGB 65% vs. SOC 50%, \( P = 0.0188 \)) and muscle relaxants (PGB 40% vs. SOC 25%, \( P = 0.0131 \)) existed in the preindex period. There were relatively few pre–post differences in both groups. Except for the specific study medications used to define the cohorts, the PGB cohort had no significant changes in medication prevalence between the pre and postindex periods. The SOC cohort, however, had several significant changes. The percent of SOC employees taking nonbenzodiazepine hypnotics increased from 19.2% to 27.5% (\( P = 0.0330 \)), and the percent taking gastrointestinal protectants increased from 1.7% to 6.7% (\( P = 0.0339 \)). Conversely, the percentages of SOC employees taking “Other antidepressants” (18.3% to 11.7%, \( P = 0.0455 \)) and SSRIs (24.2% to 14.2%, \( P = 0.0285 \)) both decreased significantly from the pre to the postindex period. In the postindex period, significant differences were noted between cohorts for gastrointestinal protectants, topical steroids, selective serotonin reuptake inhibitors (SSRIs), muscle relaxants, and short-acting opioids as shown in Figure 1. During the 6 months after treatment initiation, the use of short-acting opioids, muscle relaxants, and SSRIs was more prevalent in PGB than in SOC. Likewise, the use of topical steroids and gastrointestinal protectants was more prevalent in the SOC cohort.

**Burden to Employers of Employees Initiating PGB Treatment vs. SOC Treatment**

Health benefit cost estimates from regression modeling are shown in Table 5. No significant differences were found in employee-related health benefit cost categories when comparing the PGB and SOC cohorts.

When medical costs (all-cause, FM-specific, and FM-related) were compared by the location where the service was provided, no significant differences between PGB and SOC were found in inpatient hospital, emergency department, laboratory, or “other”
costs. Most doctor’s office and outpatient hospital or clinic cost differences were also insignificant. However, PGB’s FM-specific doctor’s office costs were significantly higher than SOC’s ($202 vs. $124, P = 0.0198), and PGB’s FM-related outpatient hospital or clinic costs were significantly lower than SOC’s ($200 vs. $567, P = 0.0016).

Comparisons of days absent using two-part regression models are shown in Table 6. PGB cohort sick leave days were significantly greater than SOC cohort sick leave days, while no significant differences were noted for short- or long-term disability.

The expected likelihood of an inpatient hospital visit was 11.3% in the PGB cohort and 7.2% in the SOC cohort, but this difference was not statistically significant (P = 0.2604). Similarly, the expected likelihood of an emergency department visit was 19.8% for PGB and 28.4% for SOC, but again, the difference was not statistically significant.

### Persistence, Discontinuance, and Adherence

No significant difference was found in medication persistence during the 6-month postindex period between the PGB and SOC cohorts. Median PGB persistence was 90 days, while the SOC cohort’s median persistence was 89 days (P = 0.9319).

The difference in median time until medication discontinuance between cohorts was larger than the difference in persistence, but still not statistically significant. Median time until discontinuance was 138 days for PGB and was 113 days for SOC (P = 0.2721).

Proportion of days covered was also higher in the PGB cohort (52%) than in the SOC cohort (47%), but not significantly higher (P = 0.3076).

A similar regression model was used to compare the effect that copay had on PDC, controlling for the other factors.
independent variables (Figure 2). There was a significant difference in the effect of copay per day supplied on adherence between the PGB and SOC cohorts. Unlike the SOC cohort, the PGB cohort showed a significant relationship between copay per day supplied and adherence. As copay per day supplied increased, adherence decreased. Specifically, a $0.00 PGB copay per day supplied (ie, no cost to the user) was associated with 69% adherence, while a copay of $1.75 was associated with only a 34% adherence rate. Conversely, over their distribution ($0.00 to $1.00 per day supplied), SOC medications had no significant differences in adherence.

Association of Adherence with Outcomes

The regression modeling used to measure the association of postindex medication adherence (PDC) with postindex outcomes (medical, drug, sick leave, and short-term disability costs and sick leave and

Table 5. Health Benefit Costs during the 6 Months after Initiating Treatment

<table>
<thead>
<tr>
<th>Cost Category</th>
<th>PGB Adjusted* Values</th>
<th>SOC Adjusted* Values</th>
<th>PGB vs. SOC; P Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical – all conditions</td>
<td>Eligible N</td>
<td>Adjusted Mean Costs</td>
<td>Eligible N</td>
</tr>
<tr>
<td>FM-specific medical</td>
<td>120</td>
<td>$298</td>
<td>120</td>
</tr>
<tr>
<td>FM-related medical</td>
<td>120</td>
<td>$1,617</td>
<td>120</td>
</tr>
<tr>
<td>Prescription drug</td>
<td>120</td>
<td>$1,291</td>
<td>120</td>
</tr>
<tr>
<td>Total health care</td>
<td></td>
<td>$5,546</td>
<td></td>
</tr>
<tr>
<td>Sick leave</td>
<td>72</td>
<td>$608</td>
<td>65</td>
</tr>
<tr>
<td>Short-term disability</td>
<td>105</td>
<td>$811</td>
<td>107</td>
</tr>
<tr>
<td>Long-term disability</td>
<td>101</td>
<td>$98</td>
<td>105</td>
</tr>
<tr>
<td>Total absence cost</td>
<td></td>
<td>$1,517</td>
<td></td>
</tr>
<tr>
<td>Overall total cost</td>
<td></td>
<td>$7,064</td>
<td></td>
</tr>
</tbody>
</table>

*Two-part regression models control for age, gender, marital status, race, prior comorbidity differences, log of weekly salary, index year, pre-period Charlson Index, and preindex benefit cost.

Table 6. Adjusted Absence Day Comparisons between PGB and SOC Cohorts

<table>
<thead>
<tr>
<th>Absence Days Category</th>
<th>PGB</th>
<th>SOC</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eligible N</td>
<td>Adjusted* Days Absent</td>
<td>Eligible N</td>
<td>Adjusted* Days Absent</td>
</tr>
<tr>
<td>Sick leave</td>
<td>72</td>
<td>9.76</td>
<td>65</td>
</tr>
<tr>
<td>Short-term disability</td>
<td>105</td>
<td>6.29</td>
<td>107</td>
</tr>
<tr>
<td>Long-term disability</td>
<td>101</td>
<td>1.05</td>
<td>105</td>
</tr>
</tbody>
</table>

*Two-part regression models control for age, gender, marital status, race, prior comorbidity differences, log of weekly salary, index year, pre-period Charlson Index, and preindex absence days.
short-term disability absence days) did not find any significant differences between the PGB and SOC cohorts. Differences in outcomes within each of the PGB and SOC cohorts were also examined by PDC level. A PDC of at least 80% was significantly associated with higher drug costs in both the PGB ($P = 0.0016$) and SOC cohorts ($P = 0.0070$). In addition, a PDC of at least 80% was significantly associated with higher FM-related costs in the PGB cohort ($P = 0.0334$). All other within-cohort comparisons by PDC level were statistically insignificant.

**DISCUSSION**

Results Summary

Few significant differences were found between the PGB and SOC cohorts. In terms of preindex prevalence of specific comorbid conditions, PGB users were more likely to have muscle pain or dizziness, and less likely to have depression than SOC users. In major diagnostic condition categories, PGB users were more likely to have musculoskeletal/connective tissue disorders and less likely to have diseases of the skin and subcutaneous tissue when compared with SOC employees.

When comparing medication usage prior to the index prescription, PGB users were more likely to have taken muscle relaxants or short-acting opioids than SOC users. In the postindex period, short-acting opioid use was statistically higher in the PGB cohort; however, the relative increase was higher in the SOC cohort (23.3% vs. 8.3%). PGB users were also more likely to use SSRIs and less likely to use topical steroids or gastrointestinal protectants such as misoprostol or sucralfate than SOC users after the index date. The lower postindex SSRI utilization in the SOC cohort may be influenced by the prescribers’ desire to avoid confounding the effects of the SOC medications themselves.

No differences in total health care, total absence, and overall total costs were found between cohorts following the index date. There was a difference in sick leave absence days favoring the SOC cohort; however, this did not affect any of the cost categories mentioned above.

Persistence, time to discontinuance, and adherence were all better for the PGB cohort than for the SOC cohort, but the differences were not statistically significant. The copay paid by the employee for PGB was significantly associated with medication adherence (PDC). After controlling for other differences, including salary, employees paying higher copays had significantly lower PDC than employees paying lower copays.

Not surprisingly, greater adherence was significantly associated with higher drug costs in both cohorts, but greater adherence was also associated with higher FM-related medical costs in the PGB cohort. Examining employees of similar adherence levels with each other yielded no significant differences in cost and absence outcomes between the PGB and SOC cohorts.
Comparisons to Prior Research

A study by Zhao et al. comparing pregabalin to duloxetine was the only study found in the literature that directly compared cost outcomes of patients taking pregabalin vs. any of the SOC medications (duloxetine, amitriptyline, or venlafaxine). The all-cause total health care cost results presented here are in contrast to those found by Zhao et al., which reported that patients initiated on duloxetine had significantly lower health care costs relative to those initiated on pregabalin. However, while that study evaluated a longer follow-up period (12 months) than the 6 months in the current study, several other important study design differences should be noted. The Zhao et al. manuscript required only a single FM-related ICD-9 diagnosis code for inclusion, which increases the likelihood for misclassification of patients. Zhao et al. did attempt to reduce the potential for misclassification by excluding non-FM approved indications for the respective drugs; however, these exclusion criteria rendered the two cohorts noncomparable. For example, even though there is a high comorbidity between FM and depression, patients with a diagnosis of depression were excluded, but only in the duloxetine cohort. It is interesting to note that generalized anxiety disorder was not an exclusion criterion in the duloxetine cohort despite the approved indication. These exclusions created an imbalance in the cohorts; only 2% of duloxetine patients had claims for postherpetic neuralgia or epilepsy, whereas more than a quarter of the pregabalin cohort had claims for depression. Therefore, caution should be exercised when interpreting the results in Zhao et al.

Significance of the Current Research

The current study appears to be the first to compare costs and other outcomes between FM patients using PGB and SOC medications. Furthermore, comparisons of a broad array of outcomes are reported, including preindex comorbidity prevalence, pre and postindex medication usage; medical, drug, sick leave, and short- and long-term disability costs; medical costs by place of service; days absent from work; and persistence, discontinuance, and adherence. The study is also the first to make these comparisons in an employed population where the consequences of the comparisons are of direct importance to the employers who sponsor health benefits and work to promote a productive workforce.

Limitations

The findings in this study may be subject to potential drawbacks common to retrospective database analyses such as using medical claims data and ICD-9-CM diagnosis codes to identify employees with FM. In addition, claims data do not contain information about the severity of a person’s FM, thus it would be difficult to control for any potential differences in FM severity between the PGB and SOC cohorts other than by controlling for preindex cost and absence values. Finally, the results of this study are limited by the small size of the PGB and SOC cohorts, which diminishes the ability to assign statistical significance to potentially meaningful differences, and we encourage further similar studies with larger sample sizes.

CONCLUSIONS

Employees with FM in this study who used pregabalin generally did not significantly differ in their health-related employee benefit costs and absences from employees taking duloxetine, amitriptyline, or venlafaxine. None of the incremental differences in persistence, time to discontinuance, or PDC seen in the PGB cohort vs. the SOC cohort were statistically significant. Finally, use of pregabalin was found to be sensitive to the copay level paid by the employee.

ACKNOWLEDGEMENTS

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