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Healthcare Costs and Medication Adherence Among Patients with Fibromyalgia: Combination Medication vs. Duloxetine, Milnacipran, Venlafaxine, and Pregabalin Initiators

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Abstract

Objective—To examine medication adherence and healthcare costs for combination prescription initiators (duloxetine/milnacipran/venlafaxine with pregabalin) versus monotherapy initiators (duloxetine, milnacipran, venlafaxine, and pregabalin) among patients with fibromyalgia syndrome (FMS).

Methods—Our retrospective cohort study used claims data for the South Carolina Blue Cross Blue Shield State Health Plan (SHP). Patients with FMS aged ≥18 years, with prescription initiation from July 1, 2007 through June 30, 2010, and SHP enrollment for 12-months pre- and post-index periods were included (combination: N=100, pregabalin: N=665, duloxetine: N=713, milnacipran: N=131, venlafaxine: N=272). Medication adherence measures included high adherence (medication possession ratio ≥80%) and total supply days. Healthcare costs comprised direct medical expenditures. Propensity score methods of inverse probability of treatment weights were used to control for selection bias due to differing pre-index characteristics.

Results—Odds ratios for high adherence were significantly increased ($p<0.05$) among the combination cohort versus the venlafaxine (2.15), duloxetine (1.39), and pregabalin (2.20) cohorts. Rate ratios for total supply days were significantly higher ($p<0.05$) for combination versus venlafaxine (1.23), duloxetine (1.08), and pregabalin (1.32) cohorts. Expenditures for total healthcare were significantly higher ($p<0.05$) for combination versus duloxetine (\$26291 versus \$17190), milnacipran (\$33638 versus \$22886), and venlafaxine (\$26586 versus \$16857) cohorts.

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Conclusions—Medication adherence was considerably better for combination prescription initiators; however, expenditures for total healthcare were higher. Still, our findings suggest important clinical benefits with the use of combination prescription therapy, and prospective studies of medication adherence are warranted to examine causal relationships with outcomes not captured by healthcare claims databases.

Keywords

fibromyalgia syndrome; pharmacotherapy; adherence; healthcare costs; comparative effectiveness research

Introduction

Fibromyalgia syndrome (FMS) is a chronic widespread musculoskeletal pain disorder that affects an estimated 5 million Americans.¹ After osteoarthritis, FMS is the second most common rheumatic disease.^{2,3} It frequently occurs with other chronic pain conditions,⁴ and symptoms result in functional limitations (potentially disability) and negative influences on quality of life and social and occupational productivity.^{5–10}

In addition to being an illness that is complex to diagnose and treat, FMS is a costly public health problem. FMS-related disability affects 9% to 26% of patients,^{9,11–13} as compared to the general population (2%) and patients with other chronic pain (10%).^{7,9,14,15} Direct healthcare costs are three times higher for patients with FMS than individuals without FMS,^{6,16} and indirect costs (i.e., work loss and reduced productivity) are more than twice that of employees without FMS.^{6,16} Chandran and colleagues¹⁷ reported that indirect cost comprised 52.5%, 78.4%, and 78.1% of total FMS-related costs for those with mild, moderate, and severe FMS, respectively.

A multi-dimensional treatment strategy is recommended, including prescription medications, behavioral interventions, physical therapy, and exercise.^{18–25} Prescription medications used to treat the pain of FMS include analgesics, antidepressants, anticonvulsants, opioids, dopamine agonists, and others.^{18–21,23} Pregabalin (an $\alpha_2\delta$ modulator anticonvulsant) was the first prescription medication licensed by the U.S. Food and Drug Administration for treating FMS in 2007.²⁶ Duloxetine and milnacipran (serotonin-norepinephrine reuptake inhibitor [SNRI] antidepressants) were approved by the FDA for FMS in 2008 and 2009, respectively,^{27–30} and venlafaxine (a SNRI) is frequently prescribed for off-label treatment of FMS.³¹ Combined use of prescription medications with complementary mechanisms of action have also been described, such as a SNRI with anticonvulsant;^{32–36} additionally, a randomized controlled trial (RCT) illustrated that the addition of milnacipran to pregabalin, versus pregabalin monotherapy, was both tolerable and produced significant improvements in pain, physical and mental functioning, fatigue, and cognition.³⁷ However, population-based evidence regarding the patterns and effects of combination prescription medication approaches (e.g., SNRI with anticonvulsant) on health outcomes and costs are vastly lacking.

The relationship between initiation of pregabalin or duloxetine and associated medical costs have previously been studied using administrative claims, but the results are inconsistent.

FMS patients 65 years of age who initiated pregabalin showed no significant changes in individual medication costs when comparing six month pre- and post-index periods.³⁸ Harnett and colleagues' study in employees 18 years of age comparing the pre- to post-index periods showed that changes in average expenditures for all-cause medications was greater in duloxetine than pregabalin.³⁹ When examining predictors associated with adherence and health-care costs among insured patients with FMS who initiated duloxetine, the 12 months post-initiation showed that high adherence was significantly associated with lower total healthcare costs for commercially insured patients as well as lower outpatient healthcare costs for those with the Medicare supplement.⁴⁰ In patients aged 18–64 years or 65 years diagnosed with FMS, Gore and colleagues showed no differences between the duloxetine or pregabalin for healthcare costs during the pre- or post-index periods.⁴¹ In a separate analysis, exploring treatment patterns and costs among FMS, analyses of the post-index period showed higher costs among pregabalin initiators for medication and total healthcare costs when compared to duloxetine.³⁴ Burke and colleagues' study of FMS patients aged 18 years who initiated pregabalin or duloxetine, showed no significant differences between treatment cohorts for all-cause total healthcare costs as well as FMS-related total healthcare costs.⁴²

Several publications have explored medication adherence among FMS patients initiating duloxetine or pregabalin, but the results have been mixed. A study using commercially insured or Medicare claims showed higher medication adherence in the pregabalin cohort compared to gabapentin.³⁸ Zhao and colleagues showed that in the 12 months following medication initiation, duloxetine users that were commercially insured had significantly higher medication adherence than pregabalin users.⁴³ In a retrospective study using national managed claims, there was no significant differences in medication adherence between pregabalin and duloxetine cohorts.⁴² Sun and colleagues reported significantly more patients with high medication adherence among duloxetine initiators compared to pregabalin initiators.⁴⁴

Comparative effectiveness research (CER) studies provide considerably more external validity to “real-world” clinical practice and patient outcomes than RCTs. As summarized above, previous results from CER studies of prescription medications utilizing healthcare claims data have been mixed; additionally, study conclusions have been limited by not examining combination prescription medication approaches, particularly a SNRI with anticonvulsant. Using South Carolina (SC) administrative claims for patients with FMS, the main objective of this study was to examine prescription medication adherence and healthcare costs for monotherapy initiators (duloxetine, milnacipran, venlafaxine, or pregabalin) compared to combination therapy initiators (duloxetine/milnacipran/venlafaxine with pregabalin).

Methods

Study Design

Study approval by the Institutional Review Board for Human Research (IRB) of the University of Florida was attained (IRB201500121) with respect to the study of human subjects as adequately protecting the rights and welfare of the individuals involved,

employing adequately methods of securing informed consent from these individuals and not involving undue risk in the light of potential benefits to be derived therefrom. This was a retrospective cohort study of FMS patients who initiated one of four prescription medication therapies (duloxetine, milnacipran, venlafaxine, pregabalin) or combinations thereof from July 1, 2007 through June 30, 2010. Medication initiation was defined as no prescription coverage for the medication in the prior 90 days, and the index-date was defined as the medication initiation date.⁴³ Individuals were grouped into treatment cohorts based on the prescription(s) of their index-date claim. The cohort study period consisted of 12-months prior and 12-months after the index-date.

Data Source

We utilized population-based administrative claims data for FMS patients in South Carolina. The SC Office of Research and Statistics (ORS) routinely manages administrative claims databases for individuals in SC with State Health Plan (SHP) commercial insurance. Data from July 1, 2006 through June 30, 2011 for patients with FMS were extracted from these databases by the SC ORS for our proposed study, including individual enrollment files as well as inpatient, outpatient, and pharmacy claims files. The predominate advantages of using the SC ORS database include that they are considerably affordable and readily accessible, as SC is very interested in improving the health of its population.

The patient enrollment data included information on individual demographic characteristics and enrollment status: age (in year of first claim), sex, and total months enrolled in the SHP in each 12 month time span from selection into cohort through end of study period. Inpatient, outpatient, and pharmacy claims included *International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM)* diagnosis and procedure codes,⁴⁵ *Clinical Procedure Terminology (CPT)* codes,⁴⁶ date of service (month/year), length of stay (for inpatient records), prescription medications filled (including date dispensed (month/year), NDC code, therapeutic class code, dose, frequency dosed, days supplied), payments per claim (patient + deductible + SHP), provider/service type, encrypted provider IDs for each service, and encrypted enrollee ID.

Sample Selection

De-identified individual-level data were obtained and linked through a unique study personal identification number, allowing for longitudinal assessments of patient care. Inclusion criteria comprised individuals enrolled in the SC SHP, ages ≥ 18 years, diagnosed with FMS (*ICD-9-CM* 729.1X), and prescribed pregabalin, venlafaxine, duloxetine, milnacipran, or combination therapy (venlafaxine/duloxetine/milnacipran with pregabalin) during July 1, 2007 – June 30, 2010. We specifically selected individuals whose FMS diagnosis preceded medication initiation in order to increase the reliability of their FMS diagnosis. We did not select individuals who were naïve to all 4 medications prior to the index-date; however, use of these medications during the 12-month pre-index period was considered for inclusion in propensity score models. We also specifically selected individuals with 12 months of SHP enrollment during the pre- and post-index periods. Exclusion criteria consisted of those having less than 31 total drug supply days for the medication(s) of interest of during the 12-month post-index period, due to their inadequate medication use and/or adherence during

this follow-up period.⁴³ Additionally, to reduce indication bias and ensure that medications of interest were used for treating FMS and not other comorbidities, enrollees with an index medication of pregabalin and any pre-index period claims containing an *ICD-9-CM* diagnosis code for epilepsy (345.XX, 780.39), post-herpetic neuralgia (053.1X), or diabetic peripheral neuropathy (357.2, 250.6X) were excluded. Additionally, patients with an index medication of milnacipran, duloxetine, or venlafaxine and diagnostic evidence of depression (*ICD-9-CM* 290.21, 292.84, 296.20–296.XX, 298.0, 300.4, 309.0, 309.1) were excluded, and patients with an index medication of venlafaxine were also excluded if they had evidence of migraine or tension headache disorders (*ICD-9-CM* 307.81, 346.XX, 784). Patients had to possess at least 2 claims for one of these comorbidities (with the *ICD-9-CM* diagnosis code in any position) for that comorbidity to be counted, to increase the reliability of the diagnosis. Sample selection criteria are shown in a flowchart in Figure 1.

Study Measures

The population's baseline characteristics were described, including age at medication initiation, year of index date, gender, and time from first FMS diagnosis to medication initiation. Presence of comorbidities (Appendix 1) during the 12-month pre-index period was estimated, including the top 10 FMS-related conditions and symptoms of interest as noted by Silverman et al.,⁴⁷ the total number of these FMS-related conditions and symptoms, select chronic pain conditions,⁴⁸ and the Charlson Comorbidity Index.⁴⁹ Concomitant medications^{39,48} (Appendix 2) were evaluated as any patient use (yes/no) of other pain or FMS-related prescription medications during the 12-month pre- and post-index periods, including short-acting opioids, long-acting opioids, first generation anticonvulsants, other second generation anticonvulsants, tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), selective serotonin-norepinephrine reuptake inhibitors (SNRIs), cyclo-oxygenase-2 specific and nonspecific nonsteroidal anti-inflammatory drugs (COX-2/NSAIDs), tramadol, tetracyclic and miscellaneous antidepressants (TCAs), topical agents approved for neuropathic pain, triptans and other antimigraines, attention deficit hyperactivity disorder (ADHD) drugs, benzodiazepines, sedatives/hypnotics, and muscle relaxants.

Medication adherence was evaluated according to the medication possession ratio (MPR) of the initiated prescription medication during the 12-month post-index period, and the MPR was calculated by totaling the drug days-supply and dividing it by the fixed interval of 365 days for follow-up.^{50,51} Calculated MPRs in the study sample ranged from 0.08 (for patients having 31 days supply during the post-index period) up to 1.0. Patients having MPR 0.8 was determined, indicating high adherence.^{51,52} Lastly, total supply days of therapy for each medication group were ascertained.

Healthcare costs were evaluated as total expenditures (patient + deductible + SHP payments) during the 12-month pre- and post-index periods. The following expenditure outcomes were estimated: total all-cause medical, total inpatient and/or outpatient, total prescription medications, total pain/FMS-related prescription medications, and total initiated prescription medication therapy.

Statistical Analysis

All analyses were conducted using SAS ® Proprietary Software, Version 9.4.⁵³ Descriptive statistics of patient characteristics and the measures of interest were performed, and chi-square and Wilcoxon tests were used in these analyses to test for subgroup differences in categorical and continuous variables, respectively. The threshold for statistical significance was set at 0.05, using two-sided *p-values*. Propensity score methods of inverse probability of receiving treatment weights (normalized by the mean weight) were used to control for selection bias due to differing demographic and clinical characteristics prior to baseline for each patient group. Four separate propensity score models were estimated based on factors that predicted the prescription medication initiation group: combination medication versus (1) duloxetine, (2) milnacipran, (3) venlafaxine, and (4) pregabalin monotherapy. The analysis covariates comprised those that have shown significant associations with the propensity of medication choice in FMS patients. The following baseline and 12 month pre-index period characteristics were included: age (at index date), year (of index date), time from first FMS diagnosis to index date (years), gender, Charlson Comorbidity Index,⁴⁹ use (yes/no) of concomitant pain/FMS-related prescription medications, total FMS-related conditions and symptoms,⁴⁷ and presence (yes/no) of other chronic pain comorbidities.⁴⁸ Propensity scores were produced based on the probability of combination medication selection (duloxetine/milnacipran/venlafaxine with pregabalin).

Outcome 1 – Medication adherence—Comparisons of SNRI data were made for combination medication versus monotherapy of duloxetine, venlafaxine and milnacipran, while pregabalin data was evaluated for the fourth comparison. Logistic regression models were used assess differences in likelihood of having high adherence (MPR ≥ 0.8) between the medication groups (combination therapy versus duloxetine, milnacipran, venlafaxine, and pregabalin monotherapy). Lastly, differences in days of medication therapy were evaluated using negative binomial regression models.

Outcome 2 – Healthcare Costs—Differences in post-index healthcare expenditure outcomes (all-cause medical, inpatient and/or outpatient, all prescription medications, pain/FMS-related prescription medications, initiated prescription medication therapy) between the medication groups (combination therapy versus duloxetine, milnacipran, venlafaxine, and pregabalin monotherapy) were evaluated using generalized linear models (GLMs) with a log-link and gamma distributions that controlled for pre-index healthcare expenditures specific to the outcome being evaluated.

Results

Using our study inclusion criteria, the following medication initiation groups of FMS patients were identified: 1274 for duloxetine, 286 for milnacipran, 753 for venlafaxine, 1122 for pregabalin, and 156 for combination. After applying exclusions, the final analytical study population comprised 713 for duloxetine, 131 for milnacipran, 272 for venlafaxine, 665 for pregabalin, and 100 for combination therapy groups (Figure 1).

Baseline and Pre-Index Patient Characteristics

Baseline demographic and clinical characteristics of the patient cohorts are displayed in Tables 1 through 3. The median age at prescription medication initiation was 52.00 years, and the median time from the initial FMS claim until prescription medication initiation was 1.74 years. Patients were predominately female (82%), and year of prescription medication initiation comprised 17% during 2007, 31% during 2008, 32% during 2009, and 19% during 2010. Median direct healthcare expenditures during the pre-index period according to resource category included \$10034 for all-cause medical, \$6249 for inpatient and/or outpatient services, \$2569 for all prescription medications, and \$457 for other pain/FMS-related prescription medications, Table 1.

The median Charlson Comorbidity Index was 0 during the pre-index period, and the median for total FMS-related conditions and symptoms was 1.00. The highest proportion were diagnosed with muscle pain (62%), followed by nervousness (22%), fatigue (18%), abdominal pain (17%), headache (15%), and insomnia (13%); less than 5% had depression, irritable bowel syndrome, muscle weakness, and thinking or remembering problems. About one third of patients had one FMS-related condition or symptom (36%), while 25% had 2, 13% had 3, and 7% had 4 or more. The most common chronic pain-related comorbidities included osteoarthritis and other arthropathies (34%), low back pain (28%), rheumatism – excluding the back (32%), other musculoskeletal pain conditions (28%), and back and neck pain with neuropathic involvement (21%), Table 2.

A high burden of pain/FMS-related concomitant prescription medication use characterized the patient cohorts during the pre-index period, Table 3. More than half (58%) were prescribed short acting opioids (SAOs), and considerably high proportions were prescribed NSAIDs (47%), benzodiazepines (39%), muscle relaxants (38%), SSRIs (36%), and/or sedatives/hypnotics (29%). Additionally, there were moderate usages of tramadol (19%), anticonvulsants other than pregabalin (15%), and antidepressants other than SSRIs and SNRIs (19%).

Medication Adherence by Prescription Therapy Group

Our results showed that proportions of each prescription medication cohort with high medication adherence (MPR ≥ 80%) included 43.00% for SNRI among combination therapy users, 34.00% for pregabalin among combination therapy users, 44.74% among duloxetine users, 31.30% for milnacipran users, 33.46% for venlafaxine users, and 22.11% for pregabalin users (Table 4). The odds of high SNRI adherence was 39% higher for the combination therapy cohort (OR=1.39, 95% CI: 1.05–1.83) compared to the duloxetine cohort, while the odds of high SNRI adherence was 69% higher for the combination therapy cohort compared to the milnacipran cohort (OR=1.69, 95% CI: 0.97–2.98). Also, the odds of high SNRI adherence was 115% higher for the combination therapy cohort compared to the venlafaxine cohort (OR=2.15, 95% CI: 1.42–3.27). Lastly, the odds of high pregabalin adherence was 120% higher for the combination therapy cohort (OR=2.20, 95% CI: 1.60–3.02).

The mean days medication supply among the duloxetine cohort was 242.09 ± 106.38 (range: 35–365), while for the milnacipran cohort it was 201.49 ± 106.86 (range: 50–365). For the venlafaxine cohort the mean days medication supply was 205.99 ± 110.75 (range: 31–365), and the pregabalin cohort had days medication supply of 172.28 ± 108.76 (range: 31–365). Among the combination therapy cohort the mean for days supply of duloxetine/milnacipran/venlafaxine was 240.29 ± 106.86 (31–365); while, the mean for days of pregabalin therapy was 224.06 ± 104.34 (31–365), Table 5. The rates for prescription medication therapy days were significantly higher among the combination cohort compared to the pregabalin and venlafaxine cohorts. The rate of SNRI therapy days was 8% higher for the combination cohort (rate ratio: 1.08, 95% CI: 1.01–1.16) compared to the duloxetine cohort, while the rate of SNRI therapy days was 13% higher for the combination cohort compared to the milnacipran cohort (rate ratio: 1.13, 95% CI: 1.13–1.31). Also, the rate of SNRI therapy days was 23% higher for the combination cohort compared to the venlafaxine cohort (rate ratio: 1.23, 95% CI: 1.10–1.28). Lastly, the rate of pregabalin therapy days was 32% higher for the combination cohort (rate ratio: 1.32, 95% CI: 1.21–1.43).

Post-Index Adjusted Healthcare Costs by Prescription Therapy Group

Figure 2 displays estimates for the adjusted mean healthcare expenditures during the post-index period, with comparisons derived from multivariable GLMs applying propensity score inverse probability of treatment weights, adjusted for pre-index expenditures. Total healthcare, all pharmacy, and initiated prescription medication therapy expenditures were significantly higher for the combination therapy cohort compared to the duloxetine (\$26291, \$6266, and \$2487, versus \$17190, \$4153, and \$1253, respectively), milnacipran (\$33638, \$7590, and \$2356, versus \$22886, \$5159, and \$808, respectively), and venlafaxine (\$26586, \$6569, and \$2640, versus \$16857, \$3618, and \$909, respectively) cohorts. However, there were no significant differences observed for total healthcare expenditures between the combination cohort compared to the pregabalin cohort (\$25668 versus \$23568). Expenditures for concomitant pain/FMS-related prescription medications were also significantly higher for the combination cohort compared to the duloxetine (\$1028 versus \$712), milnacipran (\$1285 versus \$947), and venlafaxine (\$967 versus \$573) cohorts. Meanwhile, there were no significant differences observed for concomitant pain/FMS-related prescription medication expenditures for the combination cohort compared to the pregabalin (\$1015 versus \$940) cohort.

Discussion

We hypothesized that medication adherence would be higher, while post-index direct healthcare expenditures use would be lower, for patients initiating combination medication therapy (milnacipran/duloxetine/venlafaxine with pregabalin). Our rationale was that patients who initiate combination therapy would be more likely to have comprehensive symptom control and, therefore, have higher medication adherence, decreased concomitant medication use, and fewer medical visits as well as hospital admissions. Our regression results demonstrated that medication adherence was superior for patients initiating combination therapy as opposed to monotherapy with venlafaxine, duloxetine, or pregabalin. These results suggest that patients in the combination therapy cohort were better able to

achieve a therapeutic effect given the complementary pharmacologic activities of this treatment regimen, specifically a SNRI with pregabalin.

Our adherence results for duloxetine and pregabalin monotherapy initiators are comparable to previous retrospective cohort studies. Zhao and colleagues⁴³ reported high medication adherence for 46.5% of duloxetine users and 26.4% of pregabalin users. In a separate study Zhao and colleagues reported that less than one third of duloxetine initiators had high adherence.⁴⁰ In a recent study Liu and colleagues⁵⁴ reported high medication adherence for 20% of milnacipran users, 38% of duloxetine users, and 24% of pregabalin users. Sun and colleagues⁴⁴ reported high adherence among 45.1% of duloxetine users and 29.4% of pregabalin users. Wu and colleagues⁵⁵ examined medication adherence among duloxetine initiators according to average daily dose (ADD, in mg) and observed high adherence for 17.5% among those with <30mg, 16.4% for 30mg, 36.7% for 31–59mg, 31.7% for 60mg, and 41.1% for >60mg.

Contrary to our hypothesis, expenditures for all healthcare as well as all prescriptions filled were significantly higher for the combination therapy cohort. Our results for total healthcare and all pharmacy expenditures among the duloxetine and pregabalin cohorts are comparable to previous retrospective cohort studies with similar inclusion and exclusion criteria and, additionally, analogous propensity score methods to control for selection bias.^{34,41} The increased expenditures for all healthcare among the combination therapy cohort were partially driven by the increased expenditures for all prescriptions filled, as well as the increases in expenditures observed for inpatient and/or outpatient services. Concurrently, the increased expenditures for all prescriptions filled were mainly driven by the increased expenditures for the use of combination therapy (milnacipran/duloxetine/venlafaxine with pregabalin) versus monotherapy with duloxetine, milnacipran, venlafaxine, or pregabalin. This increase can also be partially explained by the higher medication adherence among the combination therapy cohort; more prescriptions filled during a year produces greater medication expenditures.

Limitations

Several limitations of our study are worth noting. Our study design was retrospective; therefore, causality cannot be assessed. We also made use of an administrative health claims database, which may contain errors in coding and/or billing items. We used *ICD-9-CM* codes for diagnoses of FMS and comorbidities of interest, and these were not validated with medical chart review procedures. However, any errors in coding and/or billing items are expected to be non-differential across our study groups.

We were unable to determine whether patients filled their prescriptions specifically for FMS. However, our inclusion criteria did require that the index-date for each medication cohort followed the date of FMS diagnosis. We limited our patient population to individuals with no medication group prescription coverage for 90 days prior to their index-date, consistent with previously reported retrospective cohort studies^{40,43,55–58} as well as the prerequisite of a medication wash-out period before enrollment in the clinical trials. Although, patients may still have had access to medications due to free samples and/or an unexhausted use of previously filled prescriptions. Also, individuals who were previous users of the medication

type captured at their index-date may have been more, or perhaps less, likely to respond to the medication during follow-up. The impact of these phenomena is unknown, especially without data regarding patterns of symptom severity during the pre- and post-index periods. However, we did use methods to control for potential selection bias by including propensity score methods (based on pre-index patient characteristics, presence of FMS- and pain-related comorbidities, and prescriptions used) in regression models.⁵⁹

Our medication adherence measures were based on prescriptions being filled and the generation of pharmacy claims, which may not indicate true consumption. However, no method of examining medication use is precise,^{60–64} and we do not expect any differential errors between groups. Similar to the pre-index period, patients may have had access to medications in the post-index period from free samples and/or unexhausted prescriptions that were filled, particularly if patients were unable to take the medication as prescribed and instead made use of the extra pill coverage during a titration process.⁵⁹ A related limitation is that administrative claims data cannot capture exactly how patients take medications on a daily basis, which may influence their adherence to therapy.

As with any naturalistic study that is neither interventional nor randomized, the impact of possible selection bias on our results remains unknown. We did control for this phenomenon as best as possible by applying propensity score methods of inverse probability of treatment weights. Nonetheless, there is a potential treatment channeling effect⁵⁹ for combination medication being used in patients with greater FMS severity. Patients with more severe FMS may be less likely to respond to therapy and, consequently, more likely to discontinue treatment due to lack of response. Alternatively, those with more severe FMS may be more likely to adhere to treatment regimens that prove to be clinically beneficial. The significantly greater expenditures for concomitant pain/FMS medication among the combination medication cohort compared to the duloxetine, milnacipran, and venlafaxine cohorts is suggestive of some residual confounding due to greater FMS severity experienced by the combination medication cohort. However, the differences in these expenditures were small, and the impact on our results is not likely to be appreciable.

There is the potential for unmeasured confounding as well as other direct and indirect costs related to FMS, factors which cannot be captured by administrative health claims data. We did not have information regarding over-the-counter medication consumption, which may further complicate the risks with high use of NSAIDs, and also may impact medication adherence. Use of alternative medicine resources (such as acupuncture and massage therapy), which may have their own influence on medication adherence, are also underrepresented due to lack of reimbursement from the SC SHP. Other patient factors that we were unable to consider for their potential impact on medication adherence included use of nutritional supplements, lifestyles, exercise, income, education, marital status, race/ethnicity, family/friend support, and employment status.

Our study period was coincided with the time that milnacipran was penetrating the market post FDA approval, reflected by the relatively small sample size of our milnacipran and combination therapy cohorts. Future studies are needed to assess the additional uptake of milnacipran in more recent years. Our inclusion criteria also required 12 months continuous

enrollment in the SC SHP during the pre- and post-index periods, which may limit generalizability of results. Lastly, our results may not be generalizable to other populations, especially outside of South Carolina and those enrolled in Medicaid, Medicare without private insurance, or other public insurance plans.

Conclusions

As long as medication adherence can be improved, better patient outcomes are more likely for medications associated with high adherence. Our findings have considerable implications for multiple domains of improved patient outcomes with the use of combination therapy, such as symptom severity and health-related quality of life (HRQoL), which may explain the increased medication adherence observed for this cohort. Alternatively, patients in the combination therapy cohort may have achieved and maintained a therapeutic effect from lower doses of one or both medications (given their complementary pharmacologic activities), and they, therefore, had significantly higher medication adherence due to better tolerance of potential medication side-effects. However, we could not directly examine FMS symptom severity, functional limitations, disability, HRQoL, or medication side-effects during the post-index period, all of which could affect medication adherence. Naturalistic prospective studies of medication adherence among patient populations with FMS are warranted to appropriately examine causal relationships with these clinical outcomes. Furthermore, while we observed increased direct healthcare costs among the combination therapy cohort, higher medication adherence may lead to indirect costs benefits, including work disability and absenteeism, outcomes not captured by healthcare claims databases.

Notably, no single treatment has proven effective for relieving the full range of FMS symptoms nor do the current treatments benefit all patients. Patients may first present with one symptom (such as pain) as most pronounced; and later, with reductions in pain, other symptoms may become more prominent (such as insomnia, fatigue, and cognitive difficulties), which progressively suggests the need for combination pharmacotherapy.³² The use of duloxetine/milnacipran/venlafaxine with pregabalin has complementary mechanisms of pharmacological action, and, when done sequentially and with cautious titration procedures, is likely to be safe and well tolerated for patients. Clinical practice guidelines for managing FMS symptoms should continue to evolve with newly available treatment options as well as the introduction of evidence from population-based naturalistic studies. Our results are suggestive of important clinical benefits for patients with FMS who include duloxetine/milnacipran/venlafaxine with pregabalin combination pharmacotherapy as part of their multi-modal treatment regimen.

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Appendix 1: Comorbidities of Interest

Top 10 FMS-related conditions[*]:	
muscle pain	720.1, 723.1, 723.9, 724.1, 724.2, 724.5, 726.19, 726.32, 726.39, 726.5, 726.71, 726.72, 726.79, 726.90, 729.1
headache/migraine	307.81, 346.XX, 784
irritable bowel syndrome	564.1
pain/cramps in abdomen	789.0X
insomnia	307.4X, 333.99, 780.5X
fatigue/tiredness	780.71, 780.79
muscle weakness	728.87
thinking or remembering problem	780.93
depression	290.21, 292.84, 296.20–296.XX, 298.0, 300.4, 309.0, 309.1
nervousness	293.84, 300.0X–300.3, 309.21, 309.81, 780.4, 785.0–785.1, 786.01, 786.05, 786.09
Chronic Pain Conditions[†]:	
lupus & other diffuse connective tissue diseases	710.0, 710.1, 710.2, 710.3, 710.4, 710.5, 710.8, 710.9
rheumatoid arthritis	714.0, 714.1, 714.2
osteoarthritis and other arthropathies	711.XX, 712.XX, 713.X, 714.4X, 714.8X, 714.9X, 716.XX, 717.XX, 718.XX, 719.XX
low back pain	720.0, 720.1, 720.2, 721.3, 722.10, 722.32, 722.5, 722.83, 722.93, 724.00, 724.02, 724.2, 724.5, 724.6, 724.70, 724.71, 724.79, 738.4, 739.3, 739.4, 756.11, 756.12, 805.4, 805.6, 846.0, 846.1, 846.2, 846.3, 846.8, 846.9, 847.2, 847.3, 847.4
back and neck pain – other than 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, 722.6, 722.80, 722.81, 722.82, 722.90, 722.91, 722.92, 723.X (except 723.4), 724.01, 724.1, 724.8, 724.9, 737.10, 737.11, 737.12, 737.19, 737.20, 737.21, 737.22, 737.29, 737.30, 756.10, 756.13, 756.14, 756.15, 756.16, 756.17, 756.19, 805.8, 847.9
rheumatism – excluding the back	725–728.9, 729.3–729.9
other musculoskeletal pain conditions (those not previously captured)	730.00–739.X
carpal tunnel syndrome	354.X
causalgias	337.2X, 354.4, 355.71, 355.9
neuritis radiculitis – unspecified	729.2
facial neuropathies/neuralgias	350.1, 350.2
back and neck pain with neuropathic involvement	721.1, 721.41, 721.42, 721.91, 722.7X, 723.4, 724.3, 724.4
other neuropathic pain conditions	353.6, 337.1, 337.9, 344.6, 353.0, 353.1, 353.8, 353.9, 354.1, 354.2, 354.3, 354.5, 354.8, 354.9, 355.0, 355.1, 355.2, 355.3, 355.4, 355.5, 355.6, 355.79, 355.8, 357.1, 357.3, 357.4, 357.5, 357.6, 357.7, 357.8, 357.9

^{*} As referenced in Silverman et al.⁴⁷

[†] As referenced in Gore et al.⁴⁸

Appendix 2: Concomitant Medications of Interest

Concomitant Medications	
<i>Short-Acting Opioids (SAOs):</i>	codeine, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, morphine sulfate, oxycodone, oxymorphone, propoxyphene, tapentadol
<i>Long-Acting Opioids (LAOs):</i>	buprenorphine, controlled release oxycodone, extended release hydromorphone, extended release morphine, extended release oxymorphone, extended release tapentadol, methadone, transdermal fentanyl
<i>1st Generation Anticonvulsants:</i>	carbamazepine, divalproex, ethosuximide, phenytoin, primidone, valproate sodium, valproic acid
<i>2nd Generation Anticonvulsants:</i>	gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate, zonisamide
<i>Tricyclic Antidepressants (TCAs):</i>	amitriptyline and its combinations, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine
<i>Selective Serotonin Reuptake Inhibitors (SSRIs):</i>	citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline
<i>Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs):</i>	duloxetine, desvenlafaxine, nefazodone, venlafaxine
<i>Cyclo-Oxygenase-2 Specific (COX-2) & Nonspecific Nonsteroidal Anti-Inflammatory Drugs (NSAIDs):</i>	celecoxib, diclofenac, etodolac, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac tromethamine, mefenamic acid, meloxicam, nabumetone, naproxen, naproxen sodium, oxaprozin, piroxicam, sulindac, tolmetin sodium, salsalate
<i>Tramadol</i>	tramadol
<i>Tetracyclic (TeCAs) & Miscellaneous Antidepressants:</i>	bupropion, isocarboxazid, maprotiline, mirtazapine, phenelzine, selegiline, tranlycypromine, trazodone
<i>Topical Agents Approved for Neuropathic Pain:</i>	capsaicin, lidocaine patch
<i>Topical Corticosteroids:</i>	betamethasone, desoximetasone
<i>Injectables:</i>	bupivacaine, lidocaine
<i>Triptans & Other Antimigraines:</i>	almotriptan, dihydroergotamine, eletriptan, ergotamine, frovatriptan, methysergide, naratriptan, rizatriptan, sumatriptan, zolmitriptan, migraine combinations
<i>Attention Deficit Hyperactivity Disorder (ADHD) Drugs:</i>	amphetamine-dextroamphetamine, atomoxetine, dextmethylphenidate, dextroamphetamine, methamphetamine, methylphenidate, modafinil, pemoline
<i>Benzodiazepines:</i>	alprazolam, buspirone, chlordiazepoxide, clonazepam, clorazepate, diazepam, halazepam, lorazepam, oxazepam
<i>Sedatives/Hypnotics:</i>	amobarbital, amobarbital/secobarbital, aprobarbital, barbital/hyoscy/passifl/valerian, butabarb/phenobarb/secobarb, butabarbital, chloral hydrate, estazolam, eszopiclone, ethchlorvynol, ethinamate, flurazepam, glutethimide, mephobarbital, meprobamate, metharbital, methypylon, midazolam, paraldehyde, pentobarbital, phenobarbital, prazepam, pyrilamine/pentobarbital, quazepam, ramelteon, secobarbital, temazepam, triazolam, zaleplon, zolpidem
<i>Muscle Relaxants:</i>	carisoprodol, cyclobenzaprine, chlorphenesin, chlorzoxazone, dantrolene, metaxalone, methocarbamol, orphenadrine, baclofen, tizanidine and combinations

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Figure 1.

Derivation of study population, South Carolina Blue Cross Blue Shield State Health Plan (SHP) enrollees with fibromyalgia syndrome (FMS).

Figure 2.

Adjusted mean direct healthcare expenditures during 12 month post-index period for patients with fibromyalgia syndrome (FMS); multivariable regression models with gamma distribution and log-link, adjusted for pre-index expenditures; applying propensity score method of inverse probability of treatment weights (N=1881).

Table 1

Baseline characteristics of South Carolina Blue Cross Blue Shield State Health Plan (SHP) enrollees with fibromyalgia syndrome (FMS) and eligible for analyses according to study inclusion criteria, N=1881.

Characteristic	Milnacipran No=131	Duloxetine No=713	Venlafaxine No=272	Pregabalin No=665	Combination* No=100	Total N=1881
Age at index date	53(47.59)	51(43.57)	50 (41.57)	53(46.58) [‡]	52 (43.57)	52 (44.58)
Years from first FMS diagnosis to index date	3.00 (1.08,4.41)	1.66 (0.58,2.92) [‡]	1.92 (1.00,3.25)	1.58 (0.41,2.67) [‡]	2.21 (0.95,3.50)	1.75(0.59,3.00)
Year of index date	[‡]	[‡]	[‡]	[‡]		
2007	0 (0%)	117 (16%)	44 (16%)	158 (24%)	6 (6%)	325 (17%)
2008	0 (0%)	219(31%)	68 (25%)	264 (40%)	40 (40%)	591 (31%)
2009	75 (57%)	266 (37%)	54 (20%)	172 (26%)	37 (37%)	604 (32%)
2010	56 (43%)	111 (16%)	106 (39%)	721(11 %)	17 (17%)	361 (19%)
Females	120 (92%)	581 (81%)	223 (82%)	525 (79%)	87 (87%)	1536 (82%)
Pre-index healthcare expenditures [‡]						
All-cause medical	\$13460 (\$7399,\$27363)	\$8702 (\$4489,\$17464) [‡]	\$8354 (\$4206,\$17230) [‡]	\$10964 (\$5232,\$22555) [‡]	\$12946 (\$7718,\$24178)	\$10036 (\$4963,\$20410)
Inpatient and/or outpatient	\$8570 (\$3592, \$18752)	\$5759 (\$2122,\$13454) [‡]	\$5736 (\$2263,\$13755) [‡]	\$6817 (\$2572,\$17081)	\$7760 (\$3890,\$16339)	\$6249 (\$2469,\$15162)
All Rx	\$4036 (\$1781,\$6595)	\$2189 (\$959, \$4298) [‡]	\$1827 (\$609,\$3682) [‡]	\$2846 (\$1266,\$5068) [‡]	\$3554 (\$1976,\$7045)	\$2569 (\$1088,\$4768)
Other pain/FMS-related Rx	\$830 (\$256,\$2447)	\$414 (\$86,\$1149) [‡]	\$303 (\$56,\$906) [‡]	\$580 (\$150,\$1524)	\$567 (\$226, \$1681)	\$457 (\$119,\$1322)

All results presented as No(%) for categorical variables or median (IQR) for continuous variables

* Milnacipran/duloxetine/venlafaxine with pregabalin

[‡] Significant p-value 0.05 based on Wilcoxon Rank Sum for continuous variables or Chi-Square for categorical variables; Monotherapy as compared to the combination group

[‡]Total \$ = Patient + deductible + SHP payments

Table 2

Comorbidities during the 12 month pre-index period among patients with fibromyalgia syndrome (FMS), N=1881.

Comorbidities	Milnacipran No=131	Duloxetine No=713	Venlafaxine No=272	Pregabalin No=665	Combination* No=100	Total N=1881
Charlson Comorbidity Index	0 (0.1)	0 (0.1)	0 (0.1) [†]	0 (0.1)	0 (0.1)	0 (0.1)
FMS-related conditions and symptoms (Silverman et al. ⁴⁷) [‡]						
Muscle pain	109 (83%)	419 (59%) [†]	147 (54%) [†]	420 (63%) [†]	80 (80%)	1175 (62%)
Fatigue/tiredness	38 (29%)	138 (19%)	40 (15%)	106 (16%)	21 (21%)	343 (18%)
Insomnia	17 (13%)	92 (13%)	31 (11%)	92 (14%)	18 (18%)	250 (13%)
Depression	0 (0%)	0 (0%)	0 (0%)	69 (10%) [†]	0 (0%)	69 (4%)
Thinking or remembering problem	2 (2%)	3 (<1%)	1 (<1%)	5 (1%)	1 (1%)	12 (1%)
Nervousness	25 (19%)	159 (22%)	69 (25%)	133 (20%)	23 (23%)	409 (22%)
Muscle weakness	2 (2%)	9 (1%)	7 (3%)	16 (2%)	3 (3%)	37 (2%)
Headache	24 (18%)	124 (17%)	0 (0%)	109 (16%)	19 (19%)	276 (15%)
Irritable bowel syndrome (IBS)	5 (4%)	19 (3%)	4 (1%)	23 (3%)	0 (0%)	51 (3%)
Pain/cramps in abdomen	27 (20%) [†]	114 (16%)	52 (19%) [†]	118 (18%) [†]	9 (9%)	319 (17%)
Total FMS-related conditions and symptoms	2 (1.3)	1 (1.2) [†]	1 (0.2) [†]	1 (1.2)	2 (1.2)	1 (1.2)
0	12 (9%)	136 (19%)	73 (27%)	122 (18%)	10 (10%)	353 (19%)
1	50 (38%)	259 (36%)	96 (35%)	241 (36%)	37 (37%)	683 (36%)
2	30 (23%)	188 (26%)	63 (23%)	155 (23%)	29 (29%)	465 (25%)
3	20 (15%)	89 (12%)	33 (12%)	81 (12%)	18 (7%)	241 (13%)
4	19 (15%)	41 (6%)	7 (3%)	66 (10%)	6 (6%)	139 (7%)
Other chronic pain-related comorbidities (Gore et al. ⁴⁸)						
Diffuse connective tissue diseases	5 (4%)	18 (3%)	2 (1%) [†]	23 (3%)	5 (5%)	53 (3%)
Osteoarthritis and other arthropathies	51 (39%)	224 (31%) [†]	75 (28%) [†]	243 (37%)	46 (46%)	639 (34%)
Rheumatoid arthritis	6 (5%)	15 (2%)	7 (3%)	21 (3%)	4 (4%)	53 (3%)
Low back pain	36 (27%)	209 (29%)	69 (25%)	190 (29%)	27 (27%)	531 (28%)
Other back and/or neck pain	23 (18%)	122 (17%) [†]	44 (16%) [†]	115 (17%) [†]	26 (26%)	330 (18%)

Comorbidities	Milnacipran No=131	Duloxetine No=713	Venlafaxine No=272	Pregabalin No=665	Combination* No=100	Total N=1881
Rheumatism, excluding the back	47 (36%)	203 (28%) [‡]	76 (28%) [‡]	237 (36%)	39 (39%)	602 (32%)
Other musculoskeletal pain conditions	37 (28%)	199 (28%)	91 (33%)	181 (27%)	27 (27%)	535 (28%)
Carpal tunnel syndrome	4 (3%)	18 (3%)	4 (1%)	20 (3%)	4 (4%)	50 (3%)
Causalgias	0 (0%) [‡]	6 (1%) [‡]	4 (1%)	4 (1%) [‡]	4 (4%)	18 (1%)
Neuritis radiculitis unspecified	2 (2%)	8 (1%)	5 (2%)	5 (1%)	2 (2%)	22 (1%)
Facial neuropathies/neuralgias	2 (2%)	0 (0%) [‡]	1 (<1%)	4 (1%)	1 (1%)	8 (<1%)
Neuropathic back and/or neck pain	30 (23%)	153 (19%)	51 (19%)	142 (21%)	25 (25%)	401 (21%)
Other neuropathic pain conditions	5 (4%)	22 (3%)	5 (2%)	15 (2%)	3 (3%)	50 (3%)

All results presented as No(%) for categorical variables or median (IQR) for continuous variables

* Milnacipran/duloxetine/venlafaxine with pregabalin,

[‡] Significant p-value 0.05 based on Wilcoxon Rank Sum for continuous variables or Chi-Square for categorical variables; Monotherapy as compared to the combination group.

[‡] Refer to Appendix 1 for a detailed list of *ICD-9-CM* diagnosis codes per comorbidity group.

Use of other pain/FMS-related prescription medications* during 12 month pre-index period among patients with fibromyalgia syndrome (FMS), N=1881.

Table 3

Prescription medication class	Milnacipran No=131	Duloxetine No=713	Venlafaxine No=272	Pregabalin No=665	Combination [†] No=100	Total N=1881
Short acting opioids (SAOs)	83 (63%)	387 (54%) [‡]	148 (54%) [‡]	406 (61%) [‡]	69 (69%)	1093 (58%)
Long acting opioids (LAOs)	7 (5%)	27 (4%) [‡]	9 (3%) [‡]	19 (3%) [‡]	6 (6%)	68 (4%)
Other anticonvulsants:1 st generation	2 (2%)	6 (<1%)	1 (<1%)	14 (2%)	3 (3%)	26 (1%)
Other anticonvulsants:2 nd generation	36 (27%)	76 (11%)	27 (10%)	119 (18%)	19 (19%)	277 (15%)
Tricyclic antidepressants (TCAs)	25 (19%)	59 (8%) [‡]	21 (8%)	69 (10%)	16 (16%)	190 (10%)
Serotonin-selective reuptake inhibitors (SSRIs)	42 (32%)	289 (40%)	102 (38%)	197 (30%) [‡]	38 (38%)	668 (36%)
Other serotonin-norepinephrine reuptake inhibitors (SNRIs)	5 (4%)	3 (<1%)	3 (1%)	4 (<1%)	1 (1%)	16 (<1%)
Other antidepressants	33 (25%)	113 (16%) [‡]	53 (19%)	128 (19%)	24 (24%)	351 (19%)
Non-steroidal anti-inflammatory drugs (NSAIDs)	64 (49%) [‡]	311 (43%) [‡]	93 (34%) [‡]	351 (53%) [‡]	63 (63%)	882 (47%)
Tramadol	28 (21%)	118 (17%) [‡]	27 (10%) [‡]	161 (24%)	25 (25%)	359 (19%)
Dopamine agonists	3 (2%)	21 (3%)	5 (2%)	28 (4%)	4 (4%)	61 (3%)
Topicals for neuropathic pain	8 (6%)	38 (5%)	16 (6%)	39 (6%)	6 (6%)	107 (6%)
Topical corticosteroids	5 (4%)	22 (3%)	10 (4%)	19 (3%)	0 (0%)	56 (3%)
Injectables	1 (1%)	1 (<1%)	0 (0%)	4 (<1%)	1 (1%)	7 (<1%)
Antimigraines	16 (12%)	86 (12%)	19 (7%)	99 (15%)	17 (17%)	237 (13%)
Stimulant medications	12 (9%)	42 (6%)	15 (6%)	50 (8%)	7 (7%)	126 (7%)
Benzodiazepines	50 (38%)	273 (38%)	99 (36%)	269 (40%) [‡]	47 (47%)	738 (39%)
Sedatives/hypnotics	42 (32%)	197 (27%) [‡]	70 (26%) [‡]	202 (30%) [‡]	41 (41%)	552 (29%)
Muscle relaxants	63 (48%)	248 (35%) [‡]	68 (25%) [‡]	294 (44%)	47 (47%)	720 (38%)

* Refer to Appendix 2 for a detailed list of medications per prescription class.

[‡] Milnacipran/duloxetine/venlafaxine with pregabalin.

[‡] Significant p-value 0.05 based on Wilcoxon Rank Sum for continuous variables or chi-square for categorical variables: Monotherapy as compared to the combination group.

Table 4

Likelihood of high medication adherence (medication possession ratio [MPR] ≥ 80%) during 12 month post-index period for patients with fibromyalgia syndrome (FMS) using logistic regression models with the propensity score method of inverse probability of treatment weights (N=1881).

Parameters & Referent Cohort	Proportion MPR ≥ 80%	Odds Ratio (95% CI)	p-value
High adherence: SNRI [*]			
Combination [†] therapy (No=100)	43.00%	1.39 (1.05–1.83)	0.02
Duloxetine (No=713)	44.74%	1.00	---
High adherence: SNRI [*]			
Combination [†] therapy (No=100)	43.00%	1.69 (0.97–2.98)	0.07
Milnacipran (No=131)	31.30%	1.00	---
High adherence: SNRI [*]			
Combination [†] therapy (No=100)	43.00%	2.15 (1.42–3.27)	0.0003
Venlafaxine (No=272)	33.46%	1.00	---
High adherence: Pregabalin [*]			
Combination [†] therapy (No=100)	34.00%	2.20 (1.60–3.02)	<0.0001
Pregabalin (No=665)	22.11%	1.00	---

^{*} Comparisons of SNRI data were made for combination medication therapy versus monotherapy of duloxetine, venlafaxine, and milnacipran, while pregabalin data was evaluated for the fourth comparison.

[†] Milnacipran/duloxetine/venlafaxine with pregabalin

Table 5

Days of prescription medication therapy during 12 month post-index period for patients with fibromyalgia syndrome (FMS) using negative binomial regression models with the propensity score method of inverse probability of treatment weights (N=1881).

Parameters & Referent Cohort	Days of Rx Mean $\pm$ SD	Rate Ratio (95% CI)	<i>p-value</i>
Total Prescription Supply: SNRI *			
Combination [†] therapy (No=100)	240.49 $\pm$ 106.86	1.08 (1.01–1.16)	0.03
Duloxetine (No=713)	242.09 $\pm$ 106.38	1.00	---
Total Prescription Supply: SNRI *			
Combination [†] therapy (No=100)	240.49 $\pm$ 106.86	1.13 (0.97–1.31)	0.13
Milnacipran (No=131)	201.49 $\pm$ 111.14	1.00	---
Total Prescription Supply: SNRI *			
Combination [†] therapy (No=100)	240.29 $\pm$ 106.86	1.23 (1.10–1.28)	0.0003
Venlafaxine (No=272)	205.99 $\pm$ 110.75	1.00	---
Total Prescription Supply: Pregabalin *			
Combination [†] therapy (No=100)	224.06 $\pm$ 104.34	1.32 (1.21–1.43)	<0.0001
Pregabalin (No=665)	172.28 $\pm$ 108.76	1.00	---

* Comparisons of SNRI data were made for combination medication therapy versus monotherapy of duloxetine, venlafaxine, and milnacipran, while pregabalin data was evaluated for the fourth comparison.

[†] Milnacipran/duloxetine/venlafaxine with pregabalin