Therapeutic and Subtherapeutic Dosing of Pregabalin: Medication Adherence, Healthcare Resource Utilization, and Costs

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ABSTRACT

Objectives: To compare adherence and direct medical costs with therapeutic and subtherapeutic doses of pregabalin for the treatment of fibromyalgia (FM), post-herpetic neuralgia (PHN), and painful diabetic peripheral neuropathy (pDPN).

Study Design: Retrospective database analysis.

Methods: Adult patients (≥18 years old) newly given pregabalin for FM, PHN, or pDPN between October 1, 2007, and October 1, 2008, were identified using the MarketScan Database. Therapeutic and subtherapeutic doses were based on the FDA-approved label. Outcomes, including proportion of days covered [PDC], persistence, and direct medical costs, were compared between dose categories using χ^2 tests, *t* tests, and multivariable analyses adjusting for clinical and demographic variables.

Results: Of 21,768 patients (70% FM, 7% PHN, 23% pDPN), 13.1% (n = 2873) were given therapeutic doses of pregabalin. Within each of the indications, the average daily subtherapeutic dose was significantly lower than the therapeutic dose (*P* <.0001). Relative to patients with subtherapeutic doses, patients with therapeutic doses had higher PDC, percent with PDC ≥80%, greater persistence, and were more likely to be on therapy after 1 year. Mean total direct costs (per patient per 6 months) were similar between therapeutic and subtherapeutic doses within each indication despite significantly higher therapeutic pharmacy costs (FM $3560 vs $3041, *P* <.0001; PHN $2352 vs $2333, *P* = .08; pDPN $4020 vs $3524, *P* <.0001).

Conclusions: Among the indications, patients with pregabalin were frequently given a subtherapeutic dose, which was associated with poorer adherence. Additionally, pharmacy costs were significantly higher with therapeutic relative to subtherapeutic dosing, but nevertheless resulted in comparable total direct medical costs between dose groups, suggesting that prescribing pregabalin at its recommended therapeutic dose may increase adherence without increasing cost relative to subtherapeutic dosing.

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Fibromyalgia (FM), post-herpetic neuralgia (PHN), and painful diabetic peripheral neuropathy (pDPN) are chronic pain conditions that are characterized by substantial patient and economic burdens resulting from reduced function and quality of life, and increased healthcare resource utilization and costs.[1-4] These conditions, which are challenging from the therapeutic perspective, share similar pharmacologic treatment modalities.[5] Among these modalities, pregabalin is recommended as first-line therapy for all 3 conditions.[5-7]

Pregabalin is a high-affinity ligand of alpha2-delta (α2-δ) subunits of voltage-gated calcium channels in the central nervous system.[8] In addition to anticonvulsant properties, pregabalin has demonstrated therapeutic efficacy for FM, PHN, and pDPN, and has been approved by the US Food and Drug Administration (FDA) for the treatment of these painful conditions.[9]

Retrospective database analyses have suggested that in clinical practice pregabalin is often prescribed and used at doses that are subtherapeutic.[10-13] Consistent subtherapeutic dosing of pregabalin may not only account for the differences in dosing patterns reported between pregabalin and duloxetine in patients with FM,[13] but may also result in reduced adherence. Such reduced adherence can also lead to higher healthcare resource utilization and costs relative to therapeutic dosing, as has been shown for duloxetine in patients with FM and pDPN.[14-17] Since the impact of pregabalin dose levels on adherence and direct medical costs has not been evaluated, the purpose of the current study was to compare these parameters between patients given therapeutic and subtherapeutic doses of pregabalin for the treatment of FM, PHN, and pDPN.

METHODS

Patients ≥18 years of age with at least 1 claim for FM (*International Classification of Diseases, Ninth Revision, Clinical Modification* [*ICD-9-CM*] code 729.1), pDPN (*ICD-9-CM* codes 250.6, 357.2), or PHN (*ICD-9-CM* code 053.1) between October 1, 2007, and October 1, 2008, and who

were newly placed on pregabalin (index event) were identified from the MarketScan Commercial Claims and Encounters and Medicare Supplemental Databases (Thomson Reuters). These databases consist of complete longitudinal records of inpatient services, outpatient services, long-term care, and prescription drug claims covered under a variety of fee-for-service and capitated health plans that include exclusive provider organizations, preferred provider organizations (PPOs), point-of-service (POS) plans, indemnity plans, and health maintenance organizations (HMOs). The data are nationally representative, quality controlled, and HIPAA (Health Insurance Portability and Accountability Act of 1996)-compliant.

Continuous enrollment 6 months preindex and 12 months postindex was required. Patients with epilepsy were excluded, as were patients with a pregabalin prescription at any time during the 6 months prior to the index date. Since the objective of the study was to examine therapeutic and subtherapeutic dosing only, we made the decision to exclude doses exceeding the FDA-approved daily doses of pregabalin (>600 mg at any point in time during the follow-up period for PHN, >300 mg for pDPN, and >450 mg for FM).

Included patients were stratified by therapeutic and subtherapeutic doses of pregabalin based on the label approved for each indication by the FDA.[9] A dose was considered subtherapeutic if the average daily dose was <300 mg daily in patients with FM, PHN, and pDPN; therapeutic doses were ≥300 mg daily for each of these indications.

Among patients who had at least 2 pregabalin prescriptions, adherence parameters and direct medical costs were evaluated for each indication. Adherence parameters included proportion of days covered (PDC), defined as the number of days with the drug divided by the number of days in the study period; proportion of patients with PDC ≥80%; persistence with therapy, defined as the number of consecutive days from the index date to the start of the first medication gap larger than 15 consecutive days during the 12 months following therapy initiation; and proportion of patients remaining on therapy at 1 year.[18] Direct medical costs were categorized as outpatient, inpatient, and pharmacy costs; total direct costs were also estimated.

Demographic variables were compared using χ^2 and *t* tests. Analyses of outcomes were performed controlling for gender, age, region, plan type, and the Carlson Comorbidity Index (CCI). The PDC and average dose were analyzed using general linear models (GLMs). Persistence and time to discontinuation were analyzed using Cox proportional hazards models, and Kaplan-Meier estimated curves are provided.[19,20] Resource utilization and cost were estimated using GLM and included preindex costs.[19,20] All analyses were conducted using SAS version 9.2 (SAS Institute, Inc, Cary, North Carolina) and a *P* value <.05 was considered statistically significant.

PRACTICAL IMPLICATIONS

Increasing the dose of pregabalin to therapeutic levels may lead to greater adherence parameters, healthcare resource use, and cost among those given pregabalin for FDA-approved indications.

- Compared with subtherapeutic dosing, therapeutic dosing generally led to better adherence.
- Despite higher pharmacy cost among the therapeutic dosing cohort, no differences in total healthcare spend existed between the groups. The higher pharmacy costs were offset by lower medical spend in the therapeutic cohort.

RESULTS

A total of 21,768 patients were identified from the database for inclusion in the analysis. The demographic characteristics of patients for whom therapeutic and subtherapeutic doses were prescribed are shown in **Table 1**. Among these patients, the greatest proportion of patients for whom a therapeutic dose was prescribed was observed for FM (14.1%), followed by PHN (11.6%) and pDPN (10.9%) (Table 1).

Patients for whom a therapeutic dose was prescribed were consistently and significantly younger than those for whom subtherapeutic doses were prescribed, but women were more likely to receive a subtherapeutic dose (Table 1). While patients with pDPN had the highest number of comorbid conditions, followed by FM and PHN, no significant differences were observed in the number of comorbid conditions between patients given therapeutic and subtherapeutic doses for any of the indications (Table 1). Based on region and type of benefit plan, there were significant differences in prescribed dosing regimens for FM and pDPN but not for PHN.

The average daily subtherapeutic doses of 164.3 mg, 167.4 mg, and 154.7 mg for FM, PHN, and pDPN, respectively, were significantly lower (*P* <.0001) than the therapeutic doses of 339.6 mg (FM), 329.6 mg (PHN), and 326.7 mg (pDPN).

The numbers of pregabalin prescriptions that were filled were statistically higher at the therapeutic dose for each of the indications relative to the subtherapeutic dose (**Table 2**), and were significant across the indications for FM (6.3 vs 5.5, *P* <.0001), PHN (5.2 vs 4.7, *P* = .024),

Table 1. Characteristics of the Study Populations Given Therapeutic and Subtherapeutic Doses of Pregabalin for Approved Pain Indications

Variable	Fibromyalgia (n = 15,309)		Post-Herpetic Neuralgia (n = 1483)		Painful Diabetic Peripheral Neuropathy (n = 4976)	
	Tx (n = 2159)	SubTx (n = 13,150)	Tx (n = 172)	SubTx (n = 1311)	Tx (n = 542)	SubTx (n = 4434)
Age, mean (SD)	50.6 (10.9)[a]	53.3 (11.9)	66.7 (12.5)[a]	69.7 (12.4)	59.6 (10.7)[a]	63.4 (11.5)
Gender, n (%)	[b]		[b]		[b]	
Male	340 (15.8)	1802 (13.7)	87 (50.6)	503 (38.4)	311 (57.4)	2227 (50.2)
Female	1819 (84.3)	11,348 (86.3)	85 (49.4)	808 (61.6)	231 (42.6)	2207 (49.8)
Number of comorbidities, mean (SD)	1.19 (1.24)	1.17 (1.24)	0.92 (1.00)	1.06 (1.15)	2.29 (1.43)	2.25 (1.45)
Geographic region, n (%)	[b]				[b]	
Northeast	147 (6.8)	868 (6.6)	18 (10.5)	113 (8.6)	31 (5.7)	345 (7.8)
North Central	679 (31.5)	3965 (30.2)	49 (28.5)	425 (32.4)	168 (31.0)	1401 (31.6)
South	930 (43.1)	6318 (48.1)	67 (39.0)	538 (41.0)	246 (45.4)	2136 (48.2)
West	396 (18.3)	1927 (14.7)	38 (22.1)	232 (17.7)	94 (17.3)	535 (12.1)
Unknown	7 (0.3)	72 (0.6)	0	3 (0.2)	3 (0.55)	17 (0.38)
Type of benefit plan, n (%)	[b]				[b]	
Comprehensive	157 (7.3)	1249 (9.5)	41 (23.8)	369 (28.2)	82 (15.1)	894 (20.2)
EPO	22 (1.0)	104 (0.8)	1 (0.6)	3 (0.2)	3 (0.6)	31 (0.7)
HMO	302 (14.0%)	1602 (12.2)	17 (9.9)	97 (7.4)	70 (12.9)	421 (9.5)
POS	285 (13.2)	1557 (11.8)	17 (9.9)	83 (6.3)	44 (8.1)	386 (8.7)
PPO	1310 (60.7)	8060 (61.3)	87 (50.6)	728 (55.5)	323 (59.6)	2557 (57.6)
POS with capitation	5 (0.2)	48 (0.4)	1 (0.6)	3 (0.2)	2 (0.37)	18 (0.4)
CDHP	41 (1.9)	240 (1.8)	1 (0.6)	14 (1.1)	6 (1.11)	91 (2.1)
Missing/Unknown	37 (1.7)	290 (2.2)	7 (4.1)	14 (1.1)	12 (2.2)	91 (2.0)

CDHP indicates consumer-directed health plan; EPO, exclusive provider organization; HMO, health maintenance organization; POS, point of service; PPO, preferred provider organization; SD, standard deviation; SubTx, subtherapeutic; Tx, therapeutic.
[a] P <.005 vs subTx dose.
[b] P <.05 vs subTx dose for the overall variable.

and pDPN (5.6 vs 5.3, P = .032). Patients with FM who were given therapeutic doses showed significantly greater persistence with pregabalin (168 days) compared with those who were given subtherapeutic doses (144 days; P <.0001), and at 1 year, the PDC was 0.62 for therapeutic compared with 0.55 for subtherapeutic (P <.0001). Likewise, significantly greater persistence was observed among PHN patients given therapeutic doses, 148 versus 133 (P <.05), while pDPN patients given therapeutic doses experienced higher persistence, 171 versus 154 days (P <.05), and PDC at 1 year, .63 for therapeutic compared with 0.59 for subtherapeutic (P <.01). Among the indications, the mean time to discontinuation was significantly higher only for FM (336 vs 297 days; P <.0001). A significantly greater proportion of patients with FM who were given therapeutic doses had PDC ≥80% relative to those given subtherapeutic doses (37.4% vs 29.1%; P <.0001) (**Figure 1a**), and were more likely to still be on therapy at 1 year (42.3% vs 36.8%; P <.0001) (**Figure 1b**). For the other indications, the proportions of patients with PDC ≥80% and those still on therapy at 1 year were generally similar between the therapeutic and subtherapeutic doses.

Survival curves for each of the 3 indications show the largest difference between subtherapeutic and therapeutic groups in the FM indication (P <.0001, unadjusted and adjusted for covariates) with median days to discontinue equal to 297 days and 336 days in the subtherapeutic and therapeutic dose groups. Survival curves show almost identical days to discontinue profiles in PHN patients (P = .75, adjusted for covariates) and pDPN patients (P = .44, adjusted for covariates). Median days to discontinue in the subtherapeutic and therapeutic dose groups was 186 and 197.5 days in PHN patients and 332 and 339.5 in pDPN patients (**Figure 2**).

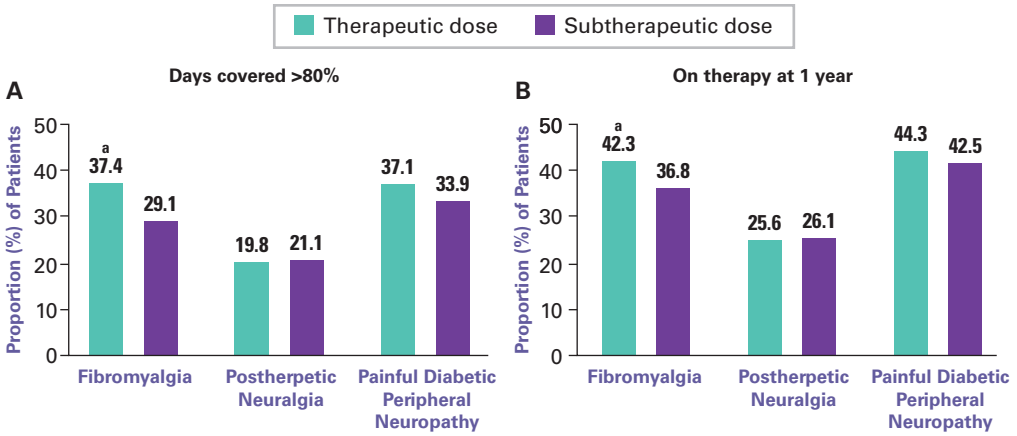
Among the indications, total direct costs for patients receiving therapeutic and subtherapeutic doses were similar

Table 2. Adherence Parameters Among Patients Given Therapeutic and Subtherapeutic Doses of Pregabalin for Approved Pain Indications

Variable	Fibromyalgia (n = 15,309)		Post-herpetic Neuralgia (n = 1483)		Painful Diabetic Peripheral Neuropathy (n = 4976)	
	Tx (n = 2159)	SubTx (n = 13,150)	Tx (n = 172)	SubTx (n = 1311)	Tx (n = 542)	SubTx (n = 4434)
Number of pregabalin prescriptions filled, mean ± SD	6.3 ± 3.7[a]	5.5 ± 3.3	5.2 ± 3.5[b]	4.7 ± 3.0	5.6 ± 3.5[b]	5.3 ± 3.1
PDC at 1 year, mean ± SD	0.62 ± 0.31[a]	0.55 ± 0.31	0.48 ± 0.30	0.46 ± 0.31	0.63 ± 0.31[c]	0.59 ± 0.31
Persistence, days, mean ± SD	168 ± 123[a]	144 ± 113	148 ± 105[b]	133 ± 102	171 ± 123[b]	154 ± 118
Time to discontinuation, days, median (25th, 75th percentiles)	336[a] (166,360)	297 (137,360)	197 (85,360)	186 (82,360)	339 (179,360)	332 (165,360)

PDC indicates proportion of days covered; SD, standard deviation; SubTx, subtherapeutic; Tx, therapeutic.
[a]*P* <.0001, [b]*P* <.05, and [c]*P* <.01, vs subtherapeutic dose.

Figure 1. Adherence to Therapy Over 12 Months Among Patients Newly Given Therapeutic and Subtherapeutic Doses of Pregabalin



A) Percent of patients with >80% of days covered. B) Percent of patients remaining on therapy at 1 year.
[a]*P* <.0001 vs subtherapeutic dose.

within each of the indications. pDPN was associated with the highest total direct costs (therapeutic, [mean, ± SD] $13,531 ± $18,311; subtherapeutic, $13,381 ± $22,612) followed by FM (therapeutic, $10,612 ± $11,768; subtherapeutic, $10,285 ± $15,464) (**Figure 3**). Although total costs were primarily driven by outpatient costs, there were no differences in outpatient costs between therapeutic and subtherapeutic cohorts for any of the indications. Within each indication, the only significant difference in resource utilization costs between therapeutic and subtherapeutic doses was for pharmacy costs, which were consistently lower with subtherapeutic (FM $3560 vs $3041, *P* <.0001; PHN $2352 vs $2333, *P* = .08; pDPN $4020 vs $3524, *P* <.0001) (Figure 3).

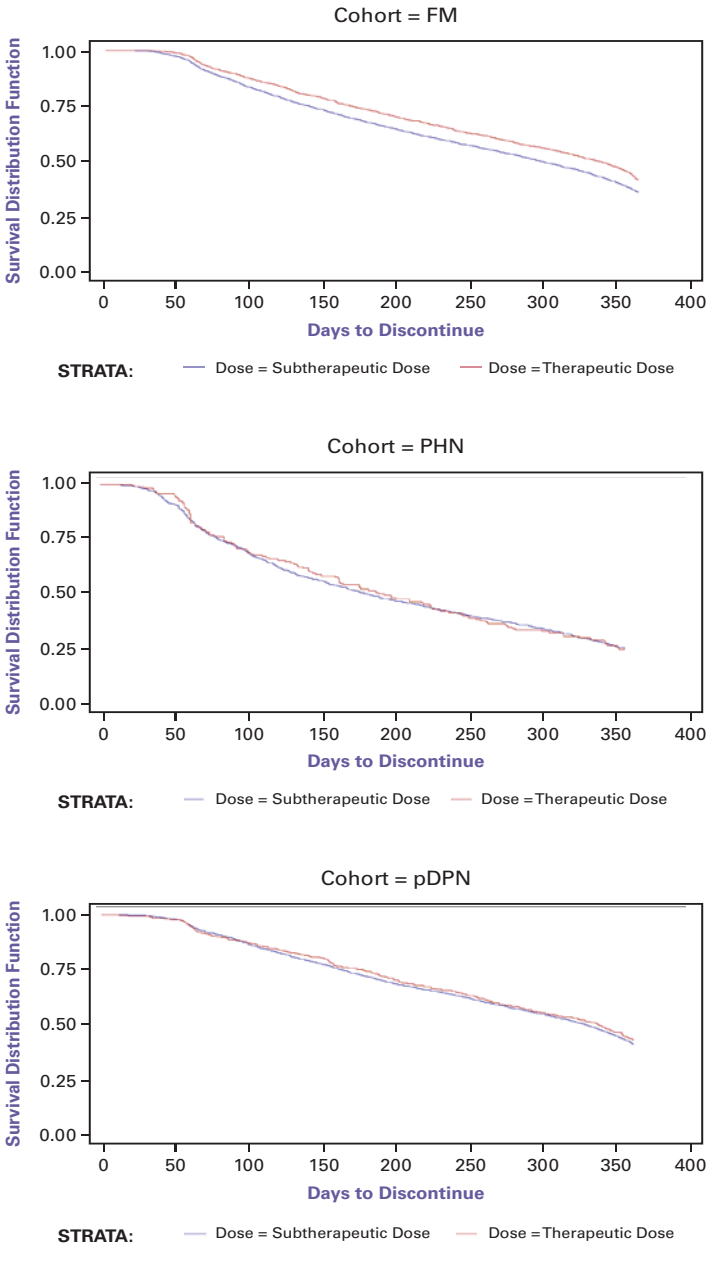
DISCUSSION

The implications of poor adherence to therapy are well recognized with regard to patient health (lack of achieving therapeutic benefits) and economic outcomes (sunk costs of unused medication, and the potential need for additional healthcare resource utilization).[21] While adherence to a particular medication is dependent on a variety of factors including the complexity of regimens among patients with polypharmacy and out-of-pocket medication costs, rapid achievement of the therapeutic goal and tolerability also represent key factors, both of which are contingent on appropriate dosing.

Results of the current study not only confirm previous observations that pregabalin is not titrated to therapeutic doses across indications,[10-12] but also indicate that the magnitude of subtherapeutic prescribing is substantial; across indications, only 13% of patients were given a therapeutic dose of pregabalin.

Several significant differences were observed in demographic characteristics between patients given therapeutic

Figure 2. Kaplan-Meier Estimates for Therapeutic and Subtherapeutic Doses of Pregabalin



pDPN indicates painful diabetic peripheral neuropathy; PHN, post-herpetic neuralgia.

and subtherapeutic dosing in each of the indications, including a younger age among those given a therapeutic dose, and differences in region and health plan type. These observations, which suggest the presence of specific prescribing patterns, warrant further investigation to determine whether dosing may be associated with patient and/or prescriber characteristics.

While there was greater adherence among patients given a therapeutic dose relative to a subtherapeutic dose for all indications, only for FM were these differences consistently significant, suggesting that patients with FM had the best adherence to dosing among the indications. The reason for this greater adherence is unclear, but it can be speculated that these patients were also younger than those with the other conditions, and at least relative to pDPN, there was likely less complexity of concomitant dosing regimens.

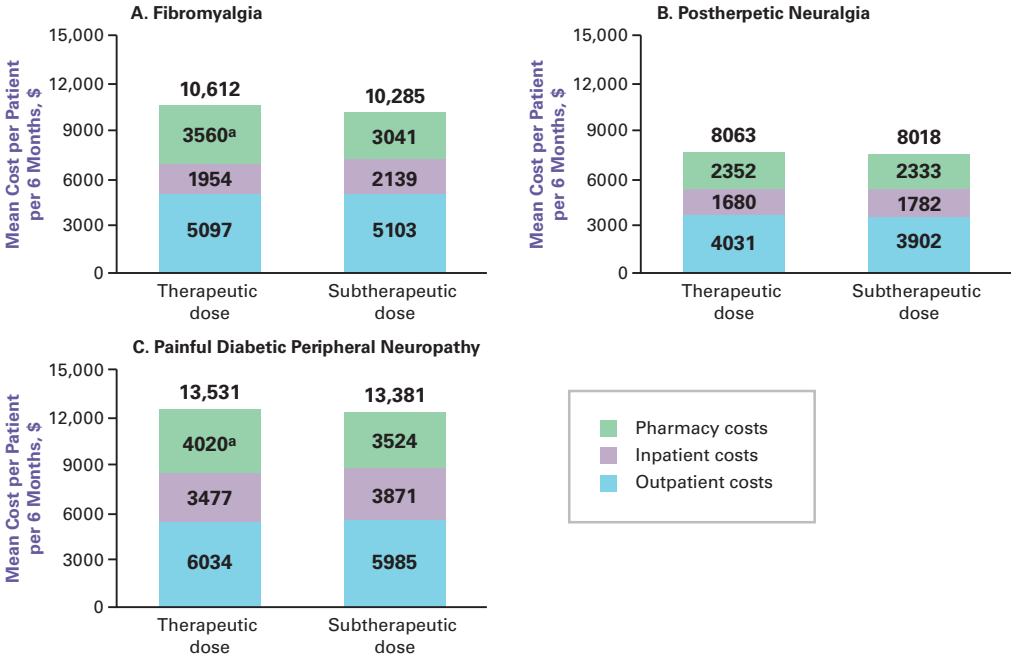
Therapeutic dosing in patients with pDPN did result in a significantly greater number of pregabalin prescriptions, PDC at 1 year, and persistence days, relative to subtherapeutic dosing. In contrast, significant differences in adherence parameters for PHN were only observed for number of pregabalin prescriptions and persistence days. This lack of significance may be a function of the relatively small number of patients with PHN who were given a therapeutic dose (n = 172).

While therapeutic dosing was associated with significantly higher pharmacy costs relative to subtherapeutic dosing for each of the indications, total costs were comparable between dose levels for each indication as well as for the composite across indications. Of note, there were no significant differences in either outpatient or inpatient costs between therapeutic and subtherapeutic dosing among any of the indications, with these costs numerically lower with therapeutic dosing except for outpatient costs in PHN and pDPN. Total costs were highest among patients with pDPN, most likely as a result of greater comorbidity and disease complexity relative to the other conditions.

Two studies that compared adherence among patients with FM and pDPN given either duloxetine or pregabalin reported less than optimal adherence with both drugs, and significantly poorer adherence with pregabalin.[22,23] However, neither study reported the mean daily doses of either drug, precluding any comparison with the adherence data reported here. Furthermore, in the absence of dosing information, the clinical relevance of the comparison presented in those studies is unclear.

Several limitations of this study should be noted, including our use of *ICD-9-CM* codes for identification of the conditions of interest. As with all retrospective database studies, use of these codes may be subject to

Figure 3. Direct Medical Costs per Patient per 6 Months Among Patients Newly Given Therapeutic and Subtherapeutic Doses of Pregabalin



[a]*P* <.0001 vs subtherapeutic dose.

potential errors in coding and recording, which could result in misclassification of patients. For example, there is not an *ICD-9-CM* code for FM; however, *ICD-9-CM* 729.1 (mylagia and myositis, unspecified, fibromyositis NOS) is used frequently. This study assumed that subjects coded with *ICD-9-CM* 729.1 had a diagnosis of FM. Additionally, no cause-and-effect inferences can be made, and thus the observed relationships should be considered associative rather than causal, including for the prescribing of pregabalin, since patients were characterized by other comorbid conditions for which pregabalin could potentially have been prescribed. Similarly, although a strength of this study is that it provides information from a real-world clinical setting, differences in demographic and other characteristics such as comorbidities may contribute to the observed healthcare resource utilization and costs, limiting our ability to more fully characterize the association between these parameters and adherence.

It should also be noted that patient adherence cannot be absolutely ascertained in retrospective database studies, since the assumption that the patient was in possession of the medication does not necessarily mean that the patient actually took it as prescribed. Consequently, PDC and persistence can only be considered as proxy measures for adherence.

Finally, neither initial disease severity nor efficacy and safety outcomes resulting from the use of a specific medication can be captured in claims databases. Thus, while it is possible that the patients who received subtherapeutic doses actually achieved improvements in pain or other outcomes, it is not possible to know the effect these outcomes or potential differences in outcomes between therapeutic and subtherapeutic doses may have had on the observed adherence and costs. However, to attain optimal pregabalin efficacy with a balanced side effect profile, dosing within the therapeutic range is desirable.[24]

In conclusion, the majority of patients who were prescribed pregabalin across indications received doses that were subtherapeutic; few patients with FM, pDPN, or PHN who were given pregabalin received a therapeutic dose. For each of the indications, pharmacy costs were significantly higher with therapeutic dosing relative to subtherapeutic dosing, but nevertheless resulted in total direct medical costs that were comparable between dose groups, suggesting that prescribing pregabalin at its recommended therapeutic dose may increase adherence without increasing costs relative to subtherapeutic doses. Further research should focus on identifying those factors that may contribute to the observed pattern of subtherapeutic dosing.

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