RESEARCH

Complexity of Pain Management Among Patients with Nociceptive or Neuropathic Neck, Back, or Osteoarthritis Diagnoses

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ABSTRACT

BACKGROUND: Approaches to pain management are diverse, requiring prescribers to evaluate an array of clinical issues and potential solutions. In addition to the difficult task of selecting a treatment option, pain treatment may be further complicated by multiple prescribers, multiple medications, and multiple mechanisms of pain origination.

OBJECTIVE: To describe patient demographics (e.g., age, gender); comorbidities; office visits (e.g., physician, chiropractor, physical therapy, psychiatry, allergist); number of different prescribers overall prescription use; pain medications as classified by the World Health Organization's (WHO) pain ladder; adjuvant medications; nonpharmacologic procedures; and potential drug interactions in a broad sample of patients with nociceptive or neuropathic neck or back diagnoses, or osteoarthritis diagnoses, in a commercial population.

METHODS: This claims-data analysis used a cross-sectional cohort comparison with a fixed 2-year observation period from September 1, 2006, to August 31, 2008, for patients in the PharMetrics national managed care database. The assigned cohorts were neuropathic-related neck/back diagnoses (NEURO); neuropathic and nociceptive neck/back diagnoses (NEURO/NOCI); nociceptive neck/back diagnoses without a neuropathic-related diagnosis (NOCI); and only osteoarthritis (OA) diagnoses. All analyses were conducted by cohort. The analysis included the following patient-descriptive variables: patient demographics, comorbidities, office visits, most frequent medical providers and number of different prescribers, all medications, pain medications as classified by the WHO pain ladder, adjuvant medications, adjuvant procedures and potential drug interactions. The goal for selecting these variables was to describe a range of data that might provide insight into the complexity of pain management decisions faced by clinicians.

RESULTS: The study included 85,014 patients, classified as NEURO (n = 2,375), NEURO/NOCI (n = 37,019), NOCI (n = 39,496), and OA (n = 6,124). The most frequently occurring comorbidities (observed in > 40% of patients) included cardiovascular and neuropathic pain conditions. Considering all types of medication claims observed among all cohorts, the overall mean prescription claim count for the 2-year observation period was 57.9 claims (standard deviation 56.2). Weak opioids (WHO pain relief ladder rung 2) accounted for the majority of pain medication claims across all cohorts. Across cohorts, 25.7% of patients had 10 or more days of overlapping drug availability (for inducers or inhibitors of the cytochrome P450 system concomitantly), a measure of potential for drug interactions.

CONCLUSIONS: Choosing the appropriate pain treatment involves assessing currently used medications for existing illnesses and deciding on the appropriate types of pain medications. However, potentially serious drug-drug interactions are a consequence of multiple drug use, and such a potential requires thoughtful consideration by those involved in patient care.

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What is already known about this subject

- Pain relief is one of the leading reasons for health-seeking behavior. Pain may be localized or general and may arise from various etiologies, including joint and arthritic injury, herpes zoster, multiple sclerosis, spinal injury, and pain-related conditions such as diabetic polyneuropathy and fibromyalgia.
- Pain is caused by different pathophysiological mechanisms, including neuropathic, nociceptive, and a mix of neuropathic and nociceptive mechanisms. Neuropathic pain is caused by a lesion or dysfunction of the peripheral or central nervous system. Nociceptive pain is associated with the stimulation of nociceptive nerve receptors that transmit signals to the central nervous system. Neuropathic pain is believed to be the most challenging to treat.
- Patients are treated with a variety of modalities to control pain, including physical therapy, psychological therapy, acupuncture, acupressure, and interventional pain procedures that include spinal cord stimulation, biofeedback, transdermal electric stimulation, complementary and alternative medicine, and pharmacological treatment.

What this study adds

- To our knowledge, this is the first study that has assessed a large population of mixed sources of pain in order to understand the characteristics of patient populations that might contribute to increased risks for complications when making medication prescribing decisions.
- This analysis highlights a breadth of pain management variables evaluated in a single population of patients, as opposed to analyses that have examined single variables.
- This study documents treatments for a range of patients with neck and back pain diagnoses for whom clinicians might have to make pain management decisions.

Approaches to pain management are diverse, requiring prescribers to evaluate an array of clinical issues and potential solutions. Treatment options including lifestyle changes, medications, cognitive and physical therapy, surgery, and alternative medicine are weighed in consideration of other patient factors such as age and comorbid conditions. In addition to the difficult task of selecting a treatment option, pain treatment may be further complicated by the use of multiple classes of medications[1-3] and multiple mechanisms of pain origination.[4]

In addition to complaints of pain, patients often present with other multiple coexisting chronic diseases.[5-8] According to the Centers for Disease Control and Prevention, 47% of U.S. adults aged 55 or greater have 2 or more chronic conditions (e.g., arthritis, asthma, cancer, cardiovascular disease, chronic obstructive pulmonary disease, and diabetes).[9] These diseases require chronic treatment, often with multiple medications. Thus, pain treatment is often concurrent with chronic disease treatment in a large number of patients.

There are few published studies that describe the complexity of pain management. This analysis attempts to provide an in-depth description of the potential complexities associated with pain management in terms of patient characteristics, physician involvement, medication variety, and other treatment services used in a large cohort of patients receiving treatment for chronic or acute pain. The goal of the analysis was to raise awareness of the complexity of treating pain with the focus specifically on medications, since medications are a mainstay of pain treatment. Understanding the characteristics of patient populations that might contribute to increased risks for complexity may signal areas that need attention when making medication-prescribing decisions. Factors that may require specific consideration by clinicians when prescribing medications are highlighted.

Methods

Data Source

Patients with commercial coverage were selected from the PharMetrics (Watertown, MA) national managed care database. The PharMetrics database is an anonymous patient-centric database that represents more than 60 million enrollees from more than 95 health plans and provides comprehensive medical and prescription claims data. The database is a de-identified, HIPAA (Health Insurance Portability and Accountability Act of 1996) compliant database and, as such, no institutional review board approval was necessary.

Study Design

This analysis used a cohort comparison with a fixed 2-year observation period from September 1, 2006, to August 31, 2008, during which all patients were required to have continuous insurance coverage. To ensure that patients had a diagnosis of interest at the start of the period for which data were reported, at least 1 diagnosis of interest was required in the prior 1-year preperiod (September 1, 2005-August 31, 2006).

Analysis Population

The strategy for patient selection was to obtain a sample with neck and back diagnoses in which the magnitude of variables affecting pain management complexity might be inferred. The selection criteria were designed to identify patients who had any moderate pain therapy exposure, for whom there would be complete data, and in whom a common alternative reason for pain medication use (i.e., cancer) was removed. The goal was to identify a wide range of patients of the type that might be seen in clinical practice, who had neuropathic or nociceptive neck or back diagnoses.

Patients were included in this analysis if they met all of the following criteria: (a) had continuous insurance eligibility between September 1, 2006, and August 31, 2008; (b) were at least 18 and no more than 63 years of age as of 2006 (to exclude patients who may have switched to Medicare coverage during the observation period); (c) had at least 2 claims (any analysis diagnosis) separated by at least 90 days for an analysis inclusion diagnosis between September 1, 2005, and August 31, 2006, and at least 1 during the observation period (September 1, 2006-August 31, 2008); and (d) had at least 1 oral opioid prescription claim during the observation period. The opioid restriction was applied to provide some minimal evidence of pain medication use.

Patients were excluded from the analysis if they met any of the following exclusion criteria: (a) had 1 or more claims indicating a stay in a long-term care or skilled nursing facility (because of concerns about the completeness of their claims data); (b) had a diagnosis for history of alcohol and/or drug abuse; (c) had a pregnancy or pregnancy-related claim during the observation period; (d) had a surgical procedure involving the spine or intervertebral disc prior to the observation period; (e) had a diagnosed malignancy, with the exception of nonmelanoma skin cancers, during or prior to the observation period; (f) had noncommercial coverage; or (g) had invalid or missing data for key analysis variables.

Patients meeting the analysis inclusion and exclusion criteria were assigned to neuropathic and nociceptive neck and back and osteoarthritis cohorts based on the presence of diagnosis codes for 1 of the selected conditions, based on the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM; Table 1). The assigned cohorts were neuropathic-related neck/back diagnoses (NEURO); neuropathic and nociceptive neck/back diagnoses (NEURO/NOCI); nociceptive neck/back diagnoses without a neuropathic-related diagnosis (NOCI); and only osteoarthritis (OA) diagnoses. NOCI, NEURO, and NEURO/NOCI were assigned without regard to coexisting OA diagnoses. See Figure 1 for sample identification.

Statistical Analysis

Categorical variables were summarized using frequencies and percentages. Continuous measures were summarized with means, standard deviations, minimums, maximums, and medians. Comparisons between cohorts were conducted with analysis of variance for continuous measures and chi-square tests for categorical variables. While statistical tests were conducted, we note that there are large and disparate sample

TABLE 1 Description of Coding

Type of Pain	Description	Codes
NEURO	Low back pain/disorders with radicular leg pain	723.4X, 724.3X, 724.4X, 729.2X
	Neck pain with neuropathic involvement	721.1X, 722.0X, 723.0X
	Back or neck with neuropathic involvement, predominately back	721.4X, 722.1X, 724.0X
	Back or neck with neuropathic involvement, predominately neck	721.91, 722.2X, 722.7X
NEURO/NOCI[a]	Low back pain/disorders with radicular leg pain	723.4X, 724.3X, 724.4X, 729.2X, and any diagnosis below
	Neck pain with neuropathic involvement	721.1X, 722.0X, 723.0X, and any diagnosis below
	Back or neck with neuropathic involvement, predominately back	721.4X, 722.1X, 724.0X, and any diagnosis below
	Back or neck with neuropathic involvement, predominately neck	721.91, 722.2X, 722.7X, and any diagnosis below
NOCI	Back without radicular leg pain	724.2X, 724.5X, 724.6X, 724.9X, 721.2X, 721.3X, 722.5X, 724.1X, 724.7X, 724.8X, 739.2X, 739.3X, 739.4X, 846.0X, 846.1X, 846.8X, 846.9X, 847.1X, 847.2X, 847.3X, 847.4X, 847.9X, 722.3X, 846.3X
	Neck pain without neuropathic involvement	721.0X, 723.1X, 723.2X, 723.3X, 723.5X, 723.6X, 723.7X, 723.8X, 723.9X, 847.0X
	Back or neck, predominately back without neuropathic involvement	720.0X, 720.1X, 720.2X, 721.5X, 721.8X, 720.8X
	Back or neck, predominately neck without neuropathic involvement	720.9X, 721.6X, 721.7X, 721.90, 722.4X, 722.6X, 738.4X, 739.1X, 846.2X
OA[b]	Osteoarthritis cohort total	715.XX

[a]The NEURO/NOCI pain cohort consisted of patients with 1 or more diagnoses for neuropathic pain and at least 1 additional diagnosis for neck/back pain without neuropathic involvement during the observation period.

[b]Any cohort may or may not have had an osteoarthritis diagnosis. The osteoarthritis cohort had no diagnosis from any other cohort.

NEURO = neuropathic-related neck/back diagnoses; NEURO/NOCI = neuropathic and nociceptive neck/back diagnoses; NOCI = nociceptive neck/back diagnoses; OA = osteoarthritis.

sizes. In many cases, trivial differences may be statistically significant. The interpretation should rely on differences that are of clinical significance. Given the large number of comparisons, only general comments are made regarding statistical significance. No adjustments were made for multiplicity. SAS/STAT software for Windows version 9.2 (SAS Institute Inc., Cary, NC) was used for all analyses.

Variable Descriptions

The analysis included the following variables: patient demographics (e.g., age, gender); comorbidities; office visits (e.g., physician, chiropractor, physical therapy, psychiatry, allergist); the percentage of patients with visits to medical providers by specialty and number of different prescribers; the mean number of prescription claims; pain medications as classified by the World Health Organization (WHO) pain ladder; adjuvant medications; adjuvant procedures; and potential drug interactions. All analyses were conducted by cohort. Operational definitions of the key variables are presented in the following sections.

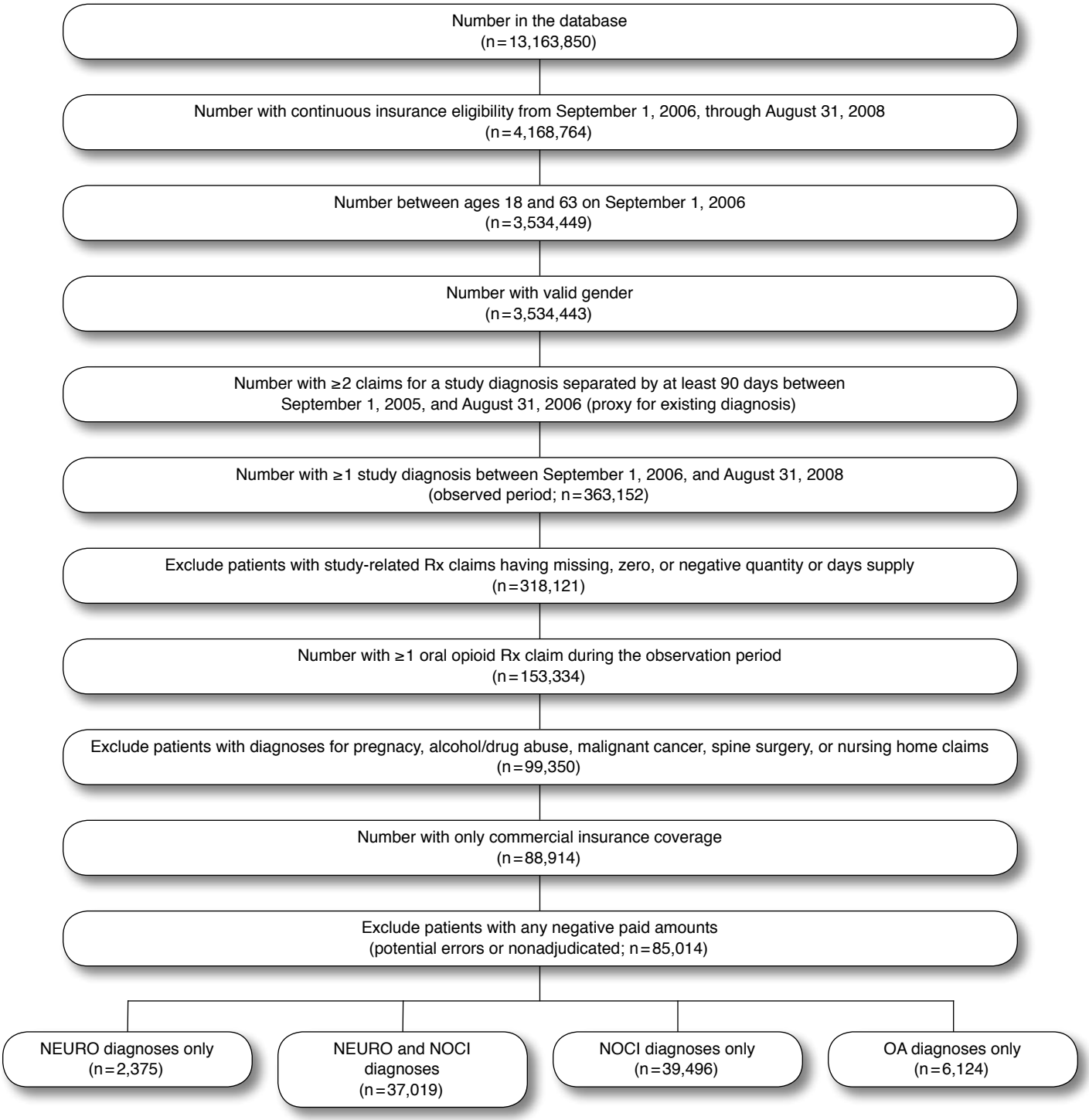
Comorbidities of interest and specific codes are presented in Appendix A (available in online article). Comorbidities were identified from a published article using the ICD-9-CM diagnosis codes and refined based on an analysis by Gore et al. (2011).[10] The percentage of patients with at least 1 claim during the 2-year observation period with each of the comorbidities was identified.

Office visit counts for the observation period were calculated for the overall group and for each cohort using claims data. The observation period was a fixed 2-year observation period from September 1, 2006, to August 31, 2008.

Most frequently appearing medical providers during the observation period were identified using the Standard Provider field included in the outpatient claims database. Standard Provider is a field provided by the data vendor that describes the provider's specialty. Each uniquely identified provider per patient per date was counted as 1 occurrence. In addition to this more general assessment, prescribing specialties were identified qualitatively from the list of Standard Provider types assigned in order to provide a count from the subset of provider types who regularly prescribe chronic medications to the patients in our analysis. Counts for the number of patients with visits to these providers were provided. Mean prescription claims counts for the entire observation period were calculated and grouped into categories using National Drug Codes. These counts included all of the prescription claims, including new or refill medications. The claims were divided into categories of all prescriptions, pain-related, adjuvant, and nonpain-related prescriptions. Claims count and categories were assessed for each cohort.

The assessment of pain medication was based on the WHO pain ladder. The pain ladder has 3 steps representing mild, moderate, and severe pain. For step 1 (mild pain), nonopioid medications with or without adjuvant analgesic therapy are recommended. Typically, the drugs used at this step are acetaminophen or nonsteroidal anti-inflammatory medications (NSAIDs; e.g., aspirin, ibuprofen, diclofenac). Step 2 on the

FIGURE 1 *Sample Identification*



NEURO = neuropathic-related neck/back diagnoses; NEURO/NOCI = neuropathic and nociceptive neck/back diagnoses; NOCI = nociceptive neck/back diagnoses; OA = osteoarthritis; Rx = prescription.

TABLE 2 Sample Characteristics

	Overall	Cohorts			
		NEURO	NEURO/NOCI	NOCI	OA
Parameter	**n = 85,014**	**(n = 2,375)**	**(n = 37,019)**	**(n = 39,496)**	**(n = 6,124)**
Mean age, years (± SD)[a]	47.8 (10.1)	49.6 (9.5)	48.3 (9.5)	46.2 (10.7)	53.6 (6.8)
Female, n (%)[b]	51,384 (60.4)	1,359 (57.2)	22,152 (59.8)	24,146 (61.1)	3,727 (60.9)

[a]*All tests for differences in age between cohorts were statistically significant (P < 0.0001).*

[b]*All tests for differences in gender distribution between cohorts were statistically significant (P < 0.002), except for NEURO/NOCI vs. NOCI (P = 0.1315) and NOCI vs. OA (P = 0.6798).*

NEURO = neuropathic-related neck/back diagnoses; NEURO/NOCI = neuropathic and nociceptive neck/back diagnoses; NOCI = nociceptive neck/back diagnoses; OA = osteoarthritis; SD = standard deviation.

ladder (moderate pain) adds the use of a weak opioid (e.g., tramadol, codeine, dihydrocodeine). The third rung (severe pain) adds the use of strong opioids (e.g., morphine, fentanyl, buprenorphine, oxycodone, hydromorphone). The medications included on the rungs of the WHO pain relief ladder are shown in Appendix B (available in online article). Medication availability was defined as the percentage of days where a patient theoretically had access to the drug based on the dispensing dates and days supply. Days of availability for pain ladder classes were categorized into >0% to <30%, 30% to <80%, and ≥80%.

Adjuvant treatments may be used at any step on the ladder and include antidepressants, anticonvulsants, steroids, muscle relaxants, exercise, psychological support, temperature therapy, physical therapy, hydrotherapy, and acupuncture. Adjuvant pain medications were categorized using the therapeutic classes and then were refined based on a published list.[11] The therapeutic class approach is broader than just the specific pain-related adjuvant treatments; however, use of any drug in the class may affect pain treatment decisions.

Drug interaction potential was also evaluated. Potential drug interactions were defined based on the interaction within the cytochrome P450 system. Pain medications were evaluated both as substrates on which other drugs could act and as inhibitors and inducers that act on other drugs as substrates. Pain medications were assessed for overlapping availability (i.e., based on dispensing dates and days supplies) for a minimum of 10 days based on dispensing dates and days supply of medication (a proxy for concomitant use).

Adjuvant therapies (e.g., chiropractic therapy, physical therapy) also are used to treat pain. Adjuvant therapies were identified using medical codes that are frequently associated with the treatment of pain. These procedures were included to provide a comprehensive view of how pain is treated.

Results

Patient Demographics and Comorbidities

The analysis included 85,014 patients, of which 2,375 were classified as NEURO; 37,019 were NEURO/NOCI; 39,496 were NOCI; and 6,124 were OA. The mean age of the overall sample was 47.8 years, and females comprised 60.4% (Table 2). The most frequently occurring comorbidities (observed in >40% of patients) included cardiovascular and neuropathic pain conditions (in the NEURO and NEURO/NOCI groups only; Table 3). Hypertension was the most commonly observed specific comorbidity, occurring in more than 60% of OA patients, followed by NEURO (46.9%), NEURO/NOCI (43.6%), and NOCI (35.2%) patients.

Hyperlipidemia occurred in 59.5% of OA patients, followed by NEURO (51.6%), NEURO/NOCI (48.9%), and NOCI (41.6%) patients. Depression was observed in 21.3% of NEURO/NOCI patients, followed by NOCI (18.4%), OA (15.8%), and NEURO (15.6%) patients. Diabetes was observed in 22.4% of OA patients, followed by NEURO (19.8%), NEURO/NOCI (15.4%), and NOCI (11.7%) patients. Sleep disturbance was observed in 20.0% of the NEURO/NOCI cohort, followed by OA (18.9%), NEURO (16.6%), and NOCI (16.6%) cohorts. Thyroid disorder was observed in 15% to 19% of the cohorts. If a significant omnibus test ($P < 0.05$) was found using ANOVA, then pairwise statistical tests were conducted. The results of these tests indicated that differences equal to or larger than the following magnitudes were statistically significant ($P < 0.05$ or less): NEURO versus NEURO/NOCI 1.5%; NEURO versus NOCI 0.5%; NEURO versus OA 1.6%; NEURO/NOCI versus NOCI 0.2%; NEURO/NOCI versus OA 0.5%; and NOCI versus OA 0.5%.

Office Visits

The mean number of office visits during the observation period for the overall population was 32.0 (standard deviation [SD] 27.9) visits (Table 4). The NEURO/NOCI cohort led the office visits with a mean of 38.1 visits (SD 31.3), followed by the NOCI, NEURO, and OA cohorts at 28.4 visits (SD 24.6), 25.1 visits (SD 23.6), and 20.8 visits (SD 18.3) during the 2-year observation period. All pairwise statistical tests were significant at $P < 0.0001$.

Medical Providers

Overall visits to prescribing specialists indicate that general and family practice (GP/FP) and internal medicine (IM) physicians accounted for the highest percentage of patients with at least 1 visit during the 2-year analysis definition period,

TABLE 3 Patient Characteristics

Comorbidity	NEURO[a] (n = 2,375) %[b]	NEURO/NOCI[a] (n = 37,019) %[b]	NOCI[a] (n = 39,496) %[b]	OA[a] (n = 6,124) %[b]
Psychiatric conditions	22.4	29.3	25.4	21.8
Depression	15.6	21.3	18.4	15.8
Anxiety	8.8	12.3	10.1	7.8
Bipolar disorder	1.1	1.1	0.8	0.7
Generalized anxiety disorder	3.2	4.1	3.2	2.7
Panic disorder	1.3	1.9	1.3	1.0
Post-traumatic stress disorder	0.5	0.9	0.8	0.6
Sleep distubances	16.6	20.0	16.6	18.9
Insomnia/sleep disorders	15.3	18.5	15.3	16.8
Sleep apnea	8.3	8.8	7.2	9.9
Cardiovascular disorders	65.6	62.7	53.7	77.8
Hypertension	46.9	43.6	35.2	60.4
Hyperlipidemia	51.6	48.9	41.6	59.5
Coronary heart disease	11.0	9.4	6.4	11.5
Myocardial infarction	1.5	1.4	1.0	1.6
Congestive heart failure	2.3	1.5	1.1	2.4
Peripheral vascular disease	3.5	2.8	1.4	3.1
Chronic obstructive pulmonary disease	5.9	4.7	3.2	5.1
Chronic renal failure	1.9	1.3	1.1	2.1
Diabetes	19.8	15.4	11.7	22.4
Musculoskeletal pain conditions	90.0	99.2	92.6	100.0
Rheumatism, excluding the back	62.0	70.8	55.7	61.6
Arthritis and other arthropathies	53.9	60.3	51.8	76.9
Back and neck pain, excluding low back pain	23.3	81.2	63.1	0.2
Lumbago	0.0	63.1	44.2	0.0
Low back pain	27.7	57.7	16.0	0.2
Osteoarthritis	33.8	32.5	25.8	100.0
Rheumatoid arthritis	3.7	3.4	2.6	6.2
Neuropathic pain conditions	71.1	77.5	11.0	10.9
Diabetic peripheral neuropathy	0.7	0.7	0.5	0.4
Postherpetic neuropathy	0.3	0.3	0.2	0.3
Other polyneuropathies	11.4	12.5	5.8	4.8
Back and neck pain with neuropathic involvement	52.3	65.7	0.0	0.0
Trigeminal neuralgia	0.4	0.4	0.3	0.2
Carpal tunnel syndrome	7.4	8.6	4.7	5.8
Causalgias	3.6	3.3	1.2	1.2
Atypical facial pain	0.4	0.5	0.3	0.3
Neuritis radiculitis, unspecified	16.2	13.5	0.0	0.0
Phantom limb pain	0.0	0.0	0.0	0.0
Autonomic neuropathies	0.4	0.4	0.2	0.2

[a]Pairwise tests following a significant omnibus ANOVA (P < 0.05) showed that differences equal to or larger than the following magnitudes were statistically significant (P < 0.05 and less): NEURO vs. NEURO/NOCI 1.5%; NEURO vs. NOCI 0.5%; NEURO vs. OA 1.6%; NEURO/NOCI vs. NOCI 0.2%; NEURO/NOCI vs. OA 0.5%; NOCI vs. OA 0.5%.

[b]Denominators for means and percentages are the number of patients within each cohort. Patients can be in more than 1 row. This table is organized according to Gore et al.[10]

NEURO = neuropathic-related neck/back diagnoses; NEURO/NOCI = neuropathic and nociceptive neck/back diagnoses; NOCI = nociceptive neck/back diagnoses; OA = osteoarthritis.

at 39.8% and 16.9%, respectively (Table 5). The NOCI group exhibited the highest percentage of patient visits to GP/FP physicians at 42.1%, followed by the NEURO/NOCI (38.9%), OA (33.1%), and NEURO (32.2%) groups. IM visits were highest in the OA group with 20.7% of patients having at least 1 visit. Other specialists such as orthopedic surgeons, cardiologists, and obstetrics/gynecology that were listed in the database are shown in the table. Nonsignificant pairwise differences are

TABLE 4 Mean Total Number of Office Visits Per Patient During the 2-Year Observation Period[a]

Cohort[b]	n	Mean	SD	Median
Overall	85,014	32.0	27.9	25.0
NEURO/NOCI	37,019	38.1	31.3	30.0
NEURO	2,375	25.1	23.6	18.0
NOCI	39,496	28.4	24.6	22.0
OA	6,124	20.8	18.3	16.0

[a]*A visit is counted as 1 unique occurrence per patient per date per provider ID.*
[b]*All pairwise differences are significant at P < 0.0001.*
NEURO = neuropathic-related neck/back diagnoses; NEURO/NOCI = neuropathic and nociceptive neck/back diagnoses; NOCI = nociceptive neck/back diagnoses; OA = osteoarthritis; SD = standard deviation.

noted in the table. When considering the average total number of different prescribing specialists that patients might have seen during the 2-year period, the overall average was 4.5 specialists (SD 2.6) per patient (Table 6). The NEURO group average was the highest at 4.9 (SD 2.7), followed by the OA group with 4.7 (SD 2.4), the NEURO/NOCI group with 4.4 (SD 2.6), and the NOCI group with 4.2 (SD 2.4). All pairwise tests were statistically significant ($P < 0.0001$).

Medication Use

Considering all types of medication claims observed among all cohorts, the overall mean prescription claim count per patient for the 2-year observation period was 57.9 claims (SD 56.2; Table 7). Across cohorts, the NEURO/NOCI cohort had the highest mean claim count of 64.6 prescriptions (SD 60.1) and was statistically significantly higher than all other cohorts with the exception of the OA cohort ($P = 0.3176$). Considering only pain-related medications, the overall mean claim count was 8.8 prescriptions (SD 13.0), and the NEURO/NOCI group had the highest mean at 11.0 prescription claims (SD 15.0) during the observation period. All pairwise comparisons of pain medication claim counts between cohorts were statistically significant at $P < 0.0001$. Considering adjuvant medication claims, the overall mean prescription claim count was 12.7 prescriptions (SD 15.5) during the period and the NEURO/NOCI mean count was the highest at 13.7 prescriptions (SD 16.5). The non-pain-related prescriptions accounted for the highest volume of claims, with the overall mean during the period of 41.2 claims (SD 42.5). In this category, the OA patients accounted for the highest mean number of prescriptions at 48.0 claims (SD 44.5; $P < 0.0001$ for all pairwise comparisons with the OA cohort).

Weak opioids (WHO pain relief ladder rung 2) accounted for the majority of pain medication claims across all cohorts (Figure 2). The percentage of patients who had nonopioids (WHO pain relief ladder rung 1), weak opioids (WHO pain relief ladder rung 2), or strong opioids (WHO pain relief ladder rung 3) available (i.e., filled) were similar across cohorts. A greater percentage of NEURO/NOCI and OA patients had nonopioid availability (53.4% and 55.5%, respectively) than patients in the other cohorts. The percentage of days where medication was available during the observation period was similar across all cohorts with the majority of patients having

TABLE 5 Medical Providers

Number and percentage of patients per cohort with at least 1 visit to top 10 overall most frequently prescribing[a] specialty types during the 2-year observation period.

	Overall	NEURO	NEURO/NOCI	NOCI	OA
	(n = 85,014)	(n = 2,375)	(n = 37,019)	(n = 39,496)	(n = 6,124)
Specialty[b]	%	%	%	%	%
General practice/family practice (GP/FP)	39.8	32.2	38.9	42.1	33.1
Internal medicine (IM)	16.9	19.6	17.2	15.8	20.7
Orthopedic surgery (OS)	6.7	8.2	6.8	5.1	16.6
Cardiology (CD)	4.2	5.3	4.7	3.5	5.7
Obstetrics and gynecology (OB)	3.1	3.3	2.7	3.8	1.4
None listed (NL)	2.5	3.2	2.2	2.8	2.2
Other specialty (Oth)	2.2	2.3	2.9	1.7	1.3
Psychiatry (PSY)	2.1	2.4	2.4	2.1	1.1
Nurse practitioner[a] (NP)	2.1	0.6	1.8	2.7	0.6
Rheumatology (RH)	1.8	1.7	1.6	1.6	4.0
Physician's assistant[a] (PA)	1.7	0.5	1.4	2.2	0.8

[a]*Prescribing abilities for controlled substances varies by state.*
[b]*Pairwise tests showed the following tests that were not significant at P < 0.05: NEURO vs. NEURO/NOCI–OS, CD, Oth, PSY, and RH; NEURO vs. NOCI–NL, PSY, RH; NEURO vs. OA–GP/FP, CD, NP, PA; NEURO/NOCI vs. NOCI–RH; NEURO/NOCI vs. OA–NL; NOCI vs. OA. All are significant at P < 0.05.*
NEURO = neuropathic-related neck/back diagnoses; NEURO/NOCI = neuropathic and nociceptive neck/back diagnoses; NOCI = nociceptive neck/back diagnoses; OA = osteoarthritis.

TABLE 6 Different Prescribing Specialists

Average total number of different prescribing specialty types[a] per person during the 2-year observation period for all patients.[b]

Cohort Group[c]	n	Mean	SD	Median
Overall	85,014	4.5	2.6	4
NEURO	37,019	4.9	2.7	5
NEURO/NOCI	2,375	4.4	2.6	4
NOCI	39,496	4.2	2.4	4
OA	6,124	4.7	2.4	5

[a]Subset to specialties who generally prescribe chronic medications (e.g., general practice).

[b]Patients with no prescribing specialty physicians listed on any claims during the observation period were assigned a value of zero.

[c]All pairwise differences are significant at P<0.0001.

NEURO = neuropathic-related neck/back diagnoses; NEURO/NOCI = neuropathic and nociceptive neck/back diagnoses; NOCI = nociceptive neck/back diagnoses; OA = osteoarthritis; SD = standard deviation.

TABLE 7 Mean Prescription Claim Counts Per Patient from the Observation Period by Cohort and Pain Category[a]

Prescription Category/Cohort	n[b]	Mean	SD	Median
All prescriptions				
Overall	84,983	57.9	56.2	41
NEURO	2,375	58.4	54.5	42
NEURO/NOCI	37,010	64.6	60.1	48
NOCI	39,475	50.8	51.6	35
OA	6,123	63.8	55.0	49
NEURO/NOCI vs. OA only are not statistically significant, P = 0.3176; all other pairwise comparisons are significantly different at P < 0.0001.				
Pain-related prescriptions[c]				
Overall	84,679	8.8	13.0	3
NEURO	2,360	8.7	13.5	4
NEURO/NOCI	36,895	11.0	15.0	5
NOCI	39,324	6.7	10.7	3
OA	6,100	9.6	11.6	5
All pairwise comparisons are statistically significant at P<0.0001.				
Adjuvant prescriptions[d]				
Overall	58,813	12.7	15.5	7
NEURO	1,565	12.2	14.4	7
NEURO/NOCI	28,678	13.7	16.5	7
NOCI	25,093	11.8	14.6	6
OA	3,477	12.0	14.0	7
NEURO vs. NOCI (P = 0.3249), NEURO vs. OA (P = 0.6621), and NOCI vs. OA (P = 0.4952) are not statistically significant; all other pairwise comparisons are statistically significant at P < 0.0001.				
Nonpain-related prescriptionse[e]				
Overall	83,236	41.2	42.5	28
NEURO	2,313	42.8	42.9	29
NEURO/NOCI	36,306	43.9	44.2	31
NOCI	38,575	37.5	40.1	25
OA	6,042	48.0	44.5	36
NEURO vs. NEURO/NOCI is not statistically significant, P = 0.2478; all other pairwise comparisons are statistically significant at P < 0.0001.				

[a]Claims with missing, zero, or negative days supply or quantity were not included in counts. Claims with identical National Drug Code numbers for the same date and patient were only counted once per date.

[b]The category "n" is the number of patients with pharmacy claims in each prescription category.

[c]Pain-related prescriptions include all medications listed for WHO ladder steps 1, 2, and 3.

[d]Adjuvant prescriptions include medications used as adjuvant treatment for pain in the following drug classes: muscle relaxants, antidepressants, steroids, anticonvulsants, antiarrhythmics, and antihypertensives.

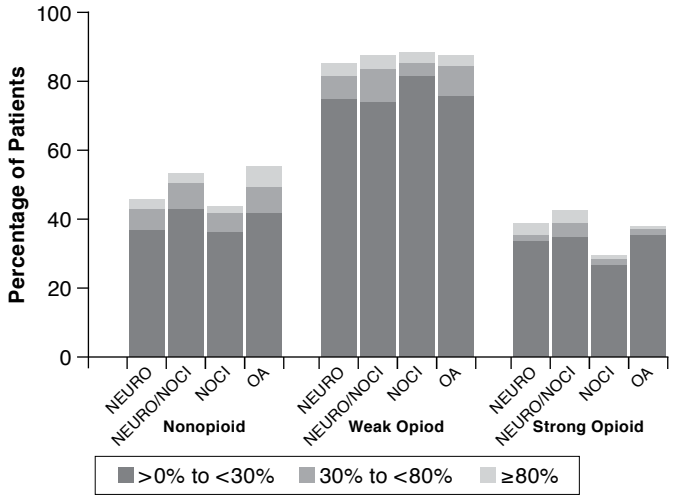
[e]Nonpain-related prescriptions include all prescriptions that are not in the pain-related or adjuvant categories.

NEURO = neuropathic-related neck/back diagnoses; NEURO/NOCI = neuropathic and nociceptive neck/back diagnoses; NOCI = nociceptive neck/back diagnoses; OA = osteoarthritis; SD = standard deviation.

0% to <30% of days with pain medication availability. At least 1 prescription for a weak opioid was filled by the majority of patients (85.1%-88.2%). However, at least 1 opioid (weak or strong) in the observation year was an analysis inclusion criterion. When strong opioids are considered, at least 1 prescription for a strong opioid was filled by a greater percentage of patients with NEURO/NOCI (42.6%) or NEURO (39.0%) diagnoses than patients with NOCI (29.6%) or OA (38.0%) diagnoses (data not shown on graph). Combination treatment, defined as claims for more than 1 pain medication of any type (i.e., within or between WHO ladder steps), was observed in more than half (54.5%) of OA patients, with NEURO/NOCI, NEURO, and NOCI patients following at 53.3%, 44.5%, and 38.9%, respectively (data not shown).

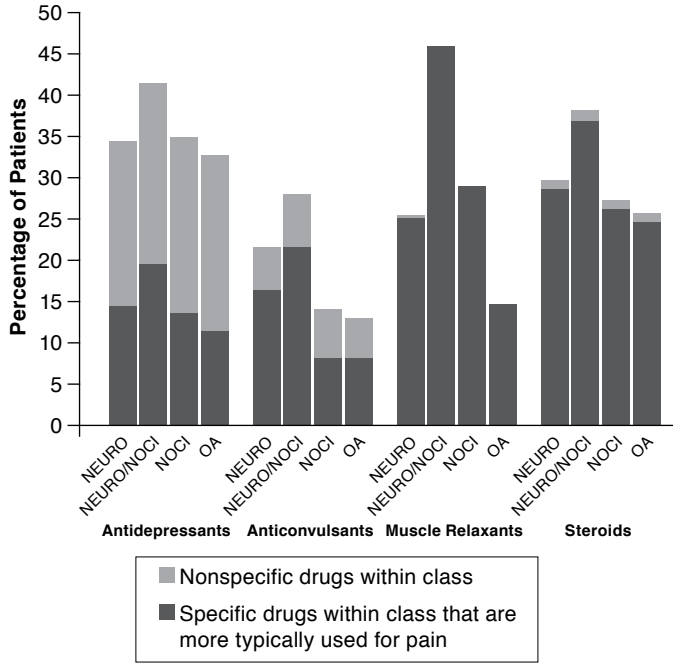
Antidepressants, anticonvulsants, muscle relaxants, and steroids were common treatments and were available to approximately 26.2%, 11.1%, and 10.6% of patients, respectively, during the observation period (Figure 3). Patients in the NEURO/NOCI group had greater availability of adjunct medications. This research also identified the subset of medications within these classes that have been described in the literature as being used as adjuvant treatments for pain. Almost all of the drugs within the muscle relaxant and steroid classes are used specifically for pain. There was less certainty with the antidepressant and anticonvulsant classes for pain. Therefore, statistics are shown for both the overall class as well as for the subset typically used for pain relief. The NEURO/NOCI cohort had the greatest percentage of patients using adjunctive medications from each class (antidepressants 41.5%; anticonvulsants 28.0%; muscle relaxants 46.1%; and steroids 38.1%) compared with the other cohorts, with the use of muscle relaxants being most common. A substantial percentage of patients in all of the cohorts had antidepressant use (range from 32.8% to 41.5%), with approximately half having an antidepressant typically associated with pain relief (tricyclics and serotonin-norepinephrine reuptake inhibitors [SNRI]).

FIGURE 2 Percentage of Patients with WHO Pain Medication by Type of Medication and Frequency of Availability Category



Note: The percentage of days medication available is presented in 3 categories as shaded portions on the bar graph. The difference between the bar height and 100% represents patients with no use of the product.
NEURO = neuropathic-related neck/back diagnoses; NEURO/NOCI = neuropathic and nociceptive neck/back diagnoses; NOCI = nociceptive neck/back diagnoses; OA = osteoarthritis; WHO = World Health Organization.

FIGURE 3 Percentage of Patients with Adjuvant Medication Use over a 2-Year Period by Medication



Note: The shaded areas on the bars represent medications within the class that are more typically used for pain (e.g., amitriptyline within the antidepressants) versus those that are not as typically used for pain (e.g., fluoxetine within the antidepressants).
NEURO = neuropathic-related neck/back diagnoses; NEURO/NOCI = neuropathic and nociceptive neck/back diagnoses; NOCI = nociceptive neck/back diagnoses; OA = osteoarthritis.

Potential Drug Interactions of the Cytochrome P450 Pathway

Considering all cohorts, 32.2% of patients had 10 or more days of overlapping drug availability (of inducers or inhibitors of cytochrome P450 used concomitantly; Table 8). The NEURO/NOCI cohort showed the highest potential for drug interactions, with 38.4% of patients having 10 or more days of overlapping drug availability. The OA, NEURO, and NOCI cohorts followed with 33.4%, 32.3%, and 26.1%, respectively. All pairwise comparisons between cohorts were significantly different at $P < 0.0001$ with the exception of NEURO versus OA, which was $P = 0.3342$.

Adjuvant Procedures

According to coding from the Healthcare Common Procedure Coding System (HCPCS), and Current Procedural Terminology (CPT), chiropractic and physical therapies were the most frequently billed coded claims for services among all cohorts except OA patients (Table 9). The NEURO/NOCI and NOCI cohorts used these adjuvant services to a much larger extent than the other cohorts. The most commonly used services among all cohorts included chiropractic therapy, physical therapy, and TENS (bioelectric therapy), but there was variability among services by cohort. Most statistical tests for differences among the cohorts were significant with a few exceptions. Pairwise tests showed the following tests that were not significant at $P < 0.05$: physical therapy for NOCI versus OA; psychological therapy for NEURO versus NOCI; neuromuscular re-education for NEURO versus NOCI and OA; neuromuscular re-education for NOCI versus OA; spinal cord stimulation for NEURO versus NOCI and NOCI versus OA; and intrathecal pump implant for NOCI versus OA. All other pairwise differences were significant at $P < 0.05$.

Discussion

This assessment provided insights into the challenges physicians face when treating patients presenting with pain. Treatment challenges are complex and encompass patient characteristics (e.g., concomitant illnesses), provider issues (e.g., multiple physician involvement), treatment choices (e.g., types of pain and adjuvants medications used), and treatment consequences (e.g., the potential for drug interactions).

TABLE 8 Patients with at Least 1 Potential Drug Interaction

Overall		NEURO		NEURO/NOCI		NOCI		OA	
n = 85,014		n = 2,375		n = 37,019		n = 39,496		n = 6,124	
n	%[a]	n	%[a]	n	%[a]	n	%[a]	n	%[a]
27,358	32.2	766	32.3	14,224	38.4	10,321	26.1	2,047	33.4

[a]*Denominator is the number of patients in each cohort. All pairwise comparisons are significantly different at P < 0.0001 except NEURO vs. OA (P = 0.3342).*
NEURO = neuropathic-related neck/back diagnoses; NEURO/NOCI = neuropathic and nociceptive neck/back diagnoses; NOCI = nociceptive neck/back diagnoses; OA = osteoarthritis.

TABLE 9 Number and Percentage of Patients by Most Frequently Billed CPT or HCPCS Categories

WHO Adjuvant Treatment	CPT/HCPCS Code for Identification	NEURO (n = 2,375)		NEURO/NOCI (n = 37,019)		NOCI (n = 39,496)		OA (n = 6,124)	
		n	%[a]	n	%[a]	n	%[a]	n	%[a]
Chiropractic therapy	98940-98943, A2000, A9170, X2010, X2020, or X2025	687	28.9	21,776	58.8	26,521	67.1	188	3.1
Physical therapy	97001, 97002, 97110, 97140, 97530, 97150	696	29.3	17,732	47.9	13,818	35	2,102	34.3
TENS unit or bioelectric therapy	97014, 97032, E0720, E0730, G0283, or M0545	423	17.8	15,110	40.8	12,222	30.9	710	11.6
Ultrasound	97035	230	9.7	8,317	22.5	6,303	16	508	8.3
Psychological therapy	90801-90899, 95883, 96100-96103, 96117-96120, G0071-G0094, S9480, W5970, W7962, W7989, W9076, X0630, X0641, X0646-X0648, X0650, X0651, X0655, X0660, X0661, X0680, or X0681	315	13.3	6,145	16.6	5,734	14.5	622	10.2
Traction	97012, E0840, E0849, E0850, E0855, E0856, or E0860	121	5.1	5,976	16.1	4,109	10.4	15	0.2
Neuromuscular re-education	97112	146	6.1	4,247	11.5	2,759	7	396	6.5
Acupuncture/acupressure	97780, 97781, 97810, 97811, 97813, 97814, S0008, X0008, X1420, or X2231	20	0.8	1,068	2.9	844	2.1	20	0.3
Spinal cord stimulation	63660, 63685, or 63688	5	0.2	130	0.4	11	0	1	0
Intrathecal pump implant	62350, 62351, 62360, 62361, 62362, 62367, 62368, or E0785	11	0.5	91	0.2	24	0.1	3	0
Epidural injection	64470, 64472, 64475, 64476, 64479, 64480, 64483, 64484, 62310, or 62311	180	7.6	9,451	25.5	747	1.9	62	1

[a]*Pairwise tests showed the following tests that were not significant at P < 0.05: physical therapy for NOCI vs. OA; psychological therapy for NEURO vs. NOCI; neuromuscular re-education for NEURO vs. NOCI and OA; neuromuscular re-education for NOCI vs. OA; spinal cord stimulation for NEURO vs. NOCI and NOCI vs. OA; and intrathecal pump implant for NOCI vs. OA. All other pairwise differences were significant at P < 0.05.*
CPT = Current Procedural Terminology; HCPCS = Healthcare Common Procedure Coding System.

A large percentage of patients had comorbid conditions. For example, hypertension, a chronic condition frequently requiring lifetime medication treatment, was observed in 36%-61% of the cohorts, with the highest percentage observed in the OA group. These results are consistent with those reported by Gore et al.,[10] who used claims data from managed care health plans to assess comorbidities and resource use among OA patients. Rates of comorbid hypertension, hyperlipidemia, and coronary heart disease reported by Gore et al. were 54.4%, 52.1%, and 10.6%, respectively. The average age of the Gore et al. analysis population was 56.9 years. In the current analysis, the average age of the OA cohort was 53.6, and hypertension, hyperlipidemia, and coronary heart disease observed in the OA cohort were somewhat higher than those reported by Gore et al., at 61.2%, 59.5%, and 11.5%, respectively. The non-OA cohorts in our analysis had comparable cardiovascular comorbidity rates, except that hypertension among the NOCI cohort was lower, at 35.6%. Concomitant rates of depression (12.4%), anxiety (8.6%), and sleep disorders (11.9%) observed by Gore et al. were somewhat lower than reported here (16.5%, 10.7%, 18.9%). Many patients with a comorbid illness will require chronic medication use. Physicians treating patients presenting with pain need to identify medications used for comorbid illnesses to guard against adverse effects and drug interactions.

This analysis further demonstrated that multiple providers were involved in treating the various pain cohorts. In the current analysis, the mean number of prescribing physicians per patient was 4.5 over a 2-year period. Visiting multiple physicians would not be unexpected behavior when chronic illnesses are involved and likely reflects the need for specialists' care. For example, the mean number of specialists visited by the NEURO group was 4.9 during the 2-year period. The

data show the providers seen included GP/FP physicians, IM physicians, orthopedic surgeons, cardiologists, and obstetric gynecologists. Inquiring about medications prescribed by other providers or use of systems that allow physicians to have information from other prescribers would seem prudent.

In terms of treatment choices, weak opioids accounted for most of the pain medication claims used by all cohorts. However, many nonopioids are available without a prescription and may not appear in a paid claims database. The percentage of patients using nonopioids is likely to be an underrepresentation. The mean number of pain-related prescriptions was 8.8 per person over the 2-year period. (The prescription count did not represent consecutive months of treatment but claims that could have occurred at any time during the 2-year period.) This number is more likely indicative of acute pain treatment rather than chronic pain treatment. Chronic pain treatment would have likely resulted in more prescription claims for strong opioids.[12,13] Strong opioid prescriptions are not refillable and require a new prescription each month; therefore, a higher mean for pain-related prescriptions would be expected for chronic treatment.

Prior research has shown that adequate pain control often requires multiple medications.[14-16] In this analysis, overlapping or simultaneous prescriptions for multiple pain medications were observed in more than half (54.5%) of OA patients, with the NEURO/NOCI, NEURO, and NOCI groups following at 53.3%, 44.5%, and 38.9%, respectively. The use of simultaneous medications or perhaps combination therapy might indicate that the primary pain medications were not sufficient as monotherapy for pain relief. A report by Romanò et al. (2012),[17] discussing the treatment of low back pain, compared monotherapy with combination therapy or placebo for the treatment of low back pain and concluded that monotherapy is often only partially effective treatment and that combining drugs with different mechanisms of action might be a rational approach because of the different mechanisms that cause low back pain. Therefore, combination drug treatment for pain is likely to occur but adds another medication to the patient's overall treatment regimen. Combination therapy may also represent use of multiple opioids. For example, patients could be combining a long-acting opioid with a short-acting opioid for breakthrough pain.

In addition to simultaneous treatment with traditional pain medications, claims for adjuvant treatments including antidepressants, anticonvulsants, muscle relaxants, and steroids were observed in this analysis. The mean number of adjuvant claims was 12.7 per person over the 2-year period. These results are consistent with the report of Bair and Sanderson (2011)[18] from a comprehensive literature review of co-analgesics or adjuvant analgesics. The Bair and Sanderson analysis stated that antidepressants (particularly the SNRIs duloxetine and milnacipran), anticonvulsants, skeletal muscle relaxants, topical analgesics, and antispasmodic agents are often used as co-analgesics. According to Bair and Sanderson, the rationale for adjuvant use includes enhancing the effect of opioid analgesics or NSAIDs, providing independent analgesic activity in certain painful conditions, or counteracting the adverse effects of some analgesics. Thus, adjuvant medications are commonly found along with those indicated specifically for pain.

Given the number of prescriptions and concomitant health conditions observed in the pain cohorts, a drug interaction assessment was included to demonstrate the likelihood of interactions among medications. The cytochrome P450 interaction was used because the drugs listed in the claims data could be categorized as inhibitors or inducers of the cytochrome P450 pathway. The results showed that 25.7% of patients had 10 or more days of overlapping drug availability (of inducers or inhibitors of cytochrome P450 used concomitantly). These types of drug-drug exposures have the potential to cause significant pharmacokinetic interactions. Using a claims database of patients taking opioid analgesics, Summers et al. (2011)[19] assessed the economic impact of incident drug-drug exposures (DDEs) with the potential to cause pharmacokinetic drug-drug interactions (DDIs). The Summers et al. analysis reported that drug-drug exposures were relatively common among subjects. Furthermore, health care costs 6 months after the DDE were significantly higher in subjects with DDE versus matched subjects without DDE, providing evidence that drug-drug interactions impact health care costs.

Limitations

As with any claims-based analysis, this analysis may be limited by any coding errors that could have resulted in the misclassification of patients and other variables. Regarding adjunct medications such as antidepressants, there was no information available to verify whether the adjunct medications were used for pain or comorbidities. The claims database does not make it possible to associate prescription claims with diagnoses. Also, the database does not provide a direct link to the provider type who wrote the prescription that appears in the claims data. Several of the analyses presented claim counts. No evaluation of duration of therapy was performed for the adjuvant medications. The DDIs presented in this analysis represented potential interactions. Use of an administrative claims database provides information about drugs that were dispensed; however, there was no way to verify whether the drugs were actually taken simultaneously other than observing overlapping days of supplies. Medications that do not require a prescription are likely to be underrepresented in this analysis. The medications used for this interaction analysis were a selected list of pain-related therapies. Use of a more comprehensive list of all drugs that were actually dispensed would likely detect more potential

interactions. Furthermore, the DDI analysis is exploratory in nature, and no evaluation of the seriousness of the interactions was performed. This analysis did not include cohorts with nonpain-related diagnoses. No commentary can be provided on how patients with pain-related diagnoses compare with patients without pain-related diagnoses.

Conclusions

Treatment of patients with pain-related complaints is complex and further complicated by the existence of concomitant illnesses and treatment by multiple specialists. Choosing the appropriate pain treatment involves assessing currently used medications for existing illnesses and deciding on the appropriate types of pain medications. Use of combination and adjuvant prescription medications may be desirable to optimize efficacy. However, potentially serious drug-drug interactions are a consequence of multiple drug use and require thoughtful consideration by those involved in patient care.

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APPENDIX A Codes Used for Comorbidity Counts, Patient Counts, and Percentages for Gore et al.[10] Comorbidities Appearing on Claims Between August 31, 2006, and September 1, 2008

Comorbidity[a]	ICD-9-CM Diagnosis Code
Mental disorders	
Depression	296.2X, 296.3X, 300.4, 311
Anxiety	300.00, 300.5X, 300.09, 300.20, 300.22, 300.23, 300.29, 300.3, 308.3
Bipolar disorder	296.4X, 296.5X, 296.6X, 296.7X
Generalized anxiety disorder	300.02
Panic disorder	300.01, 300.21
Post-traumatic stress disorder	309.81
Sleep disorders	
Insomnia/sleep disorders	780.5X, 307.4X
Sleep apnea	780.51, 780.53, 780.57
Cardiovascular disorders	
Hypertension	401.XX
Hyperlipidemia	272.0, 272.1, 272.2, 272.4
Coronary heart disease	410.XX-414.XX
Myocardial infarction	410.XX, 412.XX
Congestive heart failure	428.0X
Peripheral vascular disease	440.2X, 440.3X, 443.9
Chronic obstructive pulmonary disease	491.XX, 492.XX, 496.XX
Chronic renal failure	585.XX
Musculoskeletal pain conditions	
Rheumatism, excluding the back	725.XX-728.XX, 729.2X-729.9X
Arthritis and other arthropathies	711.X, 712.X, 713.X, 714.4X, 714.8X, 714.9X, 716.X, 717.X, 718.X, 719.X
Back and neck pain, excluding low back pain	720.XX, 721.0X, 721.2X, 721.5, 721.6, 721.7, 721.8, 721.90, 722.11, 722.30, 722.31, 722.39, 722.4, 722.51, 722.6, 722.80, 722.81, 722.82, 722.90, 722.91, 722.92, 723.XX, 724.01, 724.1, 724.5, 724.8, 724.9
Lumbago	724.2
Low back pain	721.3X, 722.10, 722.32, 722.52, 722.83, 722.93, 724.02, 724.6X, 724.7X
Osteoarthritis	715.X
Rheumatoid arthritis	714.0, 714.1, 714.2
Neuropathic pain conditions	
Other polyneuropathies	344.6, 353.XX, 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
Back and neck pain with neuropathic involvement	721.1, 721.41, 721.42, 721.91, 722.7X, 724.3, 724.4
Trigeminal neuralgia	350.1
Carpal tunnel syndrome	354.0
Causalgias	337.2X, 354.4, 355.71, 355.9
Atypical facial pain	350.2
Neuritis radiculitis, unspecified	729.2
Phantom limb pain	353.6
Autonomic neuropathies	337.1, 337.9

[a]*Three categories that were not included in the manuscript referenced in the title of this table were included in the results table because of their relevance to neuropathic pain (250.XX), diabetic peripheral neuropathy (250.6X), and postherpetic neuralgia (053.19).*

ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification.

APPENDIX B World Health Organization (WHO) Category Assignments for Poly-Pain Analyses (by Ladder Step)

Drug Group	Generic Name	Category for Analysis
Analgesics–anti-inflammatory	Celecoxib	WHO–Step 1
Analgesics–anti-inflammatory	Diclofenac potassium	WHO–Step 1
Analgesics–anti-inflammatory	Diclofenac potassium	WHO–Step 1
Analgesics–anti-inflammatory	Diclofenac with misoprostol	WHO–Step 1
Analgesics–anti-inflammatory	Etodolac	WHO–Step 1
Analgesics–anti-inflammatory	Fenoprofen calcium	WHO–Step 1
Analgesics–anti-inflammatory	Flurbiprofen	WHO–Step 1
Analgesics–anti-inflammatory	Ibuprofen	WHO–Step 1
Analgesics–anti-inflammatory	Indomethacin	WHO–Step 1
Analgesics–anti-inflammatory	Ketoprofen	WHO–Step 1
Analgesics–anti-inflammatory	Ketorolac tromethamine	WHO–Step 1
Analgesics–anti-inflammatory	Lansoprazole-naproxen	WHO–Step 1
Analgesics–anti-inflammatory	Nabumetone	WHO–Step 1
Analgesics–anti-inflammatory	Naproxen	WHO–Step 1
Analgesics–anti-inflammatory	Naproxen sodium	WHO–Step 1
Analgesics–anti-inflammatory	Sulindac	WHO–Step 1
Analgesics–anti-inflammatory	Valdecoxib	WHO–Step 1
Analgesics–anti-inflammatory	Acetaminophen	WHO–Step 1
Analgesics–anti-inflammatory	Aspirin	WHO–Step 1
Analgesics–anti-inflammatory	Diflunisal	WHO–Step 1
Analgesics–anti-inflammatory	Salsalate	WHO–Step 1
Analgesics–nonnarcotic	Aspirin-APAP-salicyl-caffeine	WHO–Step 1
Analgesics–nonnarcotic	Acetaminophen-magnesium-salicylate-phenyltoloxamine-caffeine	WHO–Step 1
Analgesics–nonnarcotic	Acetaminophen- phenyltoloxamine-caffeine	WHO–Step 1
Analgesics–nonnarcotic	Acetaminophen-salicylamide-phenyltoloxamine	WHO–Step 1
Analgesics–nonnarcotic	Acetaminophen-salicylamide-phenyltoloxamine-caffeine	WHO–Step 1
Analgesics–nonnarcotic	Aspirin buffered (al hydrox-mg hydrox-ca carb)	WHO–Step 1
Analgesics–nonnarcotic	Aspirin buffered (cal carb-mag carb-mag oxide)	WHO–Step 1
Analgesics–nonnarcotic	Choline and mag salicylate	WHO–Step 1
Analgesics–narcotic	Acetaminophen-caffeine-dihydrocod	WHO–Step 2
Analgesics–narcotic	Pentazocine with APAP	WHO–Step 2
Analgesics–narcotic	Acetaminophen with codeine	WHO–Step 2
Analgesics–narcotic	Aspirin with codeine	WHO–Step 2
Analgesics–narcotic	Aspirin-caffeine-butalbital with codeine	WHO–Step 2
Analgesics–narcotic	Butalbital-aspirin-caffeine with codeine	WHO–Step 2
Analgesics–narcotic	Codeine phosphate	WHO–Step 2
Analgesics–narcotic	Codeine sulfate	WHO–Step 2
Analgesics–narcotic	Dihydrocodeine compound	WHO–Step 2
Analgesics–narcotic	Hydrocodone-acetaminophen	WHO–Step 2
Analgesics–narcotic	Hydrocodone-ibuprofen	WHO–Step 2
Analgesics–narcotic	Propoxphene compound	WHO–Step 2
Analgesics–narcotic	Propoxphene HCL	WHO–Step 2
Analgesics–narcotic	Propoxphene HCL with APAP	WHO–Step 2
Analgesics–narcotic	Propoxphene napsylate	WHO–Step 2
Analgesics–narcotic	Propoxphene-N with APAP	WHO–Step 2
Analgesics–narcotic	Tramadol HCL	WHO–Step 2
Analgesics–narcotic	Tramadol-acetaminophen	WHO–Step 2
Analgesics–opioid	Oxymorphone	WHO–Step 3
Analgesics–opioid	Fentanyl	WHO–Step 3
Analgesics–opioid	Fentanyl citrate	WHO–Step 3
Analgesics–opioid	Hydromorphone HCL	WHO–Step 3
Analgesics–opioid	Levorphanol tartrate	WHO–Step 3
Analgesics–opioid	Meperidine HCL	WHO–Step 3
Analgesics–opioid	Meperidine with promethazine	WHO–Step 3
Analgesics–opioid	Methadone HCL	WHO–Step 3
Analgesics–opioid	Morphine sulfate	WHO–Step 3
Analgesics–opioid	Morphine sulfate beads	WHO–Step 3
Analgesics–opioid	Morphine sulfate for continuous microinfusion	WHO–Step 3
Analgesics–opioid	Oxycodone HCL	WHO–Step 3
Analgesics–opioid	Oxycodone with acetaminophen	WHO–Step 3
Analgesics–opioid	Oxycodone with aspirin	WHO–Step 3
Analgesics–opioid	Oxycodone-ibuprofen	WHO–Step 3
Analgesics–opioid	Oxymorphone HCL	WHO–Step 3