Opioid Use in Patients with Ankylosing Spondylitis Is Common in the United States: Outcomes of a Retrospective Cohort Study

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ABSTRACT. ***Objective.*** To assess the prevalence of chronic opioid use in patients with ankylosing spondylitis (AS), and to compare the characteristics of patients with and without chronic opioid use.

Methods. This was a retrospective cohort study of patients with AS identified in the Truven Health MarketScan Research database between January 1, 2012, and March 31, 2017. Commercial and Medicaid claims data were examined using both specific (720.0 and M45.x) and broader (720.x and M45.x) International Classification of Diseases (ICD) coding definitions. Patients were aged ≥ 18 years on the date of first qualifying ICD code occurrence (the index date). Demographics and clinical characteristics were assessed in the 12-month period preceding the index date. The 12-month followup period was used to assess prevalence and characteristics of chronic opioid use.

Results. Chronic opioid use was common among patients with commercial claims (23.5% of ICD 720.0 patients; 27.3% of ICD 720.x patients), and especially those with Medicaid claims (57.1% and 76.7%, respectively). The proportion of patients with claims for anti–tumor necrosis factor therapies during followup was often low, and for Medicaid patients was lower among those with chronic opioid use (29.6% of ICD 720.0 patients; 2.3% of ICD 720.x patients) than those without (47.1% and 7.1%, respectively). Among chronic opioid users in all cohorts, the cumulative supply of opioids was typically high (≥ 270 days in the followup period); most opioids prescribed were Schedule II.

Conclusion. Patients with AS receive opioids with disturbing frequency. The infrequent prescription of recommended therapies to these patients reflects a need to optimize treatment further through education of patients and healthcare professionals alike. (J Rheumatol First Release June 1 2019; doi:10.3899/jrheum.180972)

Key Indexing Terms:
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Ankylosing spondylitis (AS) is a chronic inflammatory disease involving the axial skeleton that causes considerable pain and disability. Although both inflammatory and noninflammatory processes contribute to pain[1], therapies that address inflammation hold the most promise for improving signs and symptoms, and slowing disease progression[2,3,4,5]. Such therapies are recommended by current treatment guidelines[6], which specify nonsteroidal antiinflammatory drugs (NSAID) as initial pharmacotherapy, and anti–tumor necrosis factor (anti-TNF) therapy in patients who respond inadequately to NSAID. Conventional disease-modifying antirheumatic drugs (cDMARD) are recommended only for peripheral arthritis, because they are ineffective in axial disease[6].

Nevertheless, in some patients, symptoms associated with AS are inadequately controlled by NSAID, and anti-TNF therapy may be inaccessible because of cost or ineligibility. Moreover, availability of specialist care is limited in many parts of the United States, with smaller cities and/or rural areas having few or no practicing rheumatologists[7]. This is problematic, given that nonrheumatologist physicians may be unfamiliar with treatment guidelines. Uninsured patients

may also have restricted access to specialist care[8]. Thus, for many patients with AS, prescription opioids may offer immediately accessible pain management.

Standards from the US Joint Commission (formerly the Joint Commission on Accreditation of Healthcare Organizations) released in the early 2000s led to increased prescription of opioids for noncancer pain[9]. However, the use of analgesics (including opioids) is not addressed in treatment recommendations for AS[6], and guidelines published by the US Centers for Disease Control and Prevention (CDC)[10] and the American Society of Interventional Pain Physicians[11] have sought to limit opioid use.

Despite these recommendations, misuse of prescription opioids remains a major public health issue in the United States, with an estimated economic burden of about $78 billion/year[12]. In 2009, deaths from drug overdose (including prescription opioids) outnumbered those from motor vehicle accidents for the first time in US history[13]. More recently, data from the National Institute on Drug Abuse revealed that the sharpest increase in deaths from drug overdose in 2016 was related to synthetic opioids[14]. Data from the Prescription Behavior Surveillance System, an initiative jointly funded by the CDC and the Food and Drug Administration, revealed that in 2013, opioid analgesics were prescribed almost twice as frequently as stimulants and benzodiazepines, with higher rates among females and those aged ≥ 45 years[15].

In addition to these broader concerns, prescription opioids fail to target the underlying pathology of AS, resulting in suboptimal treatment. This was corroborated by a recent prospective cohort study, in which opioid use among patients with AS was associated with subjective measures such as depression, Bath Ankylosing Spondylitis Disease Activity Index, and Bath Ankylosing Spondylitis Functional Index, rather than objective markers of inflammation[16]. Thus, any trend toward greater opioid use in AS has ramifications at both individual and societal levels. However, little is known about the population of patients with AS using chronic opioids. This information could be used to guide patients and practitioners to more targeted therapy options, thereby reducing the individual, societal, and economic burdens of opioid abuse.

Here we describe a retrospective cohort study assessing the prevalence of opioid use in the AS population, and compare the characteristics of patients with and without chronic opioid use.

MATERIALS AND METHODS

Patients. Patients were aged ≥ 18 years on the date of the qualifying claim, and had ≥ 2 claims with the specified diagnosis codes [International Classification of Diseases, 9th revision (ICD-9) code 720.x or ICD-10 code M45.x] > 7 days apart by any physician (provider type on the claim), or ≥ 1 claim with the diagnosis code by a rheumatologist in an outpatient setting. In an inpatient setting, 1 claim was sufficient for inclusion and physician type was not considered. Patients were also required to have ≥ 12 months of enrollment in medical and pharmacy benefits prior to and following the index date, which was defined as the date of the first qualifying ICD code in the observation period. Because Medicare (health insurance for the elderly) data were not included, this analysis focused primarily on patients < 65 years of age.

In cases in which patients did not meet all inclusion criteria upon receiving the first diagnosis code in the observation period, this code was disregarded in the algorithm, and assessment of eligibility was repeated with the subsequent code. Patients with a history of cancer, except nonmelanoma skin cancer, were excluded from the study.

Study design. This was a retrospective cohort study of patients with AS identified in a US claims database (Truven Health MarketScan) between January 1, 2012, and March 31, 2017. Commercial Claims and Encounters and Medicaid claims data were examined, and both prevalent and incident cases (the latter being those without an AS claim during the baseline period) were included. "Commercial claims" refer to those made through private insurance companies, while "Medicaid claims" are made through the government-funded Medicaid program. Index date selection was restricted to the period between January 1, 2013, and March 31, 2016.

The 12-month period preceding the index date (baseline period) was used to assess demographics, clinical characteristics, comorbidities, and prior treatment use. The 12-month period following (and including) the index date (followup period) was used to examine opioid use and exposure to other treatments of interest (based on the presence of ≥ 1 claim for the specified medication within the followup period).

Primary objective. The primary objective was to estimate the prevalence of chronic opioid use in the study population during the followup period (defined as ≥ 90 cumulative days of opioid use, limited to tablets, capsules, and patches; for a complete list of opioids, see Supplementary Table 1, available with the online version of this article). Cumulative days of use was based on the supply value on the opioid pharmacy claims. Opioid claims occurring within ± 7 days of hospitalization, or ± 2 days of an emergency room or urgent care visit were not considered in this analysis. The prevalence of chronic opioid use was further stratified by whether a patient had seen a rheumatologist during the followup period.

Treatment exposure was described by chronic opioid user status, including concomitant use of prescription NSAID and/or anti-TNF therapies. Concomitant exposure was defined as a claim for the medication of interest within ± 30 days of an opioid claim.

Secondary objectives and other analyses. A secondary objective was to compare demographic and clinical characteristics (taken at the index date and during the baseline period) between patients with and without chronic opioid use during the followup period. Comorbidities were identified based on the presence of claims with selected diagnostic codes (Supplementary Table 2, available with the online version of this article) and/or algorithms.

The prevalence of opioid use during the followup period was stratified by drug schedule, limited to Schedule II, III, and IV. Where claims had been made for opioids with different schedules, the highest (most potent) was used for classification purposes. Chronic opioid users were also classified by duration of opioid use during the followup period (described categorically as the number and percentage of chronic users with 90 to < 180, 180 to < 270, and ≥ 270 days of opioid use). Duration was determined by summing the days' supply for all opioid claims during the followup period, which need not have been consecutive. If a patient had overlapping claims, the number of days was additive. The duration from the index date to the index opioid claim (i.e., the first claim for opioids during the followup period) was also described for chronic opioid users.

For incident chronic opioid users (i.e., those without chronic opioid use in the baseline period), exposures to treatments commonly used for AS were described in the 6 months preceding the index opioid claim.

Analysis sets. All analyses were conducted in patients with ≥ 1 ICD-9 720.0 or ICD-10 M45.x code during the baseline or followup period (the "720.0 cohort"). Each analysis was also performed in the broader population of patients who met the eligibility criteria (the "720.x cohort"). The 720.x code

encompasses various presentations of spondyloarthropathy; while there is no ICD code specific for nonradiographic axial spondyloarthritis (nr-axSpA), this may be included in one of the 720.x codes.

Analyses were performed separately for patients with commercial insurance and Medicaid.

Statistical analysis. Comparative analysis using the chi-square test was performed to compare demographic and clinical characteristics of patients who had chronic opioid use versus those who did not. An analysis comparing opioid use between the commercial claims and Medicaid populations was also performed using the same approach. Owing to the descriptive features of this study, no sample size calculations were performed. Missing data are indicated where relevant.

Ethical approval. Because the database used in this study consists of deidentified data compliant with the US Health Insurance Portability and Accountability Act of 1996, no ethics committee approval was required.

RESULTS

Truven commercial claims data for the 720.0 cohort: baseline period. The 720.0 commercial claims cohort (n = 11,945) was split broadly between the 35–44, 45–54, and ≥ 55-year age groups (23.4%, 30.1%, and 27.1%, respectively), with a slight male majority (54.3%; Table 1). More than half of patients (58.3%) had a rheumatologist listed as the provider on the index claim. Depression and anxiety were observed in 15.5% and 13.8% of patients, respectively, and most patients (61.9%) met the study criteria for prevalent AS.

Truven commercial claims data for the 720.0 cohort: followup period. Roughly one-quarter of patients (23.5%) had chronic opioid use during the followup period (Figure 1A). This was similar between patients who had (22.5%) and had not (25.1%) seen a rheumatologist. Depression and anxiety during the baseline period were more prevalent in patients with chronic opioid use than in those without (depression: 25.4% vs 12.5%; anxiety: 20.9% vs 11.7%; $p < 0.0001$ for both; Table 1). The cumulative supply of opioids was ≥ 270 days for most chronic users (61.6%; Supplementary Figure 1A, available with the online version of this article), with most prescriptions (84.1%) being for Schedule II opioids.

Claims for anti-TNF therapies, DMARD, and NSAID in the followup period were similar between patients with and without chronic opioid use, although claims for muscle relaxants and oral corticosteroids were more frequent among chronic opioid users (54.4% vs 20.2%, and 18.4% vs 9.6%, respectively; Figure 2A). When concomitant medication use was examined exclusively among chronic opioid users (n = 2812), similar proportions had claims for NSAID alone (26.5%), anti-TNF therapy alone (22.8%), both drug classes (25.8%), and neither drug class (24.9%; Supplementary Figure 2A, available with the online version of this article).

Table 1. Baseline data for patients with Truven commercial claims (720.0 cohort).

Characteristics	Total AS Study Population, n = 11,945	With Chronic Opioid Use, n = 2812	Without Chronic Opioid Use, n = 9133	p (chronic opioid use vs not)
Age, yrs				< 0.0001
Mean (SD)	46 (11.6)	48 (10.3)	45 (11.9)	
18–24	738 (6.2)	74 (2.6)	664 (7.3)	
25–34	1575 (13.2)	301 (10.7)	1274 (13.9)	
35–44	2798 (23.4)	610 (21.7)	2188 (24.0)	
45–54	3599 (30.1)	961 (34.2)	2638 (28.9)	
≥ 55	3235 (27.1)	866 (30.8)	2369 (25.9)	
Sex				< 0.0001
Female	5462 (45.7)	1401 (49.8)	4061 (44.5)	
Male	6483 (54.3)	1411 (50.2)	5072 (55.5)	
Rheumatologist as provider on index claim				< 0.0001
Yes	6958 (58.3)	1468 (52.2)	5490 (60.1)	
Comorbidities				
Depression	1853 (15.5)	715 (25.4)	1138 (12.5)	< 0.0001
Anxiety	1653 (13.8)	587 (20.9)	1066 (11.7)	< 0.0001
RA	946 (7.9)	349 (12.4)	597 (6.5)	< 0.0001
PsA	477 (4.0)	143 (5.1)	334 (3.7)	0.0007
Psoriasis	381 (3.2)	93 (3.3)	288 (3.2)	0.6848
IBD	675 (5.7)	201 (7.1)	474 (5.2)	< 0.0001
Opioid dependence or abuse	180 (1.5)	133 (4.7)	47 (0.5)	< 0.0001
Imaging or genotyping procedures				
MRI or radiograph	4559 (38.2)	1301 (46.3)	3258 (35.7)	< 0.0001
Radiograph	3946 (33.0)	1093 (38.9)	2853 (31.2)	< 0.0001
MRI	1840 (15.4)	635 (22.6)	1205 (13.2)	< 0.0001
HLA-B27 testing	1708 (14.3)	379 (13.5)	1329 (14.6)	0.1550

Values are n (%) unless otherwise specified. AS: ankylosing spondylitis; RA: rheumatoid arthritis; PsA: psoriatic arthritis; IBD: inflammatory bowel disease; MRI: magnetic resonance imaging.

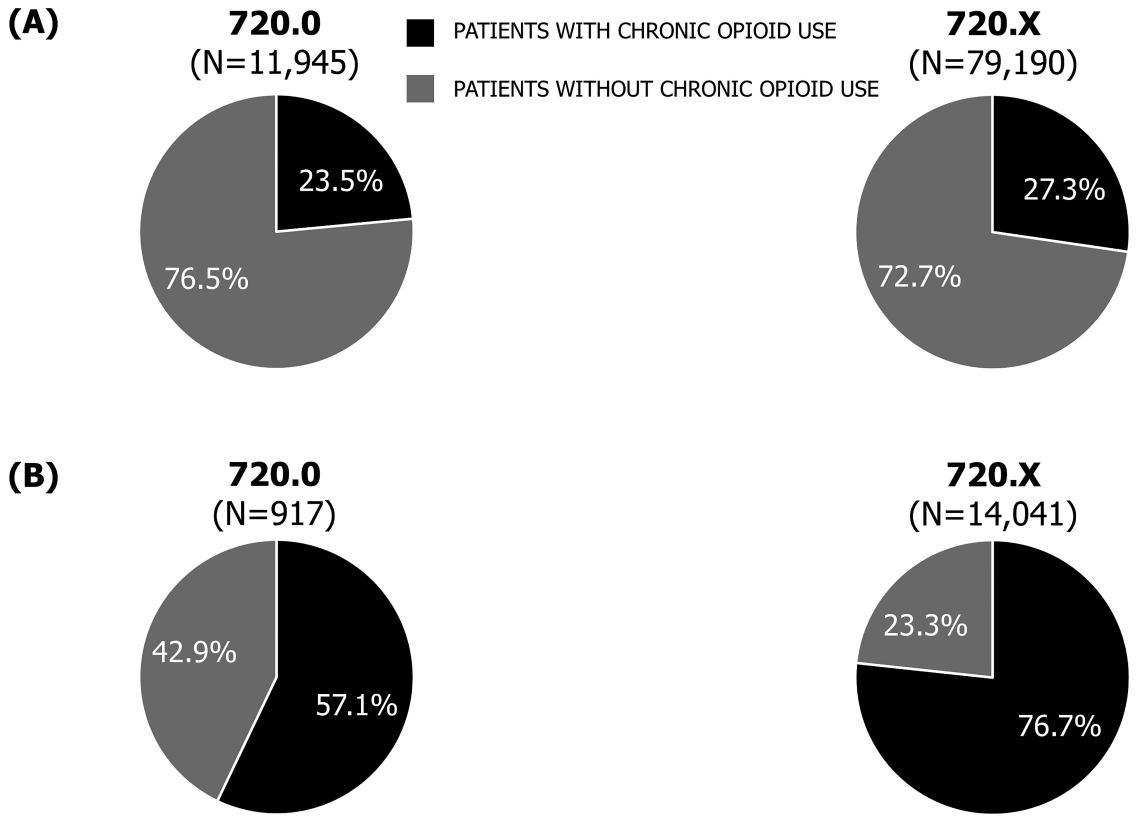

Figure 1. The prevalence of chronic opioid use among patients with (A) Truven commercial and (B) Truven Medicaid claims.

Among incident chronic opioid users (n = 443), 29.1% had no claims for either drug class in the 6 months prior to the incident opioid claim, with 35.4% having claims for NSAID alone and 16.3% for anti-TNF therapy alone.

Truven commercial claims data for the 720.x cohort. In the broader 720.x population (n = 79,190), most patients were distributed across the 45–54 and ≥ 55-year age groups (31.1% and 30.9%, respectively), with a female predominance (63.9%; Supplementary Table 3, available with the online version of this article).

As in the 720.0 cohort, about one-quarter (27.3%) of patients in the broader population had chronic opioid use during followup (Figure 1A). Again, this proportion was similar between those who had (28.9%) and had not (26.9%) seen a rheumatologist during this period.

Use of anti-TNF therapies, DMARD, and oral corticosteroids was comparable between patients with and without chronic opioid use, although NSAID and muscle relaxants were used more frequently among the former (Figure 2B). Unlike the 720.0 population, examination of concomitant medications in chronic opioid users alone (n = 21,590) revealed that most patients had claims for NSAID alone (47.9%), or no claims for either NSAID or anti-TNF therapies (43.3%; Supplementary Figure 2A, available with the online version of this article). Among incident chronic opioid users in this population (n = 4430), 46.8% of patients had no claims for either NSAID or anti-TNF therapies in the 6 months preceding the incident opioid claim, while 45.8% had claims for NSAID alone in this period.

Truven Medicaid data for the 720.0 cohort: baseline period. The 720.0 Medicaid cohort (n = 917) had about an even distribution of patients across age groups (apart from 18–24 yrs), with a sex split close to equal (53.3% female; Table 2). A rheumatologist was listed as the provider on the index claim for 14.4% of patients. Depression and anxiety were common (39.5% and 34.4% of patients, respectively), and most patients (60.1%) met study criteria for prevalent AS.

Truven Medicaid data for the 720.0 cohort: followup period. More than half of patients (57.1%) had chronic opioid use during the followup period (Figure 1B), though this proportion was lower in the subgroup who had seen a rheumatologist (44.8%). Psychiatric comorbidities were more prevalent among chronic opioid users (depression: 47.7% vs 28.5%; anxiety: 41.4% vs 24.9%; $p < 0.0001$ for both; Table 2). The cumulative supply of opioids exceeded 270 days for most chronic opioid users (70.2%; Supplementary Figure 1B, available with the online version of this article), and most opioids prescribed were Schedule II (92.2%).

The use of DMARD, oral corticosteroids, and NSAID during followup was comparable between patients with and

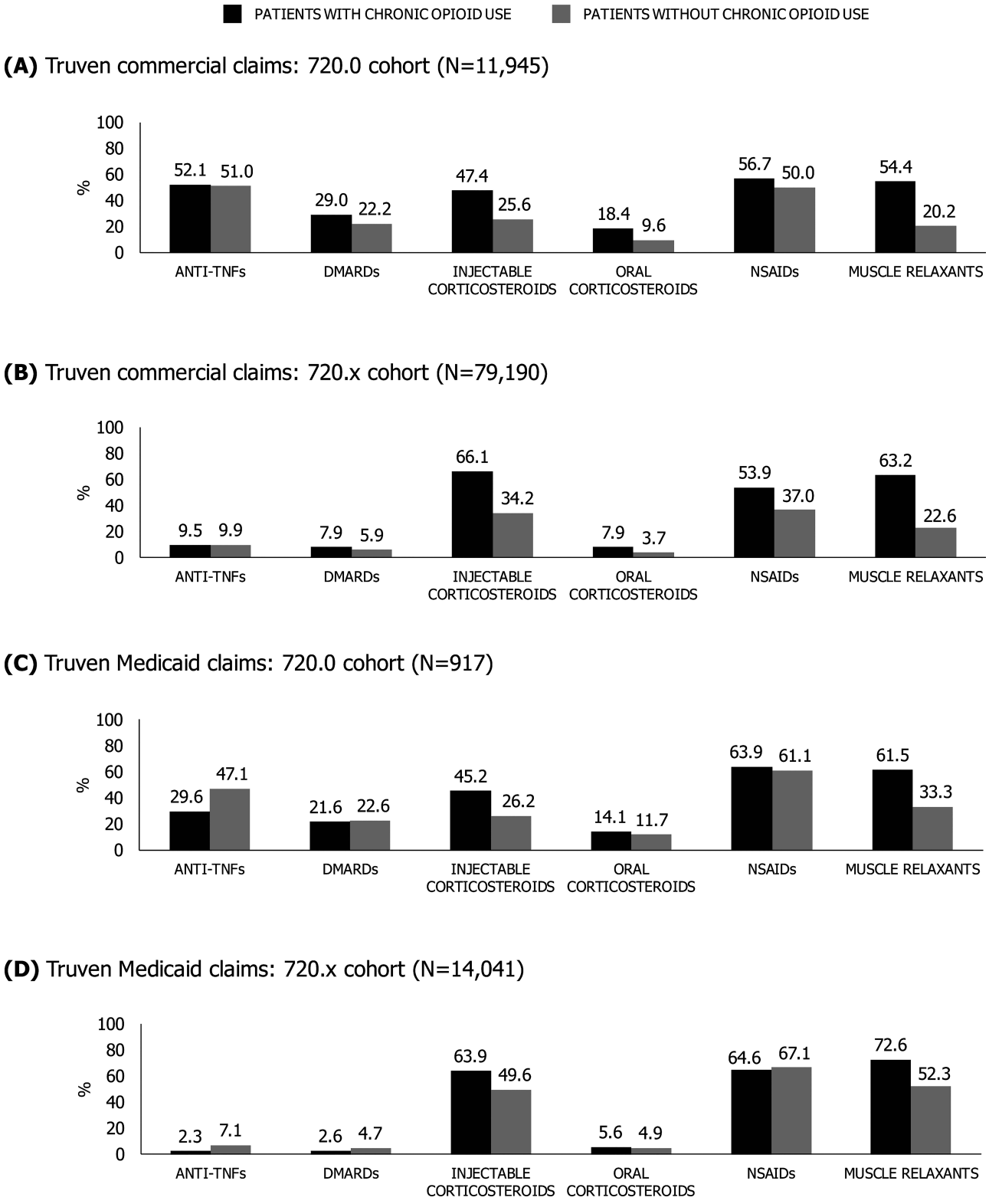

Figure 2. Medication claims during the followup period, stratified by chronic opioid user status. DMARD: disease-modifying antirheumatic drug; NSAID: nonsteroidal antiinflammatory drug; anti-TNF: anti–tumor necrosis factor.

Table 2. Baseline data for patients with Truven Medicaid claims (720.0 cohort).

Characteristics	Total AS Study Population, n = 917	With Chronic Opioid Use, n = 524	Without Chronic Opioid Use, n = 393	p (chronic opioid use vs not)
Age, yrs				< 0.0001
Mean (SD)	43 (11.6)	45 (10.9)	41 (12.2)	
18–24	53 (5.8)	14 (2.7)	39 (9.9)	
25–34	187 (20.4)	96 (18.3)	91 (23.2)	
35–44	275 (30.0)	152 (29.0)	123 (31.3)	
45–54	223 (24.3)	149 (28.4)	74 (18.8)	
≥ 55	179 (19.6)	113 (21.6)	66 (16.8)	
Sex				0.0267
Female	489 (53.3)	296 (56.5)	193 (49.1)	
Male	428 (46.7)	228 (43.5)	200 (50.9)	
Rheumatologist as provider on index claim				
Yes	132 (14.4)	60 (11.5)	72 (18.3)	0.0034
Comorbidities				
Depression	362 (39.5)	250 (47.7)	112 (28.5)	< 0.0001
Anxiety	315 (34.4)	217 (41.4)	98 (24.9)	< 0.0001
RA	97 (10.6)	60 (11.5)	37 (9.4)	0.3213
PsA	20 (2.2)	11 (2.1)	9 (2.3)	0.8448
Psoriasis	26 (2.8)	12 (2.3)	14 (3.6)	0.2507
IBD	56 (6.1)	32 (6.1)	24 (6.1)	1.0
Opioid dependence or abuse	60 (6.5)	41 (7.8)	19 (4.8)	0.0700
Imaging or genotyping procedures				
MRI or radiograph	474 (51.7)	294 (56.1)	180 (45.8)	0.0020
Radiograph	416 (45.4)	256 (48.9)	160 (40.7)	0.0142
MRI	205 (22.4)	136 (26.0)	69 (17.6)	0.0025
HLA-B27 testing	138 (15.0)	77 (14.7)	61 (15.5)	0.7289

Values are n (%) unless otherwise specified. AS: ankylosing spondylitis; RA: rheumatoid arthritis; PsA: psoriatic arthritis; IBD: inflammatory bowel disease; MRI: magnetic resonance imaging.

without chronic opioid use. However, a smaller proportion of chronic opioid users had claims for anti-TNF therapy (29.6% vs 47.1%), while a greater proportion had claims for muscle relaxants (61.5% vs 33.3%; Figure 2C). Among chronic opioid users (n = 524), many patients had concomitant claims exclusively for NSAID (41.4%) or no claims for either NSAID or anti-TNF therapies (30.0%; Supplementary Figure 2B, available with the online version of this article). Treatment patterns among incident chronic opioid users were not assessed in this population, because of the low number of such patients (n = 100).

Truven Medicaid data for the 720.x cohort. In the broader 720.x population (n = 14,041), most patients fell within the 45–54 and ≥ 55-year age groups (30.5% and 22.2%, respectively), with a female majority (74.4%; Supplementary Table 4, available with the online version of this article).

Compared to the 720.0 subpopulation, a greater proportion of these patients (76.7%) had chronic opioid use during the followup period (Figure 1B); however, as with 720.0 patients, this proportion was lower in patients who had seen a rheumatologist (63.1%) compared to those who had not (76.9%).

The prevalence of claims for anti-TNF therapy, DMARD, oral corticosteroids, and NSAID during followup were similar between patients with and without chronic opioid use in this cohort; however, as in the 720.0 subpopulation, claims for muscle relaxants were more frequent among those with chronic opioid use (72.6% vs 52.3%; Figure 2D). Similar to the 720.0 cohort, most patients with chronic opioid use (n = 10,767) had a claim suggesting concomitant use of NSAID without anti-TNF therapy (62.5%), while more than one-third (35.4%) did not have claims for either drug class (Supplementary Figure 2B, available with the online version of this article).

DISCUSSION

Misuse of prescription opioids is a major public health issue in the United States, with substantial implications at individual and societal levels. The current treatment guidelines for AS specify use of NSAID as initial pharmacotherapy, with anti-TNF therapy in cases of NSAID inefficacy or intolerance[6]. However, for many patients, prescription opioids — while not addressing the underlying inflammation — may offer an inexpensive and rapid means of achieving symptomatic relief. In this report, we describe the prevalence of chronic opioid use among patients with AS identified in the Truven MarketScan commercial and Medicaid databases. We demonstrate the worrisome frequency with which opioid analgesics are prescribed to AS

patients, while claims for recommended therapies are comparatively lacking.

Comparisons between the 720.0 and 720.x cohorts revealed that the former aligns more closely with demographic characteristics of patients with AS (e.g., higher prevalence of males[17,18]), although rates of psychiatric comorbidities were comparable between the 2 cohorts. During the followup period, more 720.0 patients had claims for anti-TNF therapy, irrespective of opioid status. The comparison between commercial and Medicaid patients revealed a greater prevalence of anxiety and depression among those with Medicaid claims.

Despite these differences, a substantial proportion of patients in all cohorts had pharmacy claims for prescription opioids. This was particularly pronounced in the Medicaid population, where more than three-quarters of patients were chronic opioid users. Given that comparatively few Medicaid patients had a rheumatologist listed as the provider type on the index claim, possibly owing to referral mechanisms or geographic constraints, the substantial number of pharmacy claims for prescription opioids may indicate that primary care physicians are unfamiliar with current treatment guidelines or are uncomfortable prescribing therapy indicated for AS. Alternatively, it may be that Medicaid patients receive improper diagnoses as a result of time constraints, which could lead to both prescription of opioids over targeted therapies, and misclassification of patients as spondyloarthropathy or AS cases. Patients in this cohort may also have limited access to effective treatments because of prescription coverage limitations. However, given the observational character of this study, these explanations are at best speculative. The difference in chronic opioid use between commercial and Medicaid patients reached statistical significance for both 720.x and 720.0 patients (data not presented in this report); however, given important differences in the characteristics of the 2 populations, identifying a reason for the difference is beyond the scope of this analysis. The magnitude of opioid use among chronic users was also considerable, with most patients, in every cohort, having a ≥ 270-day opioid supply based on claims during the followup period.

When patients were stratified by opioid status, higher rates of depression and anxiety were consistently observed among those with chronic opioid use. Further, while claims for some medications were more frequent among chronic opioid users, those for recommended treatments such as anti-TNF therapy were not. The high usage of muscle relaxants is worrisome, because concomitant use with opioids increases the risk of respiratory depression and death[19]. An understanding of the reason for prescription of opioids and muscle relaxants in this population is therefore needed.

Among incident chronic opioid users with commercial insurance, between 29.1% and 46.8% of patients did not have a claim for an NSAID or anti-TNF agent in the 6 months before filling a claim for an opioid. Supplemental analysis of these results by incident/prevalent AS status did not differ for any cohort (results not shown). This may suggest that rather than failing recommended treatments, patients are receiving opioids before initiating these treatments. If this is the case, there may be an opportunity to prevent chronic opioid use by intervening with recommended therapies earlier in the patient's treatment course. In addition, therapies such as NSAID and anti-TNF target the underlying inflammation of AS and may slow or prevent longterm progression[2,3,4,5], a distinct clinical benefit over symptomatic therapies such as opioids.

Considering established guidelines for treating AS, the reasons for frequent opioid prescription remain uncertain. While it is possible that some patients are prescribed opioids inappropriately, there is mounting evidence to suggest that misuse may occur even in cases where they are needed[20,21]. Further, there is evidence that opioid-naive patients prescribed opioids for short-term pain relief are at risk for later dependence. In one study, 17% of naive patients who received opioids in an emergency room setting became recurrent users[22].

Our analysis has limitations. First, the coding definitions used may not correlate completely with clinical diagnoses. While we used validated algorithms to minimize disease misclassification, claims data have limitations, including reliance on accurate diagnostic coding and exclusion of patients without commercial insurance. The latter means that unemployed patients (who often have the most severe disease) will be underrepresented in the database, affecting the generalizability of the results. Nevertheless, inclusion of Medicaid patients in this study enabled assessment of a population without commercial insurance.

There are also limitations regarding use of the broader 720.x population in this study. Though we conducted these analyses intending to identify patients with nr-axSpA, the broader approach likely increased inclusion of false-positive cases. For this reason, we have focused our descriptions on the 720.0 subpopulation, using the broader population for comparative purposes. Nevertheless, the inability to accurately discriminate true AS/nr-axSpA cases within the 720.x cohort should be considered when interpreting the results.

Further limitations derive from the use of databases as the primary source of information, which provided incomplete data on covariates. Moreover, there was a lack of information regarding the indication for which opioids were prescribed, as well as patient compliance with the prescribed medication, neither of which are recorded on pharmacy claims. However, by excluding patients with most cancer diagnoses, we increased the likelihood that the opioid claims identified in this study were associated with AS.

The use of opioid schedule for stratification is also subject to limitations. The majority of opioids recorded in this study were Schedule II, which encompasses a wide range of opioid potencies and causes information on dose to be lost. Future

analyses might overcome this through use of morphine milligram equivalents, though this approach was outside the scope of the present study.

A final important consideration is the use of over-the-counter NSAID, which would not have been recorded when analyzing data from pharmacy claims. This should be noted when considering concomitant or historical treatment exposure, although it is unlikely that many patients were taking these drugs in antiinflammatory doses.

Our findings suggest that opioid prescription is common among patients with AS in the United States. However, several questions remain. The timing of opioid use relative to diagnosis remains unclear. While it is possible that some patients are prescribed opioid analgesics before they receive a specialist diagnosis, for others, there may have been barriers to receiving appropriate treatment even after diagnosis. Though we did limit some analyses to incident chronic opioid users, there are many others for whom this sequence of events would remain uncertain.

Nevertheless, the high proportion of chronic opioid users with a supply for ≥ 270 days indicates that the issue is both frequent and enduring. Thus, there is a pressing need to identify barriers to optimizing AS therapy within the treatment guidelines, to further define the circumstances that underlie chronic opioid usage, and to educate patients and practitioners on more appropriate therapies for the disease.

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ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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