Opioid Analgesic Use in Patients with Ankylosing Spondylitis: An Analysis of the Prospective Study of Outcomes in an Ankylosing Spondylitis Cohort

Jonathan D. Dau, MinJae Lee, Michael M. Ward, Lianne S. Gensler, Matthew A. Brown, Thomas J. Learch, Laura A. Diekman, Amirali Tahanan, Mohammad H. Rahbar, Michael H. Weisman, and John D. Reveille

ABSTRACT. ***Objective.*** Opioid analgesics may be prescribed to ankylosing spondylitis (AS) patients with pain that is unresponsive to antirheumatic treatment. Our study assessed factors associated with opioid usage in AS.

Methods. A prospective cohort of 706 patients with AS meeting modified New York criteria followed at least 2 years underwent comprehensive clinical evaluation of disease activity and functional impairment. These were assessed by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Bath Ankylosing Spondylitis Functional Index (BASFI). Radiographic severity was assessed by the Bath Ankylosing Spondylitis Radiology Index and modified Stokes Ankylosing Spondylitis Scoring System. Medications taken concurrently with opioids, as well as C-reactive protein (CRP) levels and erythrocyte sedimentation rate (ESR), were determined at each study visit, performed every 6 months. Analyses were carried out at baseline, and longitudinal multivariable models were developed to identify factors independently associated with chronic and intermittent opioid usage over time.

Results. Factors significantly associated with opioid usage, especially chronic opioid use, included longer disease duration, smoking, lack of exercise, higher disease activity (BASDAI) and functional impairment (BASFI), depression, radiographic severity, and cardiovascular disease. Patients taking opioids were more likely to be using anxiolytic, hypnotic, antidepressant, and muscle relaxant medications. Multivariable analysis underscored the association with smoking, older age, antitumor necrosis factor agent use, and psychoactive drugs, as well as with subjective but not objective determinants of disease activity.

Conclusion. Opioid usage was more likely to be associated with subjective measures (depression, BASDAI, BASFI) than objective measures (CRP, ESR), suggesting that pain in AS may derive from sources other than spinal inflammation alone. (J Rheumatol First Release December 1 2017; doi:10.3899/jrheum.170630)

Key Indexing Terms:
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From the Department of Internal Medicine, Division of Rheumatology, and the Division of Clinical and Translational Sciences, McGovern Medical School at The University of Texas Health Science Center Houston, Houston, Texas; National Institute of Arthritis and Musculoskeletal and Skin Diseases, US National Institutes of Health, Bethesda, Maryland; Department of Medicine, Division of Rheumatology, University of California San Francisco (UCSF), San Francisco, California, USA; University of Queensland Diamantina Institute, Translational Research Institute, and Institute of Health and Biomedical Innovation, Queensland University of Technology, Princess Alexandra Hospital, Queensland, Australia; Division of Rheumatology, Cedars Sinai Medical Center, Los Angeles, California, USA.

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J.D. Dau, MD, Department of Internal Medicine, Division of Rheumatology, McGovern Medical School at The University of Texas Health Science Center Houston; M.J. Lee, PhD, Department of Internal Medicine, Division of Clinical and Translational Sciences, McGovern Medical School at The University of Texas Health Science Center Houston; M.M. Ward, MD, MPH, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health; L.S. Gensler, MD, Department of Medicine, Division of Rheumatology, UCSF; M.A. Brown, FRACP, University of Queensland Diamantina Institute, Translational Research Institute, Princess Alexandra Hospital, and Institute of Health and Biomedical Innovation, Queensland University of Technology, Translational Research Institute, Princess Alexandra Hospital; T.J. Learch, MD, Division of Rheumatology, Cedars Sinai Medical Center; L.A. Diekman, MS, Department of Internal Medicine, Division of Rheumatology, McGovern Medical School at The University of Texas Health Science Center Houston; A. Tahanan, BS, Department of Internal Medicine, Division of Clinical and Translational Sciences, McGovern Medical School at The University of Texas Health Science Center Houston; M.H. Rahbar, PhD, Department of Internal Medicine, Division of Clinical and Translational Sciences, McGovern Medical

School at The University of Texas Health Science Center Houston; M.H. Weisman, MD, Division of Rheumatology, Cedars Sinai Medical Center; J.D. Reveille, MD, Department of Internal Medicine, Division of Rheumatology, McGovern Medical School at The University of Texas Health Science Center Houston.

Address correspondence to Dr. J.D. Reveille, McGovern Medical School at the University of Texas Health Science Center Houston, 6431 Fannin, Houston, Texas 77030, USA. E-mail: John.D.Reveille@uth.tmc.edu

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Data regarding pain management in ankylosing spondylitis (AS), particularly on opioid usage, are extremely limited. The current treatment guidelines from the Assessments in Spondyloarthritis International Society (ASAS)/European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR)/Spondyloarthritis Research and Treatment Network (SPARTAN)/Spondylitis Association of America (SAA) approach the pharmacological management of AS with the primary goal of reducing symptoms with agents such as nonsteroidal antiinflammatory drugs (NSAID), tumor necrosis factor inhibitor (TNFi) agents, and interleukin 17 inhibitors, as well as disease-modifying antirheumatic drugs (DMARD) such as sulfasalazine[1,2]. Management with NSAID has shown to relieve pain and stiffness, though there has been conflicting evidence as to whether they slow radiographic progression[3]. More recently, it was suggested that TNFi treatment was associated with less radiographic progression in AS[4,5]. DMARD such as sulfasalazine have been shown to be helpful for peripheral synovitis in the disease[6]. However, these medications do not always successfully control somatic pain in patients with AS. This is especially true when the pain stems from processes other than inflammation, thus requiring opioids as an alternative for pain control.

Recommendations for the use of opioid analgesics are few, with the ASAS/EULAR guidelines recommending use of opioids and opioid-like drugs solely by expert opinion, with no evidence in the literature to reinforce this recommendation[1]. Opioid usage was not addressed by the ACR/SPARTAN/SAA treatment guidelines[2]. While many patients respond well to both NSAID and TNFi agents, the frequency and chronicity of opioid use is unknown. Also, little attention has been paid to the effects of opioid use on patients, their frequency and chronicity of use, as well as the effects of other co-administered psychoactive agents (antidepressants, anxiolytics, muscle relaxants, etc.).

In our study, factors associated with opioid usage in a large prospective observational cohort of patients with AS were examined. Specifically, 2 questions were addressed: (1) What were the characteristics of patients with AS who used opioids over time, especially with chronic versus intermittent opioid usage; and (2) what other psychoactive medications are concomitantly used by patients with AS?

MATERIALS AND METHODS

Study population. Patients were participants in the Prospective Study of Outcomes in AS (PSOAS), an observational study of predictors of AS severity that included 706 patients followed at least 2 years at the time of this analysis. Patients were recruited from the investigators' clinics, patient support groups (such as SAA), and community rheumatologists. Patients were at least 18 years old and met the modified New York criteria for AS[7]. Patients were included from 5 study sites: Cedars-Sinai Medical Center in Los Angeles, California, the McGovern Medical School at The University of Texas Health Science Center Houston (UTH), the US National Institutes of Health Clinical Center (NIH), the University of California San Francisco (UCSF), and the Princess Alexandra Hospital in Brisbane, Australia (PAH). Each institution at which the study was conducted had review and approval by their respective institutional review boards (IRB): UTH-HSC-MS-07-0022; Cedars CR00011435/Pro00010016; UCSF 1-01695, Ref 183280; PAH/QUT HREC/05/QPAH/221; NIH Clinical Center 03-AR-0131. Each subject signed informed consent to participate.

Data collected. Clinical evaluation of these patients was performed using a standardized protocol every 6 months by a study site investigator. The evaluation included questionnaires assessing disease activity and functional impairment [Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Bath Ankylosing Spondylitis Functional Index (BASFI), respectively][8,9]. Other demographic, social, and psychological variables collected included the Center for Epidemiologic Studies Depression Scale (CES-D), where a score > 16 indicates depression[10], and the Patient Health Questionnaire 9 (PHQ-9), a validated depression screening test used for a fixed period in the study[11]. Other factors recorded were disease comorbidities, including cardiovascular disease, diabetes, hypertension, and hip surgery; patient habits such as prior and current smoking; and exercise, including duration and frequency. C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) levels were determined at each study visit. All medications used in the preceding 6 months were recorded at each study visit, including interval dosage, frequency, and duration. These medications included NSAID, DMARD, TNFi, corticosteroids, and muscle relaxants, as well as both opioid analgesics such as hydromorphone, morphine, hydrocodone, codeine, and tramadol, and non-opioid analgesics such as acetaminophen, gabapentin, and pregabalin (Table 1). All other medications were recorded qualitatively (i.e., whether they had been taken in the past 6 months). These included psychoactive medications such as anxiolytics (mostly benzodiazepines), antidepressants, hypnotics (prescription sleep aids), antipsychotic drugs and stimulants, as well as statins, antihypertensive agents, cardiac, osteoporosis, gout, hormonal, diabetes, thyroid medications, and supplements. All medication data for the duration of the study were entered from the case report forms into Research Electronic Data Capture (REDCap)[12] by a physician investigator (JDR), and the medication entries were then reviewed for accuracy by the other site investigators and Data Management and Statistical Core (DMSC) personnel. All other data were also entered into REDCap and quality assurance of data for our study was performed by the DMSC, housed in the Biostatistics/ Epidemiology/Research Design component of the Center for Clinical and Translational Sciences at the McGovern Medical School at The University of Texas Health Science Center Houston.

Radiographs of the pelvis (anterior-posterior), lumbar spine (anterior-posterior and lateral), and cervical spine (lateral) were taken at the baseline visit (and every 2 years) to assess radiographic severity (and progression) using the Bath Ankylosing Spondylitis Radiology Index (BASRI) and the modified Stokes Ankylosing Spondylitis Scoring System (mSASSS)[13,14]. The BASRI and mSASSS scores were calculated for each radiograph set by an expert musculoskeletal radiologist (TJL).

Statistical analysis. Univariable cross-sectional associations of clinical characteristics with opioid usage were conducted using chi-square tests for categorical variables and Student t tests for continuous variables, or their nonparametric counterparts when necessary. The data were reported as mean (SD) or median [interquartile range (IQR)] according to their distributions. Demographics and other characteristics of the study population were categorized based on known cutoff values. If there was no biological determination that could be used to categorize the data, we used cutpoints based on medians

Table 1. Association of clinical characteristics at baseline with chronic and intermittent usage of opioid analgesics (n = 706). Values are % or median (IQR) unless otherwise specified.

Variables	Non-opioid User, n = 486 (68.8%)	Intermittent Opioid User, n = 153 (21.7%)	Chronic Opioid User, n = 67 (9.5%)	Overall p*
Male†	74.9	68.0	82.1	0.07[3]
Education ≥ gr 12† [a]	83.1	78.3	80.0	0.38
HLA-B27–positive†	82.3	88.9	80.6	0.13
Married†	51.2	53.6	70.2	0.01 [2,3]
White♦	79.0	81.1	86.6	0.33
Employed for compensation†	38.7	27.5	22.4	0.003[1,2]
Receiving disability benefits†	4.1	6.5	9.0	0.16
Age at baseline visit, yrs, mean (SD)♦	40.8 (13.5)	44.2 (12.7)	50.8 (12.9)	< 0.0001[1,2,3]
Age at disease onset, yrs, mean (SD)♦ [b]	24.8 (9.7)	24.1 (8.9)	26.2 (10.6)	0.54
Disease duration at baseline, yrs, mean (SD)♦ [b]	16.3 (12.3)	19.6 (13.5)	23.7 (13.8)	< 0.0001[1,2,3]
Exercise ≥ 120 min/wk† [c]	56.1	48.5	36.1	0.007[2]
Ever smoke tobacco† [d]	35.8	52.7	58.7	< 0.0001[1,2]
Currently smoking† [d]	9.6	16.7	14.3	0.05[1]
BASDAI, 0–10 cm VAS◊ [e]	2.4 (1.3–4.2)	4.4 (2.2–6.3)	5.5 (4.0–6.6)	< 0.0001[1,2,3]
BASFI, 0–100 cm VAS◊ [f]	16.0 (5.7– 32.7)	36.0 (14.0–55.5)	50.7 (33.6–70.0)	< 0.0001[1,2,3]
ESR, mm/h◊ **	10.0 (5.0–21.0)	11.0 (5.0–20.0)	10.0 (6.0–25.0)	0.68
CRP, mg/dl◊ **	0.4 (0.2–0.9)	0.4 (0.2–1.0)	0.5 (0.2–0.8)	0.12
Baseline BASRI, 0–16◊ ** [g]	5.5 (3.0–10.0)	6.0 (3.0–10.0)	7.5 (5.0–11.0)	0.01
Baseline mSASSS, 0–64◊ ** [h]	4.4 (0–22.0)	4.4 (0–28.0)	18.0 (5–43.0)	0.0004 [2,3]
CES-D baseline score ◊ [i]	7.0 (3.0–14.0)	13.0 (6.0–21.0)	15.0 (9.0–19.0)	< 0.0001[1,2]
CES-D baseline total > 16† [i]	16.7	36.2	40.7	< 0.0001[1,2]
PHQ-9 baseline score ◊	3.0 (1.0–6.0)	5.0 (3.0–9.0)	7.0 (4.0–9.0)	< 0.0001[1,2,3]
Depression (self-reported)† [j]	11.8	26.9	25.0	< 0.0001[1,2]
PtGA, pain	19.5 (10.0–32.5)	39.5 (18.0–60.0)	41.0 (28.0–60.0)	< 0.0001[1,2,3]
Hypertension (self-reported)† [k]	19.8	28.7	51.5	< 0.0001[1,2,3]
Cardiovascular disease† [l]	23.3	32.9	53.0	< 0.0001[1,2,3]
Diabetes† [m]	4.0	6.0	9.2	0.15

Chronic opioid user is defined as daily usage of opioids for greater than 6 months. Intermittent opioid user is defined as usage "as needed" and not daily. [1]p values < 0.05 for comparison of non-opioid user vs intermittent opioid user; [2] p values < 0.05 for comparison of non-opioid user vs chronic opioid user; [3]p values < 0.05 for comparison of intermittent opioid user vs chronic opioid user. †chi-square test; ♦ANOVA; ◊Kruskal-Wallis test; *p values of overall comparison of 3 groups; **first observed data due to missing values at baseline. Data are missing for the following: [a]n = 16; [b]n = 62; [c] n = 47; [d]n = 26; [e]n = 65; [f]n = 36; [g]n = 28; [h]n = 45; [i]n = 63; [j]n = 20; [k]n = 15; [l]n = 12; [m]n = 16. IQR: interquartile range; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; VAS: visual analog scale; BASFI: Bath Ankylosing Spondylitis Functional Index; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; BASRI: Bath Ankylosing Spondylitis Radiology Index; mSASSS: modified Stokes Ankylosing Spondylitis Scoring System; CES-D: Center for Epidemiologic Studies Depression Scale; PHQ-9: Patient Health Questionnaire 9; PtGA: patient's global assessment.

or means if the data were normally distributed. Longitudinal univariable and multivariable mixed-effects logistic regression models accounted for the possible variations between and within patients, and were conducted to assess the longitudinal associations between clinical/demographic/laboratory features and opioid usage as a binary dependent variable. The variables that were potentially associated with opioid usage by clinical rationalization, or the variables that were significantly associated with opioid usage in our univariable analyses, were included in the multivariable models. We also carefully considered the possibility of multicollinearity among medications. Medication usage and clinical factors that are nested within a patient were considered level 1 variables, and patient-level data such as baseline characteristics were considered level 2 variables for the mixed-effect models. We maintained a random intercept at the patient level in all models when analyzing our data. Each level 1 variable, including time, was treated as a random slope, while interaction effects between level 1 and level 2 variables were tested. Possible interaction effects between medication usage in relation to opioid usage were also evaluated while developing the final multivariable model. Analyses were performed using SAS 9.4 (SAS Institute Inc.) and all hypotheses were tested at 5% level of significance.

RESULTS

Medication usage and cohort characteristics. There were 706 patients included in our study after being followed for at least 2 years as of August 1, 2016. Of these patients, 67 (9.5%) were taking chronic opioids (defined as taking opioids daily for at least 6 months); 153 (21.7%) were using intermittent or "on demand" opioids (taking opioids "as needed" but not daily), and 486 (68.8%) never used opioids (Table 1). Of the 706 patients, 20% were from UCSF, 26% from UTH, 27% from Cedars Sinai, 15% from the NIH, and 13% were from PAH. Although the referral source of the patients varied between sites, nearly all the UCSF and PAH patients, and majority of the patients at UTH, were recruited from the rheumatology clinics at the respective institutions, whereas most of the patients seen at Cedars-Sinai and the NIH Clinical Center came from community rheumatologist referrals or

were self-referred. However, at all institutions, the opioids were mostly prescribed by the patients' primary care providers or from local pain clinics, not by the study rheumatologists. The use of narcotics did not vary significantly between centers on multivariable analysis (data not shown). The most commonly taken opioids were high potency such as hydrocodone-containing drugs, followed by oxycodone-containing preparations, with or without acetaminophen and morphine (Appendix 1). Less commonly consumed were low-potency opioids such as codeine-containing preparations, propoxyphene (discontinued in the United States in 2010 and in Australia in 2012), and tramadol (Appendix 1). Whereas it would have been desirable to describe why the opioids were being given, this was not an aim of the original study design; therefore, whether the opioids were being prescribed for AS or for a comorbidity was not examined.

Patients taking opioids were more likely to be older and married and less likely to be actively employed, especially those with chronic opioids usage (Table 1). No significant differences were seen in opioid use between the participating centers. Those taking opioids were more likely to have a smoking history and were less likely to be exercising regularly (Table 1). They also had longer disease duration and a greater number of comorbidities, specifically hypertension and cardiovascular disease, particularly in those with chronic opioid usage. Patients taking opioids reported greater subjective functional impairment (by median BASFI scores) and disease activity (by median BASDAI scores), with the highest levels in those with chronic opioid usage. This was not corroborated by objective measures of inflammation such as CRP and ESR. Patients taking opioids also had worse median patient global assessment of health as well as higher frequency of depression, both by self-report and by validated measures (CES-D, PHQ-9). No association with opioid usage was seen with educational status and age at disease onset. Chronic opioid users showed greater radiographic severity with higher mSASSS and BASRI scores at baseline.

In general, patients taking opioids were more likely to be taking muscle relaxants, and in the case of intermittent users, oral prednisone. More notably, anxiolytics, antidepressants, and hypnotics were most likely to be taken by chronic opioid users (Table 2). NSAID, DMARD, and TNFi, as well as antipsychotic agents and stimulants did not differ by opioid usage.

Multivariable longitudinal analyses. Of those 706 patients included in the multivariable longitudinal analyses and followed at least 2 years [median = 5.0 yrs; IQR (2.8, 6.7)], the likelihood of opioid usage was higher among those with the following characteristics: worse patient assessment of health; greater depression (CES-D > 16), functional impairment (BASFI > 40 mm), and subjective disease activity (BASDAI); > 2 comorbidities; and medication usage (anxiolytics, hypnotics, prednisone, Table 3). TNFi usage was negatively associated with opioid usage. The use of NSAID, baseline CRP elevation, baseline BASRI, and smoking were not significantly associated with taking opioids in this analysis. Because of the high correlation between mSASSS and BASRI scores, only the BASRI was included in the multivariable analysis to avoid confounding by collinearity. A trend ($p = 0.1$) toward an interaction effect between muscle relaxant and antidepressant usage was found in relation to opioid usage, which indicates that the association between antidepressant and opioid usage is modified by muscle relaxant usage. Specifically, antidepressant usage was associated with more opioid usage when subjects did not take muscle relaxants (adjusted OR = 2.2; $p = 0.004$), but no significant association was found between antidepressant usage and opioid usage when muscle relaxants were used concomitantly (adjusted OR = 0.9; $p = 0.85$). No significant interaction effect was found among other medication usages.

DISCUSSION

While striking advances have been made in controlling disease-related inflammation with biologic drugs, the issue of pain persisting beyond control of inflammation has been little addressed. Conventionally, this is done with analgesics such as acetaminophen and opioids; however, anxiolytics and antidepressants are also used for chronic pain. Concomitant usage of benzodiazepines, other psychoactive drugs, and muscle relaxants with opioids significantly increases the risk of oversedation and overdose[15–21]. To deal with these concerns, the US Centers for Disease Control and Prevention, and the US Food and Drug Administration have issued guidelines for opioid prescription for chronic noncancer pain[22,23].

In this longitudinal cohort analysis (Table 1), these characteristics were associated with opioid usage, especially with chronic opioids, though not all these associations remained on multivariable analyses (Table 3): older age, greater disease duration, smoking, not being actively employed, having greater reported disease activity and functional impairment, depression, less regular exercise, and greater baseline radiographic severity. Patients taking opioid medications were also more likely to be taking psychoactive medications including anxiolytics, antidepressants, and hypnotics, as well as muscle relaxants, many of which having sedative properties (i.e., cyclobenzaprine, carisoprodol), which is of concern, whereas no relationship was found with TNFi, NSAID, or DMARD (Table 2). Of note, opioid use was not independently associated with objective measures of disease activity, such as elevated ESR and CRP levels, nor on multivariable analysis, with radiographic severity as determined by BASRI and mSASSS scores. Opioid use could stem from pain owing to noninflammatory sources (i.e., neuropathic, mechanical, or psychogenic sources) and heightened by depression. In 2 other cohorts, patients with AS were 60% more likely to become depressed in comparison to case controls in the general population[24,25]. In addition, it has been shown in a longitudinal analysis of patients with AS that

Table 2. Cross-sectional association of medication use with opioid usage at baseline visits (n = 706). Values are %.

Medication Usage	All	Non-opioid User, n = 486 (68.8%)	Intermittent Opioid User, n = 153 (21.7%)	Chronic Opioid User, n = 67 (9.5%)	Overall p*
Baseline NSAID	70.3	68.3	75.2	73.1	0.23
Baseline TNFi	43.5	43.8	41.8	44.8	0.89
DMARD	15.3	13.8	19.6	16.4	0.21
Prednisone	5.7	4.1	11.1	4.5	0.004
Anxiolytic	6.2	2.1	12.4	22.4	< 0.0001
Muscle relaxants	7.8	2.3	18.3	23.9	< 0.0001
Hypnotics	4.8	2.7	7.2	14.9	< 0.0001
Antidepressant	9.9	4.9	18.3	26.9	< 0.0001
Antipsychotic	0.9	0.6	2.0	0	0.21
Stimulant	0.1	0.2	0	0	0.80

*Chi-square test p values of overall comparison of 3 groups. Chronic opioid user is defined as daily usage of opioids for > 6 months. Intermittent opioid user is defined as usage "as needed" and not daily. DMARD: disease-modifying antirheumatic drugs; NSAID: nonsteroidal antiinflammatory drug; TNFi: tumor necrosis factor inhibitor.

Table 3. Factors associated with opioid usage based on multivariable longitudinal mixed-effects logistic regression model (n = 706).

Variables	Adjusted OR (95% CI)	p
Antidepressant usage (use vs no use) by muscle relaxants usage*		
When muscle relaxants taken	0.9 (0.3–2.9)	0.85
When muscle relaxants not taken	2.2 (1.3–3.8)	0.004
PtGA ≥ 23	2.6 (1.5–4.6)	0.0006
CES-D total > 16	1.6 (1.1–2.3)	0.02
BASFI ≥ 40/100 mm	1.9 (1.2–2.9)	0.004
BASDAI ≥ 4/10 cm	2.0 (1.4–2.9)	0.0005
Exercise ≥ 3×/wk	0.7 (0.5–1.1)	0.13
> 2 comorbidities	1.2 (0.7–2.1)	0.46
Medication usage		
Hypnotics	5.4 (2.6–11.3)	< 0.0001
Prednisone	2.5 (1.4–4.7)	0.003
Anxiolytics	4.0 (2.2–7.1)	< 0.0001
TNFi agents	0.7 (0.5–1.0)	0.05
NSAID	1.1 (0.7–1.5)	0.76
DMARD	1.3 (0.8–2.1)	0.33
Antipsychotics	21.8 (0.4–8.4)	0.32
BASRI baseline ≥ 6**	0.8 (0.5–1.4)	0.41
Elevated CRP	1.5 (0.9–2.5)	0.13
Education (> gr 12)	1.1 (0.5–2.2)	0.84
Marital status: married	1.9 (1.1–3.2)	0.02
Race: white (compared to others)	1.5 (0.7–2.9)	0.29
Male sex	1.2 (0.7–2.2)	0.48
Age ≥ 40 yrs	1.9 (0.7–3.4)	0.03
Smoking (> 100 packs within lifetime)	1.8 (1.1–3.0)	0.02

*OR for antidepressant usage were calculated separately by muscle relaxants usage (i.e., when muscle relaxants were taken or not taken) based on an interaction effect between muscle relaxants and antidepressant usage in the multivariable model. ** Because of a high correlation between BASRI and mSASSS and the greater completeness of the data in the former, it was decided to adjust BASRI instead of mSASSS in the final multivariable model. BASFI: Bath Ankylosing Spondylitis Functional Index; BASRI: Bath Ankylosing Spondylitis Radiological Index; CES-D: Center for Epidemiologic Studies Depression Scale; DMARD: disease-modifying antirheumatic drugs; mSASSS: modified Stokes Ankylosing Spondylitis Scoring System; NSAID: nonsteroidal antiinflammatory drugs; PtGA: patient's global assessment; TNFi: tumor necrosis factor inhibitors; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CRP: C-reactive protein.

psychological correlates of depression such as coping scales, PHQ-9 score, and arthritis helplessness index were associated with higher self-reported disease activity and functional limitation[25,26]. TNFi have been shown elsewhere to relieve depression in AS, perhaps by lowering CRP, IL-1, and IL-6 levels, or by their effect on diminishing inflammation[27], and have been proposed as a potential therapy for severe depression[28]. Our study shows only a marginally negative association of TNFi usage with opioid use. Moreover, CRP and ESR elevation was not associated with opioid use. These results support those of a randomized controlled clinical trial that compared aceclofenac versus aceclofenac plus tramadol with acetaminophen, which demonstrated a statistically significant reduction in the percentage of ASAS20 responders in those taking both drugs, compared to aceclofenac alone at 12 weeks of therapy[29]. One would expect to find a statistically significant percentage of ASAS20 responders because ASAS20 is not calculated by ESR, CRP, BASRI, or mSASSS, but is calculated by patient global pain, BASFI, and BASDAI questionnaires[29]. Therefore, the component contributing to pain in patients with AS who use opioids may not be predominantly owing to inflammation. It is important to distinguish in patients with AS whether pain derives from inflammatory versus neuropathic, mechanical, other comorbid, or psychogenic factors.

The concomitant usage of opioid analgesics with muscle relaxants and benzodiazepines in our study raises concerns of an interaction effect that these drugs may be providing with opioids. It is well known that the concomitant usage of benzodiazepines and certain muscle relaxants may enhance the effect of the pain relief and sedation that opioid analgesics provide[30]. Studies in healthy volunteers of combined usage of alprazolam and oxycodone, as well as of carisoprodol and oxycodone showed that there was a greater magnitude of psychomotor inhibition when these drugs were taken together rather than taken alone[31,32,33,34,35]. Specifically, carisoprodol may be contributing because its active metabolite mepro-

bamate is a known barbiturate-like drug that is also a benzodiazepine potentiator[35]. In our cohort, the second most widely prescribed muscle relaxant was carisoprodol (data not shown). The usage of benzodiazepines and certain muscle relaxants could contribute to the development of drug dependence[35,36,37], which raises a note of caution to prescribers.

Interestingly, another avenue of treatment that may have less side-effect potential than benzodiazepines and muscle relaxants could be antidepressants. Antidepressants in 1 study were shown to be just as efficacious as opioids in treating chronic low back pain of unknown etiology[38]. The initiation of duloxetine for treatment of chronic low back pain lowered the rates of adding opioids to the treatment regimen[38]. However, a Cochrane review found that antidepressants were not superior to placebo in a metaanalysis of randomized clinical trials for chronic low back pain[39]. Given the frequency of clinical depression in our study and other studies of patients with AS and increased usage of muscle relaxants in this study, a possible role for antidepressants in the management of chronic pain in AS merits further study. An antidepressant may be a better initial choice rather than a muscle relaxant, given an improved safety profile over muscle relaxants, and because muscle relaxants may have greater sedative properties. Comparative studies should be conducted to address this question.

There was a trend toward interaction between antidepressant and muscle relaxant usage in relation to opioid use. While the use of antidepressants and muscle relaxants separately was associated with opioid usage, this association was not present when muscle relaxants and antidepressants were taken concomitantly. This raises the possibility that using antidepressants and muscle relaxants in combination may lessen the need for opioids.

The strengths of our study include the large sample size and longitudinal analysis. However, limitations include the ability to effectively compare opioid usage for pain relief and disease activity because it was not a randomized clinical trial; thus the ability to infer from an observational prospective cohort is limited. In addition, we did not address the strength or dosage of the opioids used in our study and did not specifically separate opioid use for treatment of AS versus for treatment of other conditions these patients may have had in our analyses. We did not attempt to comprehensively examine for concomitant fibromyalgia, which could have confounded these results, especially given the associations of opioid usage and depression. Given that those taking opioids exhibited greater functional limitation and subjective disease activity, a role for opioids in suppressing inflammation is not suggested. It was not the purpose of our study to examine the role of opioids in AS treatment; our purpose was to study the factors associated with their usage in AS, hence we did not assess the response rates to TNFi and NSAID. Although we examined all ethnic groups, our cohort of patients was predominantly white and > 40 years, which may affect the study's applicability to other ethnic and age groups.

In our study, subjective disease activity (measured by a high BASDAI score), self-reported depression, and reports of greater pain were correlated with opioid usage in patients with AS. None of the objective measures of AS disease activity, severity, or objective measures of disease activity (such as ESR, CRP, BASRI, and mSASSS) were found to be independently associated with opioid usage on multivariable analysis. This adds support to the hypothesis that pain perception associated with AS may develop from sources other than spinal inflammation alone. Alternatively, these data may also suggest the inadequacy of the biomarkers examined (ESR, CRP) in assessing active inflammation, and concomitant magnetic resonance imaging was not available in our study. Also, taking opioids was highly associated with concomitant use of anxiolytics (mostly benzodiazepines), as well as with other psychoactive substances such as antidepressants, hypnotics, and muscle relaxants. The reason could be because opioids in combination with certain muscle relaxants and benzodiazepines may provide a greater magnitude of pain relief than when taken alone, but the combination could result in dependence and drug interaction that could lead to oversedation and premature death.

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APPENDIX 1. Overall AS patient use of pain, muscle relaxant, and psychiatric medication in the PSOAS cohort, 2003–2015 (from October 2015 data freeze). Values are %.

Medication	Overall, n = 961	2003–2008, n = 511	2009–2015, n = 764	p*
Propoxyphene	2.4	2.9	2.2	0.82
Codeine	5.0	2.9	5.2	0.01
Hydrocodone	15.0	12.5	14.5	0.03
Oxycodone	5.6	2.9	6.3	0.0005
Morphine	2.7	2.0	3.0	0.11
Methadone	1.0	0.4	1.4	0.04
Hydromorphone	1.0	0.2	1.57	0.005
Fentanyl	1.8	1.6	1.83	0.38
Suboxone	0.6	0.4	0.9	0.24
Tapentadol	0.21	0	0.7	0.26
Tramadol	7.3	4.7	7.6	0.007

*p values based on generalized estimating equation models for correlated data within patients. AS: ankylosing spondylitis; PSOAS: Prospective Study of Outcomes in Ankylosing Spondylitis.