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Opioid Analgesic Use in Patients with Ankylosing Spondylitis—an Analysis of the PSOAS Cohort

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Abstract

Objective—Opioid analgesics may be prescribed to patients with ankylosing spondylitis (AS) with pain unresponsive to anti-rheumatic treatment. This study assessed factors associated with opioid usage in AS.

Methods—A prospective cohort of 706 AS patients meeting modified New York Criteria followed at least two years underwent comprehensive clinical evaluation of disease activity and functional impairment, 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 (BASRI) and modified Stokes Ankylosing Spondylitis Scoring System (mSASSS). Medications taken concurrently with opioids, as well as C-reactive protein (CRP) levels and erythrocyte sedimentation rate (ESR), were

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AUTHOR CONTRIBUTIONS

JDD, JDR, ML, LSG, MMW, MHW, and MAB contributed to the study design, data acquisition. JDD and JDR wrote and drafted the manuscript. TJL scored radiographs. ML and MHR contributed to the statistical analysis of data. AT, ML, and MHR contributed to data management and quality assurance of the data. All authors approved the final version of the manuscript to be published.

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 subjective but not objective determinants of disease activity as well with smoking, older age and psychoactive drugs.

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.

Key Indexing Terms

Pain; Analgesia; Cohort Studies; Opioid; Ankylosing Spondylitis

INTRODUCTION

Data regarding pain management in ankylosing spondylitis (AS), particularly on opioid usage, are extremely limited. The current Assessments in Spondyloarthritis International Society/European League Against Rheumatism (ASAS/EULAR) and American College of Rheumatology/Spondyloarthritis Research and Treatment Network/Spondylitis Association of America (ACR/SPARTAN/SAA) treatment guidelines approach the pharmacological management of AS with the primary goal of reducing symptoms with agents such as non-steroidal anti-inflammatory drugs (NSAIDs), Tumor Necrosis Factor inhibitor (TNFi, bDMARD) agents and Interleukin 17 inhibitors, and disease-modifying anti-rheumatic drugs (DMARDs) such as sulfasalazine (1,2). Management with NSAIDs has shown to relieve pain and stiffness though there has been conflicting evidence whether they slow radiographic progression (3). More recently, it was suggested that TNFi treatment was associated with less radiographic progression in AS (4,5). DMARDs 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 AS patients. 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 NSAIDs and TNFi agents, the frequency and chronicity of opioid use is unknown. Also, little attention has been paid to their impact on patients, their frequency and chronicity of usage, as well as other co-administered psychoactive agents (antidepressants, anxiolytics, muscle relaxants, etc.).

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

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 two years at the time of this analysis. Patients were recruited from the investigators' clinics, patient support groups (such as the Spondylitis Association of America), and community rheumatologists. Patients were at least 18 years old and met the modified New York Criteria for AS (7). Patients were included from five 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 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 each of 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, and each subject sign 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, including 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 disease comorbidities, including cardiovascular disease, diabetes, hypertension, hip surgery; patient habits such as prior and current smoking, and exercise including duration and frequency of exercise were also recorded. C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) levels were determined at each study visit. All medications used in the preceding six months, including NSAIDs, DMARDs, TNFi, corticosteroids, analgesics (both opioid analgesics such as hydromorphone, morphine, hydrocodone, codeine and tramadol and non-opioids including acetaminophen, gabapentin, and pregabalin (Table 1), and muscle relaxants were recorded at each study visit including interval dosage, frequency and duration. All other medications, including psychoactive medications (anxiolytics [mostly benzodiazepines], antidepressants, hypnotics (prescription sleep aids), anti-psychotic drugs and stimulants), statins, antihypertensive agents, cardiac, osteoporosis, gout, hormonal, diabetes, thyroid medications as well as supplements, were recorded qualitatively-i.e. whether they had been taken in the

past six months. All medication data for the duration of the study were entered from the case report forms into 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 this study were performed by the DMSC, housed in the Biostatistics/ Epidemiology/Research Design component of Center for Clinical and Translational Sciences at the McGovern Medical School at The University of Texas Health Science Center Houston.

Radiographs, which include x-rays of the pelvis (Anterior-Posterior), lumbar spine (anterior-posterior and lateral), and cervical spine (lateral), were taken at the baseline visit (and every two 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's t-tests for continuous variables or their non-parametric counterparts when necessary. The data were reported as means and standard deviations or medians and interquartile ranges according to their distributions. Demographic and other characteristics of the study population were categorized based on known cut-off values. If there was no biological determination that could be used to categorize the data, we used cut points based on medians or means if the data were normally distributed. Longitudinal univariable and multivariable mixed effects logistic regression models that accounted for the possible variations between and within patients, were conducted to assess the longitudinal associations between clinical/ demographic/lab 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 included in the multivariable models. We also carefully considered the possibility of multi-collinearity among medications. Medication usages and clinical factors that are nested within a patient were considered level-1 variables and patient-level data such as baseline characteristics are considered level-2 (i.e., patient-level) variables for the mixed effect models. We maintained a random intercept at the patient-level in all models when analyzing our data. Each of level-1 variables 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 usages in relation to opioid usage were also evaluated while developing the final multivariable model. Analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC) and all hypotheses were tested at 5% level of significance.

RESULTS

Medication Utilization and Cohort Characteristics

In all, 706 patients were included in this study after being followed for at least two years as of August 1, 2016. Of these, 67 (9.5%) were taking chronic opioids (defined as taking opioids every day for at least six months); 153 (21.7%) were using intermittent or "on demand" opioids (taking opioids "as needed" but not every day), and 486 (68.8%) never used opioids, whether prescribed by the patients' primary care practitioners or rheumatologists (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 of the UCSF and PAH patients and the 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' other physicians (primary care providers, etc.) or from local pain clinics and 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 (Supp Table 1). Less commonly consumed were low potency opioids such as codeine-containing preparations, propoxyphene (discontinued in the U.S in 2010 and in Australia in 2012) and tramadol (Suppl. Table 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, married, and were less likely to be actively employed especially those using opioids chronically (Table 1). No significant differences were seen in opioid use between the participating centers. Those taking opioids were also 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 in those taking chronic opioids. 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 taking chronic opioids. This was not corroborated by objective measures of inflammation such as the CRP and ESR. They 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, age at disease onset, or radiographic severity (mSASSS or BASRI), except in chronic opioid users who had higher mSASSS and BASRI scores at baseline.

Patients taking opioids in general were more likely to be taking oral prednisone and muscle relaxants. More notably, anxiolytics, antidepressants and hypnotics were most likely to be taken by chronic opioid users (Table 2). NSAIDs, DMARDs and TNFi as well as anti-psychotic agents and stimulants did not differ by opioid usage.

Multivariable Longitudinal Analyses

Of those 706 patients followed at least two years (median=5.0 years; IQR= [2.8, 6.7]) included in the multivariable longitudinal analyses, the likelihood of opioid usage was higher among those with a worse patient assessment of health, greater depression (CES-D > 16), functional impairment (BASFI > 40mm), subjective disease activity (by BASDAI), having more than two comorbidities, as well as medication usage (anxiolytics, hypnotics, prednisone) (Table 3). TNFi usage was negatively associated with opioid usage. The use of NSAIDs, 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 relaxants usage. Specifically, antidepressant usage was associated with more opioid usage when subjects did not take muscle relaxants (Adjusted odds ratio=2.2; p=0.004), but no significant association was found between antidepressant usage and opioid usage when muscle relaxants were used concomitantly (AOR=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 also used for chronic pain are anxiolytics and antidepressants. Concomitant usage of benzodiazepines, other psychoactive drugs, and muscle relaxants with opioids significantly increases the risk of over-sedation and overdose (15–21). To deal with these concerns, the Centers for Disease Control and the Food and Drug Administration of the United States have issued guidelines for opioid prescription for chronic noncancer pain (22,23).

In this longitudinal cohort analysis (Table 1), 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 were associated with opioid usage especially with chronic opioids, though not all these associations remained on multivariable analyses (Table 3). Of concern, 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), whereas no relationship was found with TNFi, NSAID’s, or DMARDs (Table 2). Of note was that 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. This could stem from pain due to noninflammatory sources (i.e. neuropathic, mechanical or psychogenic sources) and heightened by depression. In two 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 AS patients that psychological correlates of depression such as coping scales, the PHQ-9 score, and arthritis helplessness index (AHI) 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). The present 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 AS patients using opioids may not be predominantly due to inflammation. It is important to distinguish in AS patients 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 this 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 (31–35). Specifically, carisoprodol may be contributing because its active metabolite meprobamate 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 (35–37), 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 one 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 meta-analysis of randomized clinical trials for chronic low back pain (39). Given the frequency of clinical depression in this and other studies of AS patients and increased usage of muscle-relaxants here, 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 since 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 this 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 since it was not a randomized clinical trial and 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 this study and did not specifically separate opioid use for treatment of AS vs. 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 does not suggest a role for opioids in suppressing inflammation. It was not the purpose of this study to examine the role of opioids in AS treatment, merely to study the factors associated with their usage in AS, hence response rate to TNFi and NSAIDs was not assessed in this study. Although we examined all ethnic groups, our cohort of patients was predominantly white and older than 40 years of age, which may affect the study's applicability to other ethnic and age groups.

In this study, subjective disease activity (measured by a high BASDAI score), self-reported depression, and reports of greater pain were correlated with opioid usage in AS patients. None of the objective measures of AS disease activity, severity, or objective measures of disease activity 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 MRI's were not available in this 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. This could be because opioids in combination with certain muscle relaxants and benzodiazepines may provide a greater magnitude of pain relief when taken together than when taken alone, but with possible side effects such as dependence and drug interaction leading to over-sedation and possibly premature death.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Association of Clinical Characteristics at Baseline with Chronic and Intermittent Usage of Opioid Analgesics (N=706)

variable	Non Opioid User N=486 (68.8%)	Intermittent Opioid User N=153 (21.7%)	Chronic Opioid User N=67 (9.5%)	Overall p value*
Male%†	74.9	68.0	82.1	0.07[3]
Greater than 12th grade education%†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%†	4.1	6.5	9.0	0.16
Age at baseline visit (SD) ◆	40.8 (13.5)	44.2 (12.7)	50.8 (12.9)	<0.0001[1,2,3]
age at disease onset (IQR) ◆b	24.8 (9.7)	24.1 (8.9)	26.2 (10.6)	0.54
Disease duration at baseline (years)(SD) ◆b	14.0 (7.0,23.0)	18.0 (9.0,29.0)	22.0(12.0,36.0)	<0.0001[1,2,3]
Exercise ≥120 minutes /week%†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 median (0–10 cm VAS) (IQR)◊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 median (0–100 cm VAS) (IQR)◊f	16.0 (5.7, 32.7)	36.0 (14.0, 55.5)	50.7 (33.6, 70.0)	<0.0001[1,2,3]
Median ESR mm/hr (IQR) ◊,**	10.0(5.0,21.0)	11.0(5.0,20.0)	10.0(6.0,25.0)	0.68
Median CRP mg/dL (IQR) ◊,**	0.4(0.2,0.9)	0.4(0.2,1.0)	0.5 (0.2,0.8)	0.12
Baseline median BASRI (0–16)(IQR)◊,**g	5.5(3.0,10.0)	6.0(3.0,10.0)	7.5(5.0,11.0)	0.01
Baseline median mSASSS (0–64)(IQR)◊,**h	4.4 (0,22.0)	4.4 (0, 28.0)	18.0 (5, 43.0)	0.0004[2,3]
CESD baseline median score (IQR)◊i	7.0 (3.0,14.0)	13.0 (6.0,21.0)	15.0 (9.0,19.0)	<0.0001[1,2]
CESD baseline total >16%†i	16.7	36.2	40.7	<0.0001[1,2]
PHQ9 baseline median score (IQR)◊	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]
Patient global assessment of pain, median (IQR)	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

† Chi-square test

◆ ANOVA

◊ Kruskal-Wallis test

* p-values of overall comparison of three groups

** first observed data due to missing values at baseline

[a] Data are missing for n=16;

[b] Data are missing for n=62;

[c] Data are missing for n=47;

[d] Data are missing for n=26;

[e] Data are missing for n=65;

[f] Data are missing for n=36;

[g] Data are missing for n=28;

[h] Data are missing for n=45;

[i] Data are missing for n=63;

[j] Data are missing for n=20;

[k] Data are missing for n=15;

[l] Data are missing for n=12;

[m] Data are missing for n=16;

abbreviations: IQR = interquartile range, SD = standard deviation, 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, mSASS = modified Stokes Ankylosing Spondylitis Scoring System, CESD = Center for Epidemiologic Studies Depression Scale, PHQ9 = Patient Health Questionnaire-9.

Chronic opioid user is defined as daily usage of opioids for greater than six months.
Intermittent opioid user is defined as, “as needed” usage and not every day.

[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

Table 2

Cross Sectional Association of Medication Utilizations with Opioid Usage at Baseline Visits (N=706)

variable	ALL	Non Opioid User N=486(68.8%)	Intermittent Opioid User N=153 (21.7%)	Chronic Opioid User N=67 (9.5%)	Overall p value*
Baseline NSAID use%	70.3	68.3	75.2	73.1	0.23
Baseline TNFi use%	43.5	43.8	41.8	44.8	0.89
DMARD use%	15.3	13.8	19.6	16.4	0.21
Prednisone use%	5.7	4.1	11.1	4.5	0.004
Anxiolytic use%	6.2	2.1	12.4	22.4	<.0001
Muscle relaxants use%	7.8	2.3	18.3	23.9	<.0001
Hypnotics use%	4.8	2.7	7.2	14.9	<.0001
Antidepressant use%	9.9	4.9	18.3	26.9	<.0001
Anti-psychotic use%	0.9	0.6	2.0	0	0.21
Stimulant use%	0.1	0.2	0	0	0.80

* Chi-square test- p-values of overall comparison of three groups

Abbreviations: NSAID = non-steroidal anti-inflammatory drug, TNFi = tumor necrosis factor inhibitor, DMARD = disease-modifying antirheumatic drugs

Chronic opioid user is defined as daily usage of opioids for greater than six months.
Intermittent opioid user is defined as, as-needed usage and not every day.

Table 3

Factors Associated with Opioid Usage Based on Multivariable Longitudinal Mixed Effects Logistic Regression Model (N=706)

Variables	Adjusted Odds Ratio (=AOR) (95% Confidence Interval)	P-value
Antidepressant usage (Use vs. No Use) *by Muscle Relaxants Usage* *		
when Muscle Relaxants were taken	**0.9 (0.3, 2.9)**	**0.85**
when Muscle Relaxants were not taken	**2.2 (1.3, 3.8)**	**0.004**
Patient Global Assessment ≥ 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 three times or more per week	0.7(0.5, 1.1)	0.13
> 2 Comorbidities	1.2 (0.7, 2.1)	0.46
Hypnotic Usage	5.4 (2.6, 11.3)	<0.0001
Prednisone Usage	2.5 (1.4, 4.7)	0.003
Anxiolytic Usage	4.0 (2.2, 7.1)	<0.0001
TNFi-Agent Usage	0.7(0.5, 1.0)	0.05
NSAID Usage	1.1 (0.7, 1.5)	0.76
DMARD Usage	1.3 (0.8, 2.1)	0.33
Anti-psychotic Usage	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 (> 12th grade)	1.1 (0.5, 2.2)	0.84
Marital Status: Married	1.9 (1.1, 3.2)	0.02
Race: White (ref: others)	1.5 (0.7, 2.9)	0.29
Male Gender	1.2 (0.7, 2.2)	0.48
Age ≥ 40 years	1.9 (0.7, 3.4)	0.03
Smoking (>100 packs within lifetime)	1.8 (1.1, 3.0)	0.02

* Odds ratios 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.

** Due to 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