Running head: Long-term opioid therapy in lupus

Title: Long-term opioid therapy among patients with systemic lupus erythematosus in the community. A Lupus Midwest Network ( ) study

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ABSTRACT

Objective

There is little information about the epidemiology and factors associated with opioid therapy in systemic lupus erythematosus (SLE). We aimed to assess the prevalence of opioid therapy and explore factors associated with long-term opioid therapy (LTOT) in patients with SLE.

Methods

Patients with SLE were matched with non-SLE controls in a population-based cohort on January 1, 2015. We captured demographics, manifestations of lupus, comorbidities (fibromyalgia, mood disorders, osteoarthritis, chronic low back pain [CLBP], chronic kidney disease, avascular necrosis, osteoporosis, fragility fractures, and cancer), and the area deprivation index (ADI). Opioid prescription data were used to assess prevalence of LTOT, defined as contiguous prescriptions (gaps of <30 days between prescriptions) and receiving opioid therapy ≥90 days or ≥10 prescriptions before index date.

Results

465 SLE patients and 465 non-SLE controls were included; 13% of SLE patients and 3% of non-SLE controls were receiving opioid therapy (*P*<0.001), and 11% of SLE patients were on LTOT versus 1% of non-SLE controls. Among SLE patients, acute pericarditis (OR: 3.92; 95% CI: 1.78-8.66), fibromyalgia (OR: 7.78; 95% CI: 3.89-15.55), fragility fractures (OR: 3.72; 95% CI: 1.25-11.07), CLBP (OR: 4.00; 95% CI: 2.13-7.51),

and mood disorders (OR: 2.76; 95% CI: 1.47-5.16) were associated with LTOT. We did not find an association between opioid therapy and ADI.

Conclusion

Patients with SLE have higher LTOT than controls. Among patients with SLE, LTOT was associated with pericarditis and several comorbidities. However, LTOT was not associated with kidney disease despite the limited pain control options in these patients.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by a multisystemic and heterogeneous involvement and is most common in women of childbearing age.[1,2] SLE can cause tissue inflammation, injury, and damage that may manifest as pain, but pain can also be present in the absence of inflammation and be multifactorial in origin.[3]

Pain management in SLE can be complex. Among certain subsets of SLE patients, treatment options are limited. For example, SLE patients with renal involvement, on high doses of steroids, or anticoagulant therapy are at increased risk of complications related to the use of non-steroidal anti-inflammatory drugs (e.g., gastric ulcers, gastrointestinal bleed, and kidney injury).[4] Although patients with SLE could use opioid therapy without increasing the risk of these complications, the associated long-term effects of opioid therapy, such as opioid use disorder and the ongoing opioid overdose epidemic have prompted efforts to optimize its use and achieve safer chronic pain treatment while reducing side effects and misuse of these drugs.[5] As with any treatment, opioids should only be considered for chronic pain management if the expected benefits for pain and function outweigh the risks to the patient.[5] There is little information about how opioid therapy is used in the pain management of SLE. A previous study of an SLE registry showed that 31% of SLE patients self-reported opioid therapy, and up to 21% of them were on therapy for more than one year, compared to 7.8% and 6.3% of the persons without SLE, respectively.[6] A claims-based study reported that 52.6% of SLE patients used opioids and 18.2% received this therapy for 90 days or more over 12 months.[7] However, the prior studies were limited by lack of access to prescription data or

misclassification bias due to the use of administrative data. In addition, these studies did not report which factors were associated with higher use of opioid therapy in SLE.

Based on the considerations mentioned before, we hypothesize that the prevalence of long-term opioid therapy (LTOT) will be greater among patients with SLE compared to controls and painful clinical manifestations of the disease (e.g., serositis, inflammatory arthritis), lupus nephritis, and non-SLE-associated painful comorbid conditions would be associated with LTOT among patients with SLE. In this cross-sectional study, we aimed to determine the prevalence of LTOT among patients with SLE compared to subjects without SLE and investigate the clinical characteristics associated with LTOT among patients with SLE.

METHODS

Patients

The Lupus Midwest Network (LUMEN) is a population-based registry of a 27-county region in southeast Minnesota and southwest Wisconsin nested in the Rochester Epidemiology Project (REP), a record-linkage system. The REP allows access to the medical records from health care providers for the local population, including the Mayo Clinic, the Olmsted Medical Center, their affiliated hospitals, local nursing homes, etc. This system ensures a comprehensive ascertainment of opioid prescriptions among the residents of this region.[8] The characteristics and strengths of the REP and its generalizability have been described elsewhere.[9-11] Subjects who did not provide consent to use their medical records for research purposes were excluded from the

study. The study was approved by the institutional review boards of the Mayo Clinic (20-006485) and Olmsted Medical Center (036-OMC-20).

Potential SLE cases were identified through two different strategies: 1) through Hospital International Classification of Disease Adaptation (HICDA), International Classification of Diseases (ICD)-9 and ICD-10 codes for SLE, cutaneous lupus erythematosus, and other associated diseases and 2) through laboratory measures associated with SLE: anti-nuclear antibodies (ANA) (>1:80), low complement, anti-double-stranded DNA (anti-dsDNA), anti-Sm, lupus anticoagulant, anticardiolipin (IgG, IgM, and IgA) and anti-beta 2 glycoprotein I (IgG, IgM, and IgA) antibodies (Supplementary Table S1). Individual chart reviews were performed, and data were abstracted by extensively trained reviewers. Data extraction was done using a standardized Research Electronic Data Capture (REDCap) tool. Demographic characteristics, clinical, and laboratory data included in the classification criteria were abstracted from the electronic medical record. Patients meeting the 2019 European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) classification criteria[12] were considered incident cases. Those who migrated to the 27-county region after diagnosis (and therefore were under treatment) were included if they had seven EULAR/ACR points and a physician diagnosis.

We included all patients meeting the requirements described above and living in the 27-county region on January 1, 2015 (index date). SLE patients were matched (1:1) on age, sex, race/ethnicity, and county to controls without SLE randomly selected from the same population.

Opioid prescriptions

Prescribed medications are electronically available through the REP. We retrieved all prescriptions written for opioid analgesic drugs between January 1, 2005, and the index date. The prescriptions were grouped using the National Drug File-Reference Terminology classification system.[13,14] These medications include oxycodone, morphine, hydromorphone, oxymorphone, hydrocodone (excluding cough preparations), fentanyl, meperidine, codeine (excluding cough preparations), tramadol, and methadone.

Ambulatory opioid prescription data were used to identify the current episode of opioid prescription as of the index date among SLE and non-SLE subjects. These current episodes were defined as contiguous prescriptions before January 1, 2015, with gaps of less than 30 days between prescriptions. Opioid prescribing patterns were classified as LTOT or non-LTOT. Patients receiving LTOT were defined as those with an episode of prescriptions that spans ≥90 days or ≥10 prescriptions. A schematic representation of our study is presented in Figure 1.

To evaluate the opioid dose these patients received, we retrieved all the opioid prescriptions written during December 2014. We manually reviewed the electronic prescriptions and calculated each patient's total monthly and average daily dose in morphine milligram equivalents (MMEs).[15]

Lupus clinical characteristics and comorbidities

We abstracted data on SLE duration, types of manifestations, and organ involvement. We explored the presence of conditions associated with higher use of opioid therapy in the general population, including mood disorders, osteoarthritis, chronic low back pain

(CLBP), and cancer (solid tumors and hematologic); comorbidities with higher burden in SLE patients that could be manifested as pain including fibromyalgia, avascular necrosis of bone, osteoporosis, and hip or spine fragility fractures; and the presence of chronic kidney disease, which limits or contraindicates the use of certain analgesic therapies like non-steroidal anti-inflammatory drugs. Since most of these conditions are chronic, we used a five-year lookback from January 1, 2010, to the index date using International Classification of Diseases Ninth Revision (ICD-9) codes to identify the comorbidities mentioned above for both SLE patients and non-SLE controls (Supplementary Table S2). Then, we manually reviewed a random sample of 10% of the charts identified through ICD-9 codes. If the ICD-9 codes had a percentage of agreement (where the numerator is the confirmed cases by manual review and the denominator is the total patients with that ICD-9 code x 100) of ≥90% with the physician's chart review, patients and controls were attributed to that diagnosis without review of the 90% remaining. For those ICD-9 codes where the percentage of agreement was <90%, manual verification of the diagnoses was performed according to pre-established criteria (Supplementary Table S2). Only osteoarthritis and CLBP were attributed by ICD-9 codes. The rest of the conditions were confirmed by manual review of the medical records.

We also calculated the Charlson Comorbidity Index[16] removing the rheumatologic category for comparability between cohorts. To evaluate the effect of social determinants of health and understand the role of geographic variation and neighborhood deprivation in health and opioid prescribing patterns, the area deprivation index (ADI) was used at the block level.[17,18]

Statistical analysis

Descriptive statistics (means and standard deviations [SD], medians and interquartile ranges [IQR], counts, and percentages) were used to summarize the characteristics of patients with and without SLE. Chi-square and Wilcoxon rank-sum tests were performed to compare the baseline characteristics between patients with and without SLE and the characteristics between SLE patients using or not using LTOT. Logistic regression models were used to assess whether demographics, clinical features, comorbidities, and ADI were associated with LTOT in SLE patients. These models were adjusted for age, sex, and SLE duration to account for these possible confounders. A full multivariable model was not performed to avoid overfitting. A *P*-value of <0.05 was considered statistically significant for all analyses. Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA) and R 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

465 SLE patients and 465 non-SLE controls were identified on January 1, 2015. The mean age of the patients and matched non-SLE controls was 53.1 years (SD 16.2), while 82% were female and 85-86% were non-Hispanic White. The length of medical history in the REP was similar in both groups, with a mean length of 25.3 years (SD 17.8) and 25.3 years (SD 18.0) among SLE patients and controls, respectively. The mean SLE duration was 13.8 years (SD 11.6) (Table 1).

The most common clinical manifestations in this cohort were inflammatory arthritis (60%), leukopenia (41%), and acute cutaneous lupus (23%). 21% of patients had proteinuria, and the most common lupus nephritis classes were III and IV. All patients were ANA positive, and >70% were positive for anti-dsDNA (Table 2).

Comorbidities

All included comorbidities were more common in patients with SLE than controls, except malignant solid tumors, which were not significantly different between the two groups (Table 1). We found that 65 (14%) SLE patients had comorbid fibromyalgia, and 202 (43%) had a concurrent mood disorder compared to 23 (5%) and 138 (30%) among non-SLE controls, respectively (P<0.001 for both). Osteoarthritis was present in 214 (46%) patients and 123 (26%) controls (P<0.001). CLBP was present in 168 (36%) SLE patients, whereas 124 (27%) controls had this condition. Avascular necrosis of bone was diagnosed in 11 (2%) patients and in only 1 (<1%) comparator. The frequencies of osteoporosis, hip or spine fragility fractures, and the Charlson Comorbidity Index score were higher among SLE patients.

Opioid prescription

Sixty-two (13%) SLE patients were receiving prescribed opioids as of January 1, 2015 (index date) compared to twelve (3%) non-SLE controls (P<0.001). The median duration of the current opioid episode in SLE patients was 415 days (IQR: 157-1122) versus 71.5 days (IQR: 33.5-674) in non-SLE controls (P=0.045). The median number of opioid prescriptions in the current episode was 12 (IQR: 4-39) in SLE patients and 2.5 (IQR: 2-22) in non-SLE controls (P=0.072).

The total opioid dose prescribed during the last pre-index month (December 2014) was similar in both groups, with a median of 930 MMEs (IQR: 390-1620) in SLE patients and 895 MMEs (IQR: 305-1310.4) in controls (*P*=0.56). We did not find differences in daily doses (31.9 MMEs/day [IQR:20-56.8] versus 34.5 MMEs/day [IQR:16.5-52.1], *P*= 0.7) or the number of days covered in December 2014 between patients with SLE and non-SLE controls. Among SLE patients, 50 (11%) were receiving LTOT compared with five (1%) of non-SLE controls (*P*<0.001) (Table 1).

Long-term opioid therapy in SLE patients

Table 3 depicts the characteristics of patients with SLE who were receiving LTOT compared to those who were not on LTOT. SLE patients on LTOT had a median length of opioid therapy of 614.5 days (IQR: 345-1241). The median number of opioid prescriptions was 16 (IQR: 8-47), and the total pre-index month opioid dose prescribed was a median of 982 MMEs (IQR: 520-1760). Patients with SLE receiving LTOT had similar daily doses to SLE patients who were not on LTOT (40 MMEs [IQR: 20-60] versus 30 MMEs [IQR: 20-35.9], *P*=0.30); their days covered in December 2014 were higher than SLE patients not on LTOT (31 days [IQR: 31-31] versus 12.5 days [IQR: 9.5-23.5], respectively, *P*=<0.001). SLE patients receiving LTOT were marginally older (57.2 years [SD 14.1]) than the rest of the SLE patients (52.6 years [SD 16.3], but this association did not reach statistical significance (*P*=0.058). LTOT users also had a longer duration of disease (18.1 [SD 13.9] versus 13.3 years [SD 11.2], *P*=0.018) than those that were not on LTOT. The ADI score did not differ between the groups.

When looking at lupus clinical manifestations related to pain, we observed that LTOT patients had increased pleural/pericardial effusion (26% versus 14%, *P*=0.026) and

acute pericarditis (22% versus 7%, *P*<0.001), but interestingly, inflammatory arthritis was not significantly different (68% versus 59%, *P*=0.20) from non-LTOT patients (Table 2). Conversely, thrombocytopenia (4% versus 16%, *P*=0.024) was less frequent in the LTOT group. We did not find any significant difference in neuropsychiatric or renal domains.

When we evaluated comorbidities, fibromyalgia, mood disorders, osteoarthritis, CLBP, and hip or spine fragility fractures were more frequently present among SLE patients receiving LTOT (Table 3). The Charlson Comorbidity Index score was similar in both groups.

In the adjusted logistic regression analysis, older age (odds ratio [OR]: 1.13 per decade; 95% CI: 0.93-1.39) was not associated with LTOT (Figure 2). Among SLE patients, LTOT was associated with SLE duration (OR: 1.03 per year; 95% CI: 1.00-1.05), a history of acute pericarditis (OR: 3.92; 95% CI: 1.78-8.66), and pleural or pericardial effusion (OR: 2.11; 95% CI: 1.05-4.27). SLE patients with fibromyalgia were more than seven times as likely to be on LTOT than those without fibromyalgia (OR: 7.78; 95% CI: 3.89-15.55). The presence of mood disorders elevated the likelihood of being on LTOT more than twice among SLE patients (OR: 2.76; 95% CI: 1.47-5.16). Patients who had CLBP or a history of fragility fractures were four and three times more likely to be under LTOT (OR: 4.00; 95% CI: 2.13-7.51, and OR: 3.72; 95% CI: 1.25-11.07). Other SLE manifestations, comorbidities, Charlson Comorbidity Index, or ADI scores were not significantly associated with LTOT use.

DISCUSSION

In this study, 13% of SLE patients received opioid therapy compared to 3% of the non-SLE population. One out of ten (11%) SLE patients were on LTOT with a median duration of more than 1.5 years (614.5 days). The use of LTOT among SLE patients was significantly associated with a history of acute pericarditis, fibromyalgia, hip or spine fragility fractures, CLBP, and mood disorders. We did not find an association between area-based measures of social determinants of health measured by ADI scores and opioid therapy or LTOT. These findings suggest that SLE patients are more likely to receive opioid therapy because of the pain that SLE could cause directly and because of their comorbid conditions.

A previous study described a prevalence of opioid use of 31% among a sample of SLE patients from the Michigan Lupus Epidemiology and Surveillance Program (MILES) and 7.8% among a matched cohort without SLE. They found that 21% of SLE patients fulfilled their definition of long-term opioid use (more than one year). The median duration of opioid use in SLE patients was three years, which was similar to matched persons.[6] In two claims-based studies, between 46-52.6% of SLE patients received opioids during their 12-month period of observation, and 16-18.2% received opioids for 90 days or more.[7,19] Compared to these prior studies, we found a lower prevalence of opioid therapy in our SLE population and matched controls. Differences in study design and populations likely explain the differences between the studies. The MILES study was based on a sample of patients from the initial registry; possibly, the patients participating in the study may have had a more severe disease or comorbidities than those identified in the registry but did not participate, resulting in a greater prevalence of

opioid use. We also need to consider the higher dispensing rates in Michigan at the time of the MILES study compared with the rates in Minnesota or Wisconsin at the time of our study,[20] which might account for some of these differences. The MILES study was based on interviews, which is subject to response bias, as the investigators acknowledged. We were able to avoid this by using prescription data. Finally, the study population from the MILES cohort was more diverse, with more representation of racial or ethnic minorities.[6] Claims-based studies suffer from misclassification and are performed in populations of beneficiaries of a specific insurance type limiting their generalizability,[7] while we included all patients in a well-defined geographic area, irrespective of their insurance status or access to care. In a study of SLE patients who frequently visited the emergency department (ED), the prevalence of LTOT (defined as having a prescription for daily or near-daily use of opioids for at least 90 days, or total days of opioid supply >120 days) was also higher (37.7%) than ours; they also found that ADI scores in SLE patients who were receiving LTOT were higher than the regional average, but they did not compare SLE patients to a sample matched on key demographic characteristics, limiting the usefulness of the comparison.[21] Our study did not find a difference in ADI scores between SLE patients and the rest of the non-SLE population or between LTOT patients and the rest of SLE patients. The patient population and setting likely explain the differences in findings between our study and the ED study; our study included SLE patients in the community, while Lee *et al.* included SLE patients seen in the ED in a different geographic area.[21] Recently, a study from Germany derived from an insurance database reported that 8.8% of patients had a long-term prescription for opioids (defined as a prescription in ≥3 consecutive

quarters).[22] This is lower than our estimates (10%), but in general, the German population has a lower use of opioids than the US population, and their cases were identified based on diagnosis codes, which may risk misclassification.[5,23]

Among patients with SLE, we found that those who had serositis (pleural/pericardial effusion) and in particular acute pericarditis were more likely to be on LTOT. Other painful manifestations like inflammatory arthritis were as frequent among those on LTOT and the rest of the patients. One of our hypotheses was that renal involvement would be associated with LTOT, given the more limited options to treat pain (e.g., nephrotoxicity from non-steroidal anti-inflammatory drugs). However, those with and without kidney involvement were equally likely to receive LTOT. Lee *et al.* described in their group of SLE patients who frequently visited the ED that 44.2% had a history of renal involvement and 18.2% had a history of pericarditis, but they did not include a comparison group and did not analyze associations.[21]

We found that SLE patients receiving LTOT were more likely to have fibromyalgia and mood disorders than SLE patients who were not on LTOT. In contrast, the MILES study did not find associations between long-term opioid users and self-reported fibromyalgia, depression, or anxiety. They also did not find any association with damage index score (a proxy for comorbidities), the prescription of opioids, or the disease duration. It is important to note that their population was derived from a cohort diagnosed more than ten years before the interview.[6] Differences in findings could be explained by the different methods used to detect the presence of fibromyalgia and depression and the limitations intrinsic to an interview study. While the MILES study relied on self-reported diagnoses, our study identified diagnoses through medical record reviews. We explored

other conditions associated with pain. We identified that SLE patients with a history of CLBP and hip or spine fragility fractures were also considerably more likely to be on LTOT. Our results about higher LTOT in SLE patients with comorbid back pain are in agreement with reports about the general population, where a prevalence of 18.8% of back pain patients receiving LTOT has been reported.[24] Opioid therapy and fragility fractures have been associated both as cause and consequence in the general population, with a higher probability of receiving opioid therapy after a fracture and as a risk factor for fractures.[25] Fibromyalgia and depression have been previously associated with higher use of opioid therapy in the general population.[26,27] Although there is no evidence of efficacy of opioid therapy in fibromyalgia, it is frequently used in these patients, with rates of opioid use ranging from 11.3 to 69%.[27]

Our study has some limitations. The cross-sectional design does not allow us to infer causality between LTOT and the factors associated with it, more studies are needed to better understand this association among patients with SLE. The principal ethnic composition of our cohort, derived from a limited geographic area in the upper midwest of the United States, where most of the population is non-Hispanic White, may restrict the generalizability of our findings to other populations. Nevertheless, the non-Hispanic White population had the highest opioid-involved overdose death rates during 2014-2015.[28] Opioid prescribing has decreased since its height in 2012;[29,30] it is possible that after the release of the 2016 CDC guideline for prescribing opioids, fewer patients might be on LTOT; however, associations identified in this study may still apply to current practice.

In conclusion, 13% of SLE patients in this population were receiving opioid therapy as of January 1, 2015. One of every ten patients was on LTOT. Patients with a history of acute pericarditis, pleural or pericardial effusion, fibromyalgia, depression, CLBP, and hip or spine fragility fractures were more likely to receive LTOT. These findings will help clinicians identify factors that are associated with opioid therapy in SLE patients and optimize their pain management. Given the lack of evidence of the efficacy of opioid therapy in SLE and its comorbid conditions, a multidisciplinary pain management approach, including maximizing non-pharmacological and non-opioid therapies, is needed to preserve or improve the quality of life and function.

STATEMENTS

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FIGURES

Figure 1. Study schematic representation. All opioid prescriptions present on January 1, 2015 (index date, arrow) were identified. A ten-year lookback period was used to identify episodes of opioid use, defined as contiguous prescriptions before January 1, 2015, with gaps less than 30 days between prescriptions (dashed line). A 5-year lookback period between 2010 and 2014 was used to ascertain comorbidities on the index date (dotted line).

Figure 2. The Forest plot shows factors associated with long-term opioid therapy use among patients with systemic lupus erythematosus (SLE) in 27 southeast Minnesota and southwest Wisconsin counties. OR: odds ratio (age-, sex- and SLE duration adjusted); CI: confidence interval; SLE: systemic lupus erythematosus.

TABLE 1. General characteristics of patients with systemic lupus erythematosus (SLE) and matched controls without SLE within a region of 27-counties in southeast Minnesota and southwest Wisconsin on January 1, 2015.

	SLE N=465	Non-SLE N= 465	*P*-value*
Age, years, mean (SD)	53.1 (16.2)	53.1 (16.2)	0.99
Female, n (%)	382 (82)	382 (82)	1.00
Race/Ethnicity, n (%)			0.92
Non-Hispanic White	392 (85)	400 (86)	
Hispanic	27 (6)	22 (5)	
Non-Hispanic Black	18 (4)	19 (4)	
Non-Hispanic Asian	15 (3)	17 (4)	
American Indian	2 (<1)	2 (<1)	
Other/Mixed	8 (2)	5 (1)	
Unknown	3	0	
Length of medical history, years, mean (SD)	25.3 (17.8)	25.3 (18.0)	0.91
SLE duration, years, mean (SD)	13.8 (11.6)	--	--
Comorbidities (within 5 years prior), n (%)			
Fibromyalgia	65 (14)	23 (5)	<0.001
Mood disorder	202 (43)	138 (30)	<0.001
Osteoarthritis	214 (46)	123 (26)	<0.001
Chronic low back pain (CLBP)	168 (36)	124 (27)	0.002

Chronic kidney disease[a]	52 (11)	10 (2)	<0.001
Avascular necrosis of bone	11 (2)	1 (<1)	0.004
Osteoporosis	58 (12)	21 (5)	<0.001
Hip or spine fragility fractures	17 (4)	3 (1)	0.002
Cancer (solid tumors)	13 (3)	9 (2)	0.39
Hematologic cancer	8 (2)	0 (0)	0.005
Charlson Comorbidity Index[b], mean (SD)	2.2 (2.6)	0.9 (1.6)	<0.001
Area Deprivation Index, mean (SD)	94.1 (12.7)	94.4 (12.4)	0.82
Opioid therapy[c], n (%)	62 (13)	12 (3)	<0.001
Long-term[d], n (%)	50 (11)	5 (1)	<0.001
Days of opioid therapy, median (IQR)	415 (157-1122)	71.5 (33.5-674)	0.045
Opioid prescriptions, median (IQR)	12 (4-39)	2·5 (2-22)	0.072
December 2014 total opioid dose, MMEs, median (IQR)	930 (390-1620)	895 (305-1310)	0.56
Days covered in December 2014, median (IQR)	31 (29-31)	30 (14-31)	0.13
December 2014 daily doses, MMEs, median (IQR)	31.9 (20-56·8)	34.5 (16.5-52.1)	0.70

SLE= systemic lupus erythematosus; SD= Standard deviation; IQR= Interquartile range; MMEs= Morphine milligram equivalents.

*Kruskal Wallis or Chi-Square test. [a]Stage ≥3a (Glomerular filtration rate <60 ml/min/1.73m^2). [b]Excluding rheumatologic category. [c]Current at index date (January 1,

2015). [d]Was defined as those with an episode of prescription use that spans ≥90 days or ≥10 prescriptions.

TABLE 2. Clinical manifestations and organ involvement according to 2019 European League Against Rheumatism/American College of Rheumatology classification criteria among patients with systemic lupus erythematosus (SLE) within a region of 27-counties in southeast Minnesota and southwest Wisconsin on January 1, 2015; overall and subdivided by long-term opioid therapy (LTOT).

Clinical domains and criteria	All N=465	LTOT[a] N= 50	Non-LTOT N= 415	*P*-value*
Constitutional				
Fever, n (%)	26 (6)	2 (4)	24 (6)	0.60
Hematologic domain				
Leukopenia, n (%)	191 (41)	18 (36)	173 (42)	0.44
Thrombocytopenia, n (%)	68 (15)	2 (4)	66 (16)	0.024
Autoimmune hemolysis, n (%)	14 (3)	1 (2)	13 (3)	0.66
Neuropsychiatric domain				
Delirium, n (%)	2 (<1)	0 (0)	2 (<1)	0.62
Psychosis, n (%)	1 (<1)	0 (0)	1 (<1)	0.73
Seizure, n (%)	6 (1)	0 (0)	6 (1)	0.39
Mucocutaneous domain				
Non-scarring alopecia, n (%)	18 (4)	2 (4)	16 (4)	0.96
Oral ulcers, n (%)	35 (8)	4 (8)	31 (7)	0.89
Subacute cutaneous or discoid lupus, n (%)	63 (14)	10 (20)	53 (13)	0.16

Acute cutaneous lupus, n (%)	106 (23)	10 (20)	96 (23)	0.62
Serosal domain				
Pleural or pericardial effusion, n (%)	71 (15)	13 (26)	58 (14)	0.026
Acute pericarditis, n (%)	38 (8)	11 (22)	27 (7)	<0.001
Musculoskeletal domain				
Inflammatory arthritis, n (%)	277 (60)	34 (68)	243 (59)	0.20
Renal domain				
Proteinuria >0·5g/24hrs, n (%)	96 (21)	9 (18)	87 (21)	0.62
Class II or V lupus nephritis, n (%)	35 (8)	3 (6)	32 (8)	0.66
Class III or IV lupus nephritis, n (%)	73 (16)	7 (14)	66 (16)	0.73
Immunology domains				
Antiphospholipid antibodies, n (%)	103 (22)	9 (18)	94 (23)	0.45
Low C3 or low C4, n (%)	161 (35)	16 (32)	145 (35)	0.68
Low C3 and low C4, n (%)	144 (31)	11 (22)	133 (32)	0.15
Anti-dsDNA, n (%)	329 (71)	34 (68)	295 (71)	0.65
Anti-Smith, n (%)	92 (20)	5 (10)	87 (21)	0.066

LTOT= long-term opioid therapy; SLE= systemic lupus erythematosus; dsDNA= double-stranded DNA.

*Comparison of SLE patients under LTOT vs. non-LTOT patients. Kruskal Wallis or Chi-Square test. [a]Was defined as those with an episode of prescription use that spans ≥90 days or ≥10 prescriptions.

TABLE 3. Characteristics of systemic lupus erythematosus (SLE) patients receiving long-term opioid therapy (LTOT) compared with SLE patients not under LTOT on January 1, 2015.

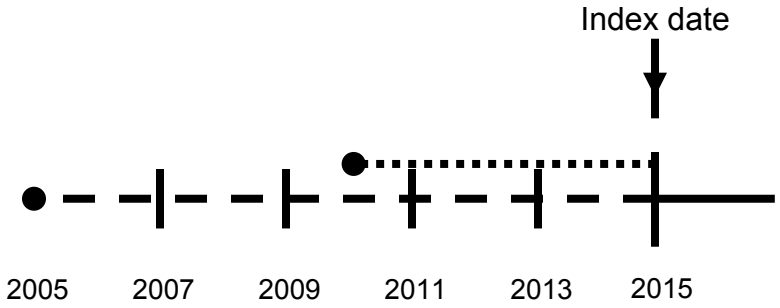
	LTOT[a] N= 50	Non-LTOT N= 415	*P*-value*
Age, years, mean (SD)	57.2 (14.1)	52.6 (16.3)	0.058
Female, n (%)	43 (86)	339 (82)	0.45
Race, n (%)			0.17
Non-Hispanic White	42 (86)	350 (85)	
Hispanic	5 (10)	22 (5)	
Non-Hispanic Black	0 (0)	18 (4)	
Non-Hispanic Asian	0 (0)	15 (4)	
American Indian	0 (0)	2 (<1)	
Other/Mixed	2 (4)	6 (1)	
Unknown	1	2	
Length of medical history, years, mean (SD)	30.3 (16.9)	24.7 (17.9)	0.018
SLE duration, years, mean (SD)	18.1 (13.9)	13.3 (11.2)	0.018
Comorbidities (within 5 years prior), n (%)			
Fibromyalgia	22 (44)	43 (10)	<0.001
Mood disorder	33 (66)	169 (41)	0.001
Osteoarthritis	31 (62)	183 (44)	0.016

Chronic low back pain (CLBP)	33 (66)	135 (33)	<0.001
Chronic kidney disease[b]	7 (14)	45 (11)	0.50
Avascular necrosis of bone	2 (4)	9 (2)	0.42
Osteoporosis	8 (16)	50 (12)	0.42
Hip or spine fragility fractures	6 (12)	11 (3)	0.001
Cancer (solid tumors)	2 (4)	11 (3)	0.58
Hematologic cancer	1 (2)	7 (2)	0.87
Charlson Comorbidity Index[c], mean (SD)	2.5 (2.3)	2.2 (2.6)	0.13
Area Deprivation Index, mean (SD)	93.4 (10.4)	94.2 (13.0)	0.50
Opioid therapy[d], n (%)	50 (100)	12 (3)	--
Days of opioid therapy, median (IQR)	614.5 (345-1241)	14.5 (9.5-39.5)	--
Opioid prescriptions, median (IQR)	16 (8-47)	1.5 (1-2)	--
December 2014 total opioid dose, MMEs, median (IQR)	982 (520-1760)	256 (158-495)	0.003
Days covered in December 2014, median (IQR)	31 (31-31)	12.5 (9.5-23.5)	<0.001
December 2014 daily doses, MMEs, median (IQR)	40 (20-60)	30 (20-35.9)	0.30

LTOT= long-term opioid therapy; SD= Standard deviation; SLE= systemic lupus erythematosus; IQR= Interquartile range; MMEs= Morphine milligram equivalents.

*Kruskal Wallis or Chi-Square test. [a]Was defined as those with an episode of prescription use that spans ≥90 days or ≥10 prescriptions. [b]Stage ≥3a (Glomerular

filtration rate <60 ml/min/1.73m^2). [c]Excluding the rheumatologic category. [d]Current at index date (January 1, 2015).



Factors associated with long-term opioid therapy in SLE. OR (95% CI)