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Long-Term Opioid Therapy Among Patients With Systemic Lupus Erythematosus in the Community: A Lupus Midwest Network (LUMEN) 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 controls without SLE in a population-based cohort on January 1, 2015. We captured demographics, manifestations of SLE, comorbidities (ie, fibromyalgia, mood disorders, osteoarthritis, chronic low back pain [CLBP], chronic kidney disease (CKD), avascular necrosis, osteoporosis, fragility fractures, and cancer), and the Area Deprivation Index (ADI). Opioid prescription data were used to assess the prevalence of LTOT, defined as contiguous prescriptions (gaps of < 30 days between prescriptions) and receiving opioid therapy for ≥ 90 days or ≥ 10 prescriptions before the index date.

Results. A total of 465 patients with SLE and 465 controls without SLE were included. In total, 13% of patients with SLE and 3% of controls without SLE were receiving opioid therapy ($P < 0.001$), and 11% of patients with SLE were on LTOT vs 1% of controls without SLE. Among patients with SLE, acute pericarditis (odds ratio [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 are more likely to receive LTOT than controls. Among patients with SLE, LTOT was associated with pericarditis and several comorbidities. However, LTOT was not associated with CKD despite the limited pain control options among these patients.

Key Indexing Terms: comorbidity, long-term opioid therapy, opioids, pain management, systemic lupus erythematosus

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Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by 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 patients with SLE, treatment options are limited. For example, patients with SLE with renal involvement on high doses of steroids or on anticoagulant therapy are at increased risk of complications related to the use of nonsteroidal antiinflammatory drugs (NSAIDs; eg, 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 patients with SLE self-reported opioid therapy, and up to 21% of them were on therapy for more than 1 year, compared to 7.8% and 6.3% of persons without SLE, respectively.[6] A claims-based study reported that 52.6% of patients with SLE 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 because of 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 (eg, serositis and inflammatory arthritis), lupus nephritis, and non-SLE–associated painful comorbid conditions will 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 healthcare providers for the local population, including the Mayo Clinic, the Olmsted Medical Center, their affiliated hospitals, and local nursing homes, among others. 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 2 different strategies: (1) through Hospital International Classification of Disease Adaptation; International Classification of Diseases, 9th revision (ICD-9); and ICD-10 codes for SLE, cutaneous lupus erythematosus, and other associated diseases; and (2) through laboratory measures associated with SLE: antinuclear antibodies (ANAs; > 1:80), low complement, anti-dsDNA, anti-Sm, lupus anticoagulant, anticardiolipin (IgG, IgM, and IgA), and anti–β_2 glycoprotein I (IgG, IgM, and IgA) antibodies (Supplementary Table S1, available with the online version of this article). 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 data, and laboratory data included in the classification criteria were abstracted from the electronic medical record. Patients meeting the 2019 European Alliance of Associations for Rheumatology (EULAR)/American College of Rheumatology (ACR) classification criteria[12] were considered incident cases. Those who migrated to the 27-county region after diagnosis—and were, therefore, under treatment—were included if they had 7 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). Patients with SLE 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 patients with SLE and subjects without SLE. 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 spanned 90 or more days or 10 or more 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]

SLE 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 (OA), chronic low back pain (CLBP), and cancer (solid tumors and hematologic); comorbidities with a higher burden in patients with SLE 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 such as NSAIDs. Since most of these conditions are chronic, we used a 5-year look-back from January 1, 2010, to the index date using ICD-9 codes to identify the comorbidities mentioned above for both patients with SLE and controls without SLE (Supplementary Table S2, available with the online version of this article). 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 × 100—of 90% or higher with the physician's chart review, patients

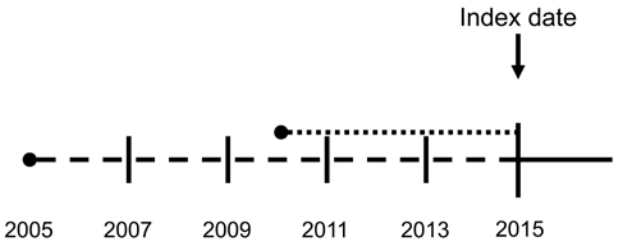

Figure 1. Study schematic representation. All opioid prescriptions present on January 1, 2015 (index date, arrow), were identified. A 10-year look-back period was used to identify episodes of opioid use, defined as contiguous prescriptions before January 1, 2015, with gaps < 30 days between prescriptions (dashed line). A 5-year look-back period between 2010 and 2014 was used to ascertain comorbidities on the index date (dotted line).

and controls were attributed to that diagnosis without review of the 90% remaining. For those ICD-9 codes where the percentage of agreement was less than 90%, manual verification of the diagnoses was performed according to preestablished criteria (Supplementary Table S2). Only OA 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 (CCI),[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 SDs, medians and IQRs, and counts and percentages—were used to summarize the characteristics of patients with SLE and controls without SLE. Chi-square and Wilcoxon rank-sum tests were performed to compare the baseline characteristics between patients with SLE and controls without SLE, and to compare the characteristics between patients with SLE using LTOT and those not using LTOT. Logistic regression models were used to assess whether demographics, clinical features, comorbidities, and ADI were associated with LTOT in patients with SLE. These models were adjusted for age, sex, and SLE duration to account for these possible confounders. A full multivariable model was not performed in order to avoid overfitting. A P value < 0.05 was considered statistically significant for all analyses. Analyses were performed using SAS (version 9.4; SAS Institute Inc) and R (version 3.6.2; R Foundation for Statistical Computing).

RESULTS

A total of 465 patients with SLE and 465 controls without SLE were identified on January 1, 2015. The mean age of the patients and matched controls was 53.1 (SD 16.2) years; 82% were female, and 85% to 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 (SD 17.8) years among patients with SLE and 25.3 (SD 18.0) years among controls. The mean SLE duration was 13.8 (SD 11.6) years (Table 1).

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

Comorbidities. All included comorbidities were more common in patients with SLE than in controls, except for malignant solid tumors, which were not significantly different between the 2 groups (Table 1). We found that 65 (14%) patients with SLE had comorbid fibromyalgia (FM) and 202 (43%) had a concurrent mood disorder, compared to 23 (5%) and 138 (30%) controls without SLE, respectively (P < 0.001 for both). OA was present in 214 (46%) patients and 123 (26%) controls (P < 0.001). CLBP was present in 168 (36%) patients with SLE, whereas 124 (27%) controls had this condition. Avascular necrosis of bone was diagnosed in 11 (2%) patients and in only 1 (0.2%) comparator. The frequencies of osteoporosis, hip or spine fragility fractures, and the CCI score were higher among patients with SLE.

Opioid prescription. In total, 62 (13%) patients with SLE were receiving prescribed opioids as of January 1, 2015 (index date), compared to 12 (3%) controls without SLE (P < 0.001). The median duration of the current opioid episode among patients with SLE was 415 (IQR 157-1122) days vs 71.5 (IQR 33.5-674) days among controls without SLE (P = 0.045). The median number of opioid prescriptions in the current episode was 12 (IQR 4-39) among patients with SLE and 2.5 (IQR 2-22) among controls without SLE (P = 0.07).

The total opioid dose prescribed during the last preindex month (December 2014) was similar in both groups, with a median of 930 (IQR 390-1620) MMEs in patients with SLE and 895 (IQR 305-1310.4) MMEs in controls (P = 0.56). We did not find differences in daily doses (median 31.9 MMEs/day, IQR 20-56.8; vs median 34.5 MMEs/day, IQR 16.5-52.1; P = 0.70) or in the number of days covered in December 2014 between patients with SLE and controls without SLE. Among patients with SLE, 50 (11%) were receiving LTOT, compared with 5 (1%) controls without SLE (P < 0.001; Table 1).

LTOT in patients with SLE. Table 3 depicts the characteristics of patients with SLE who were receiving LTOT compared to those who were not receiving LTOT. Patients with SLE on LTOT had a median length of opioid therapy of 614.5 (IQR 345-1241) days. The median number of opioid prescriptions was 16 (IQR 8-47), and the total opioid dose prescribed during the preindex month was a median of 982 (IQR 520-1760) MMEs. Patients with SLE receiving LTOT had similar daily doses to patients with SLE who were not receiving LTOT: 40 (IQR 20-60) MMEs vs 30 (IQR 20-35.9) MMEs, respectively (P = 0.30). In addition, their days covered in December 2014 were higher than those for patients with SLE not on LTOT: 31 (IQR 31-31) days vs 12.5 (IQR 9.5-23.5) days, respectively (P < 0.001). Patients with SLE receiving LTOT were marginally older (mean 57.2 yrs, SD 14.1) than the rest of the patients with SLE (mean 52.6 yrs, SD 16.3), but this association did not reach statistical significance (P = 0.06). LTOT users also had a longer duration of disease (mean 18.1 yrs, SD 13.9) than those who were not on LTOT (mean 13.3 yrs, SD 11.2; P = 0.02). The ADI score did not differ between the groups.

When looking at SLE clinical manifestations related to pain, we observed that patients receiving LTOT, compared to those not receiving LTOT, had increased pleural/pericardial effusion (26% vs 14%; P = 0.03) and acute pericarditis (22% vs 7%; P < 0.001). Interestingly, inflammatory arthritis among patients

Table 1. General characteristics of patients with 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**
Age, yrs, mean (SD)	53.1 (16.2)	53.1 (16.2)	0.99
Female gender	382 (82)	382 (82)	> 0.99
Race/ethnicity[a]			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 (0.4)	2 (0.4)	
Other/mixed	8 (2)	5 (1)	
Unknown	3	0	
Length of medical history, yrs, mean (SD)	25.3 (17.8)	25.3 (18.0)	0.91
SLE duration, yrs, mean (SD)	13.8 (11.6)	–	–
Comorbidities, within 5 yrs prior			
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	168 (36)	124 (27)	0.002
Chronic kidney disease[b]	52 (11)	10 (2)	< 0.001
Avascular necrosis of bone	11 (2)	1 (0.2)	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[c], 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			
Current at index date (January 1, 2015)	62 (13)	12 (3)	< 0.001
Long term[d]	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)	0.07
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

Data are in n (%) unless otherwise indicated. * Kruskal-Wallis or chi-square test. [a] The denominator excludes unknown. [b] Stage ≥ 3a (glomerular filtration rate < 60 mL/min/1.73 m^2). [c] Excluding rheumatologic category. [d] Was defined as those with an episode of prescription use that spans ≥ 90 days or ≥ 10 prescriptions. MME: morphine milligram equivalent; SLE: systemic lupus erythematosus.

receiving LTOT (68%) was not significantly different from that among patients not receiving LTOT (59%; $P = 0.20$; Table 2). Conversely, thrombocytopenia was less frequent in the LTOT group compared to the non-LTOT group (4% vs 16%; $P = 0.02$). We did not find any significant difference in the neuropsychiatric or renal domains.

When we evaluated comorbidities, FM, mood disorders, OA, CLBP, and hip or spine fragility fractures were more frequently present among patients with SLE receiving LTOT (Table 3). The CCI 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 patients with SLE, 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). Patients with SLE with FM were more than 7 times as likely to be on LTOT than those without FM (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 patients with SLE (OR 2.76, 95% CI 1.47-5.16). Patients who had CLBP (OR 4.00, 95% CI 2.13-7.51) or a history of fragility fractures (OR 3.72, 95% CI 1.25-11.07) were 4 and 3 times more likely to be on LTOT, respectively. Other SLE manifestations, comorbidities, CCI values, or ADI scores were not significantly associated with LTOT use.

DISCUSSION

In this study, 13% of patients with SLE received opioid therapy compared to 3% of the non-SLE population. Only 1 out of 10 (11%) patients with SLE were on LTOT, with a median duration of more than 1.5 years (614.5 days). The use of LTOT among patients with SLE was significantly associated with a history of acute pericarditis, FM, hip or spine fragility fractures, CLBP,

Table 2. Clinical manifestations and organ involvement according to 2019 EULAR/ACR classification criteria among patients with SLE within a region of 27 counties in southeast Minnesota and southwest Wisconsin on January 1, 2015.

Clinical Domains and Criteria	All, N = 465	LTOT[a], n = 50	Non-LTOT, n = 415	*P*[b]
Constitutional				
Fever	26 (6)	2 (4)	24 (6)	0.60
Hematologic domain				
Leukopenia	191 (41)	18 (36)	173 (42)	0.44
Thrombocytopenia	68 (15)	2 (4)	66 (16)	0.02
Autoimmune hemolysis	14 (3)	1 (2)	13 (3)	0.66
Neuropsychiatric domain				
Delirium	2 (0.4)	0 (0)	2 (0.4)	0.62
Psychosis	1 (0.2)	0 (0)	1 (0.2)	0.73
Seizure	6 (1)	0 (0)	6 (1)	0.39
Mucocutaneous domain				
Nonscarring alopecia	18 (4)	2 (4)	16 (4)	0.96
Oral ulcers	35 (8)	4 (8)	31 (7)	0.89
Subacute cutaneous or discoid lupus	63 (14)	10 (20)	53 (13)	0.16
Acute cutaneous lupus	106 (23)	10 (20)	96 (23)	0.62
Serosal domain				
Pleural or pericardial effusion	71 (15)	13 (26)	58 (14)	0.03
Acute pericarditis	38 (8)	11 (22)	27 (7)	< 0.001
Musculoskeletal domain				
Inflammatory arthritis	277 (60)	34 (68)	243 (59)	0.20
Renal domain				
Proteinuria > 0.5 g/24 h	96 (21)	9 (18)	87 (21)	0.62
Class II or V LN	35 (8)	3 (6)	32 (8)	0.66
Class III or IV LN	73 (16)	7 (14)	66 (16)	0.73
Immunology domains				
Antiphospholipid antibodies	103 (22)	9 (18)	94 (23)	0.45
Low C3 or low C4	161 (35)	16 (32)	145 (35)	0.68
Low C3 and low C4	144 (31)	11 (22)	133 (32)	0.15
Anti-dsDNA	329 (71)	34 (68)	295 (71)	0.65
Anti-Sm	92 (20)	5 (10)	87 (21)	0.07

Data are in n (%). [a] Was defined as those with an episode of prescription use that spanned ≥ 90 days or ≥ 10 prescriptions. [b] Comparison of patients with SLE under LTOT vs those not under LTOT; Kruskal-Wallis or chi-square test. ACR: American College of Rheumatology; EULAR: European Alliance of Associations for Rheumatology; LN: lupus nephritis; LTOT: long-term opioid therapy; SLE: systemic lupus erythematosus.

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 patients with SLE 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 patients with SLE from the Michigan Lupus Epidemiology and Surveillance Program (MILES) and 7.8% among a matched cohort without SLE.[6] They found that 21% of patients with SLE fulfilled their definition of long-term opioid use (ie, > 1 yr). The median duration of opioid use in patients with SLE was 3 years, which was similar to that of matched persons.[6] In 2 claims-based studies, between 46% and 52.6% of patients with SLE received opioids during their 12-month period of observation, and 16% to 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 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 are 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] whereas we included all patients in a well-defined geographic area, irrespective of their insurance status or access to care. In a study of patients with SLE who frequently visited the

Table 3. Characteristics of patients with SLE receiving LTOT compared to those not receiving LTOT on January 1, 2015.

	LTOT[a], n = 50	Non-LTOT, n = 415	*P**
Age, yrs, mean (SD)	57.2 (14.1)	52.6 (16.3)	0.06
Female gender	43 (86)	339 (82)	0.45
Race/ethnicity[b]			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 (0.5)	
Other/mixed	2 (4)	6 (1)	
Unknown	1	2	
Length of medical history, yrs, mean (SD)	30.3 (16.9)	24.7 (17.9)	0.02
SLE duration, yrs, mean (SD)	18.1 (13.9)	13.3 (11.2)	0.02
Comorbidities, within 5 yrs prior			
Fibromyalgia	22 (44)	43 (10)	< 0.001
Mood disorder	33 (66)	169 (41)	0.001
Osteoarthritis	31 (62)	183 (44)	0.02
Chronic low back pain	33 (66)	135 (33)	< 0.001
Chronic kidney disease[c]	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[d], 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			
Current at index date (January 1, 2015)	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

Data are in n (%) unless otherwise indicated. * Kruskal-Wallis or chi-square test. [a] Was defined as those with an episode of prescription use that spanned ≥ 90 days or ≥ 10 prescriptions. [b] The denominator excludes unknown. [c] Stage ≥ 3a (glomerular filtration rate < 60 mL/min/1.73 m^2). [d] Excluding the rheumatologic category. LTOT: long-term opioid therapy; MME: morphine milligram equivalent; SLE: systemic lupus erythematosus.

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 of more than 120 days—was also higher (37.7%) than ours; they also found that ADI scores in patients with SLE who were receiving LTOT were higher than the regional average, but they did not compare patients with SLE 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 patients with SLE and the rest of the non-SLE population or between patients receiving LTOT and the rest of the patients with SLE. The patient population and setting likely explain the differences in findings between our study and the ED study: our study included patients with SLE in the community, whereas Lee et al[21] included patients with SLE seen in the ED in a different geographic area. 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 or more 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 (ie, 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 as they were among 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 (eg, nephrotoxicity from NSAIDs). However, those with and

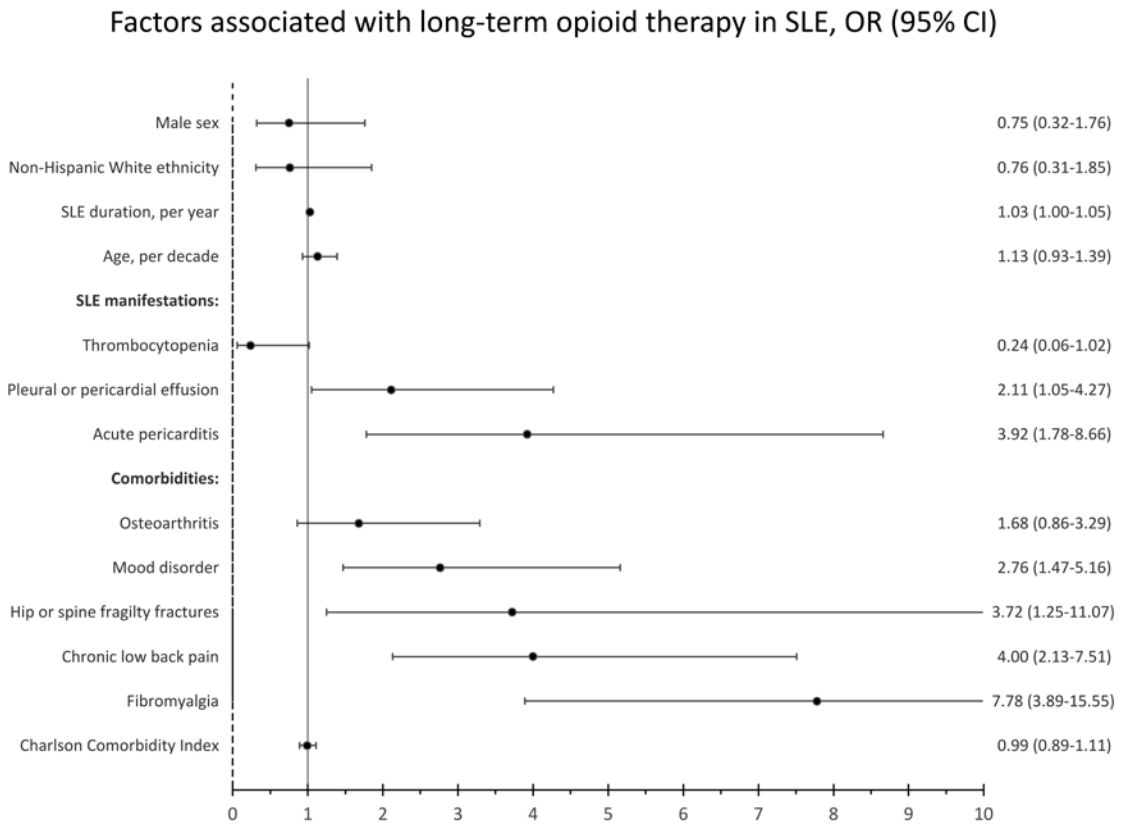

Figure 2. The forest plot shows factors associated with long-term opioid therapy use among patients with SLE in 27 southeast Minnesota and southwest Wisconsin counties. The OR was adjusted by age, sex, and SLE duration. OR: odds ratio; SLE: systemic lupus erythematosus.

without kidney involvement were equally likely to receive LTOT. In their group of patients with SLE who frequently visited the ED, Lee et al[21] found 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.

We found that patients with SLE receiving LTOT were more likely to have FM and mood disorders than patients with SLE who were not on LTOT. In contrast, the MILES study did not find associations between long-term opioid users and self-reported FM, depression, or anxiety. They also did not find any association with the damage index score (a proxy for comorbidities), the prescription of opioids, or disease duration. It is important to note that their population was derived from a cohort diagnosed more than 10 years before the interview.[6] Differences in findings could be explained by the different methods used to detect the presence of FM 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 patients with SLE 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 among patients with SLE with comorbid back pain are in agreement with reports about the general population, where a prevalence of 18.8% of patients with back pain 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] FM 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 FM, 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; therefore, 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 Centers for Disease Control and Prevention 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 patients with SLE in this population were receiving opioid therapy as of January 1, 2015, and 1 out of every 10 patients was on LTOT. Patients with a history of acute

pericarditis, pleural or pericardial effusion, FM, 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 patients with SLE 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 nonpharmacological and nonopioid therapies, is needed to preserve or improve the quality of life and function of these patients.

DATA AVAILABILITY

Deidentified data are available upon reasonable request and ethical approval.

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ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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