

Opioid use in patients with polymyalgia rheumatica

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ABSTRACT

Objective. To examine the trends of chronic opioid use in patients with polymyalgia rheumatica (PMR) over an 11-year period in Olmsted County, Minnesota, USA and compare use to subjects without the disease.

Methods. Retrospective data on opioid prescriptions were collected from 2005 to 2015 in a population-based incidence cohort of patients meeting the 2012 American College of Rheumatology classification criteria for PMR alongside comparison subjects. Poisson regression methods were used to compare opioid use between these groups.

Results. 244 patients with PMR and 211 non-PMR comparator subjects were included in the study. Rates of chronic opioid use were not significantly different between the two groups. 7.5% of patients with PMR were identified as chronic users by the end of the study period compared with 5.2% of non-PMR subjects. Any opioid use was also not significantly higher in PMR, with relative risk of 1.10 (95% CI 0.97, 1.26, $p=0.14$). Rates of chronic use among patients over 80 years were higher in both groups.

Conclusion. Patients with PMR do not appear to have higher rates of opioid use compared with the general population.

Introduction

The use of opioid analgesia for chronic pain has steadily risen in the US. Between 1980 and 2000 the total number of outpatient opioid prescriptions doubled, and the use of more potent opioids quadrupled (1). There has been a corresponding increase in opioid overdose, abuse, and addiction. Opioid poisoning death rates nearly quadrupled from 2000 to 2013, and it is estimated that 25% of patients on long-term opioid treatment become non-medical users, with 10% developing features of addiction (2, 3).

While there are established guidelines for the use of opioids for acute pain and cancer-related pain, there is little evidence supporting the long-term benefit of opioids for non-cancer related chronic pain. Recent guidelines from the American Academy of Pain Medicine

found no high quality evidence for any use of opioids for chronic pain, which includes chronic inflammatory diseases (3-6). Opioid use has also been associated with increased healthcare cost and substantial economic burden stemming from overdose and misuse (7, 8).

Polymyalgia rheumatic (PMR) is a systemic rheumatic inflammatory disease characterised primarily by musculoskeletal pain and stiffness. It is a chronic condition that affects patients over 50 years and is most common in Northern Europe and the US, with an estimated incidence rate of 50–68/100,000 population (9). Glucocorticoid treatment is the current standard of care and generally is effective in reducing PMR associated pain, however the need for additional pain management, in particular the need for opioid therapy, has not been studied. It is also unclear if opioid prescription rates for patients with PMR are higher than in the general population. The aim of this study was to identify trends in opioid use in patients with PMR over the last decade, and compare these to persons without the disease.

Methods

This is a historical cohort study to trace opioid use in each group over several decades. Residents of Olmsted County, MN with incident PMR in 1970–2014 were previously identified using the resources of the Rochester Epidemiology Project (REP), which is a record-linkage system that records all inpatient and outpatient encounters among the residents of Olmsted County, Minnesota (10, 11). Individuals were classified as having PMR if they fulfilled the 2012 American College of Rheumatology classification criteria for PMR (7). Exclusion criteria included the presence of other conditions that could lead to similar symptoms, such as rheumatoid arthritis, systemic lupus erythematosus, polymyositis, multiple myeloma, fibromyalgia or chronic infection. A comparison cohort of subjects without PMR with similar age, sex, and indexed to calendar year of PMR diagnosis of the patients with PMR was drawn randomly from the same population. Prescription data were electronically available from the REP for 2005 to

2015. Therefore, the baseline date for this study was defined as January 1st 2005. The subset of patients with incident PMR in 1970–2004 and the comparators with index dates in 1970–2004 who were alive on January 1, 2005 were included in this study. All subjects in both cohorts were followed longitudinally until death, migration, or December 31, 2015. Data on opioid outpatient prescriptions were manually converted to days of use from the prescribed frequency, dose, and days of use as previously described (12). Any opioid use was defined as one or more opioid prescriptions in the study period. Chronic use was defined as a prescription(s) for 60 or more days at usual dose and usual schedule within a 6 month period or those subjects using fentanyl, methadone and controlled/extended release oxycodone.

Diagnoses of comorbidities prior to baseline were obtained electronically for both cohorts and classified using the Mayo adaptation of the Charlson Comorbidity Index (13). These included myocardial infarction, heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, peptic ulcer, diabetes mellitus, hemiplegia, renal disease, liver disease and any malignancy (excluding non-melanoma skin cancers).

Statistical analysis

Descriptive statistics (means, percentages, etc.) were used to summarise the characteristics of each cohort. Characteristics were compared between cohorts using Chi-square and rank sum tests. Person-year methods were used to compute the overall rate of first chronic opioid use in the time period of interest as the number of patients meeting the definition of chronic opioid use divided by the number of person-years of follow-up. Patients who had any opioid prescription in 2004 were excluded from analyses of first chronic use of opioids in an attempt to estimate the rate of incident chronic use of opioids. Poisson regression models were used to estimate the relative risk of first chronic opioid use among those with PMR compared to those without PMR.

Yearly estimates of percentage of sub-

Table I. Baseline characteristics of patients with polymyalgia rheumatic (PMR) cases and non-PMR comparator subjects on January 1, 2005.

Characteristic	Non-PMR n=211	PMR n=244	p-value
Age, years, mean (SD)	79.5 (8.3)	79.8 (8.6)	0.66
Sex, female	144 (68%)	163 (67%)	0.74
Length of follow-up, years, mean (SD)	7.2 (3.8)	7.8 (3.6)	--
Comorbidities at baseline*			
Myocardial infarction	43 (20%)	31 (13%)	0.03
Heart failure	47 (22%)	55 (23%)	0.95
Peripheral vascular disease	52 (25%)	72 (30%)	0.25
Cerebrovascular disease	71 (34%)	92 (38%)	0.37
Dementia	33 (16%)	26 (11%)	0.11
Chronic pulmonary disease	89 (42%)	114 (47%)	0.33
Peptic ulcer	42 (20%)	48 (20%)	0.95
Diabetes mellitus	49 (23%)	46 (19%)	0.25
Hemiplegia	13 (6%)	7 (3%)	0.09
Moderate/severe renal disease	36 (17%)	41 (17%)	0.94
Liver disease	13 (6%)	17 (7%)	0.73
Malignancy	66 (31%)	88 (36%)	0.28

*based upon Charlson Comorbidity Index (13); SD: standard deviation.

Table II. First chronic opioid use rates in patients with polymyalgia rheumatic (PMR) compared to subjects without PMR.

Group	Category	PMR rate (per 100 py)	Non-PMR rate (per 100 py)	Relative risk (95% CI)
Total		3.44	3.20	1.07 (0.71, 1.64)
Sex	Female	3.16	3.48	0.91 (0.54, 1.53)
	Male	3.94	2.71	1.43 (0.73, 3.01)
Age	50-79 years	1.89	2.07	0.90 (0.38, 2.22)
	80+ years	4.45	3.82	1.16 (0.73, 1.88)

py: person years; CI: confidence interval.

jects with any opioid use were computed as the number of patients with any opioid prescription in a particular calendar year divided by the person-years of follow up in that calendar year. Yearly estimates of the percentage of subjects with chronic opioid use were computed similarly. To avoid overestimation of the rate of chronic use of opioids, after having met our definition of chronic use, subjects were returned to non-chronic use when there was a year without an opioid prescription. Age adjustment was necessary in order to assess trends over time because this study cohort aged over the 11-year period of the study. Yearly estimates of the percentage of subjects with opioid use were adjusted to the age and sex distribution of the entire study cohort using Poisson regression models with smoothing splines for calendar year to allow for non-linear effects. Poisson regression models adjusted for age and sex were also used to estimate the rela-

tive risk of opioid use among those with PMR compared to those without PMR. Analyses were performed using SAS v. 9.4 (SAS Institute, Cary, NC, USA) and R 3.1.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

There were 244 patients with PMR and 211 non-PMR patients included in the study. There was no significant difference in the mean age at the start of the study period and both groups were disproportionately female (66.8% of PMR and 68.2% of non-PMR; Table I). Prior to the baseline date of 1/1/2005, there was a significantly higher incidence of myocardial infarction (20.4% vs. 12.7%, $p=0.027$) in non-PMR subjects. There were no differences regarding a previous diagnosis of heart failure, peripheral vascular disease, cerebrovascular disease, dementia, peptic ulcer disease, diabetes, or chronic pulmonary, renal or liver disease (Table I).

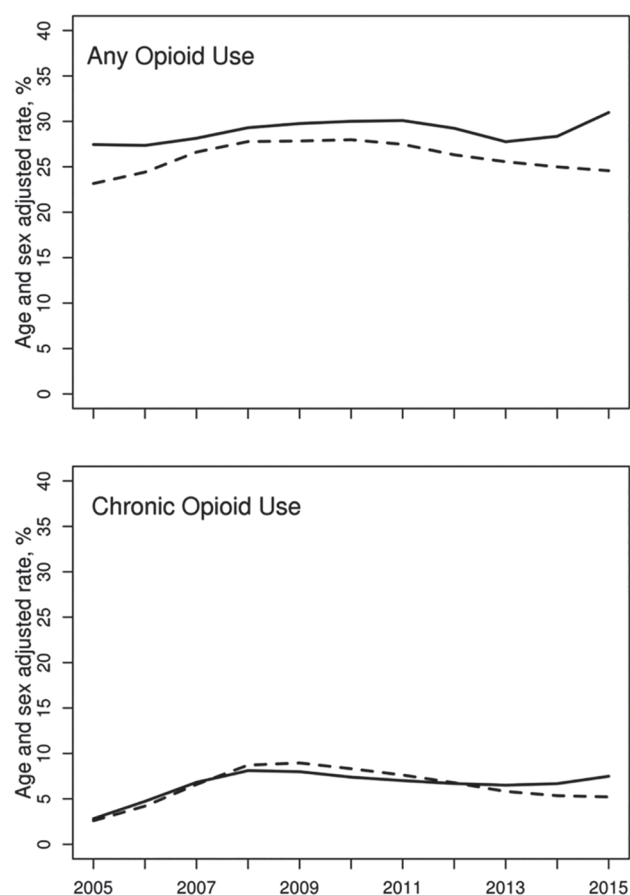


Fig. 1. Prescription trends for opioid use by age and sex for calendar years 2005–2015 in patients with polymyalgia rheumatic (PMR) and non-PMR comparator subjects. PMR shown as solid line and non-PMR as dashed line. Upper panel shows any opioid use. Lower panel shows chronic opioid use.

The prevalence of any opioid use was slightly higher in patients with PMR (relative risk [RR] 1.10, 95% CI 0.97–1.26, $p=0.14$), although this difference did not reach statistical significance and did not change over the study period (Fig. 1, upper panel). To estimate the incidence of chronic opioid use, the 60 patients with PMR and 41 non-PMR subjects who had an opioid prescription in 2004 were excluded from analysis of chronic opioid use. There was no evidence of significant differences in chronic opioid use (RR 1.02, 95% CI 0.75, 1.37). No significant trends in chronic opioid use over the 11-year period were seen in either group (Fig. 1, lower panel).

Analysis of time to first chronic opioid use by sex and age group showed that patients over 80 years were more likely to be opioid users than younger patients. For patients with PMR, the rate of chronic opioid use was 1.89 for patients between ages 50 and 79 and 4.45 for patients age 80 and over (Table II). For non-PMR subjects these rates were 2.07 and 3.82 respectively. There were

no significant differences in the rates of use between male and female patients in either group.

Of the patients with PMR who had chronic opioid use during the study period, only 8% had PMR listed as the primary indication. The most common indication was degenerative joint disease at 49%, followed by chronic back pain at 26%. Other causes included cancer-related pain, post-herpetic neuralgia, and chronic headache. The mean time from diagnosis of PMR to incidence of chronic opioid use was 11.5 years (standard deviation 6.6 years). 36% of these patients were still prescribed glucocorticoids at the time of chronic opioid use.

Discussion

In this long-term follow up population-based study, patients with PMR were not prescribed opioids for chronic use at rates that differed significantly from the general population over the 11-year study period. Older patients with or without PMR received higher rates of opioid prescriptions than younger patients.

These findings are significant from the standpoint that musculoskeletal pain is typically the defining feature of PMR. It is well established that the use of opioids for chronic non-cancer pain has risen significantly over the past several decades despite a lack of evidence supporting the effectiveness of their use (1, 4). While the current study did not gather data on other forms of pain management, these findings offer further evidence that immunosuppressive therapy alone is often adequate to treat the symptoms of PMR despite some patients having incomplete responses (14). This is in contrast to findings from patients with rheumatoid arthritis, in whom opioid use was substantially higher than in the general population (12). Of the patients with chronic opioid use, there was a significant incidence of glucocorticoid use years after the diagnosis of PMR. This is consistent with a previous report that suggests as many as 40% of patients with PMR require glucocorticoid therapy for longer than 4 years, and in many cases their use is not discontinued (15).

Opioid use rates were similar between the two groups and there was increased use among older patients in both groups. Of the PMR patients with chronic opioid use, only a very small percentage had PMR related symptoms as the primary indication. Most became chronic opioid users years after the PMR diagnosis. The most common reason for chronic use was degenerative arthritis or chronic back pain, a finding which mirrors other reports of opioid use in the older patient population. Over 40% of nursing home residents endorse moderate to severe pain on a daily basis, and 38 to 50% of these persons meet criteria for chronic pain (16). The most common conditions causing chronic pain include osteoarthritis, cancer, rheumatoid arthritis and herpes zoster. Older adults are also at higher risk for opioid misuse, and are particularly susceptible to the side effects and potential morbidities associated these medications (5, 16). While it has been shown that the glucocorticoid therapy used in PMR puts patients at an increased risk for fracture, fracture was not associated with increased opioid use in this study (14).

Chronic opioid use was defined as use for 60 days within a 6-month period or any prescription of fentanyl patches or methadone. There is a lack of strong evidence supporting the efficacy of opioids for non-cancer pain beyond 8 weeks. CDC data on opioid safety also suggests that the patients at highest risk for morbidity are those using for longer than 6 weeks or those on extended time release formulations.

This is the first study of opioid use in a large, recent cohort of patients with PMR using prescription data obtained through a rigorous epidemiological record system. Opioid prescription rates vary significantly by state and geographic region which may limit the generalisability of this study. It is possible that the threshold for prescribing opioids varies in populations outside of Olmsted County, MN, potentially affecting estimates of chronic use prevalence in other populations.

This study had a population-based comparator group. None of the comorbidities commonly associated with pain differed between patients with and without PMR. Opioid prescriptions from providers outside of Olmsted County were not accounted for though these were likely minimal due to low migration rates. The study is also limited by the population of Olmsted County, which is predominantly Caucasian and has a disproportionate number of individuals working in healthcare. This study relied on opioid outpatient prescriptions converted to days of use from the prescribed frequency, dose, and days of use rather than actual use, and there was no data on specific indications for each opioid prescription.

Despite being a condition associated with chronic pain, PMR is not associated with higher rates of chronic opioid use. This observation differs from the current general trend in opioid prescrib-

ing habits and suggests that PMR may be adequately treated from a pain standpoint with glucocorticoids and likely more conservative pain management strategies. This is reassuring for clinicians managing these patients, though there is still uncertainty regarding the rates of long-term complications such as fracture, hospitalisation, and loss of functional capacity suffered by patients with PMR. Further studies are also needed to assess the use of adjunctive pain management in PMR and the effect of chronic pain on quality of life.

Significance and innovations

- This is the first study of opioid use in patients with polymyalgia rheumatica, a chronic rheumatic condition associated with inflammation and pain.
- There was no evidence of excess chronic opioid use among patients with polymyalgia rheumatica compared to the general population.
- Older patients were more likely to be chronic opioid users. This was true for both patients with and without polymyalgia rheumatica.

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