Are pain severity and current pharmacotherapies associated with quality of life, work productivity, and healthcare utilisation for people with osteoarthritis in five large European countries?

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Abstract

Objective

Although the osteoarthritis (OA) burden is well-recognised, the benefit of currently available OA pharmacological therapy is not clear. This study aimed to assess whether the impact of OA pain on health-related quality of life (HRQoL), work, and healthcare resource utilisation (HRU) differed by both pain severity and prescription medication status.

Methods

This cross-sectional study used pooled data from the 2016/2017 European National Health and Wellness Survey. Respondents with self-reported physician-diagnosed OA and pain were included. Outcomes examined included HRQoL, health utility, health status, work productivity and activity impairment, and HRU. Groups derived from self-reported pain severity and prescription medication use were compared using chi-square tests, analysis of variance, and generalised linear models controlling for socio-demographics, health behaviours, and health status.

Results

Respondents with OA (n=2417) reported mild (40.4%, of which 44.9% prescription-treated) and moderate to severe pain (59.6%, of which 54.0% prescription-treated). HRQoL, health utility, health status, work and activity impairment were substantially worse among the moderate/severe pain prescription-treated group compared to the rest (e.g. SF-12v2 physical component score [PCS] for moderate/severe pain prescription-treated=34.5 versus mild pain prescription-treated=39.3, moderate/severe pain prescription-untreated=40.6, and mild pain prescription-untreated=45.6; p<0.01). HRU such as the mean number of emergency room visits for >6 months was higher in the prescription-treated groups (0.51–0.52, 95% CI 0.437–0.71) than the prescription-untreated groups (0.30–0.34, 95% CI 0.21–0.46; p<0.05).

Conclusion

Persons with moderate to severe OA pain treated with available prescription medications have poor health status and HRQoL and increased HRU compared to those not receiving prescription medications.

Key words

osteoarthritis, activity impairment, healthcare resource use, health-related quality of life, pain, pain severity, pharmacologic therapy, work productivity impairment
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Introduction
The hallmarks of osteoarthritis (OA) are joint pain and stiffness that lead to activity limitations, participation restrictions, sleep interruption, low mood, loss of independence and reduced quality of life (QoL) (1). The Global Burden of Disease Study has recently reported that the prevalence of OA has increased by 30% during the last 10 years and now affects more than 300 million people worldwide (2). Globally, OA of the knee and hip is the 11th highest contributor to disability, similar to if not greater than for rheumatoid arthritis (3), and about 50 million adult individuals are estimated to be affected in Europe (4).

Effective management of OA includes a holistic approach to patient assessment and aims to reduce pain, improve function and QoL and reduce comorbidities (5-7). To this end, current guidelines recommend patient education and non-pharmacological management, pharmacological treatment, and, as a last option, joint replacement surgery (5-7). Non-pharmacological management of OA may include focal muscle strengthening, exercise, injury prevention, weight loss if overweight, and use of aids (8). While pharmacological treatments typically comprise paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), COX-2 inhibitors, and opioids; however, non-pharmacological approaches are often less utilised (5-7).

In the 2019 Osteoarthritis Research Society International (OARSI) guideline for the non-surgical management of knee, hip, and polyarticular osteoarthritis (9), the use of acetaminophen/paracetamol (APAP) was conditionally not recommended, and the use of oral and transdermal opioids was strongly not recommended due to the unfavourable efficacy and safety profile of these agents on OA symptoms. Both the OARSI and the 2020 American College of Rheumatology (ACR) guidelines strongly recommend topical NSAIDs for individuals with knee OA. Appropriate patient selection is recommended before NSAID use in individuals with cardiovascular comorbidities or frailty due to evidence associating NSAID use with heightened CV risk (10). The ACR guideline conditionally recommends tramadol for patients with knee, hip, and/or hand OA, but non-tramadol opioids are conditionally recommended against (5). For many OA patients, due to the above-mentioned reasons, pharmacological treatment options for managing OA pain are therefore limited.

Research conducted in France, Germany, Italy, Spain, and the UK (EU5) showed that OA patients, who consulted a primary care physician (PCP) for their OA reported 17% current use of over-the-counter (OTC) medication alone, 38% current use of prescription medication alone, and 9% current use of both (11). Furthermore, of those taking OA prescription medication, approximately two-thirds of users were not satisfied with their medication and half reported non-adherence (likely reflecting intermittent use) (11).

In terms of healthcare burden, estimates from the UK suggest that a third of people over the age of 45 seek primary care consultations for OA (12). The personal burden of OA pain has been demonstrated among patients who report poorer self-rated health and health-related quality of life (HRQoL), including physical and psychological well-being, relative to others without OA (11, 13-16). Kingsbury et al. examined the impact of OA across the EU5 finding poorer HRQoL and higher work-related burden for those with OA, with more than one-fifth reporting depression (11).

Other studies have illustrated the high economic burden of OA. In the US, osteoarthritis results in a greater than two-fold increase in direct healthcare costs than in matched patients without OA (17), and the direct costs in a European patient with OA has been estimated to range from €534 to €1788 per year (18). Furthermore, there is a differential OA burden related to pain severity, such that self-reported pain severity, ranging from mild to severe, is linearly associated with decreasing QoL and increasing work impairment (14-16, 18, 19).

Understanding the differential impact of disease severity and pharmacotherapy use on the OA burden among sub-populations is an essential element of strategies for the overall disease management. The present study aimed to

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extend our understanding of the impact of OA and how OA pain severity and prescription medications are associated with health status, QoL, work productivity, and HRU.

**Methods**

**Sample and study design**

The National Health and Wellness Survey (NHWS) is a cross-sectional survey assessing health conditions among the general adult population (≥18 years). Opt-in online survey panels of over 1.2 million persons were invited to participate and identified using stratified random sampling to ensure sample representativeness to the corresponding adult populations in each country based on sex and age using appropriate distribution of demographic strata in the adult population of each country surveyed (20). Surveys were translated for each country. Study protocol and questionnaire were granted exemption status by Pearl Institutional Review Board (Indianapolis, IN, US) and all respondents provided informed consent prior to entering the survey.

Pooled self-reported data were taken from the NHWS 2016-2017 report from the EU5 countries. Respondent data from the most recent survey was used. Included were respondents who self-reported physician-diagnosed OA and experienced pain in the past 12 months (worst pain with or without prescription medication use [none/mild/moderate/severe]). Respondents who reported neuropathic or phantom limb pain were excluded from the study. Following inclusion/exclusion criteria, the total sample (n=2417) included 1151 (47.6%) respondents from the UK, 503 (20.8%) from France, 342 (14.1%) from Germany, 292 (12.1%) from Spain, and 129 (5.3%) from Italy who answered. Respondents who completed the arthritis module (see above) reported specific joints affected by their arthritis. Current prescription medication use (country-specific OA-approved medications) and number of days (past month) used for OA pain relief were collected. The Short Form-McGill Pain Questionnaire (SF-MPQ) was also used to evaluate pain in the past week presented as a continuous value (0=no pain to 45=worst possible pain) (22). HRQoL and health status were assessed using the SF-12v2 (23) and EuroQol-5 Dimensions (EQ-5D) (24). Two summary scores of the SF-12v2 were calculated: Physical Component Summary (PCS) and Mental Component Summary (MCS), both normed to a mean=50 (standard deviation=10) for the US population. The Short Form 6 Dimensions (SF-6D) algorithm of the SF-12v2, which is based on items from six SF-12v2 domains, was used to generate health state utilities (25). The SF-6D index has interval scoring properties and yields summary scores on a theoretical 0.3 to 1.0 scale (26). In both the SF-12v2 and the SF-6D, higher scores indicate better health status. Differences between groups exceeding 3 points for the PCS and MCS and 0.03–0.04 points for the SF-6D are considered minimal clinically important differences (MCID) (27, 28). The EQ-5D five-level scale measures current health comprising five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. These dimensions were used to create a health utility score ranging from -0.59 (“worse than dead”) to 1.00 (“best possible health”), with a published MCID of 0.05–0.13 (28). The EQ-VAS is a single visual analogue scale indicating health status from “Worst imaginable health state” (0) to “Best imaginable health state” (100) (29).

Work productivity loss and non-work activity impairment was measured using the Work Productivity and Activity Impairment-General Health (WPAI-GH) questionnaire, a six-item instrument comprised of four metrics: absenteeism (the percentage of work time missed because of one’s health in the past seven days), presenteeism (the percentage of impairment experienced while at work in the past seven days because of one’s health), overall work productivity loss (an overall impairment estimate that is a combination of absenteeism and presenteeism), and activity impairment (the percentage of impairment in daily activities because of one’s health in the past seven days) (30). Only full-time or part-time employed respondents provided data for absenteeism, presenteeism, and overall work impairment. All-cause HRU was measured using self-reported number of total healthcare visits (HCP; PCP and specialists) visits, PCP only visits, emergency room (ER) or urgent care visits, and hospitalisations, during the past six months.
### Statistical analysis

To explore differences related to both pain and pharmacotherapy, based on responses to self-reported pain severity and treatment, respondents were categorised into the following four groups:

1. **Mild pain untreated with prescription medications (herein “mild Rx-untreated”)**
2. **Mild pain treated with prescription medications (herein “mild Rx-treated”)**
3. **Moderate/severe pain untreated with prescription medications (herein “moderate/severe Rx-untreated”)**
4. **Moderate/severe pain treated with prescription medications (herein “moderate/severe Rx-treated”)**

Bivariate analyses according to patient characteristics were performed. For all analyses, a p-value of <0.05 was considered statistically significant.

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### Table I. Demographic and health characteristics among osteoarthritis groups across Europe.

|                          | Total (n=2417) | Mild pain Rx untreated (n=439) | Mild pain Rx treated (n=538) | Moderate/severe pain Rx untreated (n=777) | Moderate/severe pain Rx treated (n=663) | p-value*
|--------------------------|----------------|--------------------------------|-------------------------------|------------------------------------------|----------------------------------------|---------
| **Country, n (%)**       |                |                                |                               |                                          |                                        | 0.006   |
| United Kingdom           |                |                                |                               |                                          |                                        |         |
| France                   |                |                                |                               |                                          |                                        |         |
| Germany                  |                |                                |                               |                                          |                                        |         |
| Spain                    |                |                                |                               |                                          |                                        |         |
| Italy                    |                |                                |                               |                                          |                                        |         |
| **Age groups (years), n (%)** |                |                                |                               |                                          |                                        | 0.156   |
| 18-39                    |                |                                |                               |                                          |                                        |         |
| 40-49                    |                |                                |                               |                                          |                                        |         |
| 50-59                    |                |                                |                               |                                          |                                        |         |
| 70+                      |                |                                |                               |                                          |                                        |         |
| **Female, n (%)**        |                |                                |                               |                                          |                                        | 0.040   |
| Marital status*, n (%)   |                |                                |                               |                                          |                                        | 0.013   |
| Married/living with partner |            |                                |                               |                                          |                                        |         |
| Single                   |                |                                |                               |                                          |                                        |         |
| Divorced/separated/widowed|            |                                |                               |                                          |                                        |         |
| Household income, n (%)  |                |                                |                               |                                          |                                        | 0.048   |
| Less than Euro 50K/£40K  |                |                                |                               |                                          |                                        |         |
| Euro 50K/£40K or greater |                |                                |                               |                                          |                                        |         |
| Declined to answer       |                |                                |                               |                                          |                                        |         |
| Completed university*, n (%) |            |                                |                               |                                          |                                        | 0.004   |
| Employed*, n (%)         |                |                                |                               |                                          |                                        | 0.007   |
| BMI, n (%)                |                |                                |                               |                                          |                                        |         |
| Under/normal weight (<25.0 kg/m²) |     |                                |                               |                                          |                                        | 0.006   |
| Overweight (≥25.0 and <30.0 kg/m²) |   |                                |                               |                                          |                                        |         |
| Obese (≥30.0 kg/m²)      |                |                                |                               |                                          |                                        |         |
| Declined to answer       |                |                                |                               |                                          |                                        |         |
| Smoking status, n (%)    |                |                                |                               |                                          |                                        | 0.010   |
| Current smoker           |                |                                |                               |                                          |                                        |         |
| Former smoker            |                |                                |                               |                                          |                                        |         |
| Never smoked             |                |                                |                               |                                          |                                        |         |
| Alcohol use (past week), n (%) |            |                                |                               |                                          |                                        | <0.001  |
| No alcohol               |                |                                |                               |                                          |                                        |         |
| Low (≤3 drinks per week) |                |                                |                               |                                          |                                        |         |
| Moderate/high (>3 drinks per week) |      |                                |                               |                                          |                                        |         |
| Exercise (days in past month)† |           |                                |                               |                                          |                                        | <0.001  |
| Ever, n (%)              |                |                                |                               |                                          |                                        |         |
| Never, n (%)             |                |                                |                               |                                          |                                        | <0.001  |
| CCI, n (%)               |                |                                |                               |                                          |                                        | <0.001  |

BMI: body mass index; CCI: Charlson Comorbidity Index; Rx: prescription medication; SD: standard deviation; SF-MPQ: Short Form-McGill Pain Questionnaire.

* Chi-square tests were used for categorical variables and analysis of variance for continuous variables comparing the distributional difference between groups.

† <1% of respondents declined to answer. ** Unemployed includes disabled, retired, student, or homemaker. Employed includes full-time, part-time, or self-employed. †† Exercised vigorously at least once in past month. ‡ Self-reported diagnosis in past 12 months.
groups were performed using chi-square tests of column proportions for categorical variables and analysis of variance tests of means for continuous variables (31). Generalised linear models (GLMs) were used based on the distribution of the outcome variable: normal distribution using an identity function (e.g. HRQoL) and negative binomial distribution using a log-link function (e.g. WPAI) (32). Least squares adjusted means from the GLMs were used to evaluate whether respondents with OA differ by treatment status (treated vs. untreated) and pain severity (mild vs. moderate/severe) on HRQoL, impairment to work productivity and non-work daily activities, and HRU after controlling for covariates (socio-demographics, health behaviours, and health status). Adjusted mean values for individual countries, calculated using an interaction term of OA group x country in the overall model, are included in the supplemental tables (Supplementary Tables S1-S5). SPSS v. 23 was used for all analyses, and a p-value <0.05 was considered statistically significant.

Results
Among the 2417 OA respondents, 63.6% were over 60 years old, 64.5% were female, and the majority were of lower socioeconomic status (e.g. 76.5% household income < Euro 50K/£40K). Respondents noted an average±SD of 3.8±2.6 painful joints. The joints most affected were knees (64.1%), fingers (44.5%), hips (41.3%), and spine (40.7%). Current pain, classified as the self-reported current worst level of severity state regardless of medication use, was identified as mild for 40.4% of respondents, of which 44.9% were Rx-treated, and as moderate to severe for 59.6% of respondents, of which 54.0% were Rx-treated. In addition, 30.3% of respondents reported using OTC medication(s) for OA (type not specified).

The following severity and prescription-treated groups were examined: mild Rx-untreated (18.2%), mild Rx-treated (22.3%), moderate/severe Rx-untreated (32.1%), and moderate/severe Rx-treated (27.4%). Socio-demographic differences between groups showed overall distributional differences, but no clear pattern (Table I). A higher comorbidity burden (CCI score ≥2) was reported for 19.3% and 29.3% of the mild and moderate/severe Rx-treated groups, respectively, and 8.4% and 12.9% of the mild and moderate/severe Rx-untreated groups, respectively (overall p<0.001). Almost one-third of respondents in the moderate/severe Rx-treated group reported a self-reported physician diagnosis of anxiety, depression, or sleep disorders, which was higher than for other groups (p<0.05). Over 40% in this group were obese. The mean number of arthritis-related joints differed between groups (p<0.001) with Rx-treated respondents having on average more affected joints regardless of pain severity (Fig. 1). Among the Rx-treated groups, respondents with mild OA reported using less prescription medication in the past month, relative to those in the moderate/severe group (mean±SD number of prescriptions: 18.2±11.1 vs. 23.0±10.3, respectively, p<0.001) (Suppl. Fig. S1).

Health-related quality of life (HRQoL) and health status
After adjusting for covariates, all measures of HRQoL, health utility, and health status were substantially lower among the moderate/severe Rx-treated group, relative to all other groups (p-value for all outcomes <0.01) (Figs. 2-3). For example, compared with the mild Rx-untreated, mild Rx-treated, and moderate/severe Rx-untreated, MCS scores for this group was 38.3 vs. 41.3, 41.1, and 40.2; for PCS was 34.5 vs. 45.6, 39.3, and 40.6; for health utilities (EQ-5D-5L) was 0.38 vs. 0.63, 0.53, and 0.54 (and similarly for the SF-6D 0.52 vs. 0.64, 0.59, and 0.59); and for health status (EQ-VAS) was 41.5 vs. 62.9, 52.6, and 53.6, respectively, overall p-value for all comparisons <0.001. Aside from the MCS of the SF-12v2, respondents belonging to the mild Rx-untreated group had the highest QoL, health utility, and health status at p<0.01. However, mild Rx-treated respondents did not differ statistically from moderate/severe Rx-untreated respondents for all measures of HRQoL and health status except the PCS.

Work productivity impairment and activity impairment (WPAI)
The impact of OA on work and activity was highest among the moderate/severe Rx-treated group relative to all other groups (p<0.01) (Fig. 4). Specifically, those in this group had 2-6 times higher impairment compared with those in the mild Rx-untreated group (p<0.001),
and respondents in the other pain and treatment groups reported about 1.5–2 times greater work productivity and activity impairment compared with the mild Rx-untreated group \((p<0.001)\). In addition, mild Rx-treated respondents had a significantly higher level of presenteeism (47.2%) than the moderate/severe Rx-untreated groups (43.9%) \((p<0.001)\).

**Healthcare resource utilisation (HRU)**

In general, HRU in the past six months was significantly higher in the treated groups compared with Rx-untreated groups \((p<0.05)\) (Fig. 5). For example, mean number of PCP visits in the past six months for those in mild or moderate/severe Rx-treated groups were 3.8 and 4.0, respectively, whereas for those in the mild or moderate/severe untreated groups were 2.6 and 2.9, respectively. Similar results were observed for ER visits (mean number [past six months]: mild or moderate/severe treated).
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Discussion

We studied people with self-reported OA and identified a population consistent with other such studies in terms of age and gender, and also including the multi-site joint pains typical of such populations in the real world (33). This study found that respondents receiving prescription treatment for OA had a significantly overall lower QoL than those not receiving medications, irrespective of their OA-pain severity. Across OA severity, the use of pharmacotherapy was associated with reduced health status, lower HRQoL, impaired work productivity and activity, and increased HRU. This important finding extends previous research across Europe and provides novel insight into the complexity of OA treatment and the barriers that still exist to effectively treating this condition.

The current findings suggest that current pharmacological treatment status and disease severity are markers indicating an excess HRQoL burden. Previous studies in OA patients have independently shown that severity and prescription medication use are each related to HRQoL. In a study of employed persons with OA in the US, respondents with mild pain had better HRQoL outcomes than those with moderate or severe pain in models adjusted for demographic and clinical covariates, including use of prescription medication (14). Another study of adults with arthritis, including patient with OA showed that physical functioning was significantly lower among those taking multiple prescription medications (6+) compared to those taking fewer (34).

In the current study, EQ-5D-5L scores (index and VAS) and SF-6D health state utility scores were similar in subjects with mild pain Rx-untreated versus Rx-treated. Further, this study highlighted the substantially poorer health status of those with moderate/severe Rx-treated OA compared to the other groups. Findings from previous studies conducted in the EU5 and US that showed worsened health status with increasing OA severity as assessed by EQ-5D and in those studies, health status was adjusted for prescription medication use; however, the differen-
tial effect of this factor was not examined (15, 35).
Respondents with moderate to severe OA despite prescribed medication had overall worse work productivity and activity than the other groups, consistent with previous results from Europe and the US (14, 35). Interestingly, presenteeism was responsible for a greater loss of productivity than absenteeism since the former was approximately 1.5 times larger than the latter, as found previously (11, 35). It should be noted that all the items of WPAI studied were consistently and substantially higher in the moderate/severe pain Rx-treated group and consistently and substantially lower in the mild untreated group, indicating an effect modification by severity and medication use. In Europe and the US, work impairment is associated with individual annual productivity losses (14, 35). In Europe these losses were estimated for mild (-$9,220), moderate (-$14,861), and severe (-$27,208) OA (35) demonstrating the economic burden of OA.

Adjusted mean HRU for visits to the primary care physician and healthcare professionals in the past six months were consistently higher in the moderate/severe pain Rx-treated and untreated and mild pain Rx-treated subgroups compared with the mild pain Rx-untreated subgroup. The observed results were in line with previous studies in the US that showed higher number of visits to the physicians and hospitalisations in patients with OA than those without OA (36, 37).

Although OA is highly prevalent throughout Europe (38, 39), there is a paucity of literature that evaluates the needs of people suffering from OA-related pain as well as the variation in burden by differing pain severity and treatment status. Previously, Kingsbury et al. reported that less than half of their European sample reported prescription medication use, despite significant burden associated with their disease (11). The current study broadens this understanding by providing novel insight into the relationship between point-in-time treatment status and HRQoL, activity impairment, and HRU. The increased burden associated with more severe symptomatic disease has been well-established in the OA literature (14-16, 18, 19) and in the present study.

In addition to categorising respondents on the basis of pain severity, the current study differentiated respondents on the basis of prescription treatment (Rx-treated vs. Rx-untreated). The prescription medication use group had more comorbidities such as depression and anxiety, which may have contributed to their ranking of overall pain severity, as reported previously (40). Notably the prescription-treated group, whether with mild or moderate/severe pain, had more painful joints. It is possible that an increased number of painful joints is a driver to seeking medical care and pharmacological therapy; evidence for treating this multi-joint OA group is limited (41).

This study has limitations. First, the NHWS is cross-sectional in nature, precluding causal inference or the ascertainment of the longitudinal impact of pharmacotherapy (e.g. were these respondents worse before they received pharmacotherapy?). Moreover,
although the NHWS employs a rigorous stratified sampling methodology to represent the adult general population with respect to age and sex in the EU5 countries, it may nonetheless underrepresent segments of the population that cannot access online surveys such as ill individuals, elderly people, and institutionalised patients, as well as those with severe disabilities. Also, the data self-reported by patients, including diagnosis, treatment, and health characteristics, may be subject to recall bias and cannot be verified independently. However, recall bias may have been minimised, given that key study variables on pain and medication usage were assessed based on current experience or recent recall.

Identification of respondents with OA was based on self-reported physician diagnosis of the disease regardless of site of joint pain or comorbid condition, although only 1% of respondents reported having only shoulder or elbow pain (data not shown), indicating a low chance of misclassification bias since OA occurrence in the shoulder or elbow is uncommon (42). We used a common self-reported pain questionnaire, but may not have captured the wide variation in OA pain patient phenotypes (43).

Prescription medication use was not associated with better outcomes in this study; however, this finding must be interpreted with caution, given this cross-sectional study design. Specifically, the study methodology was unable to distinguish between individuals who previously tried prescription medication and ceased using it, those who lack access to such care, and those who prefer non-prescription or non-pharmacologic approaches. A potential explanation, to be examined in future research, is that the higher burden among prescription medication users is related to OA pain and the number of painful joint sites relative to those who do not use prescription medication. An observation that may deserve more attention in future longitudinal studies is the finding that subjects with mild pain Rx-treated had several similar health related outcomes as subjects with moderate/severe pain Rx-untreated.

Conclusion
This work suggests that a large proportion of OA patients in Europe suffer from moderate to severe pain, and the burden associated with this condition is substantial. Respondents in this cross-sectional survey reported impairment across several domains, including HRQoL, work productivity, and daily activities, as well as increased HRU. Notably, the results revealed that although pharmacotherapy use was associated with poor outcomes irrespective of OA pain severity, the impact of moderate to severe OA is considerable even in respondents who use prescription treatment. Collectively, these data suggest that irrespective of treatment history there is a need for more effective prescription medications, which could be used in conjunction with appropriate non-pharmacologic modalities, to support a comprehensive approach to OA pain management. There is also clearly a need for a better understanding of people with OA and multiple site joint pain and how therapeutic options may help in disease management of this complex group. Future longitudinal research will be necessary to clarify the relationships observed in the current study and to determine whether the association between OA pain severity, prescription medication use, and patient-reported outcomes fluctuate over time.

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