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?

P.G. Conaghan[1], M.J. Doane[2], D.H. Jaffe[3], E. Dragon[4], L. Abraham[5], L. Viktrup[6], A.G. Bushmakin[7], J.C. Cappelleri[7], S. Perrot[8]

[1]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds and NIHR Leeds Biomedical Research Centre, Leeds, UK; [2]Kantar, NY, USA; [3]Kantar, Tel Aviv, Israel; [4]Pfizer Ltd., Budapest, Hungary; [5]Pfizer Ltd., Surrey, UK; [6]Eli Lilly and Company, Indianapolis, IN, USA; [7]Pfizer Ltd., Groton, CT, USA; [8]Pain Center, Cochin Hospital, Paris Descartes University, Paris, France.

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, and 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

Philip G. Conaghan, MD
Michael J. Doane, PhD
Dena H. Jaffe, PhD
Erika Dragon, MD
Lucy Abraham, MSc
Lars Viktrup, PhD
Andrew G. Bushmakin, MS
Joseph C. Cappelleri, PhD
Serge Perrot, MD

Please address correspondence to:
Philip Conaghan,
Leeds Institute of Rheumatic and Musculoskeletal Medicine,
Chapel Allerton Hospital,
Leeds LS7 4SA, United Kingdom.
E-mail: p.conaghan@leeds.ac.uk

Received on March 19, 2020; accepted in revised form on July 6, 2020.

Funding: P.G. Conaghan is supported in part by the UK National Institute for Health Research (NIHR) Leeds Biomedical Research Centre. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, or the Department of Health.
During the research and development of the manuscript D.H. Jaffe and M.J. Doane were employed at Kantar which was paid by Pfizer and Eli Lilly and Company in connection with the research and development of this manuscript.
E. Dragon, L. Abraham, A.G. Bushmakin, and J.C. Cappelleri are employees and shareholders of Pfizer. L. Viktrup is an employee of Eli Lilly and Company.
Medical writing support was provided by Ramu Periyasamy, Indegene Pvt Ltd, Bangalore and was funded by Kantar.

Competing interests: none declared.

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 eleventh 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 subpopulations is an essential element of strategies for the overall disease management. The present study aimed to

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 all survey questions used in this study (with the exception of the specific site of joint involvement which was obtained from those completing a specific arthritis module [see below]).

The sampling methodology for the 2016 and 2017 NWHS differed slightly with regards to completion of disease-specific modules, including an arthritis module. In 2016, a probability sampling was used to select a subsample of OA respondents to complete an arthritis module that provided additional information on arthritis characteristics, and, specifically, site of arthritis-related joint pain. Such random subsampling enabled inclusion of respondents with different medical conditions to provide detailed information while limiting the average interview length and respondents' burden. In our study, 42% of the 2016 OA respondents (n=132) completed the arthritis module. Comparisons of OA respondents who did and did not complete the arthritis module in 2016 showed no statistically significant differences at $p>0.05$ by age, gender, severity of OA, or use of prescription medication for OA. In the 2017 NHWS, this sampling technique was not implemented, and all OA respondents completed the arthritis module. Respondents (n=2236; 92.5% of total sample) from the 2016 and 2017 NHWS provided responses from the arthritis module (*i.e.* site of joint pain).

Measures

All measures and diagnoses were self-reported. Respondent characteristics assessed were age, sex, marital status (married/living with partner), height, weight, body mass index, employment status, smoking status, alcohol use, and Charlson Comorbidity Index (CCI) scores (21). Self-reported physician diagnoses of anxiety, depression, or sleep disturbances (insomnia, narcolepsy, sleep apnea, or other sleep-related difficulty) during the past 12 months were also collected. 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 provider (HCP; PCP and specialists) visits, PCP only visits, emergency room (ER) or urgent care visits, and hospitalisations, during the past six months.

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 [a]
Country, n (%)						0.006
United Kingdom	1151 (47.6)	218 (49.7)	250 (46.5)	337 (43.4)	346 (52.2)	
France	503 (20.8)	73 (16.6)	110 (20.4)	183 (23.6)	137 (20.7)	
Germany	342 (14.1)	59 (13.4)	68 (12.6)	124 (16.0)	91 (13.7)	
Spain	292 (12.1)	60 (13.7)	79 (14.7)	89 (11.5)	64 (9.7)	
Italy	129 (5.3)	29 (6.6)	31 (5.8)	44 (5.7)	25 (3.8)	
Age groups (years), n (%)						0.156
18-39	94 (3.9)	21 (4.8)	16 (3.0)	41 (5.3)	16 (2.4)	
40-49	236 (9.8)	43 (9.8)	53 (9.9)	70 (9.0)	70 (10.6)	
50-59	550 (22.8)	92 (21.0)	127 (23.6)	165 (21.2)	166 (25.0)	
60-69	940 (38.9)	163 (37.1)	218 (40.5)	303 (39.0)	256 (38.6)	
70+	597 (24.7)	120 (27.3)	124 (23.0)	198 (25.5)	155 (23.4)	
Female, n (%)	1560 (64.5)	259 (59.0)	349 (64.9)	522 (67.2)	430 (64.9)	0.040
Marital status [b], n (%)						0.013
Married/living with partner	1529 (63.3)	307 (69.9)	344 (63.9)	482 (62.0)	396 (59.7)	
Single	289 (12.0)	52 (11.8)	57 (10.6)	96 (12.4)	84 (12.7)	
Divorced/separated/widowed	598 (24.7)	79 (18.0)	137 (25.5)	199 (25.6)	183 (27.6)	
Household income, n (%)						0.048
Less than Euro 50K/£40K	1849 (76.5)	323 (73.6)	424 (78.8)	584 (75.2)	518 (78.1)	
Euro 50K/£40K or greater	358 (14.8)	78 (17.8)	73 (13.6)	129 (16.6)	78 (11.8)	
Declined to answer	210 (8.7)	38 (8.7)	41 (7.6)	64 (8.2)	67 (10.1)	
Completed university [b], n (%)	696 (28.8)	145 (33.0)	151 (28.1)	239 (30.8)	161 (24.3)	0.004
Employed [c], n (%)	742 (30.7)	157 (35.8)	168 (31.2)	244 (31.4)	173 (26.1)	0.007
BMI, n (%)						0.006
Under/normal weight (<25.0 kg/m^2)	593 (24.5)	111 (25.3)	138 (25.7)	212 (27.3)	132 (19.9)	
Overweight (≥25.0 and <30.0 kg/m^2)	680 (28.1)	141 (32.1)	149 (27.7)	219 (28.2)	171 (25.8)	
Obese (≥30.0 kg/m^2)	920 (38.1)	149 (33.9)	205 (38.1)	279 (35.9)	287 (43.3)	
Declined to answer	224 (9.3)	38 (8.7)	46 (8.6)	67 (8.6)	73 (11.0)	
Smoking status, n (%)						0.010
Current smoker	544 (22.5)	76 (17.3)	130 (24.2)	171 (22.0)	167 (25.2)	
Former smoker	1013 (41.9)	189 (43.1)	225 (41.8)	310 (39.9)	289 (43.6)	
Never smoked	860 (35.6)	174 (39.6)	183 (34.0)	296 (38.1)	207 (31.2)	
Alcohol use (past week), n (%)						<0.001
No alcohol	563 (23.3)	56 (12.8)	115 (21.4)	190 (24.5)	202 (30.5)	
Low (≤3 drinks per week)	1403 (58.0)	278 (63.3)	320 (59.5)	437 (56.2)	368 (55.5)	
Moderate/high (>3 drinks per week)	451 (18.7)	105 (23.9)	103 (19.1)	150 (19.3)	93 (14.0)	
Exercise (days in past month) [d]						<0.001
Ever, n (%)	1048 (43.4)	222 (50.6)	230 (42.8)	386 (49.7)	210 (31.7)	
Never, n (%)	1369 (56.5)	217 (49.4)	308 (57.2)	391 (50.3)	453 (68.3)	
Mean (SD)	5.5 (8.5)	6.2 (8.7)	5.8 (8.8)	6.3 (8.9)	3.9 (7.4)	<0.001
CCI, n (%)						<0.001
0	1373 (56.8)	311 (70.8)	284 (52.8)	468 (60.2)	310 (46.8)	
1	644 (26.6)	91 (20.7)	150 (27.9)	209 (26.9)	194 (29.3)	
≥2	400 (16.5)	37 (8.4)	104 (19.3)	100 (12.9)	159 (24.0)	
Anxiety [e] (% yes), n (%)	600 (24.8)	79 (18.0)	125 (23.2)	184 (23.7)	212 (32.0)	<0.001
Depression [e] (% yes), n (%)	546 (22.6)	62 (14.1)	104 (19.3)	163 (21.0)	217 (32.7)	<0.001
Sleep disturbances [e] (% yes), n (%)	542 (22.4)	61 (13.9)	130 (24.2)	140 (18.0)	211 (31.8)	<0.001
SF-MPQ, mean (SD)	13.3 (9.5)	6.5 (5.8)	12.7 (8.7)	12.3 (8.2)	19.4 (10.0)	<0.001

BMI: body mass index; CCI: Charlson Comorbidity Index; Rx: prescription medication; SD: standard deviation; SF-MPQ: Short Form-McGill Pain Questionnaire. [a] Chi-square tests were used for categorical variables and analysis of variance for continuous variables comparing the distributional difference between groups. [b] <1% of respondents declined to answer. [c] Unemployed includes disabled, retired, student, or homemaker. Employed includes full-time, part-time, or self-employed. [d] Exercised vigorously at least once in past month. [e] Self-reported diagnosis in past 12 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

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.

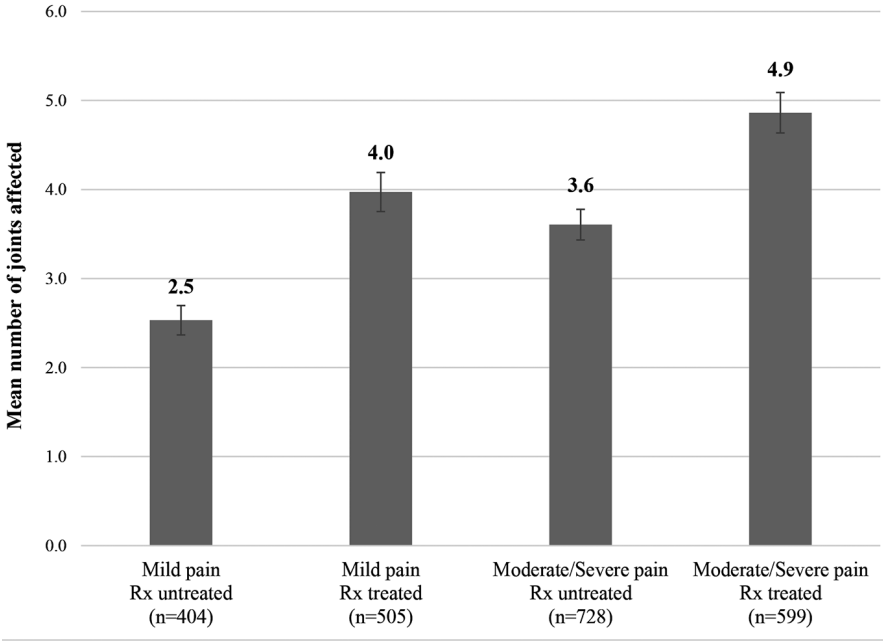

Fig. 1. Mean number of joints affected by arthritis [a].
Rx: prescription medication.
[a] Group means differed at $p<0.001$. Error bars refer to the standard deviation.

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 MCSof 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 ($p<0.001$),

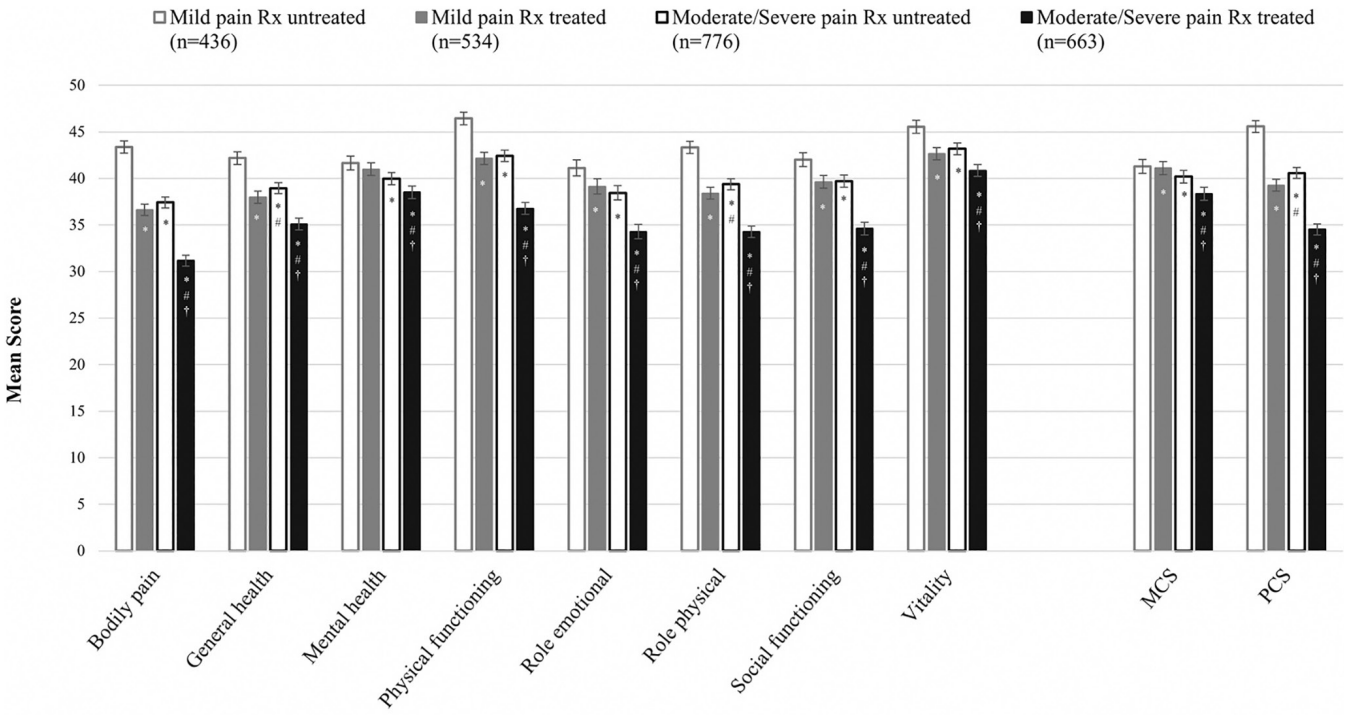

Fig. 2. Adjusted mean values for health-related quality of life (HRQoL) outcomes among respondents with osteoarthritis across Europe [a].
CCI: Charlson Comorbidity Index; MCS: mental component summary score; OA: osteoarthritis; PCS: physical component summary score; SF-12: Medical Outcomes Study 12-Item Short Form Survey Instrument version 2.
[a] Generalised linear models specifying a normal distribution and identity function were used to assess differences in health-related quality of life by OA group using component and domain scores from the SF-12v2. Covariates included: age, sex, marital status, education, income, employment status, smoking status, alcohol use, exercise, body mass index, CCI, anxiety diagnosis, depression diagnosis, insomnia diagnosis, diagnosed with sleep difficulties, and country of residence. Higher scores denote a better quality of life. Data were missing for n=8 respondents. Error bars refer to standard error of the mean.
* Differed from reference = Mild pain Rx-untreated, $p<0.05$.
# Differed from reference = Mild pain Rx-treated, $p<0.05$.
† Differed from reference = Moderate/severe pain Rx-untreated, $p<0.05$.

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 treat-

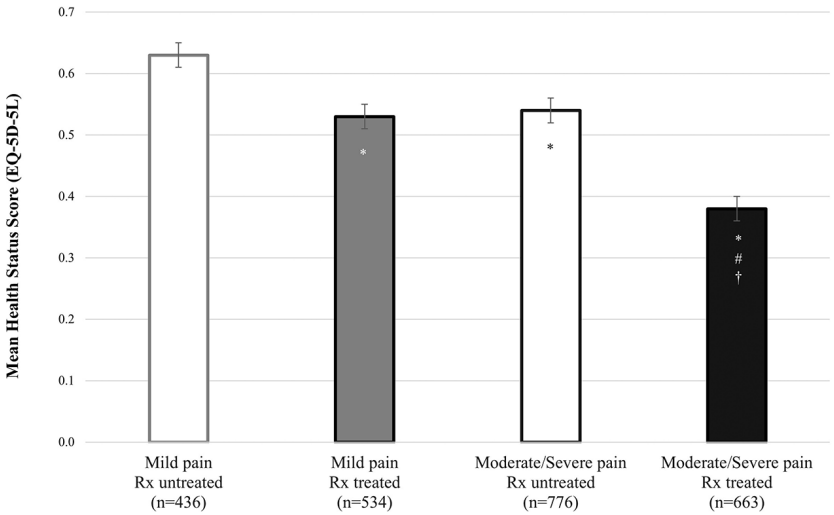

Fig. 3. Adjusted mean values for health status among respondents with osteoarthritis across Europe [a].
CCI: Charlson Comorbidity Index; EQ-5D-5L: 5-Level Euro Quality of Life-5 Dimensions; OA: osteoarthritis; Rx: prescription medication.
[a] Generalised linear models specifying a normal distribution and identity function were used to assess differences in health status by OA group using the EQ-5D-5L. Covariates included: age, sex, marital status, education, income, employment status, smoking status, alcohol use, exercise, body mass index, CCI, anxiety diagnosis, depression diagnosis, insomnia diagnosis, diagnosed with sleep difficulties, and country of residence. Higher scores denote a better quality of life. Data were missing for n=8 respondents. Error bars refer to standard error of the mean.
* Differed from reference = Mild pain Rx-untreated, $p<0.05$.
# Differed from reference = Mild pain Rx-treated, $p<0.05$.
† Differed from reference = Moderate/severe pain Rx-untreated, $p<0.05$.

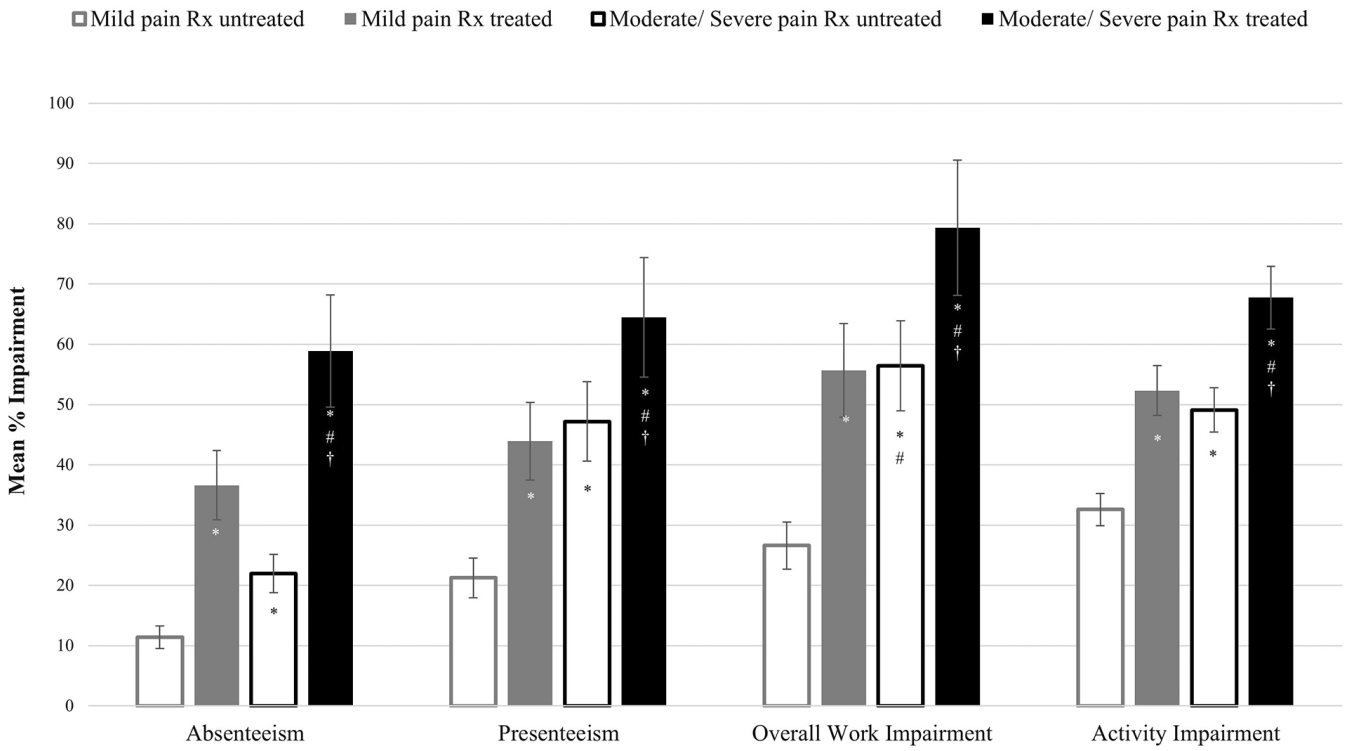

Fig. 4. Adjusted mean values for work productivity and activity impairment (WPAI) among respondents with osteoarthritis across Europe [a].
CCI: Charlson Comorbidity Index; OA: osteoarthritis; Rx: prescription medication.
[a] Generalised linear models specifying a negative binomial distribution and log-link function were used due to the highly positively skewed outcome variables. Models assess differences in work productivity and activity impairment according to group variable. Covariates included: age, sex, marital status, education, income, employment status, smoking status, alcohol use, exercise, body mass index, CCI, anxiety diagnosis, depression diagnosis, insomnia diagnosis, diagnosed with sleep difficulties, and country of residence. Higher scores denote more impairment. Error bars refer to standard error of the mean. Sample sizes varied according to employment status. For employed respondents with OA for absenteeism and overall impairment, sample sizes were: mild pain Rx-untreated n=142, mild pain Rx-treated n=153; moderate/severe pain Rx-untreated n=234, and moderate/severe pain Rx-treated n=163. For presenteeism, sample sizes were: mild pain Rx-untreated n=140, mild pain Rx-treated n=145; moderate/severe pain Rx-untreated n=222, and moderate/severe pain Rx-treated n=138. For overall activity impairment, sample sizes were: mild pain Rx-untreated n=436, mild pain Rx-treated n=534; moderate/severe pain Rx-untreated n=776, and moderate/severe pain Rx-treated n=663.
* Differed from reference = Mild pain Rx-untreated, $p<0.05$.
# Differed from reference = Mild pain Rx-treated, $p<0.05$.
† Differed from reference = Moderate/severe pain Rx-untreated, $p<0.05$.

ed groups=0.51–0.52, 95% CI 0.37–0.71 *vs*. untreated groups=0.30–0.34, 95% CI 0.21–0.46; $p<0.05$) and for hospitalisations (mean number [past six months]: mild or moderate/severe treated groups=0.20–0.24, 95% CI 0.14–0.35 *vs*. -untreated groups=0.12–0.16, 95% CI 0.08–0.24; $p<0.05$).

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-treated *versus* moderate/severe pain Rx-untreated. 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-

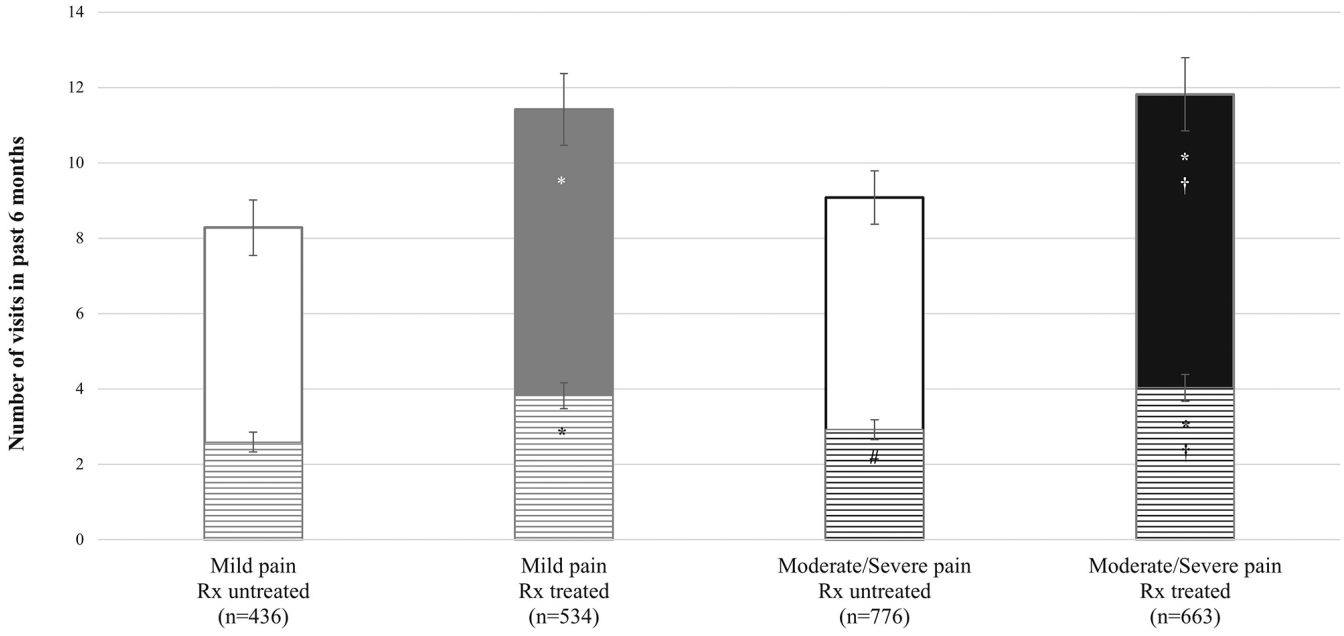

Fig. 5. Adjusted mean values for healthcare resource utilisation (HRU) among respondents with osteoarthritis across Europe [a].
CCI: Charlson Comorbidity Index; OA: osteoarthritis; Rx: prescription medication.
[a] Generalised linear models specifying a negative binomial distribution and log-link function were used due to the highly positively skewed outcome variables. Models assess differences in work productivity and activity impairment according to group variable. Covariates included: age, sex, marital status, education, income, employment status, smoking status, alcohol use, exercise, body mass index, CCI, anxiety diagnosis, depression diagnosis, insomnia diagnosis, diagnosed with sleep difficulties, and country of residence. Higher number of visits denote more healthcare utilisation. Error bars refer to standard error of the mean. Primary care visits (hashed area) are represented as proportion of total healthcare provider visits (solid area).
* Differed from reference = Mild pain Rx-untreated, $p<0.05$.
[#] Differed from reference = Mild pain Rx-treated, $p<0.05$.
[†] Differed from reference = Moderate/severe pain Rx-untreated, $p<0.05$.

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.

Acknowledgements

Data collection of the NHWS was performed independently by Kantar. The study design, analysis, interpretation, and support for manuscript writing were funded by Pfizer and Eli Lilly and Company.

References

1. Osteoarthritis Research Society International (OARSI). Osteoarthritis: A serious disease. Available at https://www.oarsi.org/sites/default/files/docs/2016/oarsi_white_paper_oa_serious_disease_12116_1.pdf. Accessed October 22, 2018.
2. VOS T, ABAJOBIR AA, ABBAFATI C *et al.*: Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990 2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet* 2017; 390: 1211-59.
3. PINCUS T, CASTREJON I, YAZICI Y, GIBSON KA, BERGMAN MJ, BLOCK JA: Osteoarthritis is as severe as rheumatoid arthritis: evidence over 40 years according to the same measure in each disease. *Clin Exp Rheumatol* 2019; 37 (Suppl. 120) :S7-17.
4. SAFIRI S, KOLAHI AA, HOY D *et al.*: Global, regional and national burden of rheumatoid arthritis 1990-2017: a systematic analysis of the Global Burden of Disease study 2017. *Ann Rheum Dis* 2019; 78: 1463-71.
5. National Institute for Health and Care Excellence (NICE). Osteoarthritis: care and management. Available at: https://www.nice.org.uk/guidance/cg177. Accessed January 4, 2019.
6. KOLASINSKI SL, NEOGI T, HOCHBERG MC *et al.*: 2019 American College of Rheumatology/Arthritis Foundation Guidelines for the Management of Osteoarthritis of the Hand, Hip, and Knee. *Arthritis Care Res* 2020; 72: 220-33.
7. KLOPPENBURG M, KROON FP, BLANCO FJ *et al.*: 2018 update of the EULAR recommendations for the management of hand osteoarthritis. *Ann Rheum Dis* 2019; 78: 16-24.
8. CALLAHAN LF, AMBROSE KR, ALBRIGHT AL *et al.*: Public Health Interventions for Osteoarthritis - updates on the Osteoarthritis Action Alliance's efforts to address the 2010 OA Public Health Agenda Recommendations. *Clin Exp Rheumatol* 2019; 37 (Suppl. 120): S31-9.
9. BANNURU RR, OSANI MC, VAYSBROT EE *et al.*: OARSI guidelines for the non surgical management of knee, hip, and polyarticular osteoarthritis. *Osteoarthritis Cartilage* 2019; 27: 1578-89.
10. ZENG C, WEI J, PERSSON MSM *et al.*: Relative efficacy and safety of topical non steroidal anti-inflammatory drugs for osteoarthritis: a systematic review and network meta analysis of randomised controlled trials and observational studies. *Br J Sports Med* 2018; 52: 642-50.
11. KINGSBURY SR, GROSS HJ, ISHERWOOD G, CONAGHAN PG: Osteoarthritis in Europe: Impact on health status, work productivity and use of pharmacotherapies in five European countries. *Rheumatology* (Oxford) 2014; 53: 937-47.
12. Osteoarthritis in General Practice. Data and Perspectives. Arthritis Research UK, Chesterfield, UK. Available at: https://healthinnovationnetwork.com/wp content/uploads /2017/01/Osteoarthritis_in_general_practice__July_2013__Arthritis_Research_ K_ PDF_421_MB.pdf. Accessed January 4, 2019.
13. VAN SCHOOR NM, ZAMBON S, CASTELL MV *et al.*: Impact of clinical osteoarthritis of the hip, knee and hand on self-rated health in six European countries: the European Project on OSteoArthritis. *Qual Life Res* 2016; 25: 1423-32.
14. DIBONAVENTURA M, GUPTA S, MCDONALD M, SADOSKY A, PETTITT D, SILVERMAN S: Impact of self-rated osteoarthritis severity in an employed population: Cross-sectional analysis of data from the national health and wellness survey. *Health Qual Life Outcomes* 2012; 10: 30.
15. SADOSKY AB, BUSHMAKIN AG, CAPPELLERI JC, LIONBERGER DR: Relationship between patient-reported disease severity in osteo-

arthritis and self-reported pain, function and work productivity. *Arthritis Res Ther* 2010; 12: R162.
16. ZAMBON S, SIVIERO P, DENKINGER M *et al.*: Role of osteoarthritis, comorbidity, and pain in determining functional limitations in older populations: European Project on Osteoarthritis. *Arthritis Care Res* (Hoboken) 2016; 68: 801-10.
17. LE TK, MONTEJANO LB, CAO Z, ZHAO Y, ANG D: Health care costs in US patients with and without a diagnosis of osteoarthritis. *J Pain Res* 2012; 5: 23-30.
18. HILIGSMANN M, REGINSTER J-Y: The economic weight of osteoarthritis in Europe. *Medicographia* 2013; 35: 197-202.
19. NEOGI T: The epidemiology and impact of pain in osteoarthritis. *Osteoarthritis Cartilage* 2013; 21: 1145-53.
20. International Data Base (IDB) of the US Census. 2018. Available at: https://www.census.gov/programs-surveys/international-programs/about/idb.html. Accessed August 27, 2019.
21. CHARLSON ME, POMPEI P, ALES KL, MACKENZIE CR: A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987; 40: 373-83.
22. HAWKER GA, MIAN S, KENDZERSKA T, FRENCH M: Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF-36 BPS), and Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP). *Arthritis Care Res* (Hoboken) 2011; 63: S240-52.
23. WARE J JR, KOSINSKI M, KELLER SD: A 12-Item Short-Form Health Survey. *Med Care* 1996; 34: 220-33.
24 HERDMAN M, GUDEX C, LLOYD A *et al.*: Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res* 2011; 20: 1727-36.
25. BRAZIER J, ROBERTS J, DEVERILL M: The estimation of a preference-based measure of health from the SF-36. *J Health Econ* 2002; 21: 271-92.
26. FERREIRA LN, FERREIRA PL, PEREIRA LN, ROWEN D, BRAZIER JE: Exploring the consistency of the SF-6D. *Value Heal* 2013; 16: 1023-31.
27. FRENDL DM, WARE JE Jr: Patient-reported functional health and well-being outcomes with drug therapy: a systematic review of randomized trials using the SF-36 health survey. *Med Care* 2014; 52: 439-45.
28. HARRISON MJ, DAVIES LM, BANSBACK NJ, INGRAM M, ANIS AH, SYMMONS DP: The validity and responsiveness of generic utility measures in rheumatoid arthritis: a review. *J Rheumatol* 2008; 35: 592-602.
29. EuroQol Research Foundation. EQ-5D-5L – EQ-5D. 2019. Available at https://euroqol.org/eq-5d-instruments/eq-5d-5l-about/. Accessed August 27, 2019
30. REILLY MC, ZBROZEK AS, DUKES EM: The validity and reproducibility of a work productivity and activity impairment instrument. *Pharmacoeconomics* 1993; 4: 353-65.
31. VAN BELLE G, FISHER LD, HEAGERTY PJ, LUMLEY T: Biostatistics: A Methodology For the Health Sciences. 2nd ed., Hoboken, John Wiley & Sons, 2004: 871.
32. AGRESTI A: Foundations of Linear and Generalized Linear Models. 1st ed., Hoboken, John Wiley & Sons, 2015.
33. KEENAN AM, TENNANT A, FEAR J, EMERY P, CONAGHAN PG: Impact of multiple joint problems on daily living tasks in people in the community over age fifty-five. *Arthritis Rheum* 2006; 55: 757-64.
34. MERAYA AM, DWIBEDI N, SAMBAMOORTHI U: Polypharmacy and health-related quality of life among US adults with arthritis, medical expenditure panel survey, 2010-2012. *Prev Chronic Dis* 2016; 13: E132.
35. BUSHMAKIN AG, CAPPELLERI JC, TAYLOR-STOKES G *et al.*: Relationship between patient-reported disease severity and other clinical outcomes in osteoarthritis: a European perspective. *J Med Econ* 2011; 14: 381-9.
36. WANG SX, GANGULI AX, BODHANI A, MEDEMA JK, REICHMANN WM, MACAULAY D: Healthcare resource utilization and costs by age and joint location among osteoarthritis patients in a privately insured population. *J Med Econ* 2017; 20: 1299-306.
37. WRIGHT EA, KATZ JN, CISTERNAS MG, KESSLER CL, WAGENSELLER A, LOSINA E: Impact of knee osteoarthritis on health care resource utilization in a US population-based national sample. *Med Care* 2010; 48: 785-91.
38. GUILLEMIN F, RAT AC, MAZIERES B *et al.*: Prevalence of symptomatic hip and knee osteoarthritis: a two-phase population-based survey. *Osteoarthritis Cartilage* 2011; 19: 1314-22.
39. VAN DER PAS S, CASTELL MV, COOPER C *et al.*: European project on osteoarthritis: design of a six-cohort study on the personal and societal burden of osteoarthritis in an older European population. *BMC Musculoskelet Disord* 2013; 14: 138.
40. SHARMA A, KUDESIA P, SHI Q, GANDHI R: Anxiety and depression in patients with osteoarthritis: impact and management challenges. *Open Access Rheumatol Res Rev* 2016; 8: 103-13.
41. COMER C, SMITH TO, DREW B, RAJA R, KINGSBURY SR, CONAGHAN PG: A systematic review assessing non-pharmacological conservative treatment studies for people with non-inflammatory multi-joint pain: clinical outcomes and research design considerations. *Rheumatol Int* 2018; 38: 331-41.
42. PEREIRA D, PELETEIRO B, ARAUJO J, BRANCO J, SANTOS RA, RAMOS E: The effect of osteoarthritis definition on prevalence and incidence estimates: a systematic review. *Osteoarthritis Cartilage* 2011; 19: 1270-85.
43. CARLESSO LC, NEOGI T: Identifying pain susceptibility phenotypes in knee osteoarthritis. *Clin Exp Rheumatol* 2019; 37 (Suppl. 120): S96-9.