Sick Leave and Costs in Active Workers With Chronic Osteoarthritis Pain in Spain: Outcomes of the OPIOIDS Real World Study

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Abstract

Objective

To evaluate sick leave and its costs in active workers who initiate opioid treatment for moderate/severe chronic osteoarthritis (OA) pain.

Methods

Secondary analysis of the longitudinal, retrospective OPIOIDS study using electronic medical records (EMR) of patients aged ≥ 18 years who started opioid treatment for chronic OA pain between 2010 and 2015 after treatment failure with usual analgesics. The follow-up period was 36 months from the index date, and the days of sick leave and their cost were analyzed.

Results

A total of 5,089 EMRs of OA chronic pain patients aged 56.8 years (SD: 4.6), 56.6% male, were analyzed: 73.3% of patients started treatment with a weak opioid and 26.7% a strong opioid. At 36 months, adherence was 21% (strong opioids 15.4%, weak opioids: 23%; p<0.001), and 77% of patients had at least one sick leave related with OA chronic pain, with a mean total days off work of 93 days in all actively working patients (120.5 days in patients with sick leaves). In 16.9% it lasted ≥ 6 months. Pain reduction was modest (-1.2 points; -4.0%, p<0.001). The cost of sick leave was € 2,594 patient/year and was associated (p<0.05) with age (β-0.043), female sex (β-0.035), comorbidity (β-0.034) and strong opioid use (β-0.037).

Conclusions

Active workers who started opioid treatment for chronic osteoarthritis pain showed an increased frequency of sick leave and cost to society, with modest pain reduction. Age, female sex, comorbidity, and strong opioids were factors associated with the cost of sick leave.

Introduction

Osteoarthritis (OA) is a degenerative joint pathology characterized by cartilage deterioration, with a proliferative reaction of the subchondral bone and inflammation of the synovial membrane [1]. It is estimated that 6-24% of adults have chronic OA pain and the incidence increases with age [2,3]. In Spain, according to the EPISER study [4], the prevalence of OA in persons aged > 40 years is 29.4%. Therapeutic approaches include non-pharmacological measures, drug treatment and joint replacement surgery in the most disabling cases [5]. Drug treatments include nonsteroidal anti-inflammatory drugs (NSAIDs), which are often used in patients who do not respond to first-choice analgesics such as acetaminophen [6]. Tramadol is the weak opioid with the greatest evidence of efficacy and safety, while strong opioids are used for moderate to severe pain with an insufficient response to other treatments [7,8]. The utility of strong opioids is proven in cancer pain relief, but their use in chronic non-cancer pain relief is unclear

[5,7,8]. Some scientific societies, such as the OARSI or the American College of Rheumatology (ACR) discourage their use in OA treatment [1,9].

The chronic pain and disability associated with OA have a negative effect on the quality of life, and are one of the main causes of days off work due to sick leave which, together with lower occupational productivity, result in high social costs [1,8,10-15]. Studies have estimated that one in four active workers with OA leave the workplace before the normal retirement age [16]. The mechanisms explaining the involvement of OA in occupational performance are not entirely clear [15]. Most studies have found that pain and/or functional joint deterioration are the main reasons for lost work productivity [10]. Joint pain may have a direct impact on occupational productivity, regardless of comorbidity or other associated factors. However, it may also have an indirect impact, in which joint pain causes physical limitations, depression, poor adaptation and poor sleep quality, which in turn lead to lost productivity [17]. In addition, opioid use in patients with OA has increased and its relationship to the incidence of days off work due to sick leave and its cost is not clear [18,19]. The OPIOIDS study, carried out under conditions of usual medical practice in Spain [20], collected information on the impact of opioids in the treatment of chronic OA pain refractory to regular analgesics on different outcomes including lost productivity due to sick leave and its costs. The objective of this study was to carry out a secondary analysis of the OPIOIDS study to assess lost occupational productivity (days of temporary sick leave) and the associated cost in active workers initiating opioid treatment for chronic pain due to OA lasting more than three months in usual clinical practice.

Patients And Methods

Design and study population

We conducted a secondary analysis of the longitudinal, multicenter, retrospective OPIOIDS (Outcomes in Patients usIng Opioids In Painful Disorders in Spain) study [20], which used electronic medical records (EMR) from the BIG-PAC registered health database (The European Network of Centers for Pharmacoepidemiology and Pharmacovigilance; http://www.encepp.eu/encepp-/viewResource.htm? *id-29236)* of records of an allocated population of 1.8 million from seven Spanish autonomous communities [21]. EMRs were anonymized according to Organic Law 3/2018, of December 5, on the Protection of Personal Data and guarantee of digital rights (*https://www.boe.es/eli/es/lo/2018/12/05/3*). The OPIOIDS study was classified by the Spanish Agency for Medicines and Health Products and approved by the Ethics Committee of the Hospital of Terrassa (Barcelona). The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement guidelines for reporting observational studies were followed [22].

We included the EMR of patients who started a new treatment with strong or weak opioids, alone or combined with other analgesics, for the treatment of moderate to severe (≥ 5 points on the numerical pain scale) chronic nociceptive pain (≥ 3 months) in any site due to OA between 1/01/2010 and 31/12/2015 [23]. Patients were followed for a maximum of 3 years. Patients had to be previously treated

with ≥ 1 first-line analgesic such as acetaminophen, metamizole and/or nonsteroidal anti-inflammatory drugs (NSAIDs). EMRs were obtained during the 12 months before the index date and over the next 36 months. The index date was the initiation of a new opioid treatment, starting from the date of diagnosis of chronic nociceptive pain due to OA. Additional inclusion criteria were (a) age ≥18 years, (b) occupationally active, c) patients active in the database (≥2 health records in the computer system) a minimum of 12 months before the start of the study, (d) ensured regular monitoring (≥2 health records in the computer system from the index date), and (c) inclusion in chronic prescription program (with a record of the daily dose, time interval and duration of each treatment administered (≥2 prescriptions during the follow-up period)). Exclusion criteria were (a) displaced or out-of-area subjects; (b) permanently institutionalized patients, c) terminal illness and/or dialysis (ICD-10:N18), d) neuropathic pain/radiculopathy (ICD-10: G50-65) or cancer (ICD-10: G89.6), and e) not occupationally active (retired, unemployed, permanent work disability, early retirement and/or maternity leave).

Definition of diagnosis and study cohorts

Diagnoses were obtained from the International Classification of Diseases (10th edition) Clinical Modification (ICD-10-CM) (*https://eciemaps. mscbs.gob.es*). Chronic pain was defined as pain that persisted for ≥ 3 months. The site of pain was a) hip and knee (M16, M17), b) lumbar (M54.5), and other sites (M15, M18, M19, M40, M41) according to medical criteria. Two study cohorts were developed according to type of opioid (weak or strong) according to the Anatomical Therapeutic Chemical Classification System (ATC)[24]. The index date was the start of a new opioid treatment (weak or strong) from the date of diagnosis of chronic nociceptive pain due to OA. Adherence, persistence, medication possession ratio (MPR) and discontinuation definitions were as previously described in the OPIOIDS study [20].

Demographic variables, comorbidity and medication administered

Demographic and comorbidity variables were age (continuous and by range: 18-44, 45-54 and ≥55 years on the index date), sex and body mass index (BMI, Kg/m^2) and the personal medical history. The Charlson comorbidity index and the number of chronic comorbidities were used as a summary variable of general comorbidity and an approximation of patient severity [25]. The medications (active ingredients) indicated for chronic OA pain were obtained (ATC N02AA01 to N02AX06) from pharmacological prescription records. The choice of medication in a specific patient was at the physician's discretion. The type and medical specialty that initiated the prescription was determined (Supplementary table S1).

Cost of days of sick leave

The cost of days of temporary work disability from the social perspective was determined by the human capital method (mean salary of the replacement of the active patient [€ 119.44 per day not worked]), source: Spanish Institute of Statistics (INE))[26]. Days of sick leave were expressed as absolute and relative values (in patients with sick leave), and as the mean days of sick leave per patient (patients with/without sick leave [0 days of sick leave]).

Clinical effectiveness

Clinical effectiveness was obtained using the variation in pain intensity on an 11-point numerical pain scale (5-7; moderate pain, >7; severe pain) from the closest date before the start date (index date) and the end date of the study [23]. The absolute variation in the natural and relative units was calculated in percentage changes from the baseline value.

Statistical analysis

A descriptive, univariate statistical analysis was made. Qualitative data were described using absolute and relative frequencies. The 95% confidence intervals (CI) for parameter estimation were based on the total number of subjects with no missing values. ANOVA and the chi-square test for independent groups were used in the bivariate analysis. Paired tests were also used to evaluate the before-after differences for each subgroup (McNemar's test and the Student's t test). A survival analysis was made by estimating the Kaplan-Meier curves (log-rank test) to analyze the persistence of opioid treatment, applying a Cox proportional risk model (corrected by covariates) to determine the hazard ratio (HR) and its 95% CI between strong and weak opioids. Covariate analysis was used to correct the cost per patient of days of sick leave. The covariates included were sex, age, general comorbidity (Charlson index), time from diagnosis, treatment persistence and the MPR. A multiple linear regression model (procedure: consecutive steps) was constructed to examine the variables associated with sick leave (dependent variable: cost per patient [all] of sick leave). The analyses used IBM SPSS, version 23.0, NY, USA software (https://www.ibm.com/analytics/spss-statistics-software).

Results

Of an initial selection of 1,280,684 subjects aged ≥ 18 years who sought care during the recruitment period, 124,798 were diagnosed with OA in any site with nociceptive pain of > 3 months duration (chronic pain). Of these patients, 34% initiated a new opioid treatment (n=42,429), who were the sample included in the OPIOIDS study. For the present analysis, 37,340 subjects (77.2%) who were not active workers were excluded. Finally, 5,089 patients who met the study selection criteria were included (Figure 1). Table 1 shows the demographic characteristics and overall comorbidity; the mean age was 56.8 (SD: 4.6) years and 56.6% were male. Only 14 patients were aged ≥ 65 years: 73.3% (n=3,732) initiated treatment with a weak opioid and 26.7% (n=1,357) with a strong opioid. Patients receiving strong opioids had greater comorbidity (Charlson index: 1.2 vs. 1.1; p=0.041). The type of opioid medication administered and the medical specialty initiating the prescription are described in Supplementary table S1. Almost all prescriptions for weak opioids were for tramadol or tramadol + acetaminophen (98.1%) while fentanyl, tapentadol and oxycodone-naloxone were the most frequently prescribed strong opioids (76.4%). Strong opioids were proportionately more frequently prescribed by specialists than by GPs (40.6% vs. 22.6%, p<0.001). Supplementary table S2 shows the concomitant medication prescribed by group and follow-up periods. During the 12 months before initiation of opioids, mean concomitant medication was 1.4 analgesics per patient compared with 1.2 at 36 months (p<0.001). The reduction was mainly due to the

lower use of acetaminophen alone (73% vs. 38.9%, p<0.001), which was compensated for by the significant increase in the use of NSAIDs and metamizole concomitantly with opioids (Supplementary table S2).

Treatment adherence, persistence, MPR, reasons for discontinuation and mortality by study group (strong/weak opioids) are shown in table 2. The median duration of opioid treatment was 187 days (interquartile range: 84-738 days). At 36 months, overall treatment adherence was 21% (95% CI: 19.9%-22.1%) and was 23% (95% CI: 21.6 - 24.4%) for weak opioids and 15.4% (95% CI: 13.5 - 17.3%) for strong opioids (p<0.001). Supplementary figure S1 shows the Kaplan-Meier curves for the persistence of opioid treatment, with a corrected mean that was 27% higher for weak compared with strong opioids (HR=1.27 [1.17–1.34], p=0.001). Pain intensity decreased significantly, but moderately (-1.2 points [-14%], p<0.001), with only 6.8% of patients stopping opioids having no moderate or severe pain (Supplementary table S3). Pain reduction was greater in patients on weak opioids in comparison with those receiving strong opioids. Rehabilitation sessions showed no significant changes in the percentage of patients using this resource or in the mean number of rehabilitation sessions per patient according to both the period of the study or the type of opioid medications used (Supplementary figure S2), although a numeric increase in the percentage of rehabilitation user throughout the follow up of the study was observed.

Table 3 shows the distribution of days of sick leave and their cost by opioid type and study periods. Compared to the 12 months pre-opioid, during the following 12 months there were 4.3% more patients with sick leave (p<0.001), with a longer duration of sick leave, both in patients on sick leave and in the overall sample; 4.5 and 4.0 days, respectively (p<0.001), which was accompanied by a significant increase in the cost of lost work productivity in the first year of opioid treatment; € 559 and € 481, respectively (p<0.001) to € 6,837 and € 2,594 per patient, in the overall sample and in patients with sick leaves respectively, after 12 months of starting opioid therapy. The increase in the cost of sick leave was slightly higher in patients receiving weak opioids. At 12 months after initiation of opioid treatment, 37.9% of patients had ≥ 1 days of sick leave (6.1% ≥ 6 months), with a mean of 57.1 (SD: 55.3) days/year in patients with sick leave and 21.7 (SD: 43.9) days/year overall. Patients receiving strong opioids had a longer duration of sick leave and a higher cost per patient than those receiving weak opioids. Table 3 also shows the evolution of the number of sick leaves and days of sick leave and their cost over the 36-month follow up.

Table 4 shows the cost per patient during the 36-month follow up, according to the different scenarios dependent on location of OA, pain reduction after opioid administration and concomitant use of NSAIDs. Patients with a relevant reduction of pain ≥ 50% of the pre-opioid severity of pain had a lower cost of sick leave in comparison to those who did not, while patients treated with strong opioids, regardless of whether or not they received concomitant NSAIDs, had a higher mean cost. In the multiple linear regression model, the mean cost of days of sick leave was associated with age (β=0.043; p=0.003), female sex (β=0.035, p=0.012), the severity of comorbidity (β=0.034, p=0.018) and treatment with strong opioids (β=0.037, p=0.011). Figure 2 shows the mean cost per patient of days of sick leave adjusted by covariates during the follow-up period according to sex and age group. The cost of sick leave was

significantly higher in women and in individuals 55 or more years in comparison with men or younger patients, either receiving weak or strong opioids. In all subgroups, patients treated with strong opioids, regardless of sex or age group, showed higher cost per patient.

Discussion

This study was an analysis of a secondary endpoint of the OPIOIDS study in usual medical practice in Spain [20]. Active workers with OA who started opioid treatment for moderate/severe chronic pain showed high job productivity losses due to days of temporary occupational disability. Opioid use had low treatment adherence and early medication discontinuation, did not reduce previous levels of sick leave, and had a modest impact on pain reduction in the present research. There were also no significant differences in the use of rehabilitation by workers on sick leave compared to those without, highlighting the need for rehabilitation in these patients as noted above [27]. In addition, older age, female sex, the severity of comorbidity, and the use of strong opioids were associated with greater occupational costs because of higher number of workdays off due to temporary disability. There is a scarcity of observational studies in real-world conditions in the literature consulted, which makes it difficult to compare the results, but which enhances the singularity of the study and also the possibility of helping health authorities and opinion leaders when making healthcare decisions in OA patients. Standard randomized clinical trials should be used with caution for justification of political, medico-legal, and economic decisions as well as generalizing the results; outcomes obtained under routine medical care, like the ones includes here, could be of help to healthcare decision makers in OA. This is because such naturalistic, non-interventional studies may be complementary to evidence-based medicine supported by traditional clinical trial research [28,29]. In addition, the large number of patients included, together with the monitoring period analyzed, may support the degree of external validity of the results in Spain, and may be considered as a strength of the study.

In this study of active workers, the mean age was approximately 57 years and 56.6% were male, results consistent with those of other studies in patients with common musculoskeletal disorders [14, 16, 17]. After 36 months of follow up, treatment adherence was low (21%). Kostev found that in a large cohort of patients (n=32,158) with chronic pain [30], adherence to opioids was low; 69% of patients discontinued treatment per year of follow up, similar to our study (64%). In the series analyzed in this research, opioid use did not result in a substantial reduction in pain and had no direct effect in reducing days of sick leave. Our results show a close relationship between pain intensity and days of sick leave. Reducing days of sick leave would require a multidisciplinary approach, including improvements in pain (new treatments), associated comorbidity (obesity, psychological states), lifestyle and/or occupational conditions (occupational risk of certain jobs). We found that, in one-third of patients, there was a significant impact of lost productivity per follow-up year, which increased to 77% at the end of the follow up. These results are in line with other reports [14]. For each follow-up year, there was a mean sick leave in patients on sick leave of 57.1 days/year; in 8.2% of patients the mean was 1-7 days and in 6.1% it was ≥ 6 months while, in all patients, the mean was 21.7 days/year at a cost of € 2,594/year/patient. At 36

months, 77% of patients had taken some days of sick leave, with a mean of lost working days of 93 days, and of ≥ 6 months in 16.9% of patients, at a cost of € 11,103/patient.

Different designs and time periods and the lack of specific studies make it difficult to compare the results. Hubertsson et al., analyzed patients aged 16-64 years and found that sick leave was more common in the 50-64 years age group and differed between males and females [17]. For lower back pain and myalgia, 27% and 26% of all sick leaves were short (8-14 days) and only 11% and 13% were long (≥90 days). Berger found that private sector employees with OA had a mean of 62.9 days of sick leave compared with 36.7 days in a control group without OA [31]. Mean total indirect costs were twice as high in patients with OA ($5,002 vs. $2,120). Pekkala highlighted the hierarchical differences in occupational classes between different musculoskeletal disorders [32], with large discrepancies in back and shoulder disorders. Rabenda and coworkers [33], in a cohort of active workers, underlined the high burden of direct and indirect costs of patients with OA (€15.2 and €23.8, respectively, per active subject per month; equivalent to 0.8 days of sick leave per patient per month), which were predominantly productivity-related costs. Mather found that 10.8% of days of sick leave were ≥90 days/year [34]. Some reports have concluded that an increase in sick leave and its cost as a result of OA is expected in forthcoming years [14]. Taking methodological differences into account, our results are broadly in line with these studies. The association with strong opioids may be motivated by a greater degree of severity of OA or associated comorbidities. Some authors are studied previously the association of opioid use and days off work and found a relationship between taking opioids, both weak or strong, and disability to work. Lalic and coworkers [35], found that among the 6.9% of people initiating strong opioids, 12.5% had persistent high sickness absence and disability pension (estimated 320 days/year) before and after opioid initiation and 72.9% had persistent low/minimum sickness absence and disability pension (estimated 30 days/year). Tao et al. reported a significant association of the use of opioid and psychotropic medications with workers' compensation claim costs and prolonged disability. In general, it is assumed that opioid abuse/dependence impose a substantial economic burden on employers [36-37].

The possible limitations of the study are those inherent to retrospective studies (under recording, coding errors, variations in professionals and patients and possible classification bias). In addition, the individual severity of OA or the interactions between different comorbidities were not considered. Neither could the associations between the intensity of chronic pain and days of sick leave be assessed because they were not available in the database (occupational risk control, work adaptation, flexibility of schedules, etc.), although this should not have influenced the study results.

Conclusions

In usual clinical practice in Spain, active workers who started opioid treatment for moderate to severe chronic OA pain showed high costs due to days of sick leave, with a modest reduction in pain. Age, female sex, severity of comorbidity and the use of strong opioids were significantly associated with the cost of lost occupational productivity.

Declarations

Availability of data and materials

he datasets (aggregated and anonymized), analyzed for the elaboration of this specific study,

are available (on reasonable request) at the following email address: ansicras@atryshealth.com.

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Contributions

The study was conceived by ASM (ansicras@atryshealth.com), JRG (javier.rejas@pfizer.com) and IL (Isabel.lizarraga@pfizer.com). ASM, CTT (carlostornero @gmail.com), FVN (fvargasnegrin@gmail.com), JRG, ASN (arsicras@atryshealth.com) and IL participated and contributed to the study design. Data collection and the statistical analysis were made by ASM and ASN. Data interpretation of data was made by all authors. All authors drafted or critically revised and approved the final version of the submitted manuscript.

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Ethics approval and consent to participate

The OPIOIDS study was classified by the Spanish Agency for Medicines and Health Products and approved by the Ethics Committee of the Hospital of Terrassa (Barcelona). The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement guidelines for reporting observational studies were followed.

Consent for publication

Not applicable.

Competing interests

Antoni Sicras-Mainar and Aram Sicras-Navarro are employees of Atrys Health SA, who were paid consultants to Pfizer in connection with this manuscript. Javier Rejas-Gutiérrez and Isabel Lizarraga are employees of Pfizer, SLU. Carlos Tornero-Tornero and Francisco Vargas-Negrín declare no competing interests.

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Tables

Table 1. Baseline characteristics (demographic and morbidity) of patients by study groups.

Study groups	Weak opioid	Strong Opioid	Total	p-value
Number of patients, %	N = 3732 (73.3%)	N = 1357 (26.7%)	N = 5089 (100%)	
Demographic features				
Mean age, years (SD)	56.8 (4.6)	56.8 (4.7)	56.8 (4.6)	0.848
Age group: 18 - 44 years	1.4%	1.4%	1.4%	
45 - 54 years	33.8%	33.2%	33.6%	
≥ 55 years	64.8%	65.4%	65.0%	0.912
Sex (female	56.2%	57.5%	56.6%	0.431
General comorbidity				
Mean diagnoses (SD)	2.3 (1.5)	2.4 (1.6)	2.4 (1.6)	0.032
Mean Charlson index (SD)	1.1 (0.3)	1.2 (0.3)	1.1 (0.3)	0.041
0	44.6%	47.5%	45.4%	
1	27.5%	22.5%	26.2%	
2	13.8%	16.0%	14.4%	
3+	6.0%	6.6%	6.2%	0.066
Associated comorbidities				
High blood pressure	39.8%	39.1%	39.6%	0.683
Diabetes	16.6%	16.9%	16.7%	0.807
Dyslipidemia	55.3%	52.5%	54.5%	0.078
Obesity	29.0%	23.0%	27.4%	<0.001
Ischemic heart disease	4.5%	4.3%	4.5%	0.783
Cerebrovascular event	2.8%	3.8%	3.1%	0.084
Heart failure	1.8%	2.9%	2.1%	0.017
Kidney failure	1.9%	1.8%	1.9%	0.710
Asthma	11.3%	11.3%	11.3%	0.967
COPD	7.2%	7.8%	7.3%	0.426
Dementia	1.3%	2.3%	1.6%	0.017
Depressive syndrome	20.3%	23.3%	21.1%	0.023
Anxiety	46.8%	50.6%	47.8%	0.018

Malignancies	5.8%	5.4%	5.7%	0.554
Osteoporosis	19.6%	21.9%	20.2%	0.071
Lifestyle				
Active smokers (daily)	23.6%	27.7%	24.7%	0.003
Alcohol consumption ≥ 30 grams/day	2.8%	2.4%	2.7%	0.521
Osteoarthritis site				
Knee/hip	49.8%	49.4%	49.7%	
Spine	31.5%	32.1%	31.7%	
Others	18.6%	18.6%	18.6%	0.939

Values expressed as percentage or mean (SD: standard deviation). COPD: chronic obstructive pulmonary disease.

Table 2. Treatment persistence and adherence, medication possession ratio and discontinuation by study groups.

Study groups	Weak opioid	Strong Opioid	Total	p-value
Number of patients, %	N = 3732 (73.3%)	N = 1357 (26.7%)	N = 5089 (100%)	
Time from diagnosis, years	3.4 (1.0)	3.5 (1.2)	3.4 (1.1)	0.002
- Median (P25 - P75)	2.9 (2.7 - 3.9)	2.9 (2.7 - 3.8)	2.9 (2.7 - 3.9)	
Duration of treatment, days	427 (417.4)	343.4 (372.9)	404.7 (407.7)	<0.001
- Median (P25 - P75)	201 (84 - 890)	155 (83 - 467)	187 (84 - 738)	
Medication possession ratio				
Percentage	74.0%	69.2%	72.7%	<0.001
95% CI	72.6 - 75.4%	66.7 - 71.7%	71.5 - 73.9%	
Treatment adherence (%)				
12 months	38.6%	29.0%	36.0%	<0.001
95% CI	37.0 - 40.2%	26.6 - 31.4%	34.7 - 37.3%	
24 months	27.4%	18.6%	25.1%	<0.001
95% CI	26.0 - 28.8%	16.5 - 20.7%	23.9 - 26.3%	
36 months	23.0%	15.4%	21.0%	<0.001
95% CI	21.6 - 24.4%	13.5 - 17.3%	19.9 - 22.1%	
Discontinuation (%)	77.0%	84.6%	79.0%	<0.001
Poor tolerability*	11.8%	8.7%	10.9%	0.004
95%CI	10.8 - 12.8%	7.2 - 10.2%	10.0 - 11.8%	
Poor response**	48.2%	60.4%	51.7%	<0.001
95% CI	46.6 - 49.8%	57.8 - 63.0%	50.3 - 53.1%	
Change from weak to strong opioid	17.3%	NA	NA	NA
95% CI	16.1 - 18.5%			
Other changes***	12.5%	21.3%	15.0%	<0.001
95% CI	11.4 - 13.6%	19.1 - 23.5%	14.0 - 16.0%	
Lost-to-follow up	10.1%	9.6%	10.0%	0.601
95% CI	9.1 - 11.1%	8.8 - 11.2%	9.2 - 10.8%	
Any cause deaths	1.1%	3.1%	1.7%	<0.001

95% CI	0.8 - 1.4%	2.2 - 4.0%	1.3 - 2.1%

Values expressed as percentage or mean (standard deviation), CI: confidence interval, P: percentile. NA: Not applicable. *Discontinuation after 1st prescription dispensed in community pharmacy without refills during study follow-up; **Pain numeric rating scale ≥ 5 points in last available measurement; ***Other changes: includes patients with hospital admission for surgical procedures (joint replacement, arthroscopy, 2.6%), referrals to the pain clinic (1.3%) and changes in non-opioid medication (0.9%).

Table 3. Distribution of days of sick leave and annual cost due to lost productivity according to opioid type and study periods.

Study groups	Weak opioid	Strong Opioid	Total	p-value
Number of patients. %	N = 3732 (73.3%)	N = 1357 (26.7%)	N = 5089 (100%)	
12 months pre-opioid				
Patients with sick leave. %	33.4%	34.5%	33.7%	0.452
Ranges according to days of sick leave				
1 - 7 days	15.3%	13.7%	14.9%	
8 - 14 days	18.6%	11.5%	16.7%	
15 - 89 days	51.9%	56.8%	53.2%	
90 - 181 days	11.0%	13.9%	11.8%	
≥ 182 days (6 months)	3.1%	4.1%	3.4%	0.003
Days of sick leave in patients with sick leave	49.9 (48.6)	59.6 (52.4)	52.6 (49.8)	<0.001
Days of sick leave in all patients	16.6 (36.6)	20.6 (41.8)	17.7 (38.1)	0.001
Cost/year for patient with sick leave (€)	5960 (5804)	7122 (6258)	6277 (5952)	<0.001
Cost/year for patient (all. €)	1988 (4374)	2456 (4996)	2113 (4552)	0.001
12 months post-opioid initiation				
Patients with sick leave. %	38.2%	37.4%	37.9%	0.605
Ranges according to days of sick leave				
1 - 7 days	9.5%	4.7%	8.2%	
8 - 14 days	15.3%	10.7%	14.1%	
15 - 89 days	59.1%	63.1%	60.1%	
90 - 181 days	10.5%	14.2%	11.5%	0.160
≥ 182 days (6 months)	5.6%	7.3%	6.1%	0.001
Days of sick leave in patients with sick leave	54.6 (54.1)	64.2 (58.1)	57.1 (55.3)	0.004
Days of sick leave in all patients	20.9 (42.7)	24.0 (47.2)	21.7 (43.9)	0.027
Cost/year for patient with sick leave (€)	6541 (6458)	7666 (6939)	6837 (6604)	0.004
Cost/year for patient (all. €)	2496 (5100)	2864 (5633)	2594 (5249)	0.027

Variations in 12 months before and 12 months after opioid initiation				
Patients with sick leave (%. 95% CI)	4.8% (4.1-5.5) ‡	2.9% (2.0-3.8) ‡	4.3% (3.7-4.9) ‡	0.007
Days of sick leave in patients with sick leave	4.7 (3.1-6.3) ‡	4.6 (2.6-6.6) ‡	4.5 (2.6-6.4) ‡	0.654
Days of sick leave in all patients	4.3 (2.5-6.1) ‡	3.4 (0.2-5.8) *	4.0 (2.4-5.6) ‡	0.455
Cost/year for patient with sick leave (€)	581 (578-585) ‡	544 (539-548) *	559 (556-561) ‡	<0.001
Cost/year for patient (all. €)	508 (458-555) ‡	408 (326-489) *	481 (439-522) ‡	<0.001
36 months post-opioid initiation				
Patients with sick leave. %	77.6%	75.5%	77.0%	0.109
Range/ intervals				
1 - 7 days	4.9%	0.5%	3.8%	
8 - 14 days	11.6%	2.2%	9.2%	
15 - 89 days	63.7%	66.4%	64.4%	
90 - 181 days	3.1%	13.5%	5.8%	
≥ 182 days (6 months)	16.7%	17.4%	16.9%	<0.001
Days of sick leave in patients with sick leave	115.5 (179.1)	134.5 (188.8)	120.5 (181.8)	0.004
Days of sick leave in all patients	89.8 (165.2)	101.6 (173.9)	93.0 (167.6)	0.026
Cost/year for patient with sick leave (€)	13823 (21421)	16084 (22548)	14414 (21741)	0.004
Cost/year for patient (all. €)	10727 (19731)	12137 (20773)	11103 (20021)	0.026
Sick leaves during follow up				
0 (none)	22.4%	24.5%	23.0%	
1	35.9%	29.9%	34.3%	
2	24.2%	29.4%	25.6%	
3+	17.5%	16.1%	17.2%	<0.001

Values expressed as percentage or mean (95% confidence interval), mean (95%) cost expressed in €. $^{‡}p<0.001$; $^{†}p<0.01$; $^{*}p<0.05$. Non-significant when not indicated.

Table 4. Mean cost per patient (€) of sick leave adjusted by covariates during the follow up (36 months) in different scenarios and associated factors.

Scenario	Cost/patient-year* (95%CI)	Difference (95%CI)	p-value
Site of osteoarthritis			
Knee/hip	11,576 (10,609-12,544)	vs. Spine;874 (-1,029-2,777)	0.869
Spine	10,702 (9,480-11,923)	vs. other; 360 (-2,620-1,901)	0.781
Other	11,936 (10,359-13,513)	vs. other; 1,234 (-2,578-110)	0.517
Type of opioid			
Weak opioid	10,987 (10,218-11,756)		
Strong opioid	12,516 (10,985-14,048)	1,529 (188-3,255)	0.044
Pain reduction (initial vs. final)			
Relative reduction in baseline pain ≥ 30%	11,265 (10,532-11,998)		
Relative reduction in baseline pain < 30%	11,983 (10,081-13,885)	718 (-1,318-2,754)	0.491
Relative reduction in baseline pain ≥ 50%	11,141 (10,432-11,851)		
Relative reduction in baseline pain < 50%	14,016 (11,471-16,561)	2,875 (232-5,518)	0.033
Pain in last record ≥5 in NRS	11,282 (10,572-11,993)		
Pain in last record <5 in NRS	12,226 (9,670-14,783)	944 (-1092-2262)	0.459
Combinations of NSAIDs + opioids			
Without NSAID + weak opioid	10,724 (9,872-11,578)		
Without NSAID + strong opioid	12,258 (10,645-13,872)	1,534 (188-2,881)	0.042
With NSAID + weak opioid	10,729 (9,783-11,675)		
With NSAID + strong opioid	12,018 (10,498-13,538)	1,289 (57-2,635)	0.046
Multiple linear regression model	Standardized coefficients (β)	t	p
Age, years	0.043	2.960	0.003
Sex (female)	0.036	2.500	0.011
Charlson index (comorbidity)	0.035	2.440	0.015
Strong opioid	0.031	2.244	0.025

Values expressed as percentage or mean (95% CI: 95% confidence intervals), t: Student's t test.

* Analysis of covariance (ANCOVA; procedure: estimate of marginal means; Bonferroni adjustment), for adjustment of cost per patient of days of sick leave. Covariates: age, sex, time from diagnosis, Charlson index, treatment persistence and relative reduction in pain). NRS: Numeric rating scale of pain. NSAID: Nonsteroidal anti-inflammatory drug.

Figures

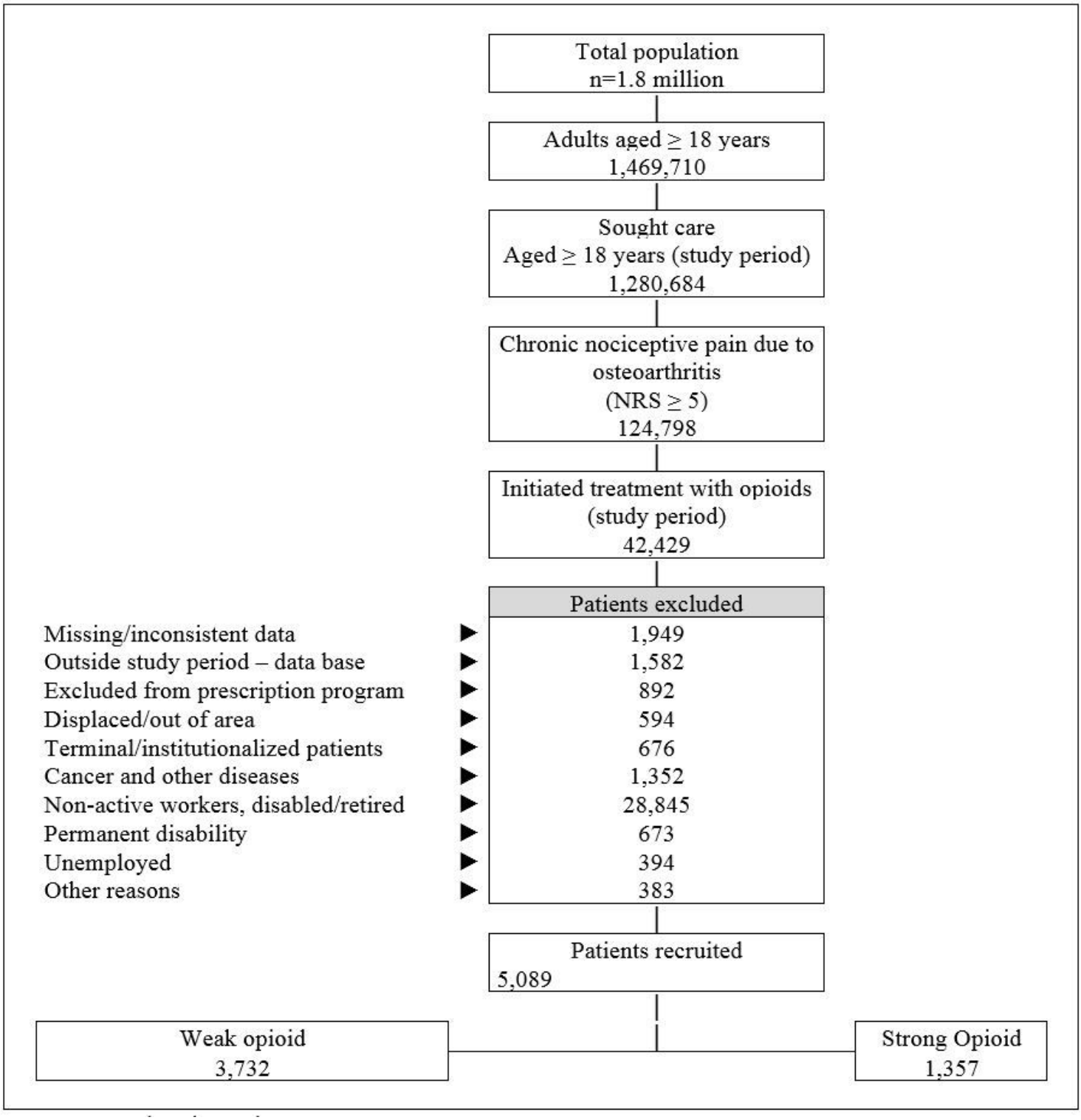

Figure 1

Study flow diagram. NRS: numeric rating scale

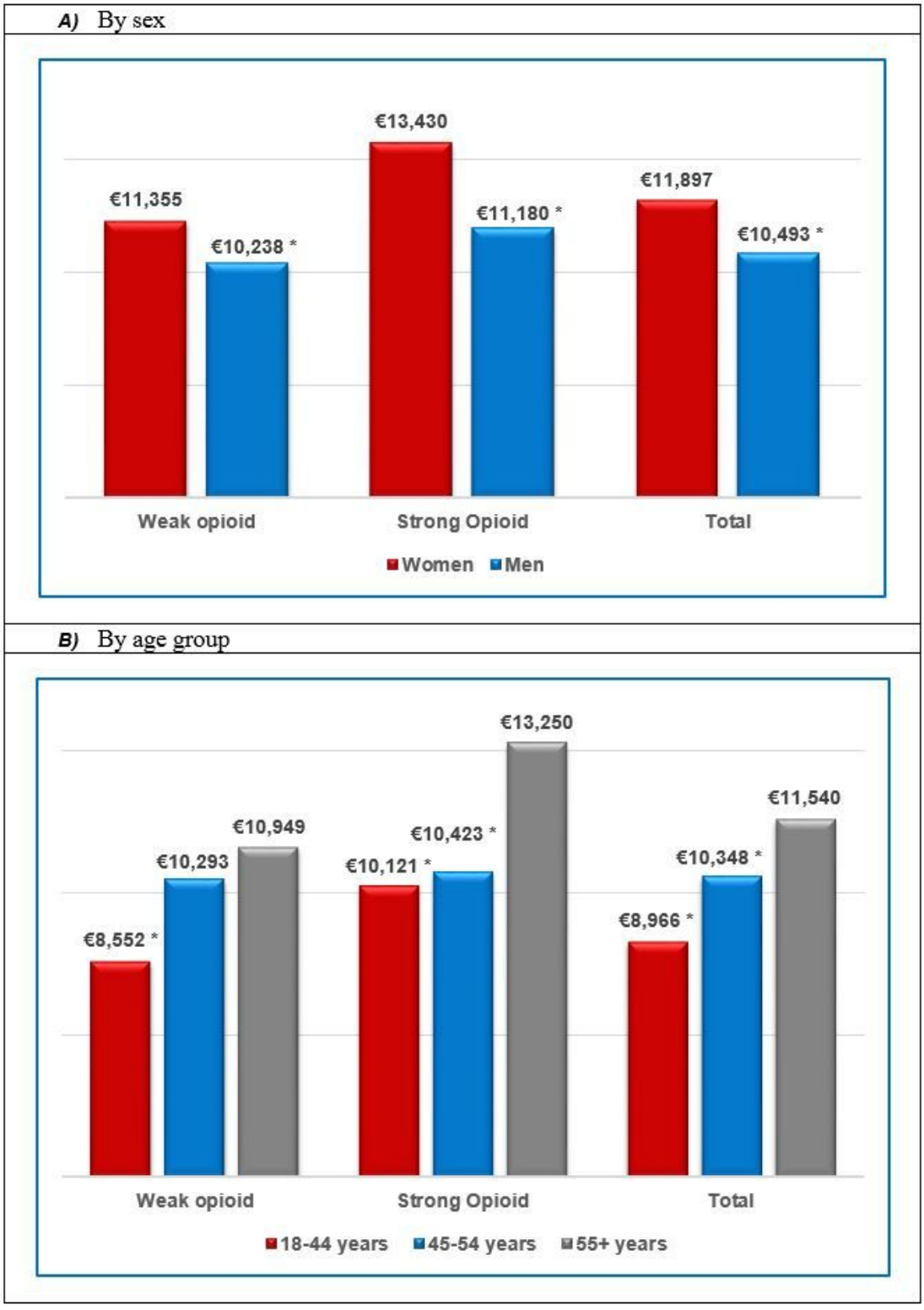

Figure 2

Mean cost per patient (€) of sick leaves adjusted by covariates during follow up (36 months) by sex and age group. Values expressed as means. * p <0.05 (reference cohort: females and 55+ years, respectively). Not significant when not indicated.

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