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## Original article

# Inadequate pain relief among patients with primary knee osteoarthritis



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## ABSTRACT

**Background:** Despite the widespread treatments for osteoarthritis (OA), data on treatment patterns, adequacy of pain relief, and quality of life are limited. The prospective multinational Survey of Osteoarthritis Real World Therapies (SORT) was designed to investigate these aspects.

**Objectives:** To analyze the characteristics and the patient reported outcomes of the Portuguese dataset of SORT at the start of observation.

**Methods:** Patients  $\geq 50$  years with primary knee OA who were receiving oral or topical analgesics were eligible. Patients were enrolled from seven healthcare centers in Portugal between January and December 2011. Pain and function were evaluated using the Brief Pain Inventory (BPI) and WOMAC. Quality of life was assessed using the 12-Item Short Form Health Survey (SF-12). Inadequate pain relief (IPR) was defined as a score  $>4/10$  on item 5 of the BPI.

**Results:** Overall, 197 patients were analyzed. The median age was 67.0 years and 78.2% were female. Mean duration of knee OA was 6.2 years. IPR was reported by 51.3% of patients. Female gender (adjusted odds ratio – OR 2.15 [95%CI 1.1, 4.5]), diabetes (OR 3.1 [95%CI 1.3, 7.7]) and depression (OR 2.24 [95%CI 1.2, 4.3]) were associated with higher risk of IPR. Patients with IPR reported worst outcomes in all dimensions of WOMAC ( $p < 0.001$ ) and in all eight domains and summary components of SF-12 ( $p < 0.001$ ).

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*Conclusions:* Our findings indicate that improvements are needed in the management of pain in knee OA in order to achieve better outcomes in terms of pain relief, function and quality of life.

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## Alívio inadequado da dor em pacientes com osteoartrite de joelho primária

### R E S U M O

#### Palavras-chave:

Osteoartrite de joelho  
Alívio inadequado da dor  
Qualidade de vida  
Incapacidade  
Desfechos relatados pelo paciente

*Antecedentes:* Apesar dos tratamentos muito difundidos para a osteoartrite (OA), dados sobre os padrões de tratamento, a adequação do alívio da dor e a qualidade de vida são limitados. O estudo multinacional prospectivo *Survey of Osteoarthritis Real World Therapies* (SORT) foi projetado para investigar esses aspectos.

*Objetivos:* Analisar as características e os desfechos relatados pelo paciente do conjunto de dados português do Sort no início da observação.

*Métodos:* Consideraram-se elegíveis os pacientes com 50 anos ou mais com OA de joelho primária que recebiam analgésicos orais ou tópicos. Os pacientes foram recrutados de sete centros de saúde de Portugal entre janeiro e dezembro de 2011. A dor e a função foram avaliadas pelo *Brief Pain Inventory* (BPI) e pelo WOMAC. A qualidade de vida foi avaliada com o 12-item *Short Form Health Survey* (SF-12). O alívio inadequado da dor (AID) foi definido como uma pontuação > 4/10 no item 5 do BPI.

*Resultados:* Foram analisados 197 pacientes. A idade média foi de 67 anos e 78,2% eram do sexo feminino. A duração média da OA de joelho foi de 6,2 anos. O AID foi relatado por 51,3% dos pacientes. O sexo feminino (*odds ratio* ajustado - OR 2,15 [IC 95% 1,1-4,5]), o diabetes (OR = 3,1 [IC 95% 1,3-7,7]) e a depressão (OR 2,24 [IC 95% 1,2-4,3]) estiveram associados a um maior risco de AID. Os pacientes com AID relataram piores desfechos em todas as dimensões do Womac ( $p < 0,001$ ) e em todos os oito domínios e nos dois componentes sumários do SF-12 ( $p < 0,001$ ).

*Conclusões:* Os resultados do presente estudo indicam que é necessário melhorar o manejo da dor na OA de joelho a fim de alcançar melhores desfechos em termos de alívio da dor, função e qualidade de vida.

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## Introduction

Osteoarthritis (OA) is a highly prevalent and debilitating disorder which seriously limits both health and well-being, particularly in the elderly population.<sup>1,2</sup> The economic burden of OA on subjects, their caregivers and society is considered quite high. In developed countries it may cost between 1.0% and 2.5% of gross domestic product.<sup>3</sup>

Approximately 13% of women and 10% of men aged 60 years and older have symptomatic knee OA. These proportions are likely to increase due to the aging of the population and the growing rate of obesity in the general population.<sup>4</sup> Other factors are associated with a higher risk for the development and progression of knee OA such as female gender, previous knee trauma, bone density, muscle weakness, joint laxity and physically demanding occupations or activities.<sup>2,5</sup>

The European League Against Rheumatism (EULAR) recommends that the clinical diagnosis of knee OA should be based on three symptoms (persistent knee pain, limited morning stiffness and reduced function) and three signs (crepitus, restricted movement and bone enlargement). The presence

of all these signs and symptoms increases the probability of radiographic knee OA to 99%.<sup>6</sup>

Pain is the most common symptom in knee OA and is the leading cause of disability due to this condition.<sup>2</sup> This symptom has also a diversity of psychological and social implications.

The clinical management of OA aims to relieve pain, maintain or improve joint function and prevent or delay disease progression and its consequences.<sup>7,8</sup> Effective pain management relies on a broad range combination of non-pharmacological and pharmacological modalities.<sup>9</sup> The pharmacological approaches and treatment modalities include paracetamol, NSAIDs, opioids, topical analgesics and intra-articular injection of corticosteroid.<sup>10,11</sup> However, variability in treatment effectiveness, as well as tolerability, often requires trials of different treatment modalities to achieve adequate pain control. Treatment should be individualized according to patient symptoms, preferences, and the therapeutic agent's safety profile.<sup>12</sup> Despite its serious consequences, most patients with knee OA can be managed in the community and the primary care setting.<sup>7,13</sup>

The Study of Osteoarthritis Real World Therapies (SORT) is a 12-month clinical prospective study conducted in six European countries (United Kingdom, France, Germany, Italy, Netherlands and Portugal)<sup>14</sup> and is designed primarily to evaluate the impact of inadequate pain relief (IPR) on patient reported outcomes (PRO) among subjects with symptomatic osteoarthritis of the knee(s) treated with oral or topic analgesics.

The present work reports the clinical characteristics, treatment patterns and PROs of the Portuguese dataset of the SORT study at the start of observation. The adequacy of pain relief from the use of analgesics is compared with the subset of patients with inadequate pain relief regarding demographic and clinical variables of interest, as well as several dimensions of other PRO such as joint stiffness, general health and quality of life.

## Methods

### Participants and variables of interest

In Portugal, the study was conducted at seven reference healthcare centers, reflecting a wide geographic distribution. The dataset included male or female patients that were enrolled between January and December of 2011. Patients were eligible if they were 50 years or older and had a clinical diagnosis of primary OA of the knee(s) according to the physician's clinical judgment. Patients had to be using oral or topical analgesics for a period no shorter than two weeks. Patients were excluded if they had other forms of arthritis, subtotal or total joint replacement in the affected knee, chronic severe pain due to causes other than arthritis or any other condition that would require long-term analgesia. Patients were also ineligible if they had previously received disease-modifying antirheumatic drugs or biologic therapies, or if they were participating in a clinical trial. Using these criteria, a total of 197 patients were included in this cross-sectional analysis.

Patients were enrolled in the study as they attended their scheduled consultation. During the consultation the information was obtained from patient's interview, self-administered questionnaires and the review of medical charts. The following variables were considered for this analysis: gender, age, professional status, self-reported height and weight (which allowed the calculation of body mass index - BMI), smoking status and OA diagnosis-related information (duration, number of affected knees and other affected joints). Comorbidities of interest included: disability (total or partial), previous hip replacement, gastro-intestinal conditions, diabetes, hypertension, hyperlipidemia, cardiovascular diseases, renal failure and depression. Use of analgesics for knee OA (by class) was also collected.

### Patient reported outcomes

The following instruments were used to collect PROs:

- The *Brief Pain Inventory* (BPI) is a validated tool that measures the intensity of pain (four items), scores ranging from 0 (no pain) through 10 (pain as bad as you can imagine) and

the interference of pain on different facets of the patient's life (seven items), ranging from 0 (do not interfere) and 10 (completely interferes).<sup>15</sup> This instrument also queries the patient about how much relief the treatments or medications have provided, the quality of their pain by choosing words among a list of verbal descriptors derived from the *McGill Pain Questionnaire*, and the patient's perception of the cause of pain.<sup>16</sup> A patient with IPR was defined as having a score >4 in the item 5 of BPI - "What is your pain on average?" (0 = no pain and 10 = pain as bad as you can imagine), indicating moderate to severe pain. The robustness of the cut-off of 4 on BPI was already examined elsewhere.<sup>14</sup>

- The *Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index* is an instrument that measures pain (5 items), stiffness (2 items) and performance of daily activities (17 items) in patients with hip and/or knee osteoarthritis. The version used in this study (WOMAC, VA3.0) consisted of twenty-four 100 mm visual analog scales. Responses range from no pain/stiffness/difficulty (0) through extreme pain/stiffness/difficulty (100).<sup>16-18</sup>
- The health status instrument *12-Item Short Form Health Survey (SF-12) (V2.0)*, measures the quality of life regarding eight health domains of functional health and well-being scores as well as physical (PCS) and mental (MCS) component summary measures.<sup>19</sup> The questions report to the previous week and the scoring ranges from 0 through 100. Higher values indicate better quality of life/general health.<sup>18</sup>

Furthermore, each patient rated his/her level of satisfaction with the prescribed analgesics taking into account two perspectives: (1) relieve of pain and symptoms caused by knee arthritis; (2) side-effects (i.e. stomach upset). A five-point Likert scale was used in both evaluations with five possible responses: very dissatisfied, dissatisfied, somewhat dissatisfied, satisfied and very satisfied. Each patient also rated his/her global response to analgesics using a five-point Likert scale (no response, poor response, fair response, good response, excellent response). These evaluations reported to the last seven days.

Finally, the physician's impression of patient's global response to the prescribed analgesics was assessed using a five-point Likert scale with the same descriptors as the scale administered to the patient.

The study was approved by each site's ethics committee and the participants were informed about the nature of the study before signing an informed consent.

### Statistical analysis

This analysis included all patients that were enrolled in Portugal according to eligibility criteria of the SORT study. Summary statistics were calculated for continuous and categorical variables. Chi-square test and Fisher exact test were used to compare IPR versus non-IPR subgroups regarding categorical variables. Mann-Whitney-Wilcoxon test was used to compare both groups regarding numerical variables including the scores of BPI, WOMAC and SF-12. A multivariable logistic regression model was employed to identify which patient characteristics were most associated with IPR. The variables were selected according to its statistical significance

**Table 1 – Socio-demographic and clinical characteristics of the sample, general and broken down by knee pain relief status.**

	Total n = 197	Adequate pain relief (non-IPR) n = 96	Inadequate pain relief (IPR) <sup>a</sup> n = 101	p-Value <sup>b</sup>
Age (years)	67.0 (8.6)	66.9 (8.4)	67.0 (9.0)	0.848
Female	154 (78.2%)	69 (71.9%)	85 (84.2%)	<b>0.040</b>
BMI (kg/m <sup>2</sup> )	29.4 (5.2)	29.1 (5.0)	29.7 (5.4)	0.502
Presently with paid job	35 (17.8%)	19 (19.8%)	16 (15.8%)	0.576
Current smoker	6 (3.1%)	3 (3.1%)	3 (3.0%)	>0.999
Duration of knee OA (years)	6.2 (6.3)	5.9 (6.2)	6.5 (6.4)	0.277
Clinical diagnosis of OA				
Both knees	142 (72.1%)	65 (67.7%)	77 (76.2%)	0.206
Hip	59 (30.0%)	31 (32.3%)	28 (27.7%)	0.535
Spine	99 (50.3%)	48 (50.0%)	51 (50.5%)	>0.999
Comorbidities of interest				
Cardiovascular disease <sup>c</sup>	35 (17.8%)	17 (17.7%)	18 (17.8%)	>0.999
Hypertension	126 (64.0%)	61 (63.5%)	65 (64.4%)	>0.999
Hyperlipidemia	115 (58.4%)	61 (63.5%)	54 (53.5%)	0.193
Disability (total or partial)	82 (41.6%)	32 (33.3%)	50 (49.5%)	<b>0.030</b>
Depression	74 (37.6%)	28 (29.2%)	46 (45.5%)	<b>0.019</b>
Diabetes	32 (16.2%)	10 (10.4%)	22 (21.8%)	<b>0.035</b>
Gastric condition <sup>d</sup>	19 (9.6%)	11 (11.5%)	8 (7.9%)	0.473
Renal failure	8 (4.1%)	2 (2.1%)	6 (5.9%)	0.280
Hip replacement (total or partial)	4 (2.0%)	1 (1.0%)	3 (3.0%)	0.622

Data are number (%) or mean (standard deviation).

OA, osteoarthritis; BMI, body mass index.

<sup>a</sup> IPR was defined as a score >4 (indicating moderate or greater pain) on the following item of Brief Pain Inventory (BPI) scale: "What is your pain on average?" (0 = no pain and 10 = pain as bad as you can imagine).

<sup>b</sup> Student's T-test was used for numerical variables and Chi-square test was used for categorical variables. Bold denotes statistical significance.

<sup>c</sup> Included congestive heart failure or established ischemic heart disease, peripheral arterial disease or cerebrovascular disease.

<sup>d</sup> Included inflammatory bowel disease, active peptic ulceration or gastrointestinal bleeding, perforation associated with previous use of non-steroidal anti-inflammatory drugs, recurrent peptic ulcer or gastrointestinal hemorrhage.

in the bivariable analysis and according to its interest for the research (including those theoretically associated with IPR). The variables were: age, female sex, BMI, duration of knee OA, clinical diagnosis of both knees, co-morbidities of interest (cardiovascular disease, diabetes, depression, hyperlipidemia, hypertension) and number of different classes of medication.

Statistical tests were 2-tailed using a significance level of 5%. All analyses were conducted using SAS<sup>®</sup> 9.3 (SAS Institute, Cary, NC, USA).

## Results

### General characteristics of the sample

Overall, the mean age was 67.0 (SD 8.6) years and most patients were female (78.2%). Only 17.8% of patients had a paid job at the time of assessment – Table 1. The average duration of knee OA was approximately six years. Both knees were affected in 72.1% of the patients and 50.3% also had their spine affected. Hypertension (64.0%) and hyperlipidemia (58.4%) were the most common comorbidities.

### Adequacy of pain relief

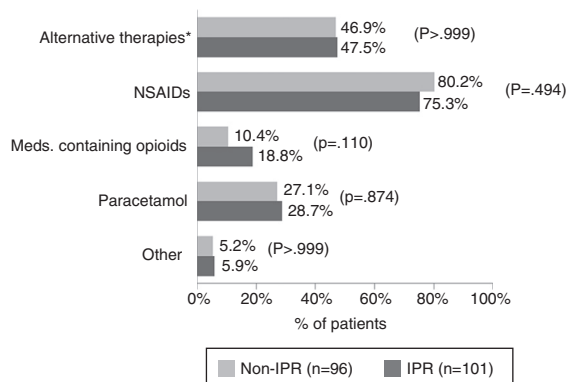
Overall, 101/197 (51.3% [95%CI 44.1%, 58.4%]) of the patients reported IPR – Table 1. Women were more likely to report

IPR than non-IPR ( $p < 0.05$ ). Disability, depression and diabetes were more frequent among patients with IPR than in patients with non-IPR ( $p < 0.05$ ). No statistically significant differences were found between both subgroups regarding the mean age (~67 years), mean duration of knee OA and other socio-demographic and clinical characteristics.

### Use of analgesics

The mean number of different classes of medication used by IPR and non-IPR patients was similar (1.76 [SD 0.78] versus 1.70 [SD 0.63];  $p = 0.866$ ). The most commonly used analgesics were the non-steroidal anti-inflammatory drugs (NSAIDs) followed by alternative therapies (including glucosamine, chondroitin and hyaluronate) – Fig. 1. There were no statistically significant differences in the use of these medications between IPR and non-IPR groups. Although non-statistically significant, higher prescription of opioid-containing medications was observed in patients with IPR (18.8% versus 10.4%;  $p = 0.110$ ).

The multivariable analysis showed that female gender (adjusted odds ratio – OR 2.15 [95%CI 1.1, 4.5]), diabetes (adjusted OR 3.1 [95%CI 1.3, 7.7]) and depression (adjusted OR 2.24 [95%CI 1.2, 4.3]) were associated with higher risk of IPR (Table 2).



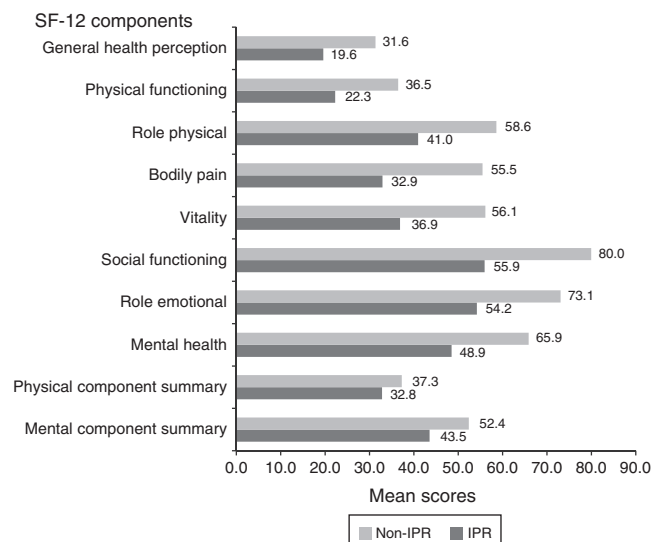
**Fig. 1 – Prescribed analgesics, broken down by knee pain relief status. \*Alternative therapies include glucosamine, chondroitin and hyaluronate. NSAIDs, non-steroidal anti-inflammatory agents; IPR, inadequate pain relief. Fisher exact test was used for comparisons.**

### Other health-related outcomes

Pain severity and interference (BPI) was higher among patients with IPR ( $p < 0.001$ ) – Table 3. Likewise, patients with IPR reported worst outcomes in the three dimensions of WOMAC (pain, stiffness and physical function) than patients with Non-IPR ( $p < 0.001$ ).

About 64% of patients with non-IPR were satisfied or very satisfied with the effects of the prescribed analgesics in relieving the pain and symptoms caused by knee OA. On the other hand, 63.4% of patients with IPR were dissatisfied or very dissatisfied with the effects of analgesics. A higher proportion of patients with IPR reported a fair response or worse to the prescribed analgesics compared to patients with non-IPR (79.2% versus 55.2%, respectively;  $p < 0.05$ ). The physicians reported patient's response to analgesics as fair or worse in 84.2% of patients with IPR as opposed to 55.2% of the patients in the non-IPR group ( $p < 0.05$ ).

A higher proportion of patients in the IPR subgroup reported fair or poor general health in the overall score of



**Fig. 2 – Mean score for each domain of SF-12, broken down by knee pain relief status. IPR: inadequate pain relief. Non-IPR (n = 101) and IPR (n = 96), unless otherwise specified. The differences were statistically significant for all comparisons (Mann-Whitney-Wilcoxon test;  $p < 0.001$ ).**

SF-12 compared to patients with non-IPR (87.1% versus 72.9%, respectively,  $p < 0.001$ ).

The distributions of responses to each of the SF-12 health domains are presented in Fig. 2. Patients with IPR had worst outcomes in all eight health domains and summary components of SF-12 compared to patients with non-IPR ( $p < 0.001$ ).

## Discussion

We found that over half of the Portuguese patients had moderate or severe pain in spite of the use of analgesics. This finding suggests that the strategies adopted at healthcare centers for managing pain in knee OA are being insufficient for the majority of patients.

Currently, the clinical management of OA is symptomatic and aims to relieve pain and stiffness, and maintain or improve joint function. In addition, the treatment of OA aims to reduce physical disability and improve health related quality of life.<sup>9</sup> For patients with knee OA, the importance of pain relief and functional improvement was evident in the results of a recently reported discrete choice experiment that assessed patient preferences with regard to NSAID-related benefits.<sup>20</sup> However, the treatment of symptomatic knee OA poses important challenges to the healthcare professionals. In order to be effective the management of OA relies on the appropriate use of a number of non-pharmacological, pharmacological and surgical therapies. Despite the fact that most commonly used pharmacologic interventions for knee OA provide clinically significant improvements in pain,<sup>21</sup> the OA literature evidences that, for a substantial proportion of patients, analgesic monotherapy does not provide adequate or complete relief of joint symptoms. Many OA patients continue to experience significant pain while taking paracetamol or NSAID (non-specific or COX-2 specific).<sup>22-24</sup> Several factors

**Table 2 – Multivariable logistic regression analysis assessing the adjusted odds of IPR.**

Independent variables	Adjusted OR	95%CI
Age	1.006	0.967 1.047
Female	2.149	1.063 4.480
BMI	1.026	0.965 1.096
Duration of knee OA (years)	1.007	0.959 1.058
Both knees	1.342	0.684 2.658
CVD	0.893	0.392 2.022
Diabetes	3.092	1.328 7.655
Depression	2.236	1.194 4.268
Hyperlipidemia	0.457	0.240 0.849
Hypertension	0.924	0.473 1.801
Number of different classes of medication	1.081	0.710 1.651

OR, odds ratio; CVD, cardiovascular disease.  
Model  $p$ -value ( $p < 0.001$ ).

**Table 3 – Scores of Brief Pain Inventory, WOMAC, patient and physician global assessment of response to therapy, broken down by knee pain relief status.**

	Adequate pain relief (non-IPR) n = 96	Inadequate pain relief (IPR) n = 101	p-Value <sup>a</sup>
BPI – pain severity	1.83 (1.58)	5.96 (1.36)	<0.001
BPI – pain interference	2.18 (2.35)	5.72 (1.98)	<0.001
WOMAC – pain	36.31 (22.28)	58.03 (21.29)	<0.001
WOMAC – stiffness	39.35 (28.90)	61.34 (25.48)	<0.001
WOMAC – physical function	40.63 (22.15)	61.83 (18.44)	<0.001
Patient satisfaction with prescribed analgesics			
Satisfied/very satisfied	61 (63.5%)	38 (37.6%)	0.004
Dissatisfied/very dissatisfied/somewhat satisfied	35 (36.5%)	63 (63.4%)	
Patient satisfaction with tolerability to analgesics			
Satisfied	67 (69.8%)	61 (60.4%)	0.181
Dissatisfied	29 (30.2%)	40 (39.6%)	
Patient assessment of response to analgesics			
Excellent/good	43 (44.8%)	21 (20.8%)	0.004
None/poor/fair	53 (55.2%)	80 (79.2%)	
Physician assessment of response to analgesics			
Excellent/good	35 (36.5%)	16 (15.8%)	0.001
None/poor/fair	61 (63.5%)	85 (84.2%)	

Data are number (%) or mean (standard deviation).

BPI, Brief Pain Inventory – higher scores on the BPI indicate worse pain or greater interference of pain with daily activities; WOMAC, Western Ontario McMaster University Osteoarthritis Index Questionnaire – higher scores on the WOMAC indicate worse pain, stiffness and greater functional limitations.

<sup>a</sup> Fisher exact test was used for categorical variables and Mann–Whitney–Wilcoxon test was used for numerical variables. All comparisons were statistically significant.

underlying the undertreatment of pain have been suggested. These can include lack of professional medical attention, failure to introduce non-pharmacological therapies such as weight loss and exercise into the management plan, and overreliance on monotherapy.<sup>25</sup>

In our study, the vast majority of patients were using NSAIDs, regardless of the reported knee pain relief status. This proportion is in line with the multinational SORT study prospective longitudinal cohort study.<sup>14</sup> This finding also corroborates other studies where high rates of NSAID use have been reported. A telephone survey of 1149 patients with OA in the UK in 2003 showed that 50% were taking NSAIDs, while only 15% were taking paracetamol.<sup>26</sup> Although the use of NSAID was higher among patients with non-IPR than patients with moderate to severe pain, the differences observed in our study were not statistically significant.

The American Academy of Orthopedic Surgeons (AAOS) strongly recommends the use of NSAIDs (oral or topic) or Tramadol in patients with symptomatic OA of the knee. The endorsement of NSAIDs was based on high quality evidence from several studies comparing either the selective, non-selective or topical analgesics to placebo. Furthermore, the recommendation on acetaminophen was downgraded from “moderate” to “inconclusive”, comparing to previous guideline published by AAOS in 2008.<sup>27</sup>

Conversely, oral NSAIDs (both non-selective and COX-2 selective) are conditionally recommended by OARSI guidelines 2013 for the management of knee OA, particularly in individuals without co-morbidities or individuals with multiple-joint OA with moderate co-morbidity risk.<sup>11</sup> Regarding the use of acetaminophen, the OARSI guidelines differ from the AAOS,

but coincides with the ACR’s 2012 guideline, by recommending its use for patients without relevant co-morbidities.<sup>10,11</sup>

A considerable proportion of participants (44%) were using alternative therapies, which included glucosamine, chondroitin and hyaluronate. The evidence is controversial regarding the benefits of glucosamine and chondroitin in knee and hip OA. *Although some studies have shown positive effects of these agents other studies showed no benefits.*<sup>9,28</sup> The AAOS are against the use of glucosamine, chondroitin and the ACR are against the use of chondroitin and conditionally against glucosamine.<sup>10,27</sup> The OARSI are more specific by evaluating these treatments separately for symptomatic relief and disease modification. Recommendation is “uncertain” regarding the symptomatic efficacy of both treatments but considered “not appropriate” their use as disease-modifying agents.<sup>11</sup> Regarding hyaluronic acid, AAOS recommend against its use in knee OA, citing a lack of efficacy, whilst OARSI provided an “uncertain” recommendation.<sup>11,27</sup>

In our study, the use of opioids was higher among patients who reported IPR, although this finding was not statistically significant. Weak opioids have increasingly been used for the treatment of refractory pain in patients with hip or knee OA. Several studies have provided evidence regarding the short-term efficacy and safety of opioids in chronic pain in OA.<sup>9</sup> A meta-analysis of a large sample of OA patients showed a moderate effect size in the reduction of pain intensity. However, a high heterogeneity between studies was observed. The benefits associated with the use of opioids are limited by the high incidence of side effects such as nausea, constipation and dizziness. Based on the body of evidence available and experts’ experience, the current OARSI guidelines provide an

“uncertain” recommendation for the use of opioids in knee OA.<sup>11</sup>

We found that the inadequacy of pain relief was more frequent in women. In addition, the regression analysis showed that women are associated with an increased risk of experiencing inadequate pain relief with analgesics. Women are more severely affected by knee OA, reporting more pain and disability than men. The etiology of knee OA in women is multifactorial and include: anatomic differences compared with men, previous trauma, genetic and hormonal issues. Women have increased incidence of anterior cruciate ligament injuries and these injuries lead to future osteoarthritis regardless of gender. In addition, postmenopausal women, due to the decrease in estrogen have an increased risk of developing OA.<sup>29</sup>

The regression analysis also showed that diabetes and depression were the comorbidities most associated with IPR, a finding that corroborates the results of the main SORT study.<sup>14</sup>

Of note, hyperlipidemia is associated with lower risk of IPR in the regression model, a finding that is consistent with the result of the bivariable analysis. We find no clear explanation for this result, other than the existence of a confounding factor or due to chance. Still, further research should examine more closely the links between these two variables.

Our analysis showed that patients who reported IPR had more severe pain and higher interference of pain with daily activities. Moreover, besides pain, these patients had worse outcomes in WOMAC's dimensions of stiffness and physical function than patients with non-IPR. Disability is a major consequence of lower limb OA.<sup>30</sup> Jordan et al. showed that severity of knee pain correlated with self-reported disability in the community.<sup>31</sup> Other authors also reported this correlation in patients attending primary care with knee OA<sup>32</sup> and in the rheumatology setting.<sup>33</sup> It is unclear the mechanism by which pain contributes to disability. Some authors suggest that pain may lead to absence of physical activity, resulting in a cycle of pain, inactivity and muscle wasting. Psychological factors such as anxiety may intensify this negative cycle.<sup>34</sup> Interestingly, our results show that depression and disability were more frequent in patients with IPR.

The participants who reported IPR had significantly worse scores on all physical and mental domains of SF-12 compared to non-IPR patients. Quality of life is a complex construct that includes several different dimensions including physical, emotional and social functioning. The body of evidence substantiates lower quality of life (QoL) scores in knee OA patients compared to age-matched norms.<sup>35</sup> Desmeules et al. observed that 197 participants with knee OA newly scheduled for total knee replacement, scored significantly lower in all eight domains and on mental and physical component summary scales of the SF-36 than the mean.<sup>36</sup> A study with Korean elders also showed that knee pain was correlated with substantial reduction in QoL and physical function.<sup>37</sup> Similar findings were reported by other authors.<sup>38,39</sup>

Our results suggest that patients with IPR were less satisfied with the effects of prescribed analgesics than patients with non-IPR. The patient perceived satisfaction with treatment is an outcome commonly used to assess treatment success. This outcome can be an adequate indicator of the quality of care given on distinct aspects of the treatment, such

as its effectiveness and tolerability. This is particularly important in patients with chronic diseases such as OA, in which treatments are frequently changed due to lack of effectiveness or adverse effects.<sup>8</sup>

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## Strengths and limitations

The strengths of this study are that it analyses real-world data, providing a realistic and valuable picture of the Portuguese population with knee OA and treatment patterns under the conditions of normal clinical practice.

Furthermore, we used reliable and validated scales to assess knee OA symptoms, particularly pain. The BPI is widely used to measure the level of pain in several chronic conditions and is recommended by the consensus panel – Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT).<sup>40</sup> This tool is validated for the Portuguese population and recent studies have shown strong support for its reliability and validity.<sup>41,42</sup> The WOMAC was developed to measure disability in patients with lower limb OA<sup>17</sup> and has been extensively used in several clinical trials that assessed pain in knee OA.

Our study has a number of limitations. We used a relatively small sample and no probability sampling methods were used. Moreover, we did not use any geographic stratification of sample. Therefore, one should be cautious when generalizing the findings to the general population with knee OA. Nonetheless, when contrasting the characteristics of the participants in our study with published literature we observed some overlapping in the distribution of gender, age and comorbid conditions.

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## Conclusions

The present work constitutes a preliminary analysis of the Portuguese sample included in prospective multinational SORT study. Despite the use of analgesics, over half of patients reported moderate to severe knee pain. These patients also reported worse outcomes regarding other symptoms of knee OA, general health and quality of life than patients with no or mild knee pain. Our findings suggest there is room for improvement in the management of knee pain due to OA in Portugal. Further investigation on the SORT study involving a longitudinal assessment of the sample will provide a clearer picture of the course of clinical care and outcomes in knee OA.

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## Conflict of interest

Pedro Laires and Stephanie D. Taylor are Merck employees.

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