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Prescription patterns and predictors of unmet pain relief in patients with difficult-to-treat osteoarthritis in the Nordics: analyses from the BISCUITS study

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Abstract

Objectives: Osteoarthritis (OA) is one of the leading causes of disability worldwide. Pain is the most important symptom in OA, driving medical care, disability, reduced functionality, and decreased quality of life. The objective of this study was to describe prescription patterns of difficult-to-treat OA and explore possible predictors of unmet pain relief in Nordic patients.

Methods: This observational cohort study included patients with a confirmed diagnosis of OA (index date) in specialty care in Sweden, Norway, Finland and Denmark between 1 January 2011 and 31 December 2012 who were followed for up to 5 years. Four subgroups were pre-defined to characterize difficult-to-treat OA: (1) ≥2 chronic comorbidities in the 3-year pre-index period; (2) top 10% of healthcare resource users, 1-year post-index; (3) ≥3 types of prescription pain medications during pre-index period to first year post-index, with ≥30 days between types; (4) having a contraindication to a nonsteroidal anti-inflammatory drug (NSAID). Patient characteristics, prescription patterns and predictors of unmet pain relief (defined as persistent opioid use, using several types of opioids or long-term NSAID use) were analyzed.

Results: We identified 288,174 OA patients and the average age was 63.5 years at time of diagnosis and 58% of them were female. After 5 years, 35–50% of the patients defined as 'difficult-to-treat' had ≥1 prescription of opioids, compared to 20–25% of all OA patients (p-value <0.05). Comorbidities and disability pension were strong predictors of unmet pain relief (p-value <0.001).

Conclusions: This study shows a substantial use of pain medications (NSAID and opioids) in difficult-to-treat OA patients. These findings suggest that pain may be inadequately managed in a considerable number of patients with OA, particularly those with contraindications to an NSAID. A high comorbid and socioeconomic burden are relevant risk factors among patients who continue to use opioids for a long period of time.

Keywords: analgesics; chronic pain; cohort study; nonsteroidal; observational study; opioid.

Previous presentation of study data at scientific meeting: Abstract at ISPOR 2020, Virtual, 20-12-2020, https://doi.org/10.1016/j.jval.2020.08.1159.

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Introduction

Osteoarthritis (OA) is a heterogeneous and chronic joint disease characterized by pain, disability, reduced functionality and decreased quality of life [1]. Worldwide, it is estimated that one in 10 individuals over the age of 60

have health issues due to OA and it is described as the fastest growing cause of disability [2–4]. Current treatment guidelines recommend arthritis education and non-pharmacological management to all patients with OA [5–9]. Pharmacological treatment with paracetamol or a nonsteroidal anti-inflammatory drug (NSAID) may be required for some patients to relieve pain but is not generally recommended over longer periods of time [9]. Opioids are debated and their use has either been explicitly discouraged due to the risk of dependency and the lack of evidence on their effectiveness for OA pain [5] or suggested to be used only in certain situations with great caution [8, 9]. Joint replacement surgery is considered an end-stage treatment option in the most severe cases where other treatments have proved insufficient [5], although up to 20% of patients may experience continued chronic pain after an otherwise successful knee joint replacement [10].

Inadequate pain relief is common in OA, affecting over 50% of patients with knee OA [11, 12]. For elderly patients, where pain management is further complicated due to the increased number of comorbidities, 20% experience inadequate pain relief [13]. It is a common reason for returning to the general practitioner after initiating treatment [14] and contributes significantly to reduced quality of life [11]. It has been reported that 45 and 16% of patients visited an orthopaedist or rheumatologist, respectively, within 2 years of their OA diagnosis. The frequent revisits may indicate that these patients received insufficient pain relief with first-line therapies, resulting in additional pain treatment provided from a specialist [15, 16]. The characteristics of this specific group of OA patients referred to specialist clinics and their medications have not previously been investigated in detail and their features related to possible inadequate pain management paths have not been investigated in large studies. Previous research on real-world treatment patterns in speciality care exists [17–20], but is limited in their study of difficult-to-treat patients and investigating predictors for inadequate management, i.e., unmet pain relief.

The Burden of Disease and Management of Osteoarthritis and Chronic Low Back Pain: Healthcare Utilization and Sick Leave in Sweden, Norway, Finland and Denmark (BISCUITS) was initiated as an observational cohort study linking longitudinal healthcare and socioeconomic registers in the Nordics and provides an opportunity to study different patient subgroups, including difficult-to-treat patients experiencing a problematic patient journey, in a real-world setting based on comprehensive nation-wide register data. The aim of the present study was to: (i) describe patients entering specialty care for their OA, (ii) describe their pain medication use, including predefined difficult-to-treat-subgroups, and (iii) explore predictors of outcomes for an increased use and/or problematic use of pain medication.

Methods

Study design and population

A multinational observational cohort study was conducted using data on healthcare visits, medication use, demographics, and socioeconomics. Data were collected as part of 'BISCUITS' and all data sources and the linkage process in the BISCUITS study are described elsewhere [submitted/if accepted: reference to "sjpain-2021-0212"].

All adult patients (≥18 years old) with a primary diagnosis of OA (ICD-10 codes: M15–M19) in specialty care between 1 January 2011 and 31 December 2012 were included in the study population. Patients with a diagnosis of OA or cancer (ICD-10 codes: C00–C43 or C45–C97) within the 3 years prior to inclusion were excluded to create a patient population representative of an incident and newly diagnosed group seeking specialty care for the first (recorded) time for OA without malignant pain. The index date was set to the inclusion date for patients fulfilling the criteria and information during the 3 years pre-inclusion was also retrieved.

Included patients were followed for up to 5 years post-index or until the following censoring events: death, a primary cancer diagnosis, or a joint replacement; whichever occurred first. Patients with cancer were censored as we aimed to study pain medication use due to non-malignant pain. Patients with a joint replacement were also censored to not capture post-operative pain requiring high use of pain medication. Patients with an orthopedic assessment or a less invasive surgery (e.g., arthroscopy) were not censored.

Subgroups

Four subgroups were pre-defined on the assumption that patients included in these subgroups were expected to be difficult-to-treat, have a potential high unmet need of pain relief and/or have a problematic treatment journey. These groups were 'Multiple comorbidities', 'Frequent healthcare visits', 'Multiple pain medications', and 'Contraindication to an NSAID'. See Appendix S1, Supplementary Table S1 (online supplement) for a list and detailed description of all subgroups.

Study outcomes and variables

Patient characteristics on demographics, comorbidities and medication use were gathered at or before index. Prescription patterns were studied by describing annual medication use after the index date. Unmet pain relief (defined as using several types of opioids, persistent opioid use or long-term NSAID use) was used as the outcome in regression analyses. All patient characteristics, prescription patterns, unmet pain relief and predictors in the regression analyses are described further in Appendix S1.

Statistical analysis

Continuous variables are presented with mean and standard deviation, and categorical variables with frequency and percentage. A two-tailed t-test was used to test for statistically significant differences in continuous variables and a chi-square test for categorical variables. The statistical significance level was set at 95% in statistical tests and in estimation of confidence intervals. Statistical tests were not performed to test differences between countries. Predictors of unmet pain relief were tested using survival analysis graphs (Kaplan-Meier [21]) and Cox proportional-hazards regression [22] with unmet pain relief, as defined earlier, as the outcome. Patients with an outcome before the index date were excluded from this analysis. All data management and statistical analyses were performed using RStudio v1.3 (RStudio Team, PBC, Boston, US) and Stata v16 (StataCorp, College Station, US).

Results

Patient characteristics

The total number of patients was 288,174 (62,300, 70,857, 54,544, and 100,473 in Denmark, Finland, Norway and Sweden, respectively). For all patients, ranges per country were relatively consistent for most of the patient characteristics (Table 1). The combined mean age was 63.5 years at the index date and 58% were female. Most patients did not have a diagnosis recorded in the Elixhauser comorbidity index based on all visits made in specialty care, but 29.5% had at least one comorbidity. A diagnosis of depression or anxiety was relatively rare (2.1%). In total, 45.3% were opioid users, of which 7.1% were persistent users and over 20% were long-term NSAID users.

Of the four subgroups of interest, the largest subgroup was 'Multiple pain prescriptions' which represented 33.1% of patients (Table 2). In the subgroups 'Multiple comorbidities' and 'Frequent healthcare visits', 13.0 and 12.3% of patients were included, respectively. The smallest subgroup was 'Contraindication to a NSAID', including 2.8% of all patients. The overlap of patients between the subgroups are presented in Appendix S2, Supplementary Figures S1–S3.

Patients in the subgroups 'Multiple comorbidities', 'Frequent healthcare visits', and 'Contraindications to NSAIDs' had substantially more comorbidities (by the Elixhauser index) (p-value <0.001), depression, and anxiety diagnoses (p-value <0.001), and the former two subgroups were more likely to have a contraindication to an NSAID than the overall group comprising all patients (p-value <0.001). Patients in these groups were also older than the overall group (p-value <0.001). Opioid use (p-value <0.001), except for the subgroups 'Multiple comorbidities' in Finland and 'Contraindication to an NSAID' in Finland, Norway and Sweden and persistent opioid use (p-value <0.001) were higher in these difficult-to-treat subgroups than the overall group with the highest ranges per country among those with multiple pain prescriptions for opioid use (63.8%) and persistent opioid use (15.0%). Among the subgroup of patients contraindicated for NSAID use, 13.4% were long-term NSAID users (at least two prescriptions within 3 months) compared to 23.6% in the overall group (p-value <0.001).

Prescription patterns

The percentage of patients with an NSAID (Figure 1A) or opioid (Figure 2A) prescription was highest in the first year following inclusion for all countries and subgroups, and decreased in subsequent years.

Table 1: Patient characteristics by country.

	Denmark	Finland	Norway	Sweden
Number of patients	62,300	70,857	54,544	100,473
Males, n, %	26,547 (42.61)	28,896 (40.78)	21,690 (39.77)	44,007 (43.8)
Age, mean, SD	63.3 (13.24)	63.4 (13.3)	62.8 (13.38)	64.2 (12.69)
Elixhauser comorbidity index, mean, SD	0.459 (0.95)	0.506 (1.02)	0.584 (1.09)	0.552 (1.06)
Number of Elixhauser categories, n, %				
No conditions	45,498 (73.03)	50,848 (71.76)	36,671 (67.23)	70,060 (69.73)
One condition	9,876 (15.85)	11,085 (15.64)	10,295 (18.87)	16,453 (16.38)
Two conditions	4,083 (6.55)	4,910 (6.93)	4,091 (7.5)	7,558 (7.52)
Three or more conditions	2,843 (4.56)	4,014 (5.66)	3,487 (6.39)	6,402 (6.37)
Patients with a depression or anxiety diagnosis, n, %	745 (1.2)	1,554 (2.19)	1,263 (2.32)	2,550 (2.54)
Non-persistent opioid users, n, %	19,662 (31.56)	26,303 (37.12)	22,826 (41.85)	41,291 (41.1)
Persistent opioid users (≥4,500 OMEQ), n, %	6,996 (11.23)	3,578 (5.05)	2,605 (4.78)	7,331 (7.3)
Long-term NSAID users, n, %	14,099 (22.63)	18,483 (26.08)	12,967 (23.77)	22,548 (22.44)
Contraindications to an NSAID, n, %	1,533 (2.46)	1,995 (2.82)	1,352 (2.48)	3,176 (3.16)

SD, standard deviation; OMEQ, oral morphine equivalent; NSAID, nonsteroidal inflammatory drug.

Table 2: Patient characteristics by subgroup and country.

Multiple comorbidities	**Denmark**	**Finland**	**Norway**	**Sweden**
Number of patients	6,926 (11.1%)	8,924 (12.6%)	7,578 (13.9%)	13,960 (13.9%)
Males, n, % [p-value]	2,912 (42.04) [0.311]	3,555 (39.84) [0.052]	3,083 (40.68) [0.079]	6,235 (44.66) [0.027]
Age, mean, SD [p-value]	68.6 (12.09) [<0.001]	69.5 (12.91) [<0.001]	69.2 (12.35) [<0.001]	70.4 (11.55) [<0.001]
Elixhauser comorbidity index, mean, SD [p-value]	2.705 (1.1) [<0.001]	2.776 (1.13) [<0.001]	2.843 (1.23) [<0.001]	2.792 (1.14) [<0.001]
Number of Elixhauser categories, n, % [p-value]				
No conditions	n/a	n/a	n/a	n/a
One condition	n/a	n/a	n/a	n/a
Two conditions	4,083 (58.95) [<0.001]	4,910 (55.02) [<0.001]	4,091 (53.99) [<0.001]	7,558 (54.14) [<0.001]
Three or more conditions	2,843 (41.05) [<0.001]	4,014 (44.98) [<0.001]	3,487 (46.01) [<0.001]	6,402 (45.86) [<0.001]
Patients with a depression or anxiety diagnosis, n, % [p-value]	426 (6.15) [<0.001]	836 (9.37) [<0.001]	606 (8) [<0.001]	1,306 (9.36) [<0.001]
Non-persistent opioid users, n, % [p-value]	2,491 (35.97) [<0.001]	3,289 (36.86) [0.579]	3,382 (44.63) [<0.001]	6,145 (44.02) [<0.001]
Persistent opioid users (≥4,500 OMEQ), n, % [p-value]	1,574 (22.73) [<0.001]	992 (11.12) [<0.001]	772 (10.19) [<0.001]	2,047 (14.66) [<0.001]
Long-term NSAID users, n, % [p-value]	1,558 (22.49) [0.774]	1,717 (19.24) [<0.001]	1,551 (20.47) [<0.001]	2,549 (18.26) [<0.001]
Contraindications to an NSAID, n, % [p-value]	958 (13.83) [<0.001]	1,522 (17.06) [<0.001]	1,001 (13.21) [<0.001]	2,387 (17.1) [<0.001]
Frequent healthcare visits	**Denmark**	**Finland**	**Norway**	**Sweden**
Number of patients	8,102 (13%)	7,966 (11.2%)	6,880 (12.6%)	12,387 (12.3%)
Males, n, % [p-value]	3,227 (39.83) [<0.005]	2,784 (34.95) [<0.005]	2,333 (33.91) [<0.005]	5,088 (41.08) [<0.005]
Age, mean, SD [p-value]	68.7 (12.05) [<0.005]	72.6 (13.22) [<0.005]	69.1 (12.16) [<0.005]	70.51 (12.38) [<0.005]
Elixhauser comorbidity index, mean, SD [p-value]	0.963 (1.39) [<0.005]	1.266 (1.56) [<0.005]	1.081 (1.52) [<0.005]	1.224 (1.59) [<0.005]
Number of Elixhauser categories, n, % [p-value]				
No conditions	4,283 (52.86) [<0.001]	3,495 (43.87) [<0.001]	3,397 (49.38) [<0.001]	5,793 (46.77) [<0.001]
One condition	1,797 (22.18) [<0.001]	1,756 (22.04) [<0.001]	1,621 (23.56) [<0.001]	2,601 (21) [<0.001]
Two conditions	1,005 (12.4) [<0.001]	1,222 (15.34) [<0.001]	843 (12.25) [<0.001]	1,680 (13.56) [<0.001]
Three or more conditions	1,017 (12.55) [<0.001]	1,493 (18.74) [<0.001]	1,019 (14.81) [<0.001]	2,313 (18.67) [<0.001]
Patients with a depression or anxiety diagnosis, n, % [p-value]	214 (2.64) [<0.001]	477 (5.99) [<0.001]	319 (4.64) [<0.001]	666 (5.38) [<0.001]
Non-persistent opioid users, n, % [p-value]	3,849 (47.51) [<0.001]	3,328 (41.78) [<0.001]	4,521 (65.71) [<0.001]	7,347 (59.31) [<0.001]
Persistent opioid users (≥4,500 OMEQ), n, % [p-value]	2,267 (27.98) [<0.001]	1,083 (13.6) [<0.001]	782 (11.37) [<0.001]	2,234 (18.04) [<0.001]
Long-term NSAID users, n, % [p-value]	2,488 (30.71) [<0.001]	1,801 (22.61) [<0.001]	1,886 (27.41) [<0.001]	3,363 (27.15) [<0.001]
Contraindications to an NSAID, n, % [p-value]	476 (5.88) [<0.001]	844 (10.6) [<0.001]	349 (5.07) [<0.001]	1,086 (8.77) [<0.001]
Multiple pain medications	**Denmark**	**Finland**	**Norway**	**Sweden**
Number of patients	16,109 (25.9%)	23,903 (33.7%)	17,669 (32.4%)	37,818 (37.6%)
Males, n, % [p-value]	5,502 (34.15) [<0.001]	8,495 (35.54) [<0.001]	5,807 (32.87) [<0.001]	14,175 (37.48) [<0.001]

Table 2: (continued)

Multiple pain medications	Denmark	Finland	Norway	Sweden
Age, mean, SD [p-value]	67.7 (12.01) [<0.001]	64.1 (12.53) [<0.001]	64.1 (13.05) [<0.001]	65.71 (11.92) [<0.001]
Elixhauser comorbidity index, mean, SD [p-value]	0.711 (1.17) [<0.001]	0.586 (1.08) [<0.001]	0.703 (1.18) [<0.001]	0.663 (1.13) [<0.001]
Number of Elixhauser categories, n, % [p-value]				
No conditions	9,915 (61.55) [<0.001]	16,193 (67.74) [<0.001]	10,861 (61.47) [<0.001]	24,143 (63.84) [<0.001]
One condition	3,304 (20.51) [<0.001]	4,203 (17.58) [<0.001]	3,804 (21.53) [<0.001]	7,300 (19.3) [<0.001]
Two conditions	1,565 (9.72) [<0.001]	1,909 (7.99) [<0.001]	1,583 (8.96) [<0.001]	3,444 (9.11) [<0.001]
Three or more conditions	1,325 (8.23) [<0.001]	1,598 (6.69) [<0.001]	1,421 (8.04) [<0.001]	2,931 (7.75) [<0.001]
Patients with a depression or anxiety diagnosis, n, % [p-value]	333 (2.07) [<0.001]	649 (2.72) [<0.001]	524 (2.97) [<0.001]	1,324 (3.5) [<0.001]
Non-persistent opioid users, n, % [p-value]	8,579 (53.26) [<0.001]	15,114 (63.23) [<0.001]	12,022 (68.04) [<0.001]	25,246 (66.76) [<0.001]
Persistent opioid users (≥4,500 OMEQ), n, % [p-value]	4,729 (29.36) [<0.001]	2,242 (9.38) [<0.001]	1,772 (10.03) [<0.001]	5,601 (14.81) [<0.001]
Long-term NSAID users, n, % [p-value]	6,729 (41.77) [<0.001]	9,589 (40.12) [<0.001]	6,811 (38.55) [<0.001]	14,244 (37.66) [<0.001]
Contraindications to an NSAID, n, % [p-value]	596 (3.7) [<0.001]	684 (2.86) [0.597]	499 (2.82) [<0.001]	1,261 (3.33) [0.015]
Contraindication to an NSAID	**Denmark**	**Finland**	**Norway**	**Sweden**
Number of patients	1,533 (2.5%)	1,995 (2.8%)	1,352 (2.5%)	3,176 (3.2%)
Males, n, % [p-value]	800 (52.19) [<0.001]	763 (38.25) [0.019]	624 (46.15) [<0.001]	1,543 (48.58) [<0.001]
Age, mean, SD [p-value]	70.1 (12.15) [<0.001]	76 (11.85) [<0.001]	72.4 (12.47) [<0.001]	73.97 (11.28) [<0.001]
Elixhauser comorbidity index, mean, SD [p-value]	2.366 (1.94) [<0.001]	2.911 (1.91) [<0.001]	3.053 (2.2) [<0.001]	2.883 (1.98) [<0.001]
Number of Elixhauser categories, n, % [p-value]				
No conditions	307 (20.03) [<0.001]	200 (10.03) [<0.001]	193 (14.28) [<0.001]	426 (13.41) [<0.001]
One condition	268 (17.48) [<0.001]	273 (13.68) [<0.001]	158 (11.69) [<0.001]	363 (11.43) [<0.001]
Two conditions	307 (20.03) [<0.001]	407 (20.4) [<0.001]	238 (17.6) [<0.001]	628 (19.77) [<0.001]
Three or more conditions	651 (42.47) [<0.001]	1,115 (55.89) [<0.001]	763 (56.43) [<0.001]	1,759 (55.38) [<0.001]
Patients with a depression or anxiety diagnosis, n, % [p-value]	44 (2.87) [<0.001]	67 (3.36) [<0.001]	62 (4.59) [<0.001]	158 (4.97) [<0.001]
Non-persistent opioid users, n, % [p-value]	547 (35.68) [<0.001]	687 (34.44) [0.012]	573 (42.38) [0.688]	1,347 (42.41) [0.126]
Persistent opioid users (≥4,500 OMEQ), n, % [p-value]	328 (21.4) [<0.001]	269 (13.48) [<0.001]	153 (11.32) [<0.001]	478 (15.05) [<0.001]
Long-term NSAID users, n, % [p-value]	280 (18.26) [<0.001]	214 (10.73) [<0.001]	202 (14.94) [<0.001]	383 (12.06) [<0.001]
Contraindications to an NSAID, n, % [p-value]	1,533 (100) [<0.001]	1,995 (100) [<0.001]	1,352 (100) [<0.001]	3,176 (100) [<0.001]
p-Values indicate difference to those not in the group.				

SD, standard deviation; OMEQ, oral morphine equivalent; NSAID, nonsteroidal inflammatory drug.

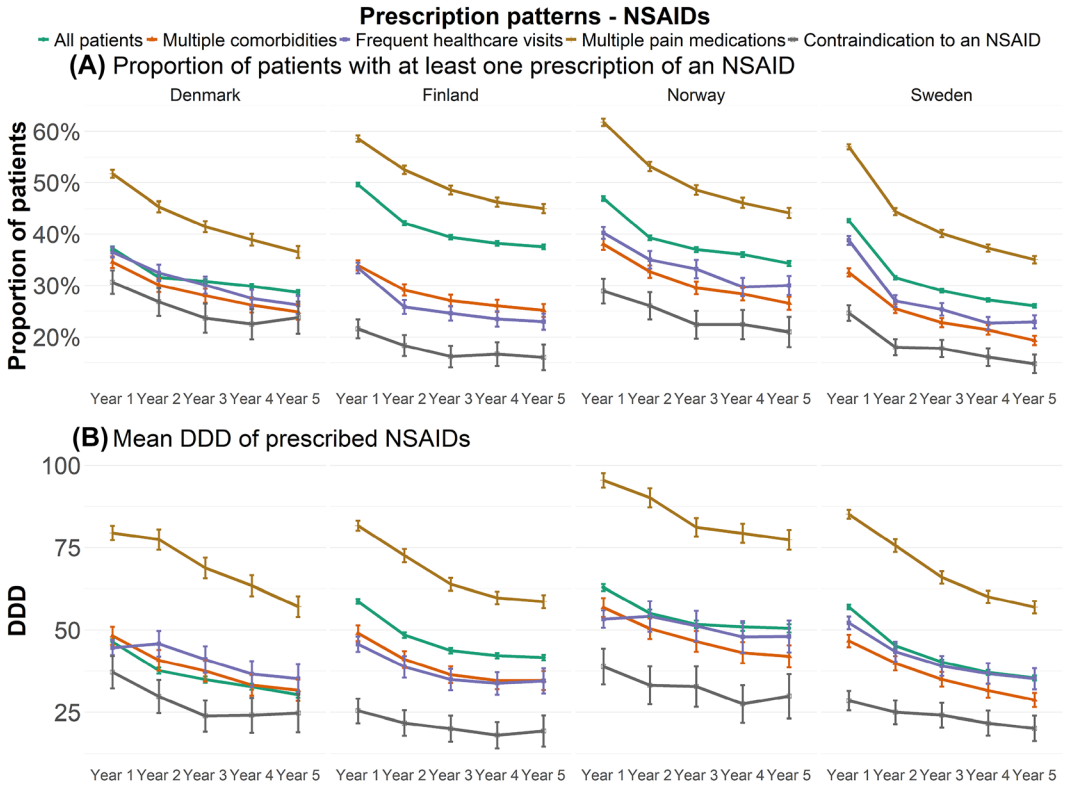

Figure 1: Prescription patterns – NSAID. Error bars indicate 95% confidence interval.
NSAID, nonsteroidal anti-inflammatory; DDD, Defined daily dose.

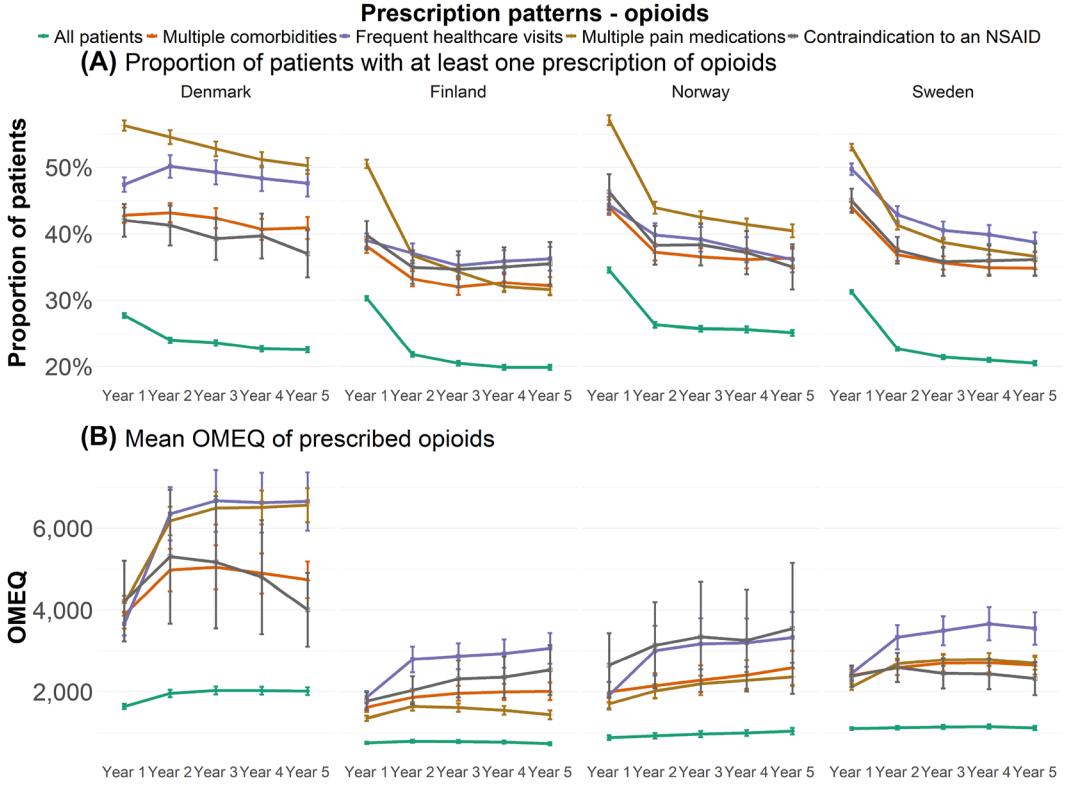

Figure 2: Prescription patterns – opioids. Error bars indicate 95% confidence interval.
NSAID, nonsteroidal anti-inflammatory drug; OMEQ, oral morphine equivalents.

NSAID use was the highest in the group with multiple pain prescriptions and lowest among those with contraindications to NSAIDs, in all countries. The 'Frequent healthcare visits' and 'Multiple comorbidities' subgroups had a lower percentage of patients with an NSAID prescription than the overall group in Finland, Norway, and Sweden (p-value <0.05) (similar percentages in Denmark). Dosing (in daily defined dose [DDD]) of NSAIDs (Figure 1B) was the highest in the first year and decreased in subsequent years, reflecting the same pattern as number of NSAID users over the same time period.

In contrast to NSAID use, all subgroups consistently had a higher number of opioid users than the overall OA group (p-value <0.001). Five years after inclusion, between 35 and 50% of patients in the subgroups were dispensed opioids, compared to 20–25% of patients in the overall group (p-value <0.05). Even though the percentage of opioid users decreased over time, dosing in oral morphine equivalents (OMEQ) (Figure 2B) was flat or increasing for patients that were dispensed opioids. The increase in dosing occurred in all Norwegian subgroups and the subgroups 'Frequent healthcare visits' and 'Multiple pain prescriptions' in Denmark and Finland. OMEQ doses for all subgroups and the overall group in Denmark was higher than for the other countries.

The number of persistent opioid users (Figure 3A) directly reflect the patterns of dosing in OMEQ as the definition of persistent use is the amount of dispensed OMEQ. More patients were dispensed several types of opioids each year (Figure 3B) in the subgroups than in the overall group (p-value <0.05) and this percentage decreased over time.

Patients were censored due to a joint replacement, cancer, or death (Appendix S2, Supplementary Figure S4). The percentage of patients that underwent a joint replacement was the highest in the first year. In total, between 30 and 40% of patients had received a joint replacement after 5 years and were censored for this reason. The percentage of patients with cancer was highest among the group with frequent healthcare visits in year one (p-value <0.05). Deaths were highest in the group with a contraindication to an NSAID (p-value <0.05) and lowest in the overall group as well as in those dispensed multiple pain prescriptions (p-value <0.05).

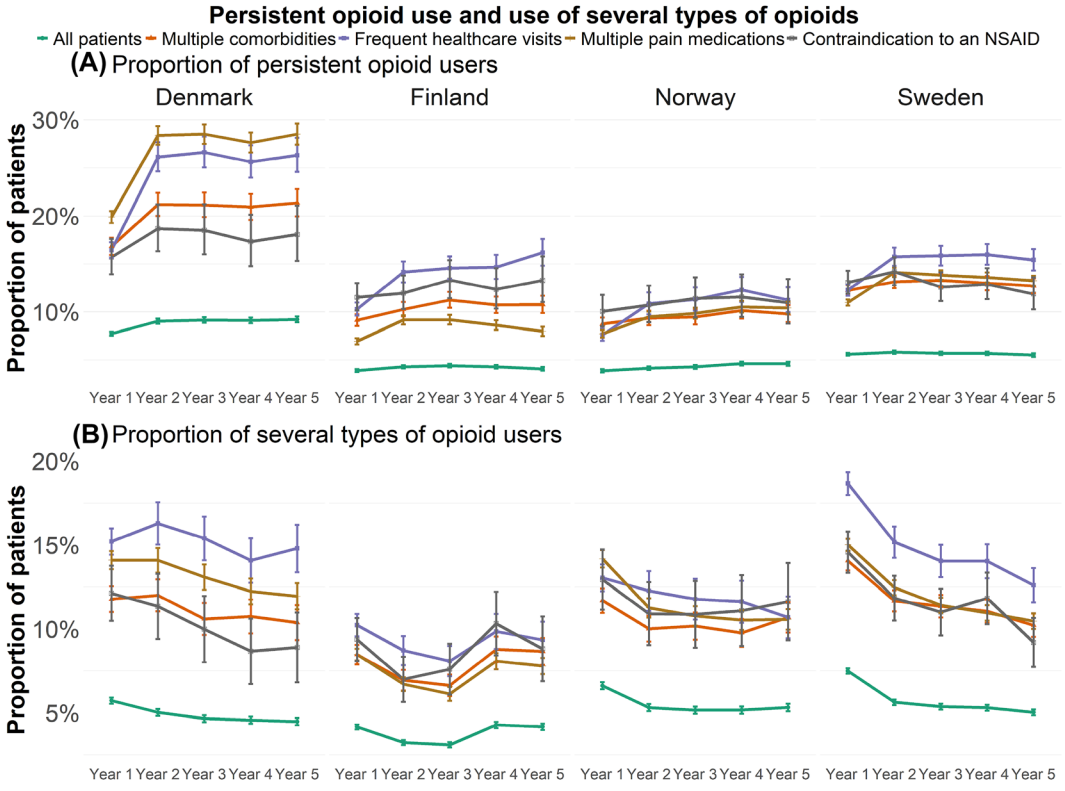

Figure 3: Persistent opioid use and use of several types of opioids. Error bars indicate 95% confidence interval. NSAID, nonsteroidal anti-inflammatory drug.

Predictors of unmet pain relief

Persistent opioid use

Predictors of persistent use are presented in Table 3. Between 7 and 13% of patients become persistent opioid users in the 5-year period after inclusion. Across all countries, being a disability pension recipient increased the risk of persistent use by 245–370% (p-value <0.001) compared to being employed. A diagnosis of depression or anxiety increased the risk by 23–60% (p-value <0.001) and a one unit increase in the Elixhauser index (corresponding to one additional diagnosis) increased the risk by almost 30% (p-value <0.001). Patients with hip OA were more likely becoming persistent opioid users by 40% (p-value <0.001) compared to patients with knee OA (Appendix S2, Supplementary Figures S5–S8).

Results from the regression models on 'Several types of opioids' are presented in Appendix S2, Supplementary Table S3 and are largely similar to the results to the models on 'Persistent opioid use'.

Long-term NSAID use

Predictors of long-term NSAID use are presented in Table 4. Long-term NSAID use was the most common unmet pain relief outcome when compared to using several types of opioids and persistent opioids. In the 5-year period after inclusion, 27–38% of patients became long-term NSAID users. Being a disability pension recipient increased the risk of long-term NSAID use in Denmark, Norway and Sweden by 25–40% (p-value <0.001). Depression and anxiety were strong predictors of long-term NSAID use, increasing the risk by 18–30% (p-value <0.001) in Finland, Norway and Sweden.

Compared to knee OA, hip OA increased the risk of long-term NSAID use by 8–22% (p-value <0.001) in Sweden, Finland and Denmark, while the results showed no

Table 3: Predictors of persistent opioid use.

	Denmark	Finland	Norway	Sweden
Number of patients (% with outcome)	60,540 (13%)	69,582 (7.4%)	53,731 (7.5%)	98,725 (10.6%)
	Hazard ratio (CI 95%)	Hazard ratio (CI 95%)	Hazard ratio (CI 95%)	Hazard ratio (CI 95%)
Type of OA diagnosis (ref: knee OA)				
Hip OA	1.372 (1.298–1.451)	1.386 (1.296–1.483)	1.405 (1.295–1.525)	1.439 (1.37–1.513)
Poly OA	1.093 (0.966–1.237)	1.506 (1.345–1.686)	1.175 (1.062–1.301)	0.898 (0.804–1.003)
First carpometacarpal joint OA	1.088 (0.977–1.213)	0.855 (0.681–1.073)	0.984 (0.833–1.162)	0.953 (0.875–1.038)
Other types of OA	1.226 (1.159–1.298)	1.131 (1.05–1.219)	1.269 (1.166–1.38)	1.184 (1.127–1.243)
Depression or anxiety before diagnosis (ref: no diagnosis)	1.221 (1.058–1.409)	1.531 (1.35–1.735)	1.552 (1.352–1.782)	1.629 (1.502–1.766)
Active pain treatment at diagnosis (ref: no)				
With NSAIDs	0.92 (0.757–1.117)	0.839 (0.706–0.998)	0.704 (0.569–0.871)	0.868 (0.788–0.956)
With opioids	4.766 (4.17–5.446)	3.473 (3.034–3.975)	3.34 (2.892–3.857)	3.29 (3.049–3.549)
With NSAIDs & opioids	3.279 (2.09–5.146)	1.099 (0.867–1.392)	1.458 (1.101–1.931)	2.439 (2.092–2.844)
Age (continuous)	1.018 (1.015–1.021)	1.012 (1.008–1.016)	0.999 (0.995–1.003)	1.007 (1.004–1.009)
Male (ref: female)	0.803 (0.765–0.841)	0.852 (0.803–0.904)	0.804 (0.75–0.862)	0.844 (0.81–0.88)
Disposable income (continuous)	0.783 (0.741–0.827)	0.567 (0.452–0.712)	0.975 (0.935–1.018)	0.857 (0.828–0.887)
Employment status (ref: employed)				
Not employed	1.55 (1.429–1.681)	1.094 (0.931–1.286)	1.966 (1.696–2.279)	1.413 (1.298–1.539)
On disability pension	3.744 (3.455–4.058)	2.514 (2.257–2.8)	3.156 (2.858–3.484)	2.467 (2.311–2.634)
Retired (>66 years of age)	1.484 (1.349–1.632)	1.714 (1.497–1.963)	2.135 (1.882–2.422)	1.304 (1.21–1.406)
Highest attained level of education (ref: <upper secondary education)				
Upper secondary education	0.86 (0.819–0.904)	0.806 (0.755–0.861)	0.745 (0.696–0.798)	0.873 (0.835–0.912)
>upper secondary education	0.639 (0.595–0.686)	0.666 (0.613–0.724)	0.581 (0.528–0.639)	0.671 (0.635–0.709)
Elixhauser comorbidity index (continuous)	1.277 (1.256–1.298)	1.288 (1.264–1.312)	1.291 (1.265–1.317)	1.273 (1.256–1.29)

OA, osteoarthritis; NSAID, nonsteroidal inflammatory drug.

Table 4: Predictors of long-term NSAID use.

	Denmark	Finland	Norway	Sweden
Number of patients (% with outcome)	60,540 (27.1%)	69,582 (34.2%)	53,731 (38%)	98,725 (30.2%)
	Hazard ratio (CI 95%)	Hazard ratio (CI 95%)	Hazard ratio (CI 95%)	Hazard ratio (CI 95%)
Type of OA diagnosis (ref: knee OA)				
Hip OA	1.08 (1.038–1.124)	1.172 (1.133–1.213)	0.983 (0.947–1.021)	1.222 (1.186–1.259)
Poly OA	0.898 (0.82–0.984)	0.934 (0.87–1.004)	0.983 (0.941–1.028)	0.854 (0.802–0.91)
First carpometacarpal joint OA	0.868 (0.805–0.935)	1.017 (0.934–1.107)	0.818 (0.761–0.878)	0.843 (0.802–0.886)
Other types of OA	0.932 (0.895–0.969)	1.038 (1.005–1.071)	0.851 (0.82–0.884)	0.9 (0.873–0.928)
Depression or anxiety before diagnosis (ref: no diagnosis)	1.132 (0.992–1.291)	1.33 (1.224–1.444)	1.179 (1.081–1.285)	1.305 (1.22–1.396)
Active pain treatment at diagnosis (ref: no)				
With NSAIDs	2.962 (2.709–3.238)	1.712 (1.624–1.804)	2.488 (2.343–2.643)	2.426 (2.333–2.522)
With opioids	1.326 (1.131–1.554)	1.098 (0.993–1.214)	0.998 (0.899–1.107)	1.156 (1.073–1.244)
With NSAIDs & opioids	5.067 (3.742–6.862)	1.332 (1.238–1.435)	1.328 (1.189–1.484)	2.77 (2.531–3.032)
Age (continuous)	1.004 (1.003–1.006)	0.993 (0.991–0.994)	0.996 (0.994–0.997)	0.999 (0.998–1.001)
Male (ref: female)	0.904 (0.876–0.934)	0.826 (0.804–0.848)	0.776 (0.752–0.8)	0.806 (0.786–0.826)
Disposable income (continuous)	0.909 (0.875–0.944)	0.877 (0.806–0.954)	1.068 (1.044–1.093)	1.047 (1.024–1.07)
Employment status (ref: employed)				
Not employed	1.058 (1.009–1.109)	0.756 (0.711–0.804)	1.133 (1.065–1.206)	1.086 (1.034–1.14)
On disability pension	1.411 (1.331–1.497)	1.018 (0.971–1.067)	1.266 (1.211–1.324)	1.423 (1.366–1.484)
Retired (>66 years of age)	0.989 (0.931–1.049)	0.657 (0.621–0.694)	0.923 (0.877–0.971)	0.901 (0.864–0.939)
Highest attained level of education (ref: <upper secondary education)				
Upper secondary education	0.973 (0.939–1.008)	1.057 (1.024–1.091)	1.021 (0.987–1.055)	1.011 (0.984–1.04)
>upper secondary education	0.812 (0.776–0.85)	0.962 (0.927–0.998)	0.896 (0.86–0.933)	0.953 (0.924–0.983)
Elixhauser comorbidity index (continuous)	0.986 (0.969–1.003)	0.891 (0.877–0.906)	0.932 (0.918–0.946)	0.92 (0.908–0.932)

OA, osteoarthritis; NSAID, nonsteroidal inflammatory drug.

statistical significance in Norway. These results are also presented in Kaplan-Meier graphs in Appendix S2, Supplementary Figures S9–S12.

Discussion

Findings from over 280,000 Nordic patients with OA treated in specialty care show that NSAID and opioid use was common, especially among subgroups of patients defined as difficult-to-treat. Compared with the index year, the percentage of patients prescribed an NSAID or opioid decreased in all groups in the years following the first visit to a specialist. This might reflect that some patients were able to control their pain or turned to alternative therapies. However, a substantial percentage (31–50%) of patients in the defined subgroups were treated with opioids 5 years after diagnosis, potentially trigged by an unmet need and insufficient pain management in many patients, as long-term opioid use is strongly discouraged [8, 9].

Predictors of unmet pain relief and prescription patterns

The association between comorbidities, in particular depression and anxiety, and unmet pain relief, defined as persistent opioid use, using several types of opioids, or long-term NSAID, was statistically very strong and in line with a previous study [23]. Disability pension was another strong predictor of all definitions of unmet pain relief, indicating a high comorbid and socioeconomic burden in some patients with OA.

Compared to the overall OA population, all difficult-to-treat subgroups had higher opioid use in all years following the index date. This may indicate that we successfully defined groups of patients with additional pain management challenges compared to the overall OA population. It was shown that the percentage of patients on opioids decreased over time, while the strength of doses in dispensed opioids increased, indicating that patients remaining on long-term opioid use required continuous

dose escalation as part of their pain treatment regimen. Continuous dose escalation is considered very problematic for these patients as it is against any recommendations for OA management [9].

Between 5 and 15% of those with a contraindication to an NSAID were prescribed an NSAID during the 5-year study period despite having a diagnosis contraindicated to NSAID use. This subgroup was dispensed as much OMEQs as the other subgroups and higher than the overall group. If these patients are prescribed opioids instead of NSAIDs for pain relief, it may highlight the challenges associated with long-term pharmacological treatment of this patient population in terms of substantial unmet need and demand for alternative therapies.

The proportions of patients treated with NSAIDs and opioids found in this study were consistent with those reported in earlier studies showing similar high levels of medications use among European patients with OA [18, 20, 24] and among US patients [25, 26]. In Denmark, the dispensed doses of opioids were higher compared to Sweden, Finland and Norway, in line with another study comparing opioid use in the general population in Denmark, Sweden and Norway [27].

The first visit in specialty care is often linked to orthopaedic assessment as observed in a Dutch study [15] and subsequent surgery, which could also be seen in our study given the high proportion of patients censored due to a joint replacement in the first year after diagnosis. The patterns of joint replacements from index to 5 years after were similar between all subgroups and the overall OA group. This may indicate that other factors than the ones used for defining difficult-to-treat subgroups are driving the decision to proceed with this procedure. As no gold standard exists for joint replacement referral [28], it remains unclear which factors that were associated with joint replacement.

Difficult-to-treat subgroups

Patients in the difficult-to-treat subgroups were dispensed higher doses of opioids in the later years of the analyses compared to the first year. This indicates that pre-operative opioid doses increased in patients waiting longer for surgery or that these groups of patients were ineligible for a joint replacement and with a substantial need for pain relief. Both reasons are troublesome as high pre-surgery use of opioids is a risk factor for continued pain and opioid use post-surgery, and the list of negative health effects of long-term opioid use is long [29, 30].

The results reflect a discrepancy between current treatment guidelines [5–9] and routine clinical practice, especially regarding long-term use of opioids. However, the long study period spans multiple iterations of clinical treatment guidelines for the management of OA. Current guidelines increasingly account for the patient's medical profile, including risks of opioid and NSAID use; thus, these findings should be considered based on these recent changes.

The differences between the difficult-to-treat subgroups and the overall OA group may indicate a sufficient sensitive identification to differentiate the difficult-to-treat patients in the cohort of OA patients referred to specialty care. However, the differences also highlight the heterogeneity within the overall OA population. Assessing the full OA population may diffuse the true heterogeneity of patients with OA and addressing the subpopulations may enable us to understand more about managing the illness.

Strength and limitations of study

A major strength of the present study is the high degree of validity, mandatory reporting, completeness, data quality and long follow-up in the Nordic national health registers.

Limitations include the inability to capture non-prescription medication, adherence to dispensed medication and the indication of prescribed medications. The OA diagnosis included in the regression analyses is the diagnosis used at the index date and does not consider the possibility of OA in multiple joints. Furthermore, no indication of pain severity or treatment satisfaction was available for the patients.

Future studies should focus on complete patient journeys from the initial contact in primary care through to treatment by specialists, prescription patterns in relation to joint replacements, and poor outcomes or adverse events because of problematic analgesic use.

Conclusions

This study shows the substantial use of pain medications in patients with OA and in the defined difficult-to-treat subgroups, which persist over time. These findings indicate that patients with pain are a challenging group to be managed pharmacologically with the current available medicines. A considerable proportion of patients with OA are on a particular problematic journey, particularly those with contraindications to an NSAID, with continued use of opioids. Furthermore, patients with comorbidities and a lower socioeconomic status have an elevated risk of developing a particular problematic journey.

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