

BMJ Open Risk factors for persistent and new chronic opioid use in patients undergoing total hip arthroplasty: a retrospective cohort study

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ABSTRACT

Objectives: To determine chronic opioid use pre-THA (total hip arthroplasty) and post-THA, and risk factors for persistent or new chronic opioid use post-THA.

Design: Retrospective cohort study.

Setting: Australian Government Department of Veterans' Affairs health claims database.

Participants: 9525 patients who had an elective unilateral THA between 1/01/2001 and 12/31/2012.

Primary outcome measure: Chronic opioid use. Defined as 90 days of continuous opioid use or 120 days of non-continuous use.

Results: Pre-THA, 6.2% (n=593) of patients were chronic users, while 5.2% (n=492) were post-THA. Among the 492 postoperative chronic users, 302 (61%) were chronic users pre-THA and post-THA and 190 (39%) became new chronic users after surgery. Risk factors for persistent chronic use were younger age (OR=0.96, 95% CI 0.93 to 0.99/1-year increment), back pain (OR=1.99, 95% CI 1.20 to 3.23), diabetes (OR=3.52, 95% CI 1.05 to 11.8), hypnotics use (OR=2.52, 95% CI 1.48 to 4.30) and higher pre-THA opioid exposure (compared with opioid use for 94–157 days, 157–224 days (OR=3.75, 95% CI 2.28 to 6.18), 225+ days (OR=5.18, 95% CI 2.92 to 9.19)). Risk factors for new chronic opioid use post-THA were being a woman (OR=1.40, 95% CI 1.00 to 1.96), back pain (OR=3.90, 95% CI 2.85 to 5.33), depression (OR=1.70, 95% CI 1.20 to 2.41), gastric acid disease (OR=1.62, 95% CI 1.16 to 2.25), migraine (OR=5.11, 95% CI 1.08 to 24.18), liver disease (OR=4.33, 95% CI 1.08 to 17.35), weight loss (OR=2.60, 95% CI 1.06 to 6.39), dementia (OR=2.19, 95% CI 1.04 to 4.61), hyperlipidaemia (OR=1.38, 95% CI 1.00 to 1.91), hypnotics (OR=1.56, 95% CI 1.13 to 2.16) and antineuropathic pain medication use (OR=3.11, 95% CI 2.05 to 4.72).

Conclusions: Patients undergoing THA are exposed to opioids for long periods of time, putting them at high risk of harm related to opioid use. We identified groups at risk of chronic opioid use, including younger patients and women, as well as modifiable risk factors of chronic opioid use, including level of opioid

Strengths and limitations of this study

- In a cohort of 9525 patients undergoing total hip arthroplasties (THAs), we found that 5% of the patients were chronic opioid users after their surgery. Of these, 61% were persistent chronic users (ie, had been chronic opioid users prior to surgery and continued after surgery), and 39% became chronic users after surgery.
- This study also identified indicators of chronic opioid use that can be used by clinicians for risk stratification prior to surgery, and to target patient groups for suitable pain management interventions presurgery and postsurgery. Specifically, back pain, diabetes and preoperative use of hypnotics were strong risk factors for the persistent and new development of chronic opioid use. Additional risk factors for persistent use included younger age and greater use of opioids prior to surgery, while for new chronic use these included being a woman, depression, migraine, gastric acid disease and antineuropathic pain medications.
- The limitations of this study include a conservative definition of chronic opioid as someone who was prescribed opioids for 90 consecutive days or 120 non-consecutive days, and inability to determine the specific reasons why analgesic medications were prescribed to patients.
- The strengths of this study include a large and fully captured patient cohort (ie, no missing data and attrition only related to death), a comprehensive assessment of patient comorbidities using three comorbidity measures, and the use of pharmacy data to determine opioid use instead of patient-reported use which can suffer from response bias.

exposure presurgery and hypnotic use. These indicators of chronic opioid use can be used by clinicians to target patient groups for suitable pain management interventions.

BACKGROUND

Total hip arthroplasty (THA) is the recommended treatment for patients with hip osteoarthritis that have failed both pharmacological and non-pharmacological treatment for the severe pain, and limited function caused by their condition.¹ THA is the fourth most common surgical procedure in the USA, with 468 000 performed in 2012²; it is one of the top 20 most common surgical procedures in Australia, with 26 000 performed in 2013.³ THA is considered a clinically effective, successful operation with reported cost-effectiveness.¹ However, while joint-related pain is expected to be resolved after surgical rehabilitation, there is a high prevalence of patients who report persistent chronic pain and some patients who report chronic pain development subsequent to the procedure.⁴

Chronic and persistent pain post-THA occurs in 7–23% of patients.^{4–5} One study reported moderate-to-severe hip pain after primary THA in 8% of patients.⁶ Other studies suggested that 3–25% of patients take opioid medications for almost 5 years after their surgery.^{6–7} There are several reasons that suggest the use of opioids in patients with THA is high, and abuse of these medications could affect these patients. First, it is well established that the use of opioids has increased worldwide for all non-cancer chronic pain management.^{8–11} In the treatment of musculoskeletal pain, opioids use increased by 50% between 2006 and 2010,¹² and surgeons are reportedly some of the highest prescribers of these medications.¹³ Second, as opioids are recommended for the treatment of osteoarthritis¹ and surgical recovery,¹⁴ patients undergoing THA are likely to be exposed to opioids for long periods of time, increasing their chance of developing tolerance, hyperalgesia,¹⁵ and other dangerous and potentially costly opioid-related side effects.¹⁶ Third, the comorbidity burden of patients undergoing THA has increased in the past two decades,^{17–19} suggesting that patients can, and are likely to, be suffering from other types of pain and taking opioids for these other conditions, which also affect their surgical outcomes.²⁰ Finally, in addition to the high exposure to these medications, there is the potential of adverse events associated with opioid use in surgical recovery.¹⁴ The higher medical complexity of the patients undergoing THA creates potential interactions between these opioid medications and the specific surgical outcomes of the procedure. Currently it is not well understood how opioids are used in this patient population and who is at risk of harm.

Understanding who is at risk of persistent chronic opioid use and developing new chronic use in this patient population can be useful to the surgeons, the patients themselves and the general healthcare system of which they are a part. Our study was conducted to identify patients at a high risk of chronic opioid use who may benefit from targeted interventions for better pain management strategies and opioid use education. Specifically, the purpose of this study was to (1)

determine the prevalence of chronic opioid use before and after THA surgery, and (2) determine the characteristics associated with persistent chronic opioid use or becoming a new chronic user after surgery.

METHODS

Study design, setting and study sample

A retrospective cohort study was conducted. Patients who underwent a THA procedure between 1/01/2001 and 12/31/2012 were included in the study. The study cohort comprised of patients who received care subsidised by the Australian Government Department of Veterans' Affairs (DVA). The DVA administrative claims database, which includes detailed information on all inpatient hospitalisations, prescription medications, medical procedures and allied health services provided to veterans, was used for the study. The DVA's client file, which contains information on gender, date of birth, date of death and family status for a treatment population of 242 000 veterans and spouses in September 2011, was also used. In the prescription data set, medications are coded according to the WHO anatomic, therapeutic and chemical classification (ATC),²¹ and the Australian Pharmaceutical Benefits Schedule (PBS) item codes.²² In the inpatient hospitalisation data set, encounters are coded using the International Classification of Diseases, 10th Revision, Australian Modification (ICD-10-AM) codes.²³

Patients older than 18 years of age were selected for the study if they underwent elective unilateral THA (identified using ICD-10-AM procedure code 4 931 800), did not have other hip or knee arthroplasties within 1 year of the index THA, and did not have history of cancer (ICD-10-AM C00.x–C26.x, C30.x–C34.x, C37.x–C41.x, C43.x, C45.x–C58.x, C60.x–C76.x, C81.x–C85.x, C88.x, C90.x–C97.x, C77.x–C80.x, C81.x–C85.x, C88.x, C96.x, C90.0, C90.2 and antineoplastic and immunomodulating agents medication history ATC codes L01*). The cohort was initially comprised of 10018 THAs belonging to 9373 patients. Of these, 493 THAs were not included in the final sample as they either experienced a revision (N=202) or died (N=290) within a year of surgery or did not have complete 1-year follow-up (N=1). Patients with revisions or who died within 1 year were excluded to reduce the effect these events could have on the amount of opioids a patient would take; thus, an accurate description of chronic opioid use could be determined. The final cohort comprised 9525 THAs given to 8925 patients (8325 patients had one THA and 600 had two surgeries more than 1 year apart).

Outcomes of interest

Chronic opioid use after surgery was the main outcome of interest. Chronic opioid use was defined as having any number of opioid prescriptions or dosing for at least 90 days continuously, or opioid prescriptions for 120

non-consecutive days.²⁴ The number of days was obtained from the number of units supplied. No gap days between one prescription supply and another were allowed when determining consecutive prescription of opioids. New chronic users were those who did not have chronic use prior to their THA. Persistent chronic opioid users were those with chronic opioid use before and after surgery.

Opioids (ATC code=N02A*, inclusive of opioid-like medications such as Tramadol) 365 days pre-THA (admission date) and post-THA (discharge date) were extracted from the DVA prescription database, and the number of dispensed prescriptions and the days of expected utilisation were calculated. Dosages were converted to oral morphine equivalents (OMEs),²⁵ and the daily OMEs were summed across the days within the pre-THA and post-THA periods to estimate the total OME for these time periods. When determining whether patients were chronic opioid users post-THA, the immediate 90-day period after THA was excluded as the use of opioids in this period is related to surgical recovery and rehabilitation. Therefore, each patient had 275 potential days of medication utilisation post-THA. To obtain a similar exposure period preoperatively, we excluded the 90-day period between 365 and 275 days prior surgery. Patients were assigned to the opioid use categories of 'chronic', 'some' and 'none' opioid use for the periods of pre-THA and post-THA. After classifying chronic users, the remaining opioid users were classified as 'some' opioid use if they did not fit the chronic criteria, and those without any opioid dispensing were assigned to the 'none' category.

Risk factors

Age, sex, surgical indication, bilaterality, opioid-related comorbidities, other medical comorbidities and other analgesic medication were evaluated as risk factors of persistent or new chronic opioid use after surgery. Comorbidities were identified using a combination of the RxRisk-V, Elixhauser and Charlson measures.^{26–27} Using these three comorbidity measures provided a comprehensive ascertainment of conditions because it used both medication dispensing history and hospital encounters of the patients in the year prior to their surgery. The opioid-related comorbidities investigated included depression, back pain, anxiety, psychoses, alcohol abuse, bipolar disorder and drug abuse. The 49 medical comorbidities investigated, which included cardiovascular and blood, endocrine, gastrointestinal, musculoskeletal, neurological, nutritional, renal, respiratory, and other body systems, can be seen in [table 1](#). Additional analgesic medication evaluated included non-steroids anti-inflammatories (ATC code=M01A*), muscle relaxants (ATC code=M03*), antineuropathic pain medications (ATC codes=N06AA09, N06AX21, N03AX12, N03AX16),²⁸ hypnotics (ATC code=N05C*, inclusive of sedatives) and corticosteroids (ATC codes=H02AA*, H02AB*). Since the comorbidities of pain treated with

opioids, pain treated with anti-inflammatory medications and steroid-responsive disorders were identified using only the RxRisk-V medication comorbidity measure we did not include them in our final analyses, as these are likely to be highly correlated to the other analgesic medication evaluated. Days of opioid use (per quartile of days) and average daily use were investigated as risk factors for persistent chronic opioid use.

Statistical analyses

Frequencies, proportions, medians, IQR, means and SD described the study sample. The prevalence of opioid use, as well as crude overall mean OME taken and days of opioid use per subgroup were calculated. The adjusted change in mean OME and mean days of opioid use from pre-THA to post-THA were calculated using generalised linear models. Logistic regression models were used to identify risk factors associated with persistent chronic opioid use and new chronic opioid use after surgery. In both models, all candidate covariates were modelled in a bivariate model with the outcome of interest. If their association with the outcome had a $p < 0.2$, then these were included in the subsequent multivariable model. Collinearity between the variables in final models was evaluated, and tolerance values were > 0.1 in all cases. ORs and 95% CIs are provided. All tests were two-sided, and $\alpha = 0.05$ was considered statistically significant. SAS V.9.4 (SAS Institute, Cary, North Carolina, USA) was used for all analyses.

Sensitivity analysis

High and long-term use of non-steroidal anti-inflammatory drugs are risk factors for gastric acid disease, a condition treated with proton-pump inhibitors;^{29–30} therefore, we tested this interaction in a sensitivity analysis—no interaction was found and data are not shown.

Patient involvement

No patients were involved in the design of this study, in developing the outcome measures nor in the conduct of the study. There are no plans to disseminate the results to study participants.

RESULTS

Our cohort of 9525 primary THAs was 51.3% (n=4891) women and had a median age of 80 years (5th–95th centile 76–84 years) at the time of surgery. [Table 1](#) describes patients' characteristics, comorbidities and other analgesic medication use pre-THA and post-THA as per their pre-THA chronic opioid use status.

Presurgery, 6.2% (n=593) of patients were considered chronic opioid users, while 5.2% (n=492) were users postsurgery. Of the 492 chronic users post-THA, 61.4% (n=302) were persistent chronic users (chronic users pre-THA and post-THA) and 38.6% (n=190) became chronic users after surgery (ie, 38 were considered 'none' and 152 were considered 'some' users pre-THA).

Table 1 Descriptive characteristics of the total hip arthroplasty study cohort

Characteristic	All	None	Some	Chronic
Total, n (%)	9525	5138 (53.9)	3794 (39.8)	593 (6.2)
Age at surgery, median (5th–95th centile), years	80 (76–84)	81 (63–88)	80 (61–89)	81 (59–89)
Sex, n (%)				
Women	4891 (51.3)	2558 (49.8)	1977 (52.1)	356 (60.0)
Men	4634 (48.7)	2580 (50.2)	1817 (47.9)	237 (40.0)
Bilateral (more than 365 days), n (%)	1200 (12.6)	669 (13.0)	473 (12.5)	58 (9.8)
Year of operation, n (%)				
2001–2002	1738 (18.2)	1001 (19.5)	694 (18.3)	43 (7.3)
2003–2004	1840 (19.3)	980 (19.1)	786 (20.7)	74 (12.5)
2005–2006	1654 (17.4)	925 (18.0)	651 (17.2)	78 (13.2)
2007–2008	1590 (16.7)	853 (16.6)	612 (16.1)	125 (21.1)
2009–2010	1454 (15.3)	750 (14.6)	572 (15.1)	132 (22.3)
2011–2012	1249 (13.1)	629 (12.2)	479 (12.6)	141 (23.8)
Surgical indication, n (%)				
ICD-10-AM M161: other primary osteoarthritis	7826 (82.2)	4241 (82.5)	3092 (81.5)	493 (83.1)
ICD-10-AM M169: osteoarthritis unspecified	882 (9.3)	513 (10.0)	342 (9.0)	27 (4.6)
Other	817 (8.6)	384 (7.5)	360 (9.5)	73 (12.3)
Opioid-related comorbidities				
Depression, n (%)	1695 (17.8)	755 (14.7)	764 (20.1)	176 (29.7)
Back pain, n (%)	1367 (14.4)	466 (9.1)	694 (18.3)	207 (34.9)
Anxiety, n (%)	1167 (12.3)	445 (8.7)	569 (15.0)	153 (25.8)
Psychoses, n (%)	191 (2.0)	96 (1.9)	74 (2.0)	21 (3.5)
Alcohol abuse, n (%)	88 (0.9)	36 (0.7)	45 (1.2)	7 (1.2)
Bipolar disorder, n (%)	26 (0.3)	14 (0.3)	11 (0.3)	1 (0.2)
Drug abuse, n (%)	11 (0.1)	4 (0.1)	3 (0.1)	4 (0.7)
Cardiovascular/blood comorbidities				
Hypertension, n (%)	5384 (56.5)	2789 (54.3)	2215 (58.4)	380 (64.1)
Anticoagulation agents/coagulopathy, n (%)	5071 (53.2)	2676 (52.1)	2077 (54.7)	318 (53.6)
Hyperlipidaemia, n (%)	3621 (38.0)	1819 (35.4)	1534 (40.4)	268 (45.2)
IHD hypertension, n (%)	3341 (35.1)	1722 (33.5)	1392 (36.7)	227 (38.3)
Antiplatelet agents, n (%)	3213 (33.7)	1594 (31.0)	1377 (36.3)	242 (40.8)
Arrhythmias, n (%)	1837 (19.3)	937 (18.2)	774 (20.4)	126 (21.2)
Congestive heart failure, n (%)	1277 (13.4)	556 (10.8)	585 (15.4)	136 (22.9)
Angina, n (%)	1112 (11.7)	484 (9.4)	530 (14.0)	98 (16.5)
Myocardial infarction, n (%)	241 (2.5)	112 (2.2)	112 (3.0)	17 (2.9)
Peripheral vascular disease, n (%)	225 (2.4)	105 (2.0)	100 (2.6)	20 (3.4)
Valvular disease, n (%)	225 (2.4)	118 (2.3)	96 (2.5)	11 (1.9)
Cerebrovascular disorders, n (%)	201 (2.1)	90 (1.8)	95 (2.5)	16 (2.7)
Pulmonary circulation disorders, n (%)	109 (1.1)	54 (1.1)	42 (1.1)	13 (2.2)
Endocrine comorbidities				
Diabetes uncomplicated, n (%)	1007 (10.6)	474 (9.2)	440 (11.6)	93 (15.7)
Hypothyroidism, n (%)	674 (7.1)	348 (6.8)	260 (6.9)	66 (11.1)
Diabetes with complications, n (%)	624 (6.6)	284 (5.5)	281 (7.4)	59 (9.9)
Pancreatic insufficiency, n (%)	15 (0.2)	4 (0.1)	10 (0.3)	1 (0.2)
Gastrointestinal comorbidities				
Gastric acid disorder, n (%)	4267 (44.8)	1981 (38.6)	1904 (50.2)	382 (64.4)
Liver disease (severe) or failure, n (%)	361 (3.8)	121 (2.4)	173 (4.6)	67 (11.3)
Peptic ulcer disease, n (%)	95 (1.0)	47 (0.9)	40 (1.1)	8 (1.3)
Inflammatory bowel syndrome, n (%)	80 (0.8)	40 (0.8)	37 (1.0)	3 (0.5)
Liver disease (mild), n (%)	25 (0.3)	9 (0.2)	13 (0.3)	3 (0.5)
Hepatitis C, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Musculoskeletal/pain-related comorbidities				
Osteoporosis/Paget's, n (%)	1189 (12.5)	564 (11.0)	496 (13.1)	129 (21.8)
Gout, n (%)	950 (10.0)	471 (9.2)	407 (10.7)	72 (12.1)
RA/collagen vascular disorders, n (%)	108 (1.1)	32 (0.6)	62 (1.6)	14 (2.4)
Migraine, n (%)	28 (0.3)	9 (0.2)	11 (0.3)	8 (1.3)

Continued

Table 1 Continued

Characteristic	All	None	Some	Chronic
Neurological comorbidities				
Dementia, n (%)	191 (2.0)	97 (1.9)	65 (1.7)	29 (4.9)
Epilepsy	421 (4.4)	143 (2.8)	210 (5.5)	68 (11.5)
Parkinson's disease, n (%)	152 (1.6)	62 (1.2)	70 (1.8)	20 (3.4)
Other neurological disorders, n (%)	119 (1.2)	60 (1.2)	47 (1.2)	12 (2.0)
Paralysis (or paraplegia/hemiplegia), n (%)	63 (0.7)	26 (0.5)	32 (0.8)	5 (0.8)
Nutritional/obesity comorbidities				
Deficiency anaemia, n (%)	152 (1.6)	65 (1.3)	72 (1.9)	15 (2.5)
Obesity, n (%)	146 (1.5)	57 (1.1)	77 (2.0)	12 (2.0)
Weight loss, n (%)	87 (0.9)	31 (0.6)	49 (1.3)	7 (1.2)
Blood loss anaemia, n (%)	60 (0.6)	24 (0.5)	29 (0.8)	7 (1.2)
Malnutrition, n (%)	16 (0.2)	9 (0.2)	5 (0.1)	2 (0.3)
Hyperkalaemia, n (%)	3 (0.0)	3 (0.1)	0 (0.0)	0 (0.0)
Renal/urological				
Renal disease/failure, n (%)	410 (4.3)	168 (3.3)	196 (5.2)	46 (7.8)
Benign prostatic hypertrophy, n (%)	352 (3.7)	189 (3.7)	137 (3.6)	26 (4.4)
Respiratory comorbidities				
Reactive airway disease, n (%)	1978 (20.8)	931 (18.1)	888 (23.4)	159 (26.8)
Chronic pulmonary disease, n (%)	504 (5.3)	230 (4.5)	228 (6.0)	46 (7.8)
Tuberculosis, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Miscellaneous comorbidities				
Allergies, n (%)	1327 (13.9)	592 (11.5)	618 (16.3)	117 (19.7)
Glaucoma, n (%)	897 (9.4)	494 (9.6)	356 (9.4)	47 (7.9)
Smoking, n (%)	90 (0.9)	32 (0.6)	53 (1.4)	5 (0.8)
Psoriasis, n (%)	46 (0.5)	19 (0.4)	24 (0.6)	3 (0.5)
Transplant, n (%)	2 (0.0)	1 (0.0)	1 (0.0)	0 (0.0)
HIV, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other analgesic medication use				
Pre-THA				
NSAIDs, n (%)	6093 (64.0)	3007 (58.5)	2722 (71.7)	364 (61.4)
Hypnotics and sedatives, n (%)	1904 (20.0)	693 (13.5)	1012 (26.7)	199 (33.6)
Corticosteroids, n (%)	1275 (13.4)	474 (9.2)	672 (17.7)	129 (21.8)
Antineuropathic pain, n (%)	657 (6.9)	205 (4.0)	333 (8.8)	119 (20.1)
Muscle relaxants, n (%)	27 (0.3)	7 (0.1)	17 (0.4)	3 (0.5)
Post-THA				
NSAIDs, n (%)	4288 (45.0)	2033 (39.6)	1969 (51.9)	286 (48.2)
Hypnotics and sedatives, n (%)	1950 (20.5)	762 (14.8)	982 (25.9)	206 (34.7)
Corticosteroids, n (%)	1242 (13.0)	497 (9.7)	623 (16.4)	122 (20.6)
Antineuropathic pain, n (%)	678 (7.1)	233 (4.5)	326 (8.6)	119 (20.1)
Muscle relaxants, n (%)	24 (0.3)	5 (0.1)	15 (0.4)	4 (0.7)

Overall and by preoperative opioid utilisation status, 2001–2012.

ICD-10-AM, International Classification of Diseases, 10th Revision, Australian Modification; NSAID, non-steroidal anti-inflammatory drugs; RA, rheumatoid arthritis; THA, total hip arthroplasty.

On average, a chronic opioid user before surgery had 55.5 (95% CI 51.4 to 59.7) OMEs mg/day and was dispensed opioids for 189.9 (95% CI 185.69 to 193.9) days. Postsurgery they had 57.5 (95% CI 52.1 to 62.8) OMEs mg/day and were dispensed opioids for 193.0 (95% CI 188.8 to 197.1) days. See table 2 for prevalence of opioid use type, daily OMEs and average number of days for each group, as well as changes in the group pre-THA and post-THA.

Risk factors for persistent chronic opioid use were younger age (OR=0.96, 95% CI 0.93 to 0.99/1-year increment), presence of back pain (OR=1.99, 95% CI 1.20 to 3.23), uncomplicated diabetes (OR=3.52, 95%

CI 1.05 to 11.8) and use of hypnotics pre-THA (OR=2.52, 95% CI 1.48 to 4.30). The number of days on opioids prior to surgery was associated with odds of continuing to be a chronic opioid user after surgery after 94 days using opioids. Compared with opioid use for 94–157 days, patients who used opioids for 157–224 days had a 3.75 (95% CI 2.28 to 6.18) higher odds of being a persistent user, and those who used it for 225+ days had a 5.18 (95% CI 2.92 to 9.19) higher odds (table 3).

Risk factors for patients to develop chronic opioid use after THA were being a woman (OR=1.40, 95% CI 1.00 to 1.96), presence of back pain (OR=3.90, 95% CI

Table 2 Prevalence of opioid use, mean daily oral morphine equivalents use, and days of use pre-THA and post-THA by opioid user status, and change in daily use and days by pre-THA to post-THA status

	Opioid use post-THA	Opioid use pre-THA		
	Total	None	Some	Chronic
Prevalence, n (%)				
Total	9525	5138 (53.39)	3794 (39.8)	593 (6.2)
None	6626 (69.6)	4369 (85.0)	2146 (56.6)	111 (18.7)
Some	2407 (25.3)	731 (14.2)	1496 (39.4)	180 (30.4)
Chronic	492 (5.2)	38 (0.7)	152 (4.0)	302 (50.9)
Daily OME use for group and change in daily OME use,* mg, mean (95% CI)				
Total		0.0 (0.0 to 0.0)	38.3 (37.6 to 39.0)	55.5 (51.4 to 59.7)
None	0.0 (0.0 to 0.0)	0.0 (−0.1 to 0.1)	−37.7 (−38.4 to −37.0)	−55.3 (−59.4 to −51.2)
Some	37.5 (36.6 to 38.4)	36.6 (35.7 to 37.5)	−1.1 (−2.1 to −0.1)	−18.7 (−22.9 to −14.5)
Chronic	57.5 (52.1 to 62.8)	56.2 (51.2 to 61.2)	18.6 (13.6 to 23.6)	0.9 (−3.2 to 5.0)
Days using opioids for group and change in days use,* mean (95% CI)				
Total		0.0 (0.0 to 0.0)	27.0 (26.1 to 27.9)	189.9 (185.9 to 193.9)
None	0.0 (0.0 to 0.0)	−0.2 (−0.3 to −0.1)	−25.9 (−26.8 to −25.0)	−187.0 (−190.9 to −183.1)
Some	24.4 (23.3 to 25.5)	22.7 (21.6 to 23.8)	−3.0 (−4.3 to −1.7)	−164.0 (−168.1 to −159.9)
Chronic	193.0 (188.8 to 197.1)	189.0 (184.8 to 193.2)	163.3 (159.1 to 167.5)	2.6 (−2.3 to 7.5)

*Adjusted for age, sex, surgical indication, bilateral status, RxRisk-V comorbidity burden, back pain, year of operation, and prior THA and post-THA other analgesic medication use.
OME, oral morphine equivalents; THA, total hip arthroplasty.

2.85 to 5.33), depression (OR=1.70, 95% CI 1.20 to 2.41), migraine (OR=5.30, 95% CI 1.12 to 25.01), liver disease (mild; OR=4.33, 95% CI 1.08 to 17.35), weight loss (OR=2.60, 95% CI 1.06 to 6.39), dementia (OR=2.19, 95% CI 1.06 to 6.39), gastric acid disease

(OR=1.62, 95% CI 1.16 to 2.25), hyperlipidaemia (OR=1.38, 95% CI 1.00 to 1.91), and preoperative use of hypnotics (OR=1.56, 95% CI 1.13 to 2.16) and anti-neuropathic pain medication (OR=3.11, 95% CI 2.05 to 4.72; table 4).

Table 3 Risk factors of persistent chronic opioid use after THA in patients who were chronic user presurgery (N=302/593)

Risk factor	Crude OR (95% CI)	p Value	Adjusted OR (95% CI)	p Value
Demographics				
Age (per 10-year increment)	0.97 (0.95 to 0.98)	<0.001	0.96 (0.93 to 0.99)	<0.001*
Opioid-related comorbidities				
Back pain	1.69 (1.20 to 2.38)	0.003	1.99 (1.20 to 3.23)	0.008*
Depression	1.60 (1.12 to 2.28)	0.009	1.14 (0.67 to 1.96)	0.629
Psychoses	1.97 (0.78 to 4.96)	0.149	1.47 (0.39 to 5.42)	0.563
Medical comorbidities				
Diabetes with complications	2.19 (1.12 to 3.87)	0.007	3.52 (1.05 to 11.8)	0.042*
IHD hypertension	0.80 (0.58 to 1.12)	0.199	0.66 (0.41 to 1.07)	0.090
Diabetes uncomplicated	2.17 (1.36 to 3.45)	0.001	1.89 (0.78 to 4.57)	0.160
Liver disease (severe) or failure	1.49 (0.89 to 2.50)	0.129	1.25 (0.59 to 2.66)	0.566
Migraine	2.93 (0.59 to 14.6)	0.190	1.76 (0.18 to 17.3)	0.628
Hypertension	1.28 (0.92 to 1.79)	0.147	0.98 (0.59 to 1.63)	0.934
RA/collage vascular disorders	2.46 (0.76 to 7.92)	0.133	1.01 (0.25 to 4.71)	0.925
Analgesic use				
Days using opioids prior to surgery		<0.001		<0.001
<94	−†		−†	
94–156	Ref		Ref	
157–224	3.75 (2.28 to 6.18)		3.63 (2.08 to 6.34)	
225+	4.85 (2.89 to 8.15)		5.18 (2.92 to 9.19)	
Average daily use of opioids (per 10 OME increment)	1.11 (1.06 to 1.15)		1.06 (1.00 to 1.11)	0.065
Pre-THA: hypnotics and sedatives	1.72 (1.21 to 2.42)	0.002	2.52 (1.48 to 4.30)	<0.001*

*Significant variables (p<0.05) in final model.

†No cases of persistent chronic users in this group, could not model this level.

IHD, ischaemic heart disease; OME, oral morphine equivalents; RA, rheumatoid arthritis; Ref, reference; THA, total hip arthroplasty.

Table 4 Risk factors for developing new chronic opioid use after THA surgery (N=190/8932)

Risk factor	Crude OR (95% CI)	p Value	Adjusted OR (95% CI)	p Value
Demographics				
Sex: women vs men	1.47 (1.09 to 1.97)	0.011	1.40 (1.00 to 1.96)	0.049*
Opioid-related comorbidities				
Back pain	5.52 (4.12 to 7.41)	<0.001	3.90 (2.85 to 5.33)	<0.001*
Depression	2.13 (1.56 to 2.93)	<0.001	1.70 (1.20 to 2.41)	0.003*
Alcohol abuse	3.08 (1.23 to 7.71)	0.016	2.16 (0.75 to 6.22)	0.152
Psychoses	2.98 (1.55 to 5.74)	0.001	1.39 (0.65 to 2.96)	0.392
Anxiety	1.66 (1.14 to 2.43)	0.009	1.00 (0.66 to 1.50)	0.990
Medical comorbidities				
Migraine	5.16 (1.19 to 22.38)	0.028	5.11 (1.08 to 24.18)	0.040*
Liver mild disease	7.37 (2.16 to 25.10)	0.001	4.33 (1.08 to 17.35)	0.039*
Weight loss	3.82 (1.64 to 8.89)	0.002	2.60 (1.06 to 6.39)	0.038*
Dementia	2.79 (1.40 to 5.56)	0.003	2.19 (1.04 to 4.61)	0.039*
Gastric acid disease	2.49 (1.84 to 3.36)	<0.001	1.62 (1.16 to 2.25)	0.004*
Hyperlipidaemia	1.76 (1.32 to 2.34)	<0.001	1.38 (1.00 to 1.91)	0.048*
Diabetes with complications	2.08 (1.34 to 3.25)	0.001	1.86 (0.97 to 3.57)	0.063
Epilepsy	3.15 (1.97 to 5.02)	<0.001	1.01 (0.58 to 1.77)	0.972
Benign prostatic hypertrophy	1.64 (0.89 to 3.05)	0.116	1.61 (0.81 to 3.22)	0.176
Peripheral vascular disease	2.44 (1.27 to 4.68)	0.008	1.57 (0.77 to 3.19)	0.215
Osteoporosis/Paget's	1.89 (1.32 to 2.71)	0.001	1.30 (0.88 to 1.93)	0.186
Myocardial infarction	2.46 (1.32 to 4.59)	0.005	1.46 (0.73 to 2.94)	0.284
Diabetes uncomplicated	1.40 (0.92 to 2.13)	0.114	0.76 (0.41 to 1.39)	0.374
Antiplatelets agents	1.38 (1.03 to 1.85)	0.032	0.85 (0.61 to 1.17)	0.317
Chronic pulmonary disease	2.10 (1.30 to 3.41)	0.003	1.31 (0.74 to 2.33)	0.349
Reactive airway disease	1.33 (0.96 to 1.85)	0.091	0.89 (0.60 to 1.30)	0.538
Hypothyroidism	1.63 (1.02 to 2.61)	0.042	1.22 (0.74 to 2.00)	0.442
Angina	1.86 (1.28 to 2.68)	0.001	1.18 (0.77 to 1.79)	0.446
RA/collage vascular disorders	2.63 (1.06 to 6.54)	0.038	1.38 (0.49 to 3.84)	0.542
Inflammatory bowel syndrome	2.55 (0.92 to 7.06)	0.071	1.37 (0.45 to 4.17)	0.583
Liver disease (severe) or failure	2.21 (1.24 to 3.93)	0.007	1.10 (0.59 to 2.04)	0.764
Congestive heart failure	1.85 (1.30 to 2.64)	0.001	1.07 (0.72 to 1.60)	0.728
Parkinson's disease	2.23 (0.97 to 5.12)	0.059	1.14 (0.43 to 3.01)	0.796
Renal disease/failure	1.91 (1.10 to 3.32)	0.022	1.06 (0.59 to 1.91)	0.849
Other neurological disorder	2.29 (0.92 to 5.68)	0.074	1.14 (0.38 to 3.44)	0.811
Other analgesic use				
Pre-THA: hypnotics and sedatives	2.31 (1.70 to 3.12)	<0.001	1.56 (1.13 to 2.16)	0.007*
Pre-THA: antineuropathic pain	4.72 (3.31 to 6.72)	<0.001	3.11 (2.05 to 4.72)	<0.001*
Pre-THA: muscle relaxants	4.22 (0.87 to 18.06)	0.053	1.95 (0.39 to 9.74)	0.416
Pre-THA: corticosteroids	1.78 (1.25 to 2.55)	0.002	1.17 (0.79 to 1.74)	0.430
Bilateral procedure (more than 365 days)	0.60 (0.36 to 1.00)	0.049	0.70 (0.41 to 1.20)	0.194

*Significant variables ($p < 0.05$) in final model.

RA, rheumatoid arthritis; THA, total hip arthroplasty.

DISCUSSION

In this large cohort of patients who had undergone THAs, we determined that 6.2% of patients were chronic opioid users before surgery, and 5.2% were chronic opioid users after surgery. After THA, 61.4% of the chronic users of opioid had been chronic users before surgery, and 38.6% of them were new chronic users postsurgery. After evaluating patient characteristics, 56 patient comorbidities and other analgesic medication, we identified several risk factors associated with chronic opioid use.

Both sex and age were associated with chronic opioid use. Being female was associated with a 40% higher risk of developing chronic opioid use after surgery. Identifying women at a higher risk of chronic use in a

THA population is consistent with studies that evaluated different aspects of the sex and pain relationship. Specifically, women are at a higher risk of acute pain after THA surgery,³¹ as well as persistent and chronic postoperative pain;³² therefore, women had higher general utilisation of opioids in the long term.^{6, 7} We also found that chronic opioid users were younger. While this was not a risk factor for development of new chronic opioid use post-THA, it was a risk factor for persistent chronic use or not reducing use after surgery. There is some evidence that younger patients are at a higher risk of persistent opioid use in the general surgical population.³³ It has also been suggested that younger patients utilise higher perioperative opioid amounts.³⁴ This higher utilisation is reported

even without consistent evidence that younger patients experience greater pain from the procedure; for example, Liu *et al*³¹ reported higher scores for moderate-to-severe pain in younger patients, but Petre *et al*³⁴ did not.

There are several opioid-related comorbidities associated with higher risk of chronic opioid use in our cohort. Back pain was the condition most consistently associated with chronic opioid use. Patients with back pain, diagnosed prior to surgery, were four times more likely to develop chronic opioid use if they did not already have it, and two times more likely to continue their chronic use after surgery. In the general population, back pain is one of the strongest predictors for opioid abuse,³⁵ and its association with the pain and utilisation of opioids in a THA population⁷ is expectedly strong.²⁰ Another condition commonly associated with high opioid utilisation and abuse, which was also found in our study, was depression.³⁶ Depression was risk factor for new chronic opioid use. This has been reported in at least two other THA cohorts, one which assessed depression using patient medication assessments and one via a patient-reported questionnaire.^{31 37}

One of the strongest general medical comorbidities risk factor for new opioid chronic use was pre-THA migraine, a condition associated with chronic pain and one where opioids are recommended for pain treatment.³⁸ Liver disease was also strongly associated with new chronic opioid use, confirming previously reported associations in non-THA cohorts.³⁹ Dementia, a moderate risk factor for new chronic use, was reportedly associated with chronic opioid use in general cohorts of patients, but to our knowledge, this is the first time it is reported in a THA cohort.⁴⁰ The dispensing of proton-pump inhibitors was used to identify patients suffering from gastric acid disorder, a condition present in 44% of our cohort. We found this condition to be weakly associated with new chronic use development, which to our knowledge has also not been previously reported. We did not assess the duration of proton-pump inhibitors use. While the majority of people who took these medications did not become chronic opioid users, long-term use of proton-pump inhibitors has been shown to increase the risk of bone fracture⁴¹ and surgical site infections,⁴² events that if present or developing after surgery could lead to the development of chronic opioid use after surgery. Weight loss, a moderate risk factor for new chronic use, and hyperlipidaemia, a borderline risk factor for chronic opioid use, were identified, but to our knowledge such associations have not been previously evaluated and we cannot, therefore, make comparisons. Finally, some established risk factors for chronic opioid use, including psychiatric comorbidities, alcohol and substance abuse, were not observed in our study. It is likely that these comorbidities were either well managed in these patients or the higher risk of opioid abuse in them was recognised and properly managed by their providers.

Diabetes was a moderate risk factor for persistent opioid use in this study. This has also been reported in other major elective surgical procedures³³ and corroborates a recent report of it being associated with persistent pain post-THA.⁵ Rajamäki *et al*⁵ suggested that either the constant chronic inflammation state that patients with diabetes are in or diabetic-related complications, such as neuropathy, could be associated with the mechanism to explain opioid use in patients with THA.

Prior opioid and adjuvant analgesics usage were also associated with risk of persistent or new chronic opioid use. The greater the number of days someone was dispensed opioids prior to surgery was associated with a higher likelihood of continuing to be a chronic user, which is consistent with studies reporting that the greater exposure to opioids, the greater the risk of abuse.⁴³ Use of other medications, such tricyclic antidepressants and anticonvulsants, recommended for neuropathic pain, was also associated with a higher risk of persistent and new chronic use; this again confirms findings from general major elective surgical populations.³³

Our study could not determine whether opioid use was associated with pain in the index joint. While we believe that opioid use is an efficient proxy for pain assessment measurement in joint replacement patients, as it identifies someone who has been prescribed a medication that is only recommended for refractory pain management,¹ we understand that measuring and evaluating pain is difficult and more complex than only using opioid prescriptions.⁴⁴ We also could not identify the reasons for the other analgesic medication patients were taking during the study timeline. It is possible they were prescribed these medications for reasons other than the joint pain. Additionally, our observational study used prescriptions to measure opioid use in this cohort of patients; therefore, we do not know whether patients were compliant to medication instructions.

Our study limitations include the conservative definition of chronic opioid user as someone who was prescribed opioids for 90 consecutive days or 120 non-consecutive days, which could miss the identification of opioid abuse (ie, overdoses or poisoning earlier on) in this patient population. We tried to include as many comorbidities, including those like migraine that is considered to be a chronic pain condition, in our analysis, but it is still possible that other chronic pain conditions, such as fibromyalgia, can be present and not accounted for in our analysis, both as a possible risk factor and as a confounder of the other relationships studied. Other confounding variables that we were unable to assess, such as body mass index, psychological well-being, function status, prescribers' preferences, as well as information regarding the index surgery, such as intraoperative complications, anaesthesia, length of stay and discharge destination, could affect the relationship between the risk factors we identified for persistent or new chronic use of opioid. Also, it is possible that due to

the relatively low proportion of patients with some of the risk factors assessed, we may have been underpowered to detect associations between these factors and the likelihood of chronic or persistent opioid use. Finally, our study was comprised of an older cohort of Australian patients, making our results possibly less generalisable to a younger joint-replacement population.

The strengths of our study include our large patient cohort, which allowed for robust estimates on various risk factors. In an attempt to provide the most comprehensive assessment of patient comorbidities, we used three comorbidity measures to identify conditions using both inpatient hospitalisations and medication history. Our use of pharmacy data to determine opioid use, which provided us with more detailed information on the medication used by the study cohort, was less subject to recall bias than other studies that relied on patient or surgeon-reported measurements. Finally, the DVA administrative data used in this study covers all services provided to the Australian veteran population, assuring that we had complete data on all the procedures, hospitalisations and medications provided to these patients. This guaranteed to our study a low risk of missing data and attrition in the cohort.

CONCLUSION

Of the 492 (5% of the total cohort) chronic opioid users after THA, 61% were persistent chronic users and 39% became chronic users after surgery. Back pain, diabetes and preoperative use of hypnotics were strong risk factors for the persistent and new development of chronic opioid use. Additional risk factors for persistent use included younger age and longer use of opioids prior to surgery, while for new chronic use these included being a woman, depression, migraine, gastric acid disease and antineuropathic pain medications. These indicators of chronic opioid use can be used by clinicians for risk stratification prior to THA surgery, and will help to target patient groups for suitable pain management interventions presurgery and postsurgery.

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REFERENCES

- Zhang W, Moskowitz RW, Nuki G, *et al.* OARSI recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evidence-based, expert consensus guidelines. *Osteoarthritis Cartilage* 2008;16:137–62.
- Healthcare Cost and Utilization Project (HCUP). Nationwide inpatient sample (NIS). Statistical Brief 186. *Secondary Healthcare Cost and Utilization Project (HCUP). Nationwide inpatient sample (NIS). Statistical Brief* 186. 2014. <http://www.hcup-us.ahrq.gov/reports/statbriefs/sb186-Operating-Room-Procedures-United-States-2012.pdf>
- Australian Institute of Health and Welfare (AIHW). Admitted patient care 2013–14: Australian hospital statistics. Secondary Australian Institute of Health and Welfare (AIHW). Admitted patient care 2013–14: Australian hospital statistics. 2014. <http://www.aihw.gov.au/publication-detail?id=60129550483>
- Beswick AD, Wylde V, Goberman-Hill R, *et al.* What proportion of patients report long-term pain after total hip or knee replacement for osteoarthritis? A systematic review of prospective studies in unselected patients. *BMJ Open* 2012;2:e000435.
- Rajamäki TJ, Jämsen E, Puolakka PA, *et al.* Diabetes is associated with persistent pain after hip and knee replacement. *Acta Orthop* 2015;86:586–93.
- Singh JA, Lewallen D. Predictors of pain and use of pain medications following primary total hip arthroplasty (THA): 5,707 THAs at 2-years and 3,289 THAs at 5-years. *BMC Musculoskeletal Disord* 2010;11:90.
- Valdes AM, Warner SC, Harvey HL, *et al.* Use of prescription analgesic medication and pain catastrophizing after total joint replacement surgery. *Semin Arthritis Rheum* 2015;45:150–5.
- Hastie BA, Gilson AM, Maurer MA, *et al.* An examination of global and regional opioid consumption trends 1980-2011. *J Pain Palliat Care Pharmacother* 2014;28:259–75.
- Morden NE, Munson JC, Colla CH, *et al.* Prescription opioid use among disabled Medicare beneficiaries: intensity, trends, and regional variation. *Med Care* 2014;52:852–9.
- Frenk SM, Porter KS, Paulozzi LJ. Prescription opioid analgesic use among adults: United States, 1999-2012. *NCHS Data Brief* 2015;189:1–8.
- Roxburgh A, Bruno R, Larance B, *et al.* Prescription of opioid analgesics and related harms in Australia. *Med J Aust* 2011;195:280–4.
- Laroche MR, Zhang F, Ross-Degnan D, *et al.* Trends in opioid prescribing and co-prescribing of sedative hypnotics for acute and chronic musculoskeletal pain: 2001-2010. *Pharmacoepidemiol Drug Saf* 2015;24:885–92.
- Levy B, Paulozzi L, Mack KA, *et al.* Trends in opioid analgesic-prescribing rates by specialty, U.S., 2007-2012. *Am J Prev Med* 2015;49:409–13.
- Kehlet H, Dahl JB. Anaesthesia, surgery, and challenges in postoperative recovery. *Lancet* 2003;362:1921–8.
- DuPen A, Shen D, Ersek M. Mechanisms of opioid-induced tolerance and hyperalgesia. *Pain Manag Nurs* 2007;8:113–21.

16. Benyamin R, Trescott AM, Datta S, *et al.* Opioid complications and side effects. *Pain Physician* 2008;11(Suppl):S105–20.
17. Caughey GE, Vitry AI, Gilbert AL, *et al.* Prevalence of comorbidity of chronic diseases in Australia. *BMC Public Health* 2008;8:221.
18. Cram P, Lu X, Kaboli PJ, *et al.* Clinical characteristics and outcomes of Medicare patients undergoing total hip arthroplasty, 1991-2008. *JAMA* 2011;305:1560–7.
19. Vogeli C, Shields AE, Lee TA, *et al.* Multiple chronic conditions: prevalence, health consequences, and implications for quality, care management, and costs. *J Gen Intern Med* 2007;22(Suppl 3):391–5.
20. Lanting BA, MacDonald SJ. The painful total hip replacement: diagnosis and deliverance. *Bone Joint J* 2013;95-B(Suppl A):70–3.
21. WHO. *Collaborating centre for drug statistics methodology, guidelines for ATC classification and DDD assignment*. 2014. Oslo, Norway, 2013. http://www.whooc.no/filearchive/publications/1_2013guidelines.pdf
22. Health AGDo. Australian Government Department of Health. Pharmaceutical Benefits Services. Secondary Australian Government Department of Health. Pharmaceutical Benefits Services. 2014. <http://www.pbs.gov.au/browse/medicine-listing>
23. International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification (ICD-10-AM). Secondary International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification (ICD-10-AM) July 2013. 2013. <https://www.accd.net.au/lcd10.aspx>
24. Von Korff M, Saunders K, Thomas Ray G, *et al.* De facto long-term opioid therapy for noncancer pain. *Clin J Pain* 2008;24:521–7.
25. Australian and New Zealand College of Anaesthetist FoPM. Opioid Conversion to oral Morphine Equivalent Daily Dose (oMEDD). Secondary Opioid Conversion to oral Morphine Equivalent Daily Dose (oMEDD). 2014. <http://www.fpm.anzca.edu.au/resources/professional-documents/OPIOID20DOSE20EQUIVALENCE.pdf>
26. Quan H, Sundararajan V, Halfon P, *et al.* Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care* 2005;43:1130–9.
27. Fishman PA, Goodman MJ, Hornbrook MC, *et al.* Risk adjustment using automated ambulatory pharmacy data: the RxRisk model. *Med Care* 2003;41:84–99.
28. Votrubec M, Thong I. Neuropathic pain—a management update. *Aust Fam Physician* 2013;42:92–7.
29. Pandeya N, Green AC, Whiteman DC, *et al.* Prevalence and determinants of frequent gastroesophageal reflux symptoms in the Australian community. *Dis Esophagus* 2012;25:573–83.
30. Ruzsniowski P, Soufflet C, Barthélémy P. Nonsteroidal anti-inflammatory drug use as a risk factor for gastro-oesophageal reflux disease: an observational study. *Aliment Pharmacol Ther* 2008;28:1134–9.
31. Liu SS, Buvanendran A, Rathmell JP, *et al.* Predictors for moderate to severe acute postoperative pain after total hip and knee replacement. *Int Orthop* 2012;36:2261–7.
32. Nikolajsen L, Brandsborg B, Lucht U, *et al.* Chronic pain following total hip arthroplasty: a nationwide questionnaire study. *Acta Anaesthesiol Scand* 2006;50:495–500.
33. Clarke H, Soneji N, Ko DT, *et al.* Rates and risk factors for prolonged opioid use after major surgery: population based cohort study. *BMJ* 2014;348:g1251.
34. Petre BM, Roxbury CR, McCallum JR, *et al.* Pain reporting, opiate dosing, and the adverse effects of opiates after hip or knee replacement in patients 60 years old or older. *Geriatr Orthop Surg Rehabil* 2012;3:3–7.
35. Deyo RA, Von Korff M, Duhkooop D. Opioids for low back pain. *BMJ* 2015;350:g6380.
36. Sehgal N, Manchikanti L, Smith HS. Prescription opioid abuse in chronic pain: a review of opioid abuse predictors and strategies to curb opioid abuse. *Pain Physician* 2012;15(Suppl):ES67–92.
37. Wylde V, Jeffery A, Dieppe P, *et al.* The assessment of persistent pain after joint replacement. *Osteoarthritis Cartilage* 2012;20:102–5.
38. Silberstein SD. Practice parameter: evidence-based guidelines for migraine headache (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2000;55:754–62.
39. Rogal SS, Winger D, Bielefeldt K, *et al.* Pain and opioid use in chronic liver disease. *Dig Dis Sci* 2013;58:2976–85.
40. Jensen-Dahm C, Gasse C, Astrup A, *et al.* Frequent use of opioids in patients with dementia and nursing home residents: a study of the entire elderly population of Denmark. *Alzheimers Dement* 2015;11:691–9.
41. Yu EW, Bauer SR, Bain PA, *et al.* Proton pump inhibitors and risk of fractures: a meta-analysis of 11 international studies. *Am J Med* 2011;124:519–26.
42. Sadoghi P, Liebensteiner M, Agreiter M, *et al.* Revision surgery after total joint arthroplasty: a complication-based analysis using worldwide arthroplasty registers. *J Arthroplasty* 2013;28:1329–32.
43. Edlund MJ, Steffick D, Hudson T, *et al.* Risk factors for clinically recognized opioid abuse and dependence among veterans using opioids for chronic non-cancer pain. *Pain* 2007;129:355–62.
44. Breivik H, Borchgrevink PC, Allen SM, *et al.* Assessment of pain. *Br J Anaesth* 2008;101:17–24.