Research Paper

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Prescription trajectories and effect of total hip arthroplasty on the use of analgesics, hypnotics, antidepressants, and anxiolytics: results from a population of total hip arthroplasty patients

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Abstract

Total hip arthroplasty (THA) has been shown to reduce pain and improve function. In addition, it is suggested that THA improves sleep and alleviates symptoms of anxiety and depression. Patients with chronic pain are frequent users of analgesic and psychotropic drugs and thereby risk adverse drug events. The impact of THA on such drug use has not been thoroughly investigated. Based on merged data from the Norwegian Prescription Database and the Norwegian Arthroplasty Register, this study sought to investigate redeemed medications in a complete population (N = 39,688) undergoing THA in 2005 to 2011. User rates and redeemed drug volume of analgesics (nonsteroid anti-inflammatory drugs (NSAIDs), opioids, and nonopioids) and psychotropics (hypnotics, anxiolytics, and antidepressants) were calculated for 4 quarters before and 4 quarters after surgery. We analysed preoperative prescription trends (Q1 vs Q4), postoperative prescription (Q4 vs Q5), and long-term effect of surgery (Q4 vs Q8). Before surgery, use of all drug groups increased from Q1 to Q4. Use of opioids, nonopioids, and hypnotics dramatically increased from Q4 to Q5. Long-term (Q4 vs Q8) surgery reduced prescriptions of analgesics, hypnotics, and anxiolytics, but not antidepressants. Overall, the present results extend the positive effects of THA to include reduced reliance on medication to alleviate symptoms.

Keywords: Register study, Total hip arthroplasty, Analgesics, Psychotropics

1. Introduction

Most patients waiting for total hip arthroplasty (THA) report constant pain and use of pain medications.[10,43] Nocturnal pain is a key indication for THA,[44] and 80% of all patients report awakening at night because of pain before surgery.[43] The prevalence of anxiety and depression in these patients is between 5% and 15%.[10,43] Consistently successful in relieving pain and improving function,[39,33] THA has also been found to have additional positive effects including reduction of sleep problems[12,26,61] and alleviation of symptoms of anxiety and depression,[31,22] all leading to improved quality of life. Notably, preoperative mental health and sleep problems have been found to predict postoperative levels of pain, functional level, and quality of life.[12,22] Overall, this reflects mutual relationships between pain, sleep, and mental health.[9,11,15,18,24,34,48,51,54]

Analgesics and psychotropic drugs are often prescribed to control pain, sleep problems, and mental health.[43] However, little is known about the corresponding use of analgesics and psychotropic drugs before and after THA. Self-reported analgesic use in these patients is as high as 97%.[52] Prescription rates are lower, not including over-the-counter medications. Most THA patients received prescriptions for nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids during the 2-year period before surgery.[10,38] The use of medication increased over time as the date of surgery approached.[10] To our knowledge, only 1 study has investigated changes in the use of analgesics after THA, reporting reduced user rates of NSAIDs during the year after surgery.[13]

Total hip arthroplasty patients experience increasing levels of pain leading up to surgery, elevated postoperative pain during a 3-month recovery phase and lower level than presurgery pain at 6 to 12 months after surgery.[2,33,37,45,53] If prescription patterns follow pain trajectories, analysis of short prescription intervals is necessary to elucidate trajectories of medication use. Knowledge about the use of medication in THA patients in large-scale,

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pre–post designs is warranted, given the risk of adverse drug reactions, drug-drug interactions, and/or postoperative costs associated with pharmacotherapy for chronic pain and frequent comorbid symptoms.[4,8,23,41,56]

Based on information from 2 nationwide registers, the Norwegian Prescription Database (NorPD) and the Norwegian Hip Arthroplasty Register, the aim of this study was to extend previous research on THA and medication use by analysing prescription patterns of 3 groups of analgesics and 3 groups of psychotropics over a 2-year window of exposure; 1 year before and 1 year after surgery. Specifically, we investigated prescription trends leading up to surgery, changes in medication use in the recovery period after surgery, and long-term effects of surgery on medication use. We hypothesized that (1) use of these medications would increase before surgery, (2) drug use would further increase in the postoperative phase, and (3) and that THA would reduce use of medications 1 year after surgery.

2. Materials and methods

2.1. Study population

The health care system in Norway is public and hip replacements are all financed by the compulsory insurance scheme.[49] Patients who undergo elective surgery are referred to a hospital by a general practitioner. Prioritization generally follows 3 criteria: the degree of severity, the expected efficiency of treatment, and the cost in relation to the expected outcome of the treatment.[5] A total of 54,402 primary THAs were performed in the period 2004 to 2012. We excluded surgeries in the opposite hip for the same person (n = 6509), reoperations within the following year (n = 742), and patients deceased within 2 years after surgery (n = 1449) from the analyses. To be able to analyse medication use during the year before and after surgery, persons undergoing THA in 2004 and 2012 were excluded (n = 6014). Thus, the study population comprised 39,688 persons. Data were then merged with prescription data from the NorPD, including redeemed prescriptions 1 year before and 1 year after the date of surgery.

2.2. Study design and data sources

This study was a register-based prospective study using data from the NorPD maintained at the Norwegian Institute of Public Health and data from the National Arthroplasty Register in Norway at Haukeland University Hospital used. Data from both sources were merged by Statistics Norway, using patients' unique encrypted identifying code, enabling us to analyse the data at the individual level while ensuring personal anonymity.

2.2.1. Norwegian prescription database

The NorPD is a national health register containing information on all prescription drugs dispensed to all home-dwelling individuals at all pharmacies in Norway from January 2004 to this time.[30] The register covers medications fully paid for by patients, and those reimbursed by the government. The database stores detailed information on items dispensed (the dispensed item's generic name, Anatomical Therapeutic Chemical code, the defined daily dose (DDD) of the prescribed drug, and date of dispensing)[47] and basic demographic information about patients (person's unique personal identifying code, age, sex, and person's year of death) about patients. However, information is lacking at the individual level concerning medications issued for institutionalized patients in nursing homes and hospitals.[35] We extracted data from NorPD from 2004 to 2012. The medications included in this study were classified according to the Anatomical Therapeutic Chemical classification system.[47] Analgesics analysed in this study include M01A—NSAIDs, N02A—opioids, and N02B—other analgesics and antipyretics, hereafter called as nonopioid analgesics. Three subgroups of psychotropic drugs were included; N05C—hypnotics and sedatives, hereafter called as hypnotics, N05B—anxiolytics, and N06A—antidepressants.

2.2.2. Norwegian national arthroplasty register

This person-identifiable health register receives data of operated joint prostheses from all 70 hospitals in Norway performing THA. Completeness is high (97%) for THA.[25] We extracted the following information from the register: the persons' unique personal identification code, date of operation, primary or secondary operation, indication for operation, type of operation, and perioperative complications. The patients were scored preoperatively by the American Society of Anesthesiologists (ASA) physical status classification system[3] as either: 1 healthy person; 2 mild systemic disease; 3 severe systemic disease; 4 severe systemic disease that is a constant threat to life; and 5 moribund person not expected to survive.

2.3. Medication use

Two measures of medication use were included. User rates were defined as number of persons who redeemed 1 or more prescriptions during the period studied. Furthermore, dispensed drug volumes were quantified as number of DDD. The DDD is a technical measuring unit determined on the basis of evaluation of international use of the substance in question and is defined as the assumed average daily maintenance dose for a drug used for its main indication in adults.[47] The DDD used in this article refers to the total number of DDDs for each redeemed prescription and is calculated by the NorPD. The dispensed drug volume in DDD was summarized per quarter.

2.4. Analysis strategy and statistics

Analyses were performed using SPSS Statistics, version 21. To examine changes in drug use over time, the 2-year observation period was divided into 8 quarters (91 days each); 4 before (Q1-Q4), and 4 after (Q5-Q8) surgery for each patient. Drug utilization trends before surgery were examined by comparing Q1 with Q4, immediate postoperative changes by comparing Q4 with Q5, and changes from preoperative to follow-up were examined by comparing Q4 with Q8. Exact McNemar tests were performed for comparison of user rates and paired sample *t* tests when comparing drug volumes. The analyses for user rates and drug volumes were supplemented by effect size (Cohen *d*) calculation using DSTAT and interpreted according to Cohen[16] whereby 0.2 equates to a small effect, 0.5 to a medium effect, and effect sizes larger than 0.8 to a strong effect. A Bonferroni correction was applied because of multiple comparisons, setting the new critical *P* value to 0.005. Effect sizes for DDDs were corrected for dependence between means.[50]

2.5. Ethics and approvals

The study was approved by the Regional Committee for Medical and Health Research Ethics, The Norwegian Directorate for Health and Social Affairs, and by The Norwegian Data Protection Authority.

3. Results

3.1. Study population

Demographic characteristics of the study population are presented in **Table 1**. The mean age of persons undergoing THR was 68.5 years, 80.4% of the study population was above 60 years and 66.4% were female. The main reason for undergoing surgery was primary osteoarthritis (77.4%), and 79.1% of the study population was classified as belonging to ASA class 1 or 2 preoperatively.

3.2. Analgesic and psychotropic drug use related to total hip arthroplasty

At least 1 type of analgesic drug was redeemed by 49.3% of the study population during the year before THA: 37.9% were dispensed NSAIDs, 16.3% opioids, and 12.4% nonopioid analgesics, **Table 2**. In the same period, 23.1% redeemed any psychotropics, 14.3% redeemed hypnotics (1.8% benzodiazepines, 12.5% Z-hypnotics, and 0.2% melatonin, data not shown), 7.8% redeemed antidepressants, and 7.6% redeemed anxiolytics, respectively. The drug utilization trajectories for all medication subgroups during the 4 quarters before, and the 4 quarters after THA are illustrated in **Figure 1** for user rates and **Figure 2** for DDDs.

3.2.1. Preoperative drug utilization trends (Q1 vs Q4)

User rates and redeemed drug volumes of analgesics increased from quarter 1 to quarter 4 preoperatively (**Figs. 1 and 2**). The increase was most pronounced for user rates and drug volume of opioids (from 16.3% to 27.8%, $P < 0.001$ and from 6.3 to 11.4 DDD, $P < 0.001$) and nonopioid analgesics (from 12.4% to 21.0%, $P < 0.001$ and from 4.6 to 9.4 DDD, $P < 0.001$). Effect sizes were small to medium (opioids: $d = 0.35$ for user rates and $d = 0.22$ for DDD; nonopioids: $d = 0.29$ for user rates and $d = 0.21$ for DDD, **Tables 2 and 3**). For NSAIDs, an increase from quarter 1 to quarter 4 (37.9% vs 39.4% and 32.9 vs 35.3 DDD) the change was also statistically significant ($P < 0.001$).

Table 1

Characteristics of study population at the time of surgery.

	n (%)
Sex	
Men	13,350 (33.6)
Women	26,338 (66.4)
Age, y	
Mean (SD)	68.5 (11.5)
Range	11-98
0-39	703 (1.8)
40-59	7056 (17.8)
60-69	11,960 (30.1)
70-79	13,329 (33.6)
80+	6640 (16.7)
Primary cause of operation	
Primary arthritis	30,737 (77.4)
ASA-class	
1	10,402 (26.2)
2	21,003 (52.9)
3	6965 (17.5)
4	113 (0.3)
Missing	1201 (3)

1 = healthy person, 2 = mild systemic disease, 3 = severe systemic disease, 4 = severe systemic disease that is a constant threat to life or moribund person.
ASA, American Society of Anesthesiologists physical status classification system.

Regarding psychotropic use, hypnotics and anxiolytics increased in user rates and drug volume during the preoperative period (hypnotics: from 14.3% to 16.8%, $P < 0.001$ and from 11.8 to 14.3 DDD, $P < 0.001$; anxiolytics: from 7.6% to 8.6% $P < 0.001$ and from 3.7 to 4.2 DDD, $P < 0.001$) while antidepressants increased significantly in drug volume only (from 8.9 to 9.8 DDD, $P < 0.001$, **Tables 2 and 3**). For changes in psychotropic user rates and drug volume effect sizes were small ($d = 0.11$-0.02).

3.2.2. Immediate postoperative changes (Q4 vs Q5)

Significant changes in medication use from quarter 4 to quarter 5 were detected (**Tables 2 and 3**). Analgesic use (both user rates and drug volume) increased the quarter after surgery regarding opioids (27.8% vs 65.4%, $P < 0.001$ and 11.4 vs 15.1 DDD, $P < 0.001$) and nonopioid analgesics (21.0% vs 60.5%, $P < 0.001$ and 9.4 vs 17.8 DDD, $P < 0.001$) Effect sizes were large for both user rates of opioids ($d = 0.8$) and nonopioids ($d = 0.85$). For NSAIDs, user rates (from 39.4% to 23.0%) and drug volumes (from 35.3 to 13.9 DDD) decreased significantly, with an effect size of 0.40 for user rates and 0.37 for drug volume. User rates of hypnotics increased from 16.8% to 25.0%, but the corresponding change in drug volume was small, from 14.3 to 15.4 DDDs, however were statistically significant ($P < 0.001$). Effect sizes were small ($d = 0.27$ for user rates and 0.03 for drug volume). Conversely, a decrease was found for antidepressants (user rates: from 8.0% to 7.2%, $P < 0.001$ and drug volume: 9.8-7.9 DDD, $P < 0.001$) and for anxiolytics (drug volume: 4.2 vs 3.6 DDD, $P < 0.001$).

3.2.3. Changes from preoperative to follow-up (Q4 vs Q8)

Total hip arthroplasty was associated with reductions in use of medications in the long-term, as shown in **Table 3**. The use of analgesics decreased from quarter 4 to quarter 8, with user rates being halved for opioids (from 27.8% to 14.1%, $P < 0.001$, $d = 0.41$) and NSAIDs (from 39.4% to 18.0%, $P < 0.001$, $d = 0.54$). User rates of nonopioid analgesics decreased (from 21.0% to 13.1%, $P < 0.001$, $d = 0.25$) in the same period. Moreover, drug volumes were reduced, especially for NSAIDs showing 35.3 DDD in quarter 4 to 13.6 DDD in quarter 8 ($P < 0.001$, $d = 0.37$). User rates and drug volumes for redeemed hypnotics and anxiolytics significantly decreased from quarter 4 to quarter 8, (hypnotics: 16.8% vs 16%, $P < 0.001$ and 14.3 vs 13.3 DDD, $P < 0.001$; anxiolytics: 8.6% vs 7.8%, $P < 0.001$ and 4.2 vs 3.7 DDD, $P < 0.001$) but with very small effect sizes. No significant changes were found for antidepressants (**Table 3**, **Figs. 1 and 2**).

4. Discussion

Prescription trajectories within a 2-year exposure window in a complete population of THA patients showed an increase in the use of analgesics (opioids and nonopioids) and hypnotics during the year before surgery, peaking in the postoperative recovery phase and decreasing after THA long-term, thus following the same trajectories as pain described in the THA literature.[37,44,53]

All medication subgroups increased in user rates and drug volume through the year before surgery. Increased pain has been reported the year before THA,[2,45] and our results support a previous study showing increased use of NSAIDs and opioids the year before total hip and knee arthroplasty.[10] The use of NSAIDs increased only until the third quarter, and then decreased. Nonsteroid anti-inflammatory drugs have several adverse side effects, especially in the elderly,[41,56] and patients

Table 2

Number and percentage of patients who have redeemed at least 1 prescription and amounts of redeemed medication (measured in DDDs) in 4 quarters preoperative (Q1-Q4) and 4 quarters postoperative (Q5-Q8).

	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8
User rates, percent (95% CI)								
Analgesics								
Any	49.3 (48.8-49.8)	53.7 (53.2-54.2)	59.8 (59.3-60.3)	58.5 (58.0-59.0)	86.7 (86.4-87.1)	35.1 (34.6-35.6)	34.4 (34.0-34.9)	32.8 (32.3-33.24)
Opioids	16.3 (15.9-16.6)	18.8 (18.4-19.2)	23.8 (23.4-24.2)	27.8 (27.3-28.2)	65.4 (64.9-65.8)	14.7 (14.4-15.0)	14.4 (14.2-14.8)	14.1 (13.7-14.4)
NSAIDs	37.9 (37.4-38.4)	40.6 (40.1-41.1)	44.2 (43.7-44.7)	39.4 (38.9-39.9)	23.0 (22.5-23.4)	19.3 (19.0-19.7)	19.3 (18.9-19.6)	18.0 (17.6-18.4)
Nonopioid analgesics	12.4 (12.1-12.8)	14.8 (14.5-15.2)	19.4 (19.0-19.7)	21.0 (20.6-21.4)	60.5 (60.1-61.0)	14.4 (14.1-14.8)	13.7 (13.4-14.1)	13.1 (12.8-13.5)
Psychotropics								
Any	23.1 (22.7-23.8)	23.4 (22.9-23.8)	24.3 (23.9-24.7)	25.8 (25.3-26.2)	32.5 (32.1-33.0)	24.3 (23.8-24.7)	24.4 (24.0-24.8)	24.6 (24.2-25.0)
Hypnotics	14.3 (14.0-14.7)	14.7 (14.3-15.0)	15.5 (15.2-15.9)	16.8 (16.4-17.1)	25.0 (24.6-25.5)	16.1 (15.7-16.5)	15.8 (15.5-16.2)	16.0 (15.6-16.3)
Antidepressants	7.8 (7.5-8.1)	7.7 (7.4-7.9)	7.9 (7.7-8.2)	8.0 (7.6-8.3)	7.2 (6.9-7.4)	7.8 (7.5-8.2)	8.1 (7.8-8.3)	8.2 (8.0-8.5)
Anxiolytics	7.6 (7.4-7.9)	7.7 (7.4-7.9)	7.9 (7.6-8.2)	8.6 (8.3-8.8)	8.5 (8.2-8.7)	7.7 (7.5-8.0)	7.8 (7.5-8.1)	7.9 (7.7-8.2)
Drug volume (DDDs), mean (SD)								
Analgesics								
Any	43.8 (69.1)	48.4 (72.6)	56.7 (77.2)	56.0 (78.3)	46.8 (56.4)	26.5 (56.9)	25.9 (55.3)	24.9 (55.6)
Opioids	6.3 (26.5)	7.1 (28.0)	9.0 (30.1)	11.4 (33.7)	15.1 (29.6)	6.0 (27.1)	5.7 (25.3)	5.8 (27.4)
NSAIDs	32.9 (57.5)	35.6 (59.4)	39.8 (62.0)	35.3 (59.2)	13.9 (36.8)	14.6 (39.8)	14.5 (39.3)	13.6 (38.3)
Nonopioid analgesics	4.6 (15.7)	5.8 (17.8)	8.0 (21.0)	9.4 (23.4)	17.8 (23.1)	5.9 (18.8)	5.7 (18.5)	5.6 (18.3)
Psychotropics								
Any	24.4 (68.7)	24.8 (70.9)	25.9 (71.0)	28.3 (75.8)	26.9 (67.0)	26.0 (70.4)	26.4 (71.2)	27.0 (75.3)
Hypnotics	11.8 (38.6)	12.1 (39.2)	12.8 (40.0)	14.3 (42.8)	15.4 (39.5)	13.3 (39.3)	13.3 (39.5)	13.6 (42.6)
Antidepressants	8.9 (40.3)	9.0 (41.5)	9.2 (41.7)	9.8 (43.7)	7.9 (37.0)	9.0 (40.3)	9.5 (41.4)	9.6 (41.8)
Anxiolytics	3.7 (20.4)	3.7 (22.6)	3.8 (21.2)	4.2 (24.1)	3.6 (21.1)	3.8 (21.8)	3.7 (21.6)	3.8 (22.4)

Persons may have redeemed medications from more than 1 medication class (N = 39,688).
CIs, Confidence Intervals; DDDs, defined daily doses; NSAIDs, nonsteroid anti-inflammatory drugs.

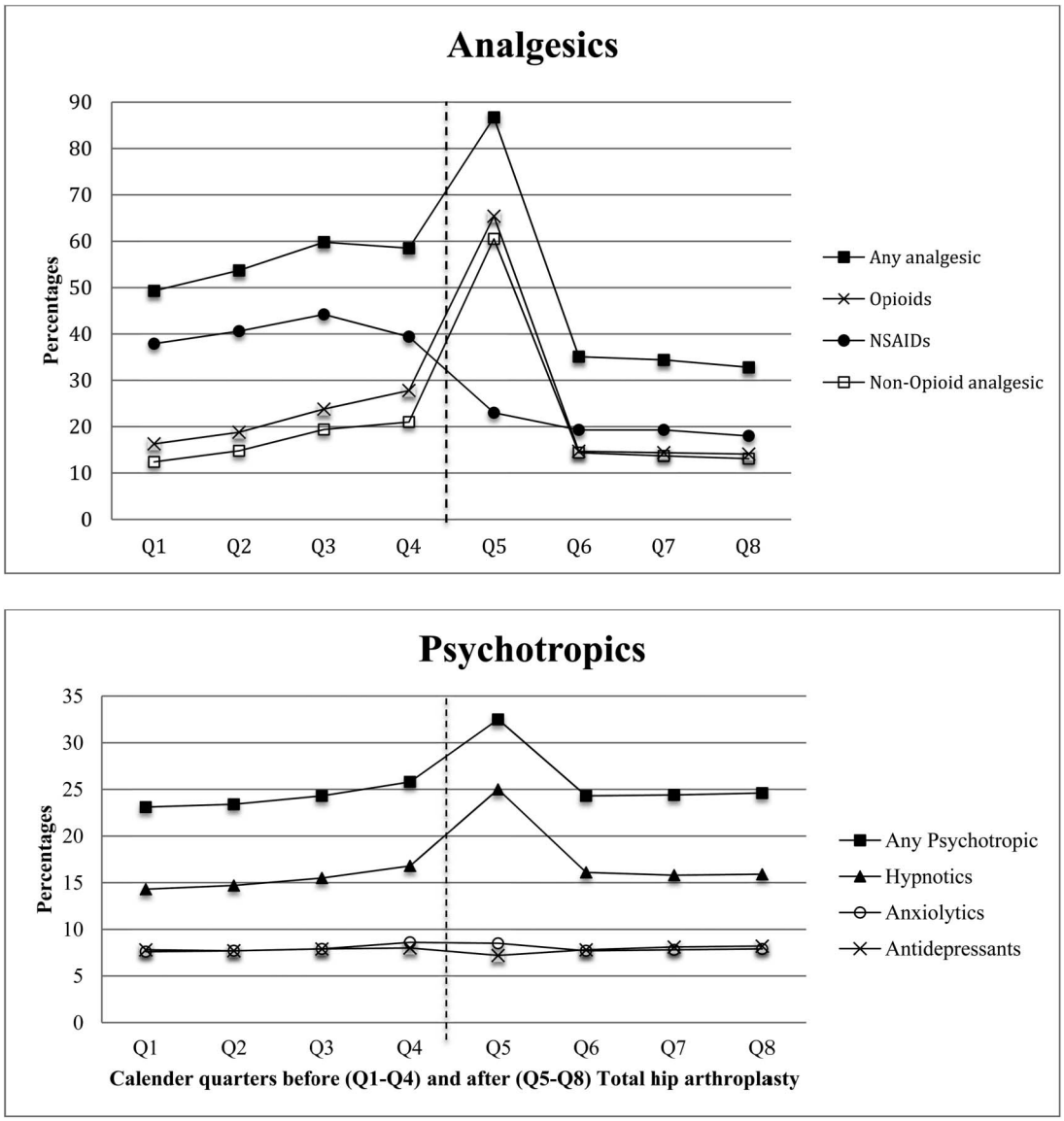

Figure 1. Prescription trajectories for user rates of redeemed prescriptions. NSAIDs, nonsteroid anti-inflammatory drugs.

might be encouraged to reduce their use of NSAIDs before surgery. Consequently, the observed increases in opioid and nonopioid use during the last quarter before surgery may be due to patients switching analgesic subgroup. Regardless, we conclude that hypothesis 1 was confirmed.

Total hip arthroplasty patients in their 3-month postoperative phase (Q5) doubled their use of opioid and nonopioid analgesics from Q4, corresponding with clinical pain trajectories previously reported.[33] It should be noted that in many patients, postoperative pain decreases earlier than 3 months after surgery,[19,33] and studies are warranted to investigate more accurately when the corresponding decrease in analgesics occurs. Interestingly, hypnotic use follows the same prescription trajectory as analgesics, supporting the link between pain and sleep. Although analgesics might be prescribed preemptively at discharge from hospital regardless of actual pain levels, patients normally have to ask their general practitioner specifically for new or repeat prescriptions of hypnotics. Hence, our finding may reflect an actual increase in sleep problems in the recovery phase after surgery. Interestingly, disturbed sleep leads to hyperalgesia and impaired endogenous pain modulation.[27,59] Furthermore, sleep disruptions postsurgically have been found to partially mediate the relationship between pain 1 month after surgery and functional limitations 3 months after surgery,[17] underscoring the importance of adequate sleep during postsurgical recovery. In that respect, increased short-term use of hypnotics may be positive, especially if non-pharmacological sleep interventions are not available. Improved sleep has both short-term and long-term effects on chronic pain[60] and may be ancillary to a positive cycle of reduced pain and improved sleep after THA. Narcotics have been found to disrupt sleep architecture and the increased need for hypnotics postsurgically found in this study may be due to adverse side effects of narcotic use.[55] The occurrence of such narcotic-induced sleep disturbance has to be taken into account to optimize the choice of analgesic and sedative medication in the treatment of THA patients. Regardless, our results warrant attention to the increased risk of adverse medication effects occurring with the use of both opioids and hypnotics increase in the recovery phase.

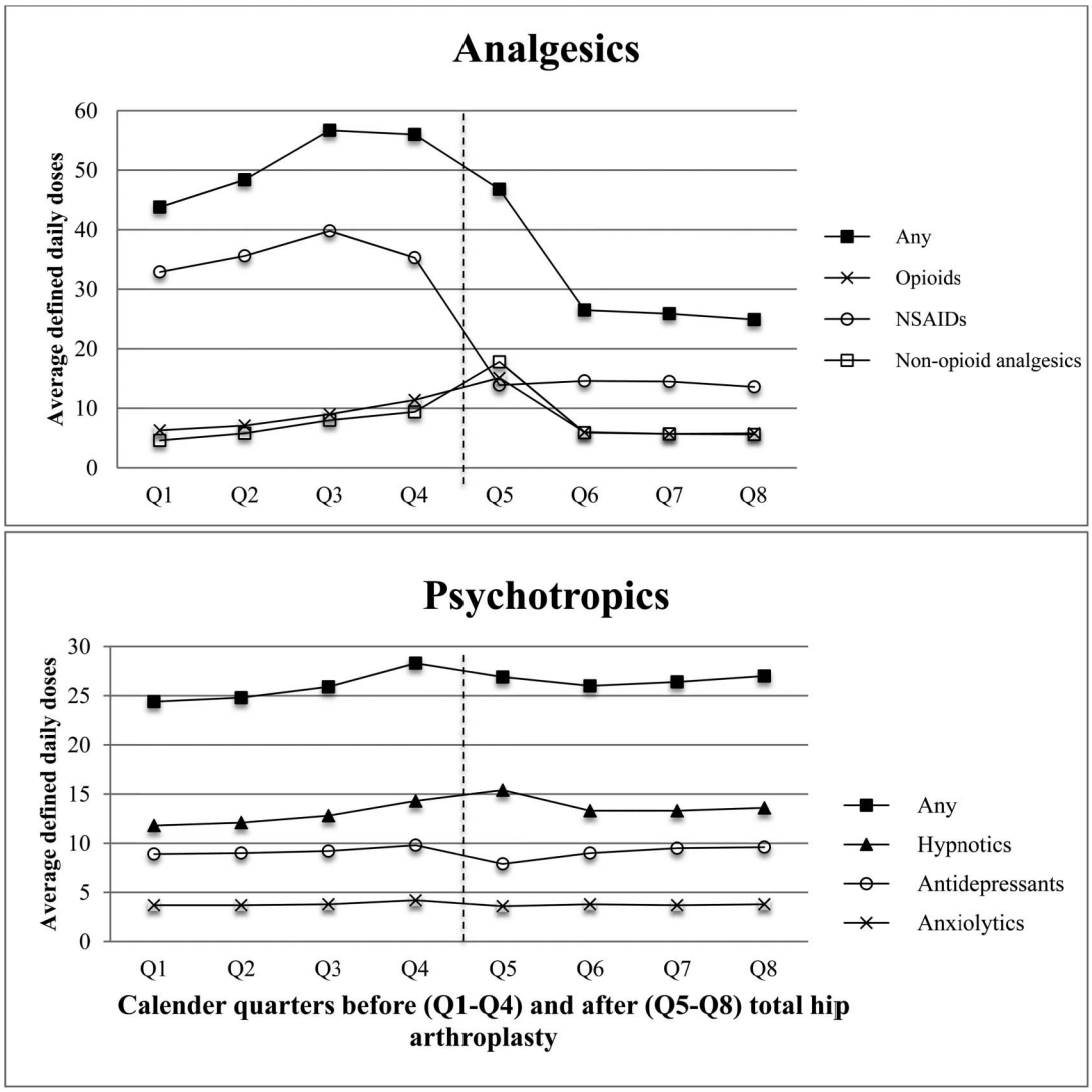

Figure 2. Prescription trajectories for drug volume DDDs. DDDs, defined daily doses; NSAIDs, nonsteroid anti-inflammatory drugs.

At odds with our expectations, user rates and drug volumes of antidepressants and drug volumes of anxiolytics decreased significantly from Q4 to Q5. This might reflect that anxiety and corresponding depression related to a forthcoming major surgical procedure declined rapidly after the surgery.[14] Still it should be noted that an increase in use of these drugs was observed after Q5, which might suggest that the anxiolytic and antidepressant effect of THA is not long-lasting. We conclude that hypothesis 2 was supported regarding analgesics and hypnotics, although not for antidepressants and anxiolytics.

Comparing preoperative levels (Q4) with long-term postoperative levels (Q8), THA was associated with decreased use of analgesics, hypnotics, and anxiolytics, but not antidepressants. The effect of THA has been thoroughly studied, with consistent findings of reduced pain after surgery,[33,39,52] and our results extend the effect to the use of analgesics. Nonsteroid anti-inflammatory drugs showed the most profound reduction, in accordance with 1 previous report.[13] Nonsteroid anti-inflammatory drugs are found to be superior to nonopioid analgesics, such as paracetamol (acetaminophen), when used to alleviate pain caused by inflammation. However, NSAIDs are not recommended for older patients and for long-term use in general because of increased risks of gastrointestinal bleeding, renal failure, and congestive heart failure.[56,41] Opioids can be an appropriate option for patients with osteoarthritis not responding to acetaminophen therapy and who have a contraindication for use of NSAIDs.[8,20,42] However, opioids also have potentially severe adverse side effects, such as cognitive impairment and falls, and risk of tolerance, dependence, and overdose.[6,8,23] In light of this, this study extends the positive effect of THA to include reduced use of all subgroups of analgesics.

Nocturnal pain is a key indication for THA,[44] and improvements in sleep have been found after surgery.[12,26,61] Accordingly, we expected user rates and drug volumes of hypnotics to be reduced after surgery, and to the best of our knowledge, this study is the first documentation of this outcome. Our findings support and extend decades of research establishing the bidirectional relationship between pain and sleep.[48] The reduction in hypnotics may indicate that many patients experience improved sleep after surgery, which may be an underrecognized benefit of THA that contributes to lower levels of pain and improved quality of life.[18,24,54] It should be noted that although pharmacological treatment is effective for short-term sleep problems, research-based guidelines do not recommend long-term use of hypnotics because of risks of dependence and tolerance.[1] Despite this, hypnotics are frequently prescribed long-term, especially in the

Table 3

Changes in medication use measured in user rates (prevalence) and drug volume (DDDs) preoperatively (Q1 vs Q4), immediately after surgery (Q4 vs Q5) and from preoperative to follow-up (Q4 vs Q8) in a population undergoing total hip replacement (N = 39,688).

	Preoperative trends (Q1 vs Q4)			Immediate postoperative change (Q4 vs Q5)			Changes from preoperative to follow-up (Q4 vs Q8)		
	χ^2	*d*		χ^2	*d*		χ^2	*d*	
User rates									
Analgesics									
Any	1016.2*	0.2		7756.0*	0.7		6722.3*	0.6	
Opioids	2309.5*	0.4		10,881.5*	0.8		3199.8*	0.4	
NSAIDs	27.5*	0.0		3103.1*	0.4		5396.7*	0.5	
Nonopioids	1580.7*	0.3		12,088.0*	0.9		1250.4*	0.3	
Psychotropics									
Any	208.1*	0.1		889.8*	0.2		39.9*	0.0	
Hypnotics	228.9*	0.1		1464.6*	0.3		24.2*	0.0	
Antidepressants	4.7			60.7*	0.1		3.5		
Anxiolytics	61.7*	0.1		0.6			27.5*	0.0	
	t	*d*	95% CI	*t*	*d*	95% CI	*t*	*d*	95% CI
Drug volume									
Analgesics									
Any	−32.4*	0.2	−13.0 to −11.5	24.8*	0.1	8.5 to 10.0	85.3*	0.4	30.4 to 31.9
Opioids	−43.6*	0.2	−5.4 to −4.9	−28.0*	0.1	−4.0 to −3.5	41.9*	0.2	5.3 to 5.8
NSAIDs	−7.5*	0.0	−3.0 to −1.8	72.7*	0.4	20.9 to 22.0	74.4*	0.4	21.2 to 22.3
Nonopioids	−42.5*	0.2	−4.9 to −4.5	−61.2*	0.3	−8.8 to −8.2	32.0*	0.2	3.6 to 4.0
Psychotropics									
Any	15.3*	0.1	−4.4 to −3.4	5.0*	0.0	0.8 to 1.9	4.6*	0.0	0.7 to 1.8
Hypnotics	−16.0*	0.1	−2.8 to −2.2	−6.3*	0.0	−1.4 to −0.8	4.1*	0.0	0.4 to 1.0
Antidepressants	−4.8*	0.0	−1.2 to −0.5	10.2*	0.1	1.5 to 2.2	1.0		−0.2 to 0.5
Anxiolytics	−7.1*	0.0	−0.7 to −0.4	8.7*	0.0	0.5 to 0.8	5.0*	0.0	0.3 to 0.6

* Indicates $P < 0.001$ (Bonferroni-corrected).

CI, confidence interval for the difference; *d*, Cohen D for effect size; DDDs, defined daily doses; NSAIDs, nonsteroid anti-inflammatory drugs; *t*, *t* test for paired samples (degrees of freedom for all variables: 1.39687); χ^2, McNemar chi-square test for related samples (continuity corrected).

elderly.[40] Sleep in chronic users of hypnotics has been found to be no better than in drug-free insomniacs,[58] further suggesting that the adverse risk associated with chronic hypnotic use outweighs the benefits in older patients.

Symptoms of depression and anxiety are prevalent among persons with chronic pain conditions such as osteoarthritis,[9,7] hence, patients with chronic pain are often prescribed both analgesics and psychotropics.[28,46] Total hip arthroplasty is shown to improve anxiety and depressive symptoms after surgery,[22] however this study only found corresponding reductions in the use of anxiolytics. The fact that no long-term effect of THA was observed regarding antidepressants might suggest that pain and depression are dissociated in these patients. Another explanation for the lack of association between THA and antidepressant use is that factors not assessed in this study influence level of depression. Still, most previous studies do support a causal link between pain and depression.[29] One-third of the patients in our study continue to use some form of prescription analgesic after 1 year, which may indicate persistent pain, comorbid pain conditions, or comorbid joint pain.[36,62] These patients have been found to report more depressive symptoms than those without.[32,36] Both clinical studies and studies on prescription data are needed to clarify the relationship between pain, depression, and medication use. We conclude that hypothesis 3 was supported regarding analgesics, hypnotics, and anxiolytics, but not for antidepressants.

The connection between a complete population of patients undergoing THA and a national prescription database comprises a major and unique asset of this study ensuring high ecologic validity. Furthermore, the large sample of participants should be considered a major strength of the study as it provided high statistical power to the analyses.

Still, our results should be considered in light of some limitations. First, redeemed drugs may not be used by the recipients or may be used for other indications. Inferences should therefore be made cautiously concerning pain, sleep, and mental symptoms. Second, information is limited to prescription drugs dispensed by retail pharmacies; hence, there is no information about purchases of over-the-counter products. Lower-dose, over-the-counter NSAIDs and non-opioid analgesics are to a nondetermined extent used to treat osteoarthritis in addition to prescription medications,[21] and we may therefore have underestimated the real extent of pharmacotherapy in this study. Additionally, in studies like this one with a very large number of participants, statistical significance should be separated from clinical relevance. We specifically added effect size estimations to overcome this limitation. Another confounder is individual differences in terms of initiatives and attitudes of treating MDs regarding drug prescriptions.[57] Some MDs may motivate patients to get their pills on a routine basis even if the patient does not want them, whereas others may adhere to a much more restrictive prescription practice. Regardless, in light of the inappropriate use of medication at the group level, the reduction in medication use may be highly valuable at the individual level.

In conclusion, THA is found to be associated with a reduction in the use of analgesics, hypnotics, and anxiolytics and extends the positive effects of this surgery to include medication use. Furthermore, the increase in the use of medication preoperatively suggests increasing symptom load in the waiting period. Last, analgesics and hypnotics showed a marked increase in the

postoperative phase. This warrants special attention from prescribers because one might reasonably assume that adverse effects (such as falls) can increase during this phase.

Conflict of interest statement

The authors have no conflicts of interest to declare.

Supplemental media

Video content associated with this article can be found online as Supplemental Digital Content at http://links.lww.com/PAIN/A233.

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