

Psychiatric Disorders and Psychopharmacologic Treatment as Risk Factors in Elective Fast-track Total Hip and Knee Arthroplasty

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ABSTRACT

Background: Psychiatric disorder (PsD) is rarely considered when evaluating perioperative risk factors. Studies on PsD are often limited by use of administrative coding, incomplete follow-up, and lack of preoperative data on psychopharmacological treatment.

Methods: A multicenter study with prospective registration on preoperative comorbidity, complete 90-day follow-up, and information on dispensed prescriptions on psychopharmacological treatment (excluding benzodiazepines). All departments used similar fast-track approaches and discharge to home. Evaluation of postoperative morbidity was based on discharge records. Odds ratios for length of stay (LOS) more than 4 days and surgery-related readmissions were calculated using multiple logistic regression adjusting for potential confounders.

Results: Of 8,757 procedures, 1,001 (11.4%) were in PsD patients. Of these, 43.4% used selective serotonin inhibitors (SSRIs), 31.6% used other antidepressants, 8.5% used a combination, and 16.5% used antipsychotics. PsD was associated with increased risk of LOS more than 4 days (16.5 vs. 7.3%; odds ratio, 1.90; 95% CI, 1.52 to 2.37), regardless of treatment with SSRIs (2.19; 1.62 to 2.97), other antidepressants (1.81; 1.25 to 2.61), or antipsychotics (1.90; 1.62 to 3.16). PsD was associated with increased 30- (9.9 vs. 5.1%; 1.93; 1.49 to 2.49) and 90-day surgery-related readmissions (12.8 vs. 7.4%; 1.68; 1.34 to 2.10), significant for SSRIs (1.97; 1.38 to 2.82 and 1.77; 1.29 to 2.43), other antidepressants (2.24; 1.51 to 3.32 and 1.82; 1.27 to 2.61), and antipsychotics (1.85; 1.03 to 3.31, 30 days only). In PsD patients, pain (1.4%), postoperative anemia (1.1%), and pulmonary complications (1.1%) were the most frequent causes of LOS more than 4 days. Hip displacements (2.8%) and falls (1.9%) were the most frequent readmissions, and 90-day surgery-related mortality was 0.7% with and 0.2% without PsD.

Conclusions: Psychopharmacologically treated PsD is a risk factor for postoperative morbidity after fast-track arthroplasty, regardless of treatment type. This may be due to PsD *per se* and/or drug-related side effects. (**ANESTHESIOLOGY 2015; 123:1281-91**)

CURRENTLY, there has been much focus on preoperative risk factors and strategies for reduction of postoperative morbidity.^{1,2} In this context, excess morbidity and mortality have been found in patients with severe psychiatric disorders (PsDs) such as schizophrenia and bipolar depression in both surgical and nonsurgical cohorts.³⁻⁷ This may be related to differences in lifestyle such as increased incidence of smoking or substance abuse and lower quality of health care,^{8,9} and similar results have been found in elderly people receiving psychopharmacological treatment for depression in primary care.¹⁰

Consequently, there is increased focus on the potential side effects of specific psychopharmacological drugs,^{6,10,11} with recent findings of an association between perioperative treatment with

What We Already Know about This Topic

- Psychiatric disorders are infrequently considered when evaluating perioperative risk factors for orthopedic surgery, and limited data are available on psychopharmacological treatment

What This Article Tells Us That Is New

- In a Danish evaluation of 8,757 knee or hip procedures, 11.4% of patients were receiving psychopharmacological treatment for mental disorders according to a preoperative questionnaire and nationwide prescription data
- Patients treated with selective serotonin inhibitors, other antidepressants, and/or antipsychotics had increased risk of postoperative morbidity after fast-track arthroplasty, regardless of treatment type and preoperative comorbidities

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selective serotonin inhibitors (SSRIs) and increased risk of in-hospital mortality and readmissions across a variety of surgical procedures.¹² In addition, long-term treatment with selective SSRIs may be associated with increased risk of gastric ulcer,¹¹ cardiac arrhythmias,¹³ and brain hemorrhage¹⁴ although the clinical relevance of these particular side effects is debatable.^{14,15} As most previous studies have used administrative and diagnostic coding when classifying psychiatric disease,^{7,12,16,17} and as detailed data on postoperative outcomes in these patients are scarce, further studies have been called for.^{3,6}

In this context, overall morbidity and hospital length of stay (LOS) have been reduced by modern multimodal “enhanced recovery” or “fast-track” programs,^{18,19} but the role of PsDs and psychopharmacologic treatment in this setting is unknown.

Consequently, the objectives of this detailed study were to investigate the occurrence of an LOS more than 4 days, 30- and 90-day surgery-related readmissions, and mortality after fast-track hip and knee replacement in patients with preoperative pharmacological treatment for PsD and in relation to specific type of psychopharmacological treatment. Secondly, we investigated the reasons for LOS more than 4 days and readmissions through review of discharge papers and medical records.

Materials and Methods

The Regional Ethics Committee waived the need for informed consent. Permission was acquired from the Danish National Board of Health, Copenhagen, Denmark, j.nr:3-3013-56/1/HKR and the Danish Data Protection Agency, Copenhagen, Denmark, j.nr: 2007-58-0015 to review and store patient records.

From 2010, all patients having total hip arthroplasty (THA) and total knee arthroplasty (TKA) at the participating orthopedic departments have completed a preoperative questionnaire on comorbidity- and patient-related factors, including whether they have mental disorders requiring psychopharmacological treatment (see Supplemental Digital Content 1, <http://links.lww.com/ALN/B141>, which lists the items on the questionnaire). Staff were available for completing the questionnaire which is subsequently entered into the Lundbeck Foundation Centre Database (LCDB). The LCDB has been established to facilitate studies on patient safety after fast-track THA and TKA with focus on both patient characteristics^{20–22} and specific complications.²³ This is an ongoing effort with an increasing number of participating departments, intended to elucidate who and why the high-risk patient is at risk.² The LCDB is registered as a study registry on ClinicalTrials.gov ID: NCT01515670.

The current study analyzed prospectively collected data on preoperative patient characteristics in primary

elective unilateral THA and TKA between January 2010 and November 2012 in seven departments reporting to the LCDB. All departments use similar standardized perioperative fast-track protocols, including spinal anesthesia, multimodal opioid-sparing analgesia, short-term thromboprophylaxis, early mobilization, functional discharge criteria, and discharge to own home.^{23,24} There are no selection criteria as to whether patients are included in the fast-track protocol as it is considered standard of care and all departments perform more than 400 procedures per year with a median LOS 2 to 3 days.

Detailed information on psychopharmacological treatment 6 months before and 3 months after surgery was acquired through the Danish National Database of Reimbursed Prescriptions (DNDRP). DNDRP collects information on all prescribed medication receiving reimbursement dispensed at any Danish pharmacy.²⁵ As psychopharmacological medication (excluding benzodiazepines) in Denmark was entitled to reimbursement during the study period, complete data on type (Anatomical Therapeutic Classification system), number of packs, pack size, and date of dispensing were available.

All prescriptions were evaluated to assure sufficient doses to include day of surgery assuming treatment according to guidelines from the Danish College of General Practitioners† and drug-specific recommended doses.

Patients with preoperative prescriptions on psychopharmacological treatment and sufficient doses to include or last beyond day of surgery were stratified according to treatment with SSRIs, other antidepressants, combination of SSRI and other antidepressants, and antipsychotics with/without antidepressants. Patients with no prescriptions and answering “no” to pharmacological treatment for PsD in the LCDB were used as controls.

Patients with insufficient doses to include day of surgery, postoperative prescriptions only, or no prescriptions in the DNDRP but answering “yes” to pharmacological treatment for PsD in the LCDB were categorized as “potential” PsD and analyzed separately. The few patients with incomplete answers on PsD in the LCDB and no prescriptions in the DNDRP were excluded from the study (0.5%).

Information on index hospitalization and 90-day follow-up on readmissions was acquired through the Danish National Patient Registry, thus insuring complete follow-up on readmissions regardless of hospital location.²⁶ LOS was calculated as postoperative nights spent in hospital, including transfer to other wards. Based on previous findings of a median LOS of 3 days,²⁰ we defined an LOS of more than 4 days as “prolonged,” in which case the patient’s discharge papers were reviewed with regard to postoperative complications. All readmissions with overnight hospital stay were reviewed with regard to relevance to index surgery using patient discharge papers and following a previously published definition of readmissions potentially related to surgery.²⁰ In case of doubts, the entire medical file was reviewed. Planned admissions and admissions

† Clinical guidelines for treatment of Anxiety and Unipolar depression (in Danish). Copenhagen, Denmark, The Danish College of General Practitioners, 2010. Available at: <http://vejledning.dsam.dk/angst/> and http://www.dsam.dk/files/9/depression_med_links.pdf. Accessed November 21, 2014.

obviously unrelated to index surgery (*i.e.*, eye surgery, admissions due to newly discovered cancer) were excluded. Causes of LOS more than 4 days and readmissions were grouped into the following categories: related to the surgical procedure (complications due to regional anesthesia, periprosthetic fractures, hematomas, prosthesis malfunction, *etc.*), prosthesis infections (including both deep and superficial infections), pulmonary (pneumonias, respiratory insufficiency, worsening of chronic obstructive pulmonary disease with/without antibiotic treatment [without antibiotic treatment included within 30 days after surgery only]), cardiac (verified myocardial infarctions, arrhythmias, cardiac insufficiency, unspecific chest pain, or electrocardiographic changes requiring observation for myocardial infarction but with no conclusive diagnosis at discharge), cerebral (postoperative delirium, cerebral stroke, and transient ischemic attack), venous thromboembolic events (deep venous thrombosis and pulmonary embolism), anemia, problems with mobilization or medication side effects, falls, hip displacements, knee manipulations, pain, and other morbidity (any complications not fitting the above). If the discharge papers described a successful fast-track procedure with no mention of postoperative morbidity, they were classified as “no registered morbidity.” Any case of in-hospital mortality was evaluated using the complete medical record, and if mortality occurred outside the hospital, the patient’s general practitioner was contacted, and the death certificate was reviewed. Review of patient records was performed by the first author, and in case of doubts, the decision on surgical relevance or category of morbidity was made by the first and senior author together.

Outcomes

Primary study outcomes were differences in fraction of procedures with LOS more than 4 days, 30- and 90-day surgery-related readmissions, and mortality in patients with and without pharmacologically treated PsD and according to type of psychopharmacological treatment.

Secondary outcomes were analyses of the different causes of postoperative morbidity resulting in either LOS more than 4 days or surgery-related readmissions. A main reason for LOS more than 4 days or surgery-related readmission was designated in each case (see table, Supplemental Digital Content 2, <http://links.lww.com/ALN/B142>, which provides details about cause of LOS >4 days and surgery-related readmissions).

Statistics and Sample Size Considerations

No *a priori* power calculation was performed as current studies are conflicting. However, considering that approximately 1 in 12 Danish citizens (including children) had redeemed a prescription on antidepressants in 2011,[‡] we expected that

‡ Use of Antidepressants in Denmark 2001–2011 (in Danish). Copenhagen, Denmark, The State Serum Institute. Available at: www.ssi.dk/~media/Indhold/DK%20-dansk/Aktuelt/Nyheder/AD_rapport_generel_2012_ver6.ashx. Accessed November 21, 2014.

at least 10% of our patient sample would fit our definition of PsD. At the time of analysis, this would correspond to a minimum of 900 patients which should provide a robust estimate of any clinically relevant effect of PsD on postoperative outcomes.

Data were analyzed for normality distribution using Kolmogorov–Smirnov test. Comparisons of continuous data were made using Mann–Whitney U test and *t* test; for categorical data, chi-square test or Fisher exact test were used as appropriate. Multivariable logistic regression was used to adjust for known or suspected confounders. These medical comorbidities or lifestyle-related factors were selected *a priori* from comorbidities known to be more common in patients with PsD (smoking, alcohol use >2 drinks per day, body mass index [BMI], and diabetes)²⁷ or previously shown to influence postoperative outcome in fast-track THA and TKA (age, preoperative use of walking aids, living alone, cardiovascular disease, pulmonary disease, and preoperative anemia as defined by the World Health Organization).^{20,21} Age was categorized into groups starting at less than 50 ending at more than 85 and using 66 to 70 yr as reference, and BMI was divided according to the World Health Organization definitions and using a BMI of 18.5 to 24.9 as reference. Finally, we included department of surgery as a random effect. We tested for relevant interactions using the Wald statistic in separate models. Model fit was evaluated using Nagelkerke R^2 and Hosmer–Lemeshow statistics. We also conducted two separate analyses using a propensity-matched dataset.²⁸ Matching of PsD and controls was done using a 1:1 greedy matching algorithm with a propensity score caliper of 0.2. Analysis was done using multiple logistic regression both with and without adjusting for baseline characteristics and taking into account the matched nature of the data.²⁹ Finally, we did a sensitivity analysis of potential influence of residual confounding using proposed imbalanced unmeasured covariates with an odds ratio (OR) of 2.0 and 1.1, respectively.³⁰ Results of multiple logistic regression analysis are presented as ORs with 95% CIs, and a two-sided *P* value of 0.05 or less considered significant.

In case of patients with multiple surgery-related readmissions, we included all readmissions with different causes, but only the first readmission if due to the same cause (*i.e.*, a patient with multiple readmissions due to infection would only be counted once). For comparisons of causes of morbidity, a *P* value of less than 0.004 was considered significant to adjust for multiple comparisons (Bonferroni). Analysis was done in SPSS v. 20 (IBM Corporation, USA).

Results

A total of 8,757 procedures with information on PsD and/or prescriptions on psychopharmacological treatment were analyzed (fig. 1). Of 1,001 (11.4%) procedures with prescriptions on psychopharmacological treatment including or beyond day of surgery, 435 (43.4%) used SSRIs, 316 (31.6%) used other antidepressants, 85 (8.5%) used both

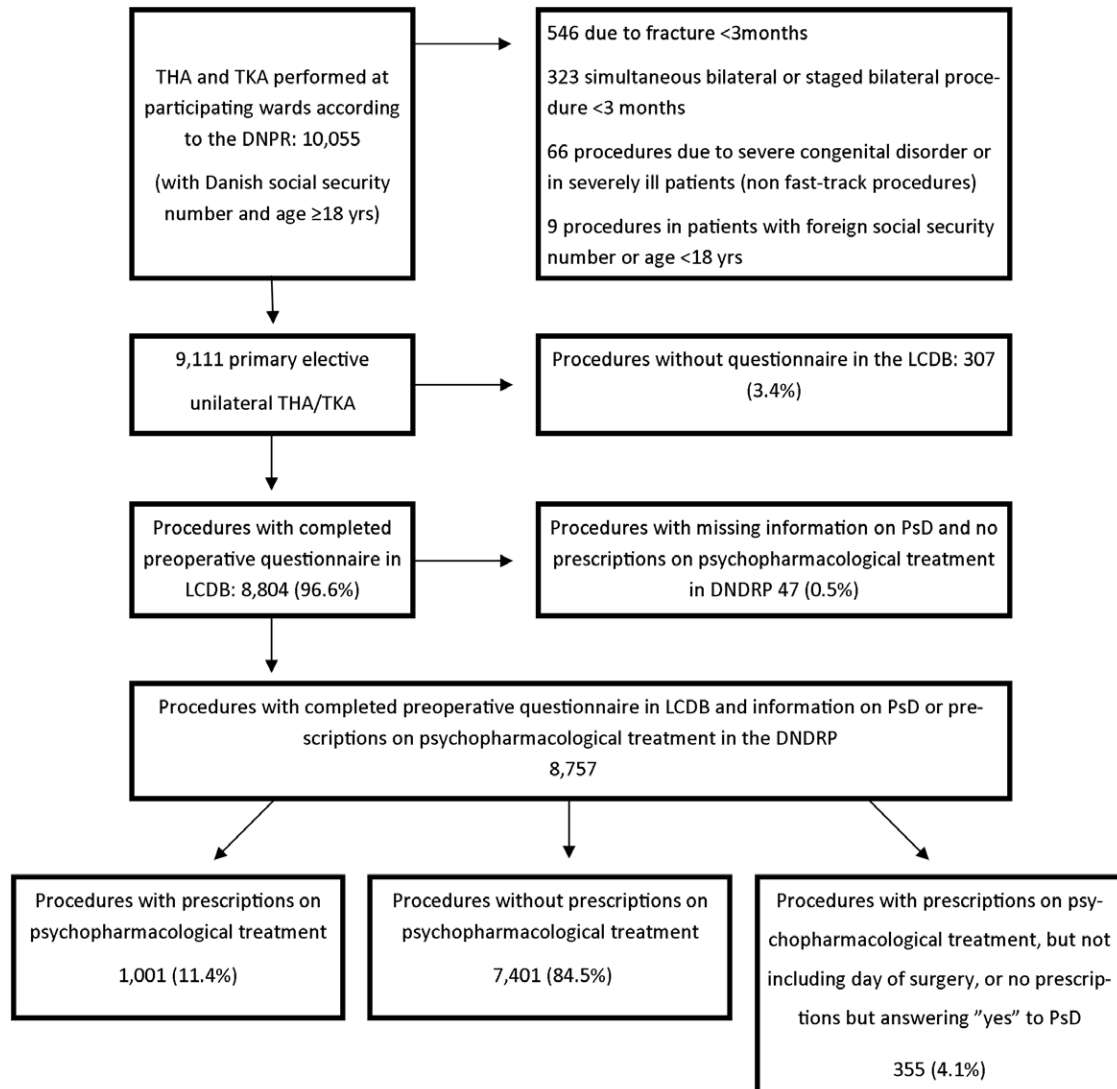


Fig. 1. Flowchart of the study population. DNDPR = Danish National Database of Reimbursed Prescriptions; DNPR = Danish National Patient Registry; LCDB = Lundbeck Foundation Centre Database; PsD = Psychiatric disorder; THA = total hip arthroplasty; TKA = total knee arthroplasty.

SSRIs and other antidepressants, and 165 (16.5%) used antipsychotics either alone or in combination with SSRIs or other antidepressants. Patients with PsD were more often female, living alone, had preoperative use of walking aids, and smoked than those without PsD. A larger fraction had preoperative anemia, pharmacologically treated cardiovascular or pulmonary disease, and diabetes (table 1). In all departments, patients with PsD constituted between 9.6 and 14.5% of all procedures.

Median LOS for the whole population was 2 days (interquartile range, 2 to 3), but the fraction of patients with LOS more than 4 days was higher in those with PsD (16.5% CI, 14.3 to 18.9 vs. 7.3% CI, 6.7 to 7.9; $P < 0.001$) (fig. 2), partly due to a larger fraction of procedures with LOS more than 4, but without registration of specific postoperative morbidity (6.0 vs. 2.8%; $P < 0.01$). Postoperative pain was the most common specific cause of morbidity resulting in LOS more than 4

days in PsD patients (1.4%, followed by postoperative anemia (1.1%) and pulmonary complications (1.1%). All were significantly increased compared with those without PsD (fig. 3A).

Thirty- and 90-day surgery-related readmission rates were 5.9 and 8.3%, respectively, but with more readmissions in patients with than without PsD at both 30-day (9.9 vs. 5.1%) and 90-day follow-up (12.8 vs. 7.4%) ($P < 0.001$) (fig. 2). When considering specific causes of surgery-related readmissions, hip displacements (2.8% of THA), falls (1.9%), and prosthesis infections (1.8%) were the most frequent reasons for 90-day surgery-related readmissions in PsD patients. The increase was significant for falls (0.5%; $P < 0.001$) but not for infections (1.1%; $P = 0.047$) or hip displacements (1.5%; $P = 0.050$) compared with non-PsD patients (Bonferroni corrected) (fig. 3B).

After adjusting for potential confounders and department of surgery, PsD patients had an overall increased risk

Table 1. Preoperative Characteristics in 8,757 Total Hip and Knee Arthroplasties

Preoperative Characteristics, n (%)	No PsD, n = 7,401 (84.6)	PsD, n = 1,001 (11.4)	P Value	“Potential” PsD, n = 355 (4.0)	P Value
Age/yr median (IQR)	68 (61–75)	69 (61–76)	0.084	70 (62–77)	0.050
<50	444 (6.0)	63 (6.3)		25 (7.0)	
50–60	1,239 (16.7)	173 (17.3)		57 (16.1)	
61–65	1,190 (16.1)	135 (13.5)		54 (15.2)	
66–70	1,474 (20.0)	180 (18.0)	0.028	54 (15.2)	0.025
71–75	1,309 (17.6)	188 (18.7)		60 (16.9)	
76–80	1,013 (13.7)	128 (12.8)		50 (14.1)	
81–85	524 (7.1)	97 (9.7)		37 (10.4)	
>85	208 (2.8)	37 (3.7)		18 (5.1)	
BMI median (IQR)	27.7 (24.8–31.1)	28.3 (24.7–32.0)	0.018	27.7 (24.8–31.5)	0.723
<18.5	50 (0.7)	16 (1.6)		4 (1.1)	
18.5–24.9	1,938 (26.3)	256 (25.8)		96 (27.1)	
25.0–29.9	3,001 (40.6)	353 (35.6)		131 (37.0)	
30.0–34.9	1,638 (22.2)	240 (24.1)	<0.001	86 (24.3)	0.443
35.0–39.9	556 (7.5)	97 (9.8)		31 (8.8)	
>39.9	198 (2.7)	32 (3.1)		6 (1.7)	
Missing	20 (0.3)	7 (0.7)		1 (0.3)	
Males	3,313 (44.8)	274 (27.4)	<0.001	127 (35.8)	0.001
THA	3,947 (53.3)	476 (47.6)	0.001	174 (49.0)	0.111
Use of walking aids	1,646 (22.7)	364 (37.2)	<0.001	136 (39.1)	<0.001
Missing	145 (2.0)	23 (2.3)		7 (2.0)	
Living alone	2,370 (32.0)	420 (42.0)	<0.001	146 (41.1)	<0.001
In institution	32 (0.4)	26 (2.6)		8 (2.3)	
Missing	0 (0.0)	0 (0.0)		0 (0.0)	
Smoking	1,033 (14.1)	231 (23.4)	<0.001	70 (20.0)	0.002
Missing	71 (1.0)	14 (1.4)		5 (1.4)	
Alcohol >2 units/day	511 (7.0)	64 (6.5)	0.586	25 (7.1)	0.918
Missing	58 (0.8)	15 (1.5)		3 (0.8)	
Anemia	874 (11.8)	178 (17.8)	<0.001	66 (18.6)	<0.001
Missing	67 (0.9)	6 (0.6)		3 (0.8)	
Type-1 diabetes	33 (0.4)	8 (0.8)	0.007	2 (0.6)	0.911
Type-2 diabetes	785 (10.6)	134 (13.5)		36 (10.1)	
Missing	23 (0.3)	10 (1.0)		0 (0.0)	
Cardiovascular disease	1,205 (16.6)	226 (23.2)	<0.001	73 (21.1)	0.029
Missing	146 (2.0)	25 (2.5)		9 (2.5)	
Pulmonary disease	521 (7.1)	108 (10.9)	<0.001	29 (8.2)	0.416
Missing	38 (0.5)	12 (1.2)		2 (0.6)	

All comparisons are vs. “no PsD.”

BMI = body mass index; IQR = interquartile range; PsD = psychiatric disorder index; THA = total hip arthroplasty.

of both LOS more than 4 days PsD (OR, 1.90; CI, 1.52 to 2.37) and 30-day (OR, 1.93; CI, 1.49 to 2.49) and 90-day surgery-related readmissions (OR, 1.68; CI, 1.34 to 2.10). In the subanalysis of psychopharmacological treatment, this remained significant with SSRI and other antidepressants, but not for 90-day surgery-related readmissions with antipsychotics or at all for combination treatment (table 2).

Of the 8,757 procedures, there were 32 (0.4%) deaths within 90 days. Eight of these were of causes considered unrelated to surgery (cancer and gastrointestinal morbidity >30 days postoperatively) and three (one in a patient using SSRIs) were in their own home of unknown causes between days 19 and 85 after surgery. Thus, of the 21 (0.2%) deaths confirmed to be related to index THA/TKA, 7 (0.7%) were in patients with and 14 (0.2%) were in patients without

PsD (unadjusted OR, 3.74; CI, 1.50 to 9.28; $P = 0.005$). Three of the seven patients were in the SSRI group (two due to respiratory insufficiency and one due to cerebral hemorrhage), two in the other antidepressants group (one pulmonary embolism and one due to renal failure), and one in both the SSRI and other antidepressants and antipsychotics group, due to respiratory insufficiency and pulmonary embolism, respectively.

Patients with “Potential” PsD

The 355 patients with “potential” PsD had similar preoperative characteristics to PsD patients (table 1). The fraction of procedures with LOS more than 4 days (17.1%) and with 30-day (8.2%) and 90-day (12.6%) surgery-related readmission were also similar to PsD patients (fig. 2) and remained

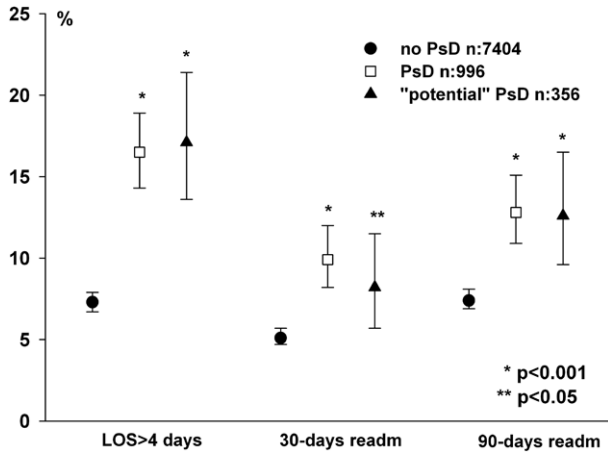


Fig. 2. Fraction of patients with hospital length of stay (LOS) >4 days and 30- and 90-day surgery-related readmissions (readm). Comparisons are versus “no psychiatric disorder (PsD)”; error bars illustrate 95% CIs.

significantly increased compared with patients without PsD in the adjusted analysis (table 2).

In contrast to procedures in patients with PsD, problems with medication side effects and mobilization (2.5%) was the most frequent specific cause of LOS more than 4 days. The fraction of procedures with LOS more than 4 days due to pain with no registered morbidity was similar to in PsD patients (fig. 3A). We also found that prosthesis infections (2.0) and falls (1.1%) were frequent causes of 90-day surgery-related readmissions in the “potential” PsD group (fig. 3B). There were no deaths in the “potential” PsD group.

Propensity-matched Data and Sensitivity Analysis

Successful propensity match was done in 901 PsD patients with a difference in propensity score between matches 0.01 or less (see table, Supplemental Digital Content 3, <http://links.lww.com/ALN/B143>, for patient characteristics in the propensity-matched dataset). The OR for all outcomes remained significantly increased for PsD, and the results were generally similar to the total cohort (table 3). There were eight surgically related deaths in the matched dataset, of which seven were in PsD patients.

When assessing sensitivity to unmeasured confounding, we found that a confounder with OR of 1.1 would have been unable to negate the association between PsD and LOS more than 4 days or readmissions. When assuming an OR of 2.0, the confounder would have to be present in twice as many PsD patients regarding LOS more than 4 days and in approximately 30% more PsD than non-PsD patients regarding surgery-related readmissions (please see Supplemental Digital Content 4, <http://links.lww.com/ALN/B144>, for complete results on sensitivity analyses).

Discussion

This large prospective detailed cohort study with complete 90-day follow-up reveals for the first time information on postoperative outcomes after fast-track THA and TKA in patients with pharmacologically treated PsD. The most important finding was that risk of LOS more than 4 days and surgery-related readmissions were almost doubled in patients with PsD and remained so after adjusting for various established confounders. Second, this association appeared not to

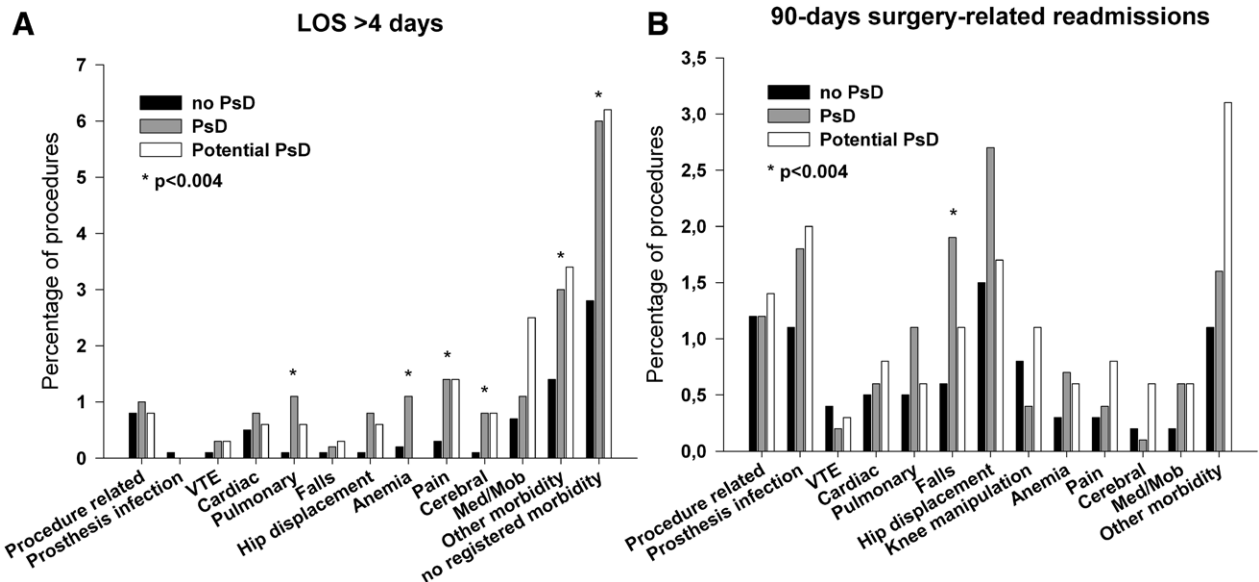


Fig. 3. Specific causes of postoperative morbidity. (A) Causes of length of stay (LOS) >4 days according to discharge papers and patient files. (B) Causes of surgery-related readmissions according to discharge papers and patient files. Procedure related include any complication due to anesthesia (complications of regional anesthesia, postoperative cramps, etc.) or surgical procedure (periprosthetic fracture, bleeding, etc.). Other morbidity includes any causes of morbidity not fitting into the other categories. Med/Mob = medication/mobilization; PsD = psychiatric disorder; VTE = venous thromboembolic events.

Table 2. Multiple Logistic Regression Analyses on Postoperative Outcomes in 8,145 Total Hip and Knee Arthroplasties*

Variable	LOS >4		30-Day Readmissions		90-Day Readmissions	
	OR (95% CI)	P Value	OR (95% CI)	P Value	OR (95% CI)	P Value
PsD overall (n = 911)	1.90 (1.52–2.37)	<0.001	1.93 (1.49–2.49)	<0.001	1.68 (1.34–2.10)	<0.001
“Potential” PsD† (n = 331)	2.00 (1.43–2.81)	<0.001	1.30 (0.84–2.02)	0.238	1.50 (1.05–2.14)	0.024
Age (yr)						
<50	1.29 (0.83–2.01)	0.251	0.60 (0.34–1.08)	0.087	0.83 (0.54–1.27)	0.387
50–60	0.68 (0.47–0.99)	0.043	0.88 (0.61–1.27)	0.491	0.85 (0.63–1.14)	0.274
61–65	0.71 (0.49–1.03)	0.068	0.80 (0.55–1.17)	0.251	0.73 (0.53–1.00)	0.048
66–70	1	Ref	1	Ref	1	Ref
71–75	1.46 (1.08–1.96)	0.013	1.42 (1.03–1.96)	0.033	1.28 (0.98–1.66)	0.073
76–80	2.18 (1.62–2.93)	<0.001	1.48 (1.05–2.08)	0.025	1.21 (0.91–1.62)	0.192
81–85	2.94 (2.13–4.07)	<0.001	1.57 (1.06–2.34)	0.024	1.44 (1.04–2.01)	0.029
<85	4.15 (2.78–6.18)	<0.001	2.49 (1.55–4.03)	<0.001	1.97 (1.30–3.00)	0.001
BMI						
<18.5	1.34 (0.61–2.94)	0.471	0.53 (0.16–1.77)	0.297	0.54 (0.19–1.54)	0.248
18.5–24.9	1	Ref	1	Ref	1	Ref
25.0–29.9	0.95 (0.77–1.17)	0.618	0.86 (0.67–1.09)	0.213	0.92 (0.75–1.13)	0.431
30.0–34.9	1.06 (0.83–1.37)	0.644	1.04 (0.79–1.37)	0.794	0.98 (0.77–1.25)	0.889
35.0–39.9	1.56 (1.12–2.18)	0.009	1.07 (0.71–1.59)	0.757	1.07 (0.76–1.49)	0.814
>39.9	1.29 (0.75–2.23)	0.361	0.53 (0.23–1.24)	0.143	0.44 (0.21–0.92)	0.030
Male vs. female	0.88 (0.73–1.06)	0.185	1.29 (1.04–1.59)	0.019	1.20 (1.00–1.44)	0.045
TKA vs. THA	1.25 (1.05–1.48)	0.013	0.95 (0.78–1.16)	0.609	0.94 (0.80–1.12)	0.507
Living with spouse/partner	1	Ref	1	Ref	1	Ref
Living alone	1.54 (1.28–1.85)	<0.001	1.14 (0.92–1.41)	0.241	1.03 (0.86–1.24)	0.735
Living in institution	1.50 (0.71–3.20)	0.291	1.44 (0.59–3.54)	0.422	1.49 (0.70–3.19)	0.301
Use of walking aids	2.13 (1.77–2.56)	<0.001	1.53 (1.23–1.91)	<0.001	1.64 (1.37–1.93)	<0.001
Smoking	1.19 (0.93–1.53)	0.165	1.61 (1.25–2.07)	<0.001	1.24 (0.99–1.55)	0.065
Alcohol >2 units a day	0.87 (0.59–1.27)	0.468	0.76 (0.50–1.14)	0.187	0.83 (0.59–1.16)	0.277
Pulmonary disease	1.41 (1.08–1.85)	0.012	1.46 (1.07–1.98)	0.017	1.48 (1.14–1.92)	0.004
Cardiovascular disease	1.48 (1.21–1.80)	<0.001	1.39 (1.10–1.75)	0.004	1.43 (1.18–1.74)	<0.001
Type-1 diabetes	2.69 (1.19–6.12)	0.018	1.97 (0.75–5.18)	0.171	2.37 (1.06–5.28)	0.035
Type-2 diabetes	1.27 (0.99–1.63)	0.061	0.97 (0.71–1.33)	0.859	1.15 (0.89–1.48)	0.290
Preoperative anemia	1.92 (1.57–2.35)	<0.001	1.43 (1.11–1.83)	0.005	1.33 (1.07–1.65)	0.010
PsD stratified by psychopharmacological treatment*†						
SSRI (n = 394)	2.19 (1.62–2.97)	<0.001	1.97 (1.38–2.82)	<0.001	1.77 (1.29–2.43)	<0.001
Other antidepressants (n = 291)	1.81 (1.25–2.61)	0.002	2.24 (1.51–3.31)	<0.001	1.82 (1.27–2.61)	0.001
SSRI plus other antidepressants (n = 73)	1.05 (0.49–2.27)	0.893	0.88 (0.31–2.47)	0.803	0.91 (0.38–2.16)	0.829
Antipsychotics (n = 153)	1.90 (1.62–3.16)	0.013	1.85 (1.03–3.31)	0.040	1.49 (0.88–2.55)	0.141

The number of patients included in analysis differs from the total number of patients due to missing data. All covariates were defined *a priori*.

* The stratified analysis was adjusted for the above confounders but excluding the “potential PsD patients.” † Patients without PsD used as reference.

BMI = body mass index; LOS = length of stay; OR = odds ratio; PsD = psychiatric disorder; SSRI = selective serotonin inhibitor; THA = total hip arthroplasty; TKA = total knee arthroplasty.

be specifically related to the type of psychopharmacological treatment (SSRIs, other antidepressants, and antipsychotics).

An increase in LOS has previously been found in patients with diagnostic codes on depression after joint arthroplasty. However, the actual increase was minimal (4.0 vs. 3.9 days),¹⁷ and in contrast to our findings of increased surgically related mortality (*albeit* unadjusted for confounders due to limited numbers) and readmissions, they found fewer major complications and decreased in-hospital mortality. Our results are also in contrast to a recent study finding no association between preoperative use of antidepressants and LOS after elective noncardiac surgery. However, this study was a secondary analysis of mixed surgical procedures which did not

account for specific preoperative differences in baseline characteristics and included much fewer patients.³¹

The recorded reasons for LOS more than 4 days in our study were mainly pain, postoperative anemia, and “unspecific” causes. It is well known that the psychological profile has influence on postoperative pain³² and, therefore, not surprising that pain management may have been more difficult in these patients. That a larger fraction of patients with PsD had LOS more than 4 days or required readmissions because of anemia could support the reports of increased risk of postoperative bleeding due to impaired platelet aggregation and thrombocyte function caused by SSRIs.^{11,12,33} However, PsD patients often had preoperative anemia, which in itself

Table 3. Multiple Logistic Regression Analyses in the Propensity-matched Cohort (n = 1,802)

Variable (n)	LOS >4		30-Day Readmissions		90-Day Readmissions	
	OR (95% CI)	P Value	OR (95% CI)	P Value	OR (95% CI)	P Value
Analysis A* PsD (901)	1.93 (1.44–2.58)	<0.001	2.24 (1.55–3.24)	<0.001	1.82 (1.33–2.48)	<0.001
Psychopharmacological treatment:						
SSRI (390)	2.19 (1.55–3.10)	<0.001	2.30 (1.47–3.58)	<0.001	1.94 (1.33–2.83)	0.001
Other antidepressants (290)	1.81 (1.22–2.70)	0.004	2.57 (1.61–4.12)	<0.001	1.97 (1.31–2.99)	0.001
SSRI plus other antidepressants (72)	1.50 (0.72–3.13)	0.285	1.14 (0.40–3.23)	0.813	1.10 (0.46–2.61)	0.836
Antipsychotics (149)	1.71 (1.02–3.13)	0.043	2.05 (1.10–3.83)	0.024	1.58 (0.90–2.76)	0.110
Analysis B† PsD (901)	2.08 (1.52–2.84)	<0.001	2.25 (1.53–3.30)	<0.001	1.81 (1.31–2.49)	<0.001
Psychopharmacological treatment:						
SSRI (390)	2.39 (1.64–3.47)	<0.001	2.38 (1.50–3.76)	<0.001	1.97 (1.34–2.91)	0.001
Other antidepressants (290)	1.92 (1.26–2.94)	0.002	2.55 (1.57–4.17)	<0.001	1.95 (1.28–2.99)	0.002
SSRI plus other antidepressants (72)	1.30 (0.60–2.82)	0.505	1.08 (0.37–3.12)	0.894	1.02 (0.42–2.45)	0.968
Antipsychotics (149)	2.02 (1.17–3.51)	0.012	1.97 (1.03–3.79)	0.041	1.54 (0.87–2.76)	0.142

* Adjusted only for hospital of surgery. † Adjusted for hospital of surgery and patient characteristics. LOS = length of hospital stay; OR = odds ratio; PsD = psychiatric disorder; SSRI = selective serotonin inhibitors.

increases both the need for transfusions and postoperative morbidity after fast-track THA and TKA.²¹ Unfortunately, we have no information on whether the preoperative anemia was caused by psychopharmacological treatment or other underlying disease, and analysis on specific causes of morbidity according to psychopharmacological treatment was not possible due to limited numbers.

The demonstrated high surgery-related readmission rate in patients with PsD may partly be due to differences in patient-perceived outcomes,³⁴ but the most common causes of readmissions were falls, hip displacements, and infections. In a smaller cohort, we have previously reported a detailed analysis on postoperative falls and also demonstrated an association with PsD.³⁵ This may be influenced by the effect of specific types of psychopharmacological treatment,^{10,36} as well as unhealthy lifestyle and decreased physical performance.^{37,38} Consequently, a potential way to reduce postoperative morbidity in PsD patients may through increased focus on fall-prevention techniques.

Mortality in PsD patients due to surgery-related causes was higher than in those without (0.7 vs. 0.2%) although adjustments for confounders were not possible due to limited numbers. It is well documented that patients with severe PsDs have decreased life expectancy due to early death of both natural and unnatural causes,^{4,5} but the association with surgery-related mortality is not well described. A previous study found increased 30-day mortality in patients with diagnostic codes for psychiatric illness, having respiratory and digestive but not musculoskeletal procedures. However, the study was based on an administrative claims database in a selected population and with a relatively small fraction of musculoskeletal procedures.¹⁶

The patients with prescriptions on psychopharmacological drugs after surgery, not enough doses for day of surgery, or answering “yes” to PsD in the LCDB but without prescriptions, had similar preoperative characteristics and postoperative outcomes as the PsD group. Considering recent findings of no effect of preoperative SSRI treatment on postoperative morbidity and mortality in nondepressed patients having coronary artery bypass,³⁹ the similarity between the PsD and “potential PsD” groups could suggest that the increased postoperative morbidity may be related rather to the PsD than medical side effects. Unfortunately, we have no data on the clinical severity and characteristics of PsD in our population to confirm this assumption.

Finally, it may be argued that as our study is in a well-defined elective surgical cohort considered “fit for surgery,” the severity of PsD and related comorbidity may be less than in studies of acute surgical procedures or in the general population. Nevertheless, we found a clinically relevant association between PsD and postoperative morbidity, apparently independent of type of psychopharmacological treatment. Thus, our findings support the previous calls for further research before institution of preoperative cessation of specific types of psychopharmacological drugs.⁶

Our study does have some caveats, primarily the lack of data on the indication for psychopharmacological treatment, the actual prescribed daily doses, and patient compliance after buying the medication. However, the similarity between the PsD and the “potential” PsD groups suggests that any “misplacements” would have minimal influence on our results. Despite a minority of these drugs may have had other indications (*i.e.*, chronic pain), the majority are prescribed for PsD.⁴⁰ Furthermore, the individual review of prescriptions likely further reduced the risk of including

patients with other indications for treatment in the PsD group. Another limitation is the lack of information on anxiolytic treatment, but these data were unavailable due to removal of reimbursements on benzodiazepines in Denmark and consequently insufficient registration in the DNDRP. This may be particularly important with regard to mortality, where an association with benzodiazepine use has been found in patients with schizophrenia.⁴¹

Regarding the classification on causes of LOS more than 4 days and readmissions, these depended mainly on discharge notes, and insufficient or missing information would lead to these data being less robust. However, we believe our attempt at classifying the causes of LOS more than 4 days and surgery-related readmissions is necessary to identify future areas of improvement and is preferable to using diagnostic codes.^{42,43} Finally, although we adjusted for a large number of relevant preoperative characteristics, there remains the risk of unmeasured confounding and under-reporting of smoking and alcohol use. In this context, it must also be mentioned that we have based our choice of covariates partly on previous studies using some of the same patients, thereby introducing the risk of a type-I error. However, the estimates for the included confounders in the multiple logistic regression analyses were similar to those we have previously reported in studies with smaller sample sizes and fewer cofounders,^{20,22} suggesting that these preoperative data are robust with regard to our outcomes.

The strengths of our study include a large prospective sample of unselected patients with a standardized perioperative setup and complete detailed 90-day follow-up through the Danish National Patient Registry and patient records.²⁶ Furthermore, previous studies have often defined PsD using administrative and diagnostic coding.^{4,12,16,17} In contrast, we used a prospective questionnaire, which, although introducing a risk of reporting bias, in combination with the DNDRP allowed a more well-defined PsD population. Such study designs have been suggested for providing solid “real-life” data not readily available in a randomized controlled trial.^{42,44,45}

In conclusion, patients with PsD requiring psychopharmacological treatment have increased postoperative morbidity after fast-track THA and TKA. Whether this is due to the underlying psychiatric disease or is related to specific psychopharmacological side effects is uncertain. Consequently, further multidisciplinary studies of the pathophysiological mechanisms are needed to direct the focus of future interventional strategies.

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Competing Interests

The authors declare no competing interests.

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References

1. Moonesinghe SR, Mythen MG, Das P, Rowan KM, Grocott MP: Risk stratification tools for predicting morbidity and mortality in adult patients undergoing major surgery: Qualitative systematic review. *ANESTHESIOLOGY* 2013; 119:959–81
2. Kehlet H, Mythen M: Why is the surgical high-risk patient still at risk? *Br J Anaesth* 2011; 106:289–91
3. Copeland LA, Zeber JE, Pugh MJ, Mortensen EM, Restrepo MI, Lawrence VA: Postoperative complications in the seriously mentally ill: A systematic review of the literature. *Ann Surg* 2008; 248:31–8
4. Hoang U, Stewart R, Goldacre MJ: Mortality after hospital discharge for people with schizophrenia or bipolar disorder: Retrospective study of linked English hospital episode statistics, 1999–2006. *BMJ* 2011; 343:d5422
5. Nordentoft M, Wahlbeck K, Hällgren J, Westman J, Osby U, Alinaghizadeh H, Gissler M, Laursen TM: Excess mortality, causes of death and life expectancy in 270,770 patients with recent onset of mental disorders in Denmark, Finland and Sweden. *PLoS One* 2013; 8:e55176
6. Mrkobrada M, Hackam DG: Selective serotonin reuptake inhibitors and surgery: To hold or not to hold, that is the question: Comment on “Perioperative use of selective serotonin reuptake inhibitors and risks for adverse outcomes of surgery.” *JAMA Intern Med* 2013; 173:1082–3
7. Bot AG, Menendez ME, Neuhaus V, Ring D: The influence of psychiatric comorbidity on perioperative outcomes after shoulder arthroplasty. *J Shoulder Elbow Surg* 2014; 23:519–27
8. Laursen TM, Munk-Olsen T, Agerbo E, Gasse C, Mortensen PB: Somatic hospital contacts, invasive cardiac procedures, and mortality from heart disease in patients with severe mental disorder. *Arch Gen Psychiatry* 2009; 66:713–20
9. De Hert M, Cohen D, Bobes J, Cetkovich-Bakmas M, Leucht S, Ndeti DM, Newcomer JW, Uwakwe R, Asai I, Möller HJ, Gautam S, Detraux J, Correll CU: Physical illness in patients with severe mental disorders. II. Barriers to care, monitoring and treatment guidelines, plus recommendations at the system and individual level. *World Psychiatry* 2011; 10:138–51
10. Coupland C, Dhiman P, Morriss R, Arthur A, Barton G, Hippisley-Cox J: Antidepressant use and risk of adverse outcomes in older people: Population based cohort study. *BMJ* 2011; 343:d4551
11. de Abajo FJ: Effects of selective serotonin reuptake inhibitors on platelet function: Mechanisms, clinical outcomes and implications for use in elderly patients. *Drugs Aging* 2011; 28:345–67
12. Auerbach AD, Vittinghoff E, Maselli J, Pekow PS, Young JQ, Lindenauer PK: Perioperative use of selective serotonin

- reuptake inhibitors and risks for adverse outcomes of surgery. *JAMA Intern Med* 2013; 173:1075–81
13. Cooke MJ, Waring WS: Citalopram and cardiac toxicity. *Eur J Clin Pharmacol* 2013; 69:755–60
 14. Hackam DG, Mrkobrada M: Selective serotonin reuptake inhibitors and brain hemorrhage: A meta-analysis. *Neurology* 2012; 79:1862–5
 15. Vieweg WV, Hasnain M, Howland RH, Hettema JM, Kogut C, Wood MA, Pandurangi AK: Citalopram, QTc interval prolongation, and torsade de pointes. How should we apply the recent FDA ruling? *Am J Med* 2012; 125:859–68
 16. Abrams TE, Vaughan-Sarrazin M, Rosenthal GE: Influence of psychiatric comorbidity on surgical mortality. *Arch Surg* 2010; 145:947–53
 17. Stundner O, Kirksey M, Chiu YL, Mazumdar M, Poultides L, Gerner P, Memtsoudis SG: Demographics and perioperative outcome in patients with depression and anxiety undergoing total joint arthroplasty: A population-based study. *Psychosomatics* 2013; 54:149–57
 18. Kehlet H, Wilmore DW: Evidence-based surgical care and the evolution of fast-track surgery. *Ann Surg* 2008; 248:189–98
 19. Kehlet H: Fast-track hip and knee arthroplasty. *Lancet* 2013; 381:1600–2
 20. Jørgensen CC, Kehlet H; Lundbeck Foundation Centre for Fast-track Hip and Knee Replacement Collaborative Group: Role of patient characteristics for fast-track hip and knee arthroplasty. *Br J Anaesth* 2013; 110:972–80
 21. Jans Ø, Jørgensen C, Kehlet H, Johansson PI; Lundbeck Foundation Centre for Fast-track Hip and Knee Replacement Collaborative Group: Role of preoperative anemia for risk of transfusion and postoperative morbidity in fast-track hip and knee arthroplasty. *Transfusion* 2014; 54:717–26
 22. Jørgensen CC, Kehlet H; Lundbeck Foundation Centre for Fast-track Hip and Knee Replacement Collaborative Group: Outcomes in smokers and alcohol users after fast-track hip and knee arthroplasty. *Acta Anaesthesiol Scand* 2013; 57:631–8
 23. Jørgensen CC, Jacobsen MK, Soeballe K, Hansen TB, Husted H, Kjærsgaard-Andersen P, Hansen LT, Laursen MB, Kehlet H: Thromboprophylaxis only during hospitalisation in fast-track hip and knee arthroplasty, a prospective cohort study. *BMJ Open* 2013; 3:e003965
 24. Husted H, Solgaard S, Hansen TB, Søballe K, Kehlet H: Care principles at four fast-track arthroplasty departments in Denmark. *Dan Med Bull* 2010; 57:A4166
 25. Johannesdottir SA, Horváth-Puhó E, Ehrenstein V, Schmidt M, Pedersen L, Sørensen HT: Existing data sources for clinical epidemiology: The Danish National Database of Reimbursed Prescriptions. *Clin Epidemiol* 2012; 4:303–13
 26. Andersen TF, Madsen M, Jørgensen J, Mellekjoer L, Olsen JH: The Danish National Hospital Register. A valuable source of data for modern health sciences. *Dan Med Bull* 1999; 46:263–8
 27. DE Hert M, Correll CU, Bobes J, Cetkovich-Bakmas M, Cohen D, Asai I, Detraux J, Gautam S, Möller HJ, Ndeti DM, Newcomer JW, Uwakwe R, Leucht S: Physical illness in patients with severe mental disorders. I. Prevalence, impact of medications and disparities in health care. *World Psychiatry* 2011; 10:52–77
 28. Stürmer T, Rothman KJ, Avorn J, Glynn RJ: Treatment effects in the presence of unmeasured confounding: Dealing with observations in the tails of the propensity score distribution—a simulation study. *Am J Epidemiol* 2010; 172:843–54
 29. Austin PC: An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate Behav Res* 2011; 46:399–424
 30. Lin DY, Psaty BM, Kronmal RA: Assessing the sensitivity of regression results to unmeasured confounders in observational studies. *Biometrics* 1998; 54:948–63
 31. Sutherland AM, Katznelson R, Clarke HA, Tait G, Beattie WS: Use of preoperative antidepressants is not associated with postoperative hospital length of stay. *Can J Anaesth* 2014; 61:27–31
 32. Ip HY, Abrishami A, Peng PW, Wong J, Chung F: Predictors of postoperative pain and analgesic consumption: A qualitative systematic review. *ANESTHESIOLOGY* 2009; 111:657–77
 33. Jeong BO, Kim SW, Kim SY, Kim JM, Shin IS, Yoon JS: Use of serotonergic antidepressants and bleeding risk in patients undergoing surgery. *Psychosomatics* 2014; 55:213–20
 34. Ellis HB, Howard KJ, Khaleel MA, Bucholz R: Effect of psychopathology on patient-perceived outcomes of total knee arthroplasty within an indigent population. *J Bone Joint Surg Am* 2012; 94:e84
 35. Jørgensen CC, Kehlet H; Lundbeck Foundation Centre for Fast-track Hip and Knee Replacement Collaborative Group: Fall-related admissions after fast-track total hip and knee arthroplasty—Cause of concern or consequence of success? *Clin Interv Aging* 2013; 8:1569–77
 36. Mion LC, Chandler AM, Waters TM, Dietrich MS, Kessler LA, Miller ST, Shorr RI: Is it possible to identify risks for injurious falls in hospitalized patients? *Jt Comm J Qual Patient Saf* 2012; 38:408–13
 37. Nyboe L, Lund H: Low levels of physical activity in patients with severe mental illness. *Nord J Psychiatry* 2013; 67:43–6
 38. Osborn DP, Nazareth I, King MB: Physical activity, dietary habits and Coronary Heart Disease risk factor knowledge amongst people with severe mental illness: A cross sectional comparative study in primary care. *Soc Psychiatry Psychiatr Epidemiol* 2007; 42:787–93
 39. Chocron S, Vandel P, Durst C, Laluc F, Kaili D, Chocron M, Etievent JP: Antidepressant therapy in patients undergoing coronary artery bypass grafting: The MOTIV-CABG trial. *Ann Thorac Surg* 2013; 95:1609–18
 40. Trifirò G, Tillati S, Spina E, Ferrajolo C, Alacqua M, Aguglia E, Rizzi L, Caputi AP, Cricelli C, Samani F: A nationwide prospective study on prescribing pattern of antidepressant drugs in Italian primary care. *Eur J Clin Pharmacol* 2013; 69:227–36
 41. Baandrup L, Gasse C, Jensen VD, Glenthoj BY, Nordentoft M, Lublin H, Fink-Jensen A, Lindhardt A, Mortensen PB: Antipsychotic polypharmacy and risk of death from natural causes in patients with schizophrenia: A population-based nested case-control study. *J Clin Psychiatry* 2010; 71:103–8
 42. Fleischut PM, Mazumdar M, Memtsoudis SG: Perioperative database research: Possibilities and pitfalls. *Br J Anaesth* 2013; 111:532–4
 43. Saucedo J, Marecek GS, Lee J, Huminiak L, Stulberg SD, Puri L: How accurately are we coding readmission diagnoses after total joint arthroplasty? *J Arthroplasty* 2013; 28:1076–9
 44. Berwick DM: The science of improvement. *JAMA* 2008; 299:1182–4
 45. Merkow RP, Ko CY: Evidence-based medicine in surgery: The importance of both experimental and observational study designs. *JAMA* 2011; 306:436–7

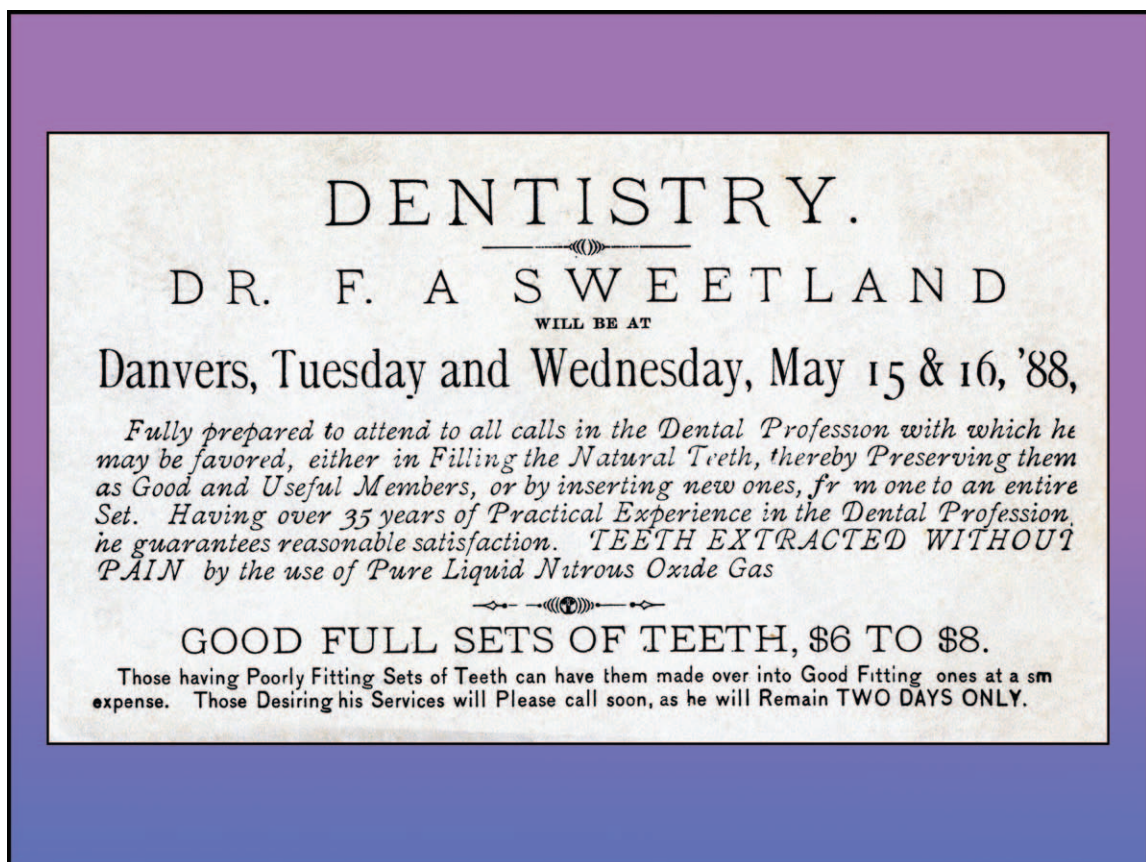
Appendix.

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ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

F. A. Sweetland's "Liquid Nitrous Oxide" Trade Card



A native of Dryden, New York, Dr. Frederick Augustus "Fred" Sweetland (1827–1908) was a dentist who practiced most of his later years about 150 miles southwest of Chicago, in Wyoming, Illinois. On his trade card (above), Sweetland advertised in May of 1888 that he would travel the 65 miles southeast in Illinois, from Wyoming to Danvers, and offer "TEETH EXTRACTED WITHOUT PAIN by the use of Pure Liquid Nitrous Oxide Gas." During the quarter century after laughing gas had been repopularized for dental anesthesia, the rising tide of postanesthetic complications were blamed frequently upon administration of impure nitrous oxide to patients. By using newer technology for furnishing "gas" from tanks filled with pure, condensed (liquid) nitrous oxide, a dental or medical practitioner could reassure patients that they were receiving safer "Pure Liquid Nitrous Oxide Gas." (Copyright © the American Society of Anesthesiologists, Inc.)

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