

RESEARCH

Rates and risk factors for prolonged opioid use after major surgery: population based cohort study

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Abstract

Objective To describe rates and risk factors for prolonged postoperative use of opioids in patients who had not previously used opioids and undergoing major elective surgery.

Design Population based retrospective cohort study.

Setting Acute care hospitals in Ontario, Canada, between 1 April 2003 and 31 March 2010.

Participants 39 140 opioid naïve patients aged 66 years or older who had major elective surgery, including cardiac, intrathoracic, intra-abdominal, and pelvic procedures.

Main outcome measure Prolonged opioid use after discharge, as defined by ongoing outpatient prescriptions for opioids for more than 90 days after surgery.

Results Of the 39 140 patients in the entire cohort, 49.2% (n=19 256) were discharged from hospital with an opioid prescription, and 3.1% (n=1229) continued to receive opioids for more than 90 days after surgery. Following risk adjustment with multivariable logistic regression modelling, patient related factors associated with significantly higher risks of prolonged opioid use included younger age, lower household income, specific comorbidities (diabetes, heart failure, pulmonary disease), and use of specific drugs preoperatively (benzodiazepines, selective serotonin reuptake inhibitors, angiotensin converting enzyme inhibitors). The type of surgical procedure was also highly associated with prolonged opioid use. Compared with open radical prostatectomies, both open and minimally invasive thoracic procedures were associated with significantly higher risks (odds ratio 2.58, 95% confidence interval 2.03 to 3.28 and 1.95 to 2.78, respectively). Conversely, open and minimally invasive major gynaecological procedures were associated

with significantly lower risks (0.73, 0.55 to 0.98 and 0.45, 0.33 to 0.62, respectively).

Conclusions Approximately 3% of previously opioid naïve patients continued to use opioids for more than 90 days after major elective surgery. Specific patient and surgical characteristics were associated with the development of prolonged postoperative use of opioids. Our findings can help better inform understanding about the long term risks of opioid treatment for acute postoperative pain and define patient subgroups that warrant interventions to prevent progression to prolonged postoperative opioid use.

Introduction

Acute postoperative pain and its treatment with opioids are important concerns for the more than 200 million patients who undergo major surgery worldwide every year.¹ After such surgery, patients often experience moderate to severe pain that interferes with postoperative rehabilitation and discharge from hospital.² Inadequate treatment of acute pain may also contribute to the development of persistent postsurgical pain,³ which in turn can have a negative impact on patients' quality of life.^{4,5}

Opioids are key analgesic agents for treating moderate to severe pain after major surgery.⁶ None the less, they have important short term limitations, including side effects and poor efficacy in movement associated pain. Furthermore, some patients develop longer term persistent opioid use,⁷ which negatively impacts on postsurgical quality of life.^{4,5} Long term use is also associated with increased risks of injury⁷ and cardiac events.⁸

Both the doctors dealing with patients perioperatively and the surgical patients themselves therefore face an important clinical

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Supplementary tables 1 and 2

challenge—namely, how best to adequately manage acute postoperative pain while tackling patients' understandable concerns about the development of long term opioid use. An important barrier to dealing with this challenge is the current poor understanding of the long term risks associated with opioid treatment for acute postoperative pain. In the setting of low risk day surgery, recent research suggests that patients prescribed opioids within seven days of discharge are almost 50% more likely to still be receiving an opioid prescription at one year after surgery.⁷ The extent to which these findings in low risk surgery can be generalised to major surgery is, however, unclear. Specifically, postoperative pain control after low risk day surgery may feasibly be managed without opioids, whereas it is unlikely that the moderate to severe postoperative pain associated with major surgery can be managed without resorting to such agents.

In a population based study we describe the rates and associated risk factors of prolonged postoperative use of opioids in patients who had never used opioids undergoing major elective surgery in Ontario, Canada. A better understanding of these factors should greatly aid the decision making of both patients and clinicians.

Methods

We conducted a retrospective cohort study using several linked population based administrative databases: the discharge abstract database of the Canadian Institute for Health Information (hospital admissions), the Ontario Health Insurance Plan database (doctor service claims), the registered persons database (vital statistics), and the Ontario Drug Benefit database (prescription drugs for outpatients aged ≥ 65 years). Although these databases lack physiological and laboratory measures (for example, blood pressure, haemoglobin), they have been validated for many outcomes, exposures, and comorbidities.⁹⁻¹¹ The approximately 13 million residents of Ontario have universal access to doctor and hospital services through a publicly funded healthcare programme. Privacy regulations relating to these databases preclude us from reporting any results for subgroups with fewer than six people.

Assembly of study cohort

We used the discharge abstract database to identify all Ontario residents who were aged 66 years or older and underwent any one of nine prespecified elective major surgical procedures between 1 April 2003 and 31 March 2010.^{12 13} An age restriction of 66 years was imposed because data on prescription drugs are only available for those aged 65 years or older, and a preoperative time window was needed for ascertaining previous drug use. The included procedures were isolated coronary artery bypass graft surgery through sternotomy, open (thoracotomy) lung resection surgery, lung resection using video assisted thorascopic surgery, open colon resection surgery, minimally invasive (laparoscopic) colon resection surgery, open radical prostatectomy, minimally invasive (laparoscopic or robot assisted) radical prostatectomy, open total or radical hysterectomy, and minimally invasive (laparoscopic or robot assisted) total or radical hysterectomy. We selected these procedures because they are common and encompass a range of anatomical sites (cardiac, thoracic, abdominal, pelvic) and degrees of surgical invasiveness (open versus minimally invasive approaches). We did not include musculoskeletal procedures such as joint arthroplasty because many patients undergoing such procedures already have considerable pre-existing pain. Procedural information in the discharge abstract database is

very accurate.¹¹ If patients underwent more than one eligible procedure during the study period, we included only the first procedure.

We used the Ontario Drug Benefit database to exclude those with pre-existing pain disorders before surgery, based on the presence of any outpatient prescriptions for specific analgesic drugs within one year before surgery. These drugs included opioids, gabapentin, tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors (for example, duloxetine), anticonvulsants (for example, valproic acid), and topical agents (for example, capsaicin). Prescription data in the Ontario Drug Benefit database are very accurate.¹⁴ In addition, we used the Ontario Health Insurance Plan database to exclude those who required doctor services for palliative care within one year before or after surgery. The objective of these restrictions was to minimise the inclusion of those who had pre-existing chronic pain disorders or required opioids for end stage cancer.

We characterised participants in the cohort for personal characteristics, socioeconomic status, residence, comorbidities, preoperative drug use, and survival. Personal information (age, sex) was obtained from the registered persons database. We estimated patients' socioeconomic status based on the median income of their neighbourhood in the Canadian census, and characterised their residence as rural versus urban using Statistics Canada definitions.¹⁵ To identify patients with diabetes or hypertension we used validated algorithms.¹⁰ We used the Ontario Health Insurance Plan database to identify patients who required dialysis before surgery. Using the discharge abstract database, we used previously described methods to identify other comorbidities based on ICD-10 codes (international classification of diseases, 10th revision) from admissions to hospital within three years before surgery: coronary artery disease, heart failure, cerebrovascular disease, peripheral vascular disease, pulmonary disease, chronic renal insufficiency, and malignancy.¹⁶ We used the Ontario Drug Benefit database to ascertain the preoperative use of drugs that may be related (selective serotonin reuptake inhibitors (SSRIs), benzodiazepines) and unrelated (β blockers, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers, statins) to postoperative opioid use. To identify outpatient prescriptions for these drugs, we used a 90 day time window before the index surgery. We ascertained postoperative survival using the discharge abstract database (in-hospital mortality) and registered persons database (mortality out of hospital).

Postoperative opioid use

The Ontario Drug Benefit database was used to ascertain opioid use after hospital discharge. These opioids included codeine, morphine, oxycodone, hydromorphone, meperidine, oxymorphone, methadone, and transdermal fentanyl. We also characterised these drugs by whether they were sustained release formulations. Early post-discharge opioid use was defined as one or more prescriptions for opioids within 1 to 90 days after surgery. Prolonged opioid use after hospital discharge was defined as one or more opioid prescriptions within 1 to 90 days after surgery along with one or more prescriptions for opioids within 91 to 180 days after surgery. This 90 day minimum interval for defining prolonged opioid use is more conservative than the 60 day interval used by the International Association for the Study of Pain to define persistent postsurgical pain,¹⁷ which has been criticised as being too short.¹⁸

Statistical analysis

All analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC), and we used a two tailed P value of less than 0.05 to define statistical significance. We initially used descriptive statistics to characterise the cohort for patterns of post-discharge opioid use. To compare the characteristics of patients who did or did not exhibit prolonged opioid use after discharge we also used bivariate tests (two sample *t* test, Mann-Whitney U test, χ^2 test, Fisher exact test).

We used multivariable logistic regression modelling to determine the adjusted association of prolonged opioid use after discharge (≥ 1 prescriptions within 1-90 days after surgery along with ≥ 1 prescriptions within 91-180 days after surgery) with age (categorised as 66-75, 76-85, and ≥ 86 years), sex, surgery, fifth of neighbourhood income, rural residence, comorbidities (coronary artery disease, heart failure, cerebrovascular disease, peripheral vascular disease, diabetes, hypertension, pulmonary disease, chronic renal insufficiency, malignancy), and preoperative drug use (β blockers, ACE inhibitors, angiotensin receptor blockers, statins, benzodiazepines, SSRIs). All predictor variables were included simultaneously in the multivariable regression model. In the primary analysis, we included all participants in the cohort regardless of whether they survived up to 180 days after surgery. In a sensitivity analysis, we repeated the analyses after restricting the cohort to only those who survived at least 180 days after surgery.

Results

The cohort consisted of 39 140 patients who had not previously used opioids and underwent major elective surgery. Of these, 49.2% (n=19 256) used opioids in the early post-discharge period, and 3.1% (n=1229) used opioids for a prolonged period after discharge. Table 1¹ presents the patterns of post-discharge opioid use across the different surgical procedures. The highest risk of prolonged opioid use was after open (8.5%) or minimally invasive (6.3%) intrathoracic procedures. Postoperative survival was 98.3% (n=38 492) at hospital discharge, 97.4% (n=38 124) at 90 days after surgery, and 96.7% (n=37 857) at 180 days after surgery.

Table 2² presents the proportion of participants with prolonged opioid use after discharge, according to their perioperative characteristics. Supplementary table 1 presents the bivariate comparisons of those who did or did not develop prolonged opioid use. In unadjusted analyses, those who developed prolonged opioid use were more likely to reside in lower income neighbourhoods and to have specific preoperative comorbidities or to use specific drugs (table 3³). Following multivariable risk adjustment, several patient characteristics had statistically significant associations with prolonged opioid use (table 3). They included younger age, lower fifth of neighbourhood income, specific comorbidities (diabetes, heart failure, pulmonary disease), and use of specific drugs preoperatively (benzodiazepines, SSRIs, ACE inhibitors). Surgical procedure was also an important determinant of prolonged opioid use (table 3). Compared with open radical prostatectomies, open and minimally invasive intrathoracic procedures were associated with higher risks of prolonged opioid use (odds ratio 2.58, 95% confidence interval 2.03 to 3.28 and 1.95, 1.36 to 2.78, respectively). Conversely, hysterectomies (open and minimally invasive) and minimally invasive radical prostatectomies were associated with lower risks of prolonged opioid use. Our results were unchanged when the analyses were repeated among patients who survived until 180 days after surgery (see supplementary table 2).

Discussion

Although almost 50% of patients who had never previously used opioids were discharged from hospital with an opioid prescription after major elective surgery, 3.1% continued to be prescribed opioids for more than three months after surgery. We identified several factors associated with development of prolonged opioid use, especially surgery type, with open intrathoracic procedures having a 2.5-fold higher risk and minimally invasive intrathoracic procedures having a 1.95-fold higher risk. Other risk factors for prolonged opioid use included younger age, lower socioeconomic status, diabetes, heart failure, pulmonary disease, and use of specific drugs preoperatively (benzodiazepines, selective serotonin reuptake inhibitors (SSRIs), ACE (angiotensin converting enzyme) inhibitors).

A key finding of our study is that only 1 in 30 patients exposed to opioids after major surgery continued to use them for more than three months. Given the types of surgical procedures included in this study, it can be reasonably assumed that all of these patients had been exposed to opioids during their in-hospital stay. The 3.1% risk of prolonged opioid use is relatively low; indeed, it is lower than the proportion of patients reported to be using opioids at one year after low risk surgery (7.7%).⁷ The discrepancy in reported risks is possibly explained by differing methodologies. Specifically, long term opioid use was defined in the previous study as any opioid prescription within 305 to 425 days after surgery, regardless of whether opioids were prescribed during the intervening postoperative period. Indeed, 90% of such long term users had not been prescribed opioids immediately after surgery. In contrast, prolonged opioid use was more strictly defined in our present study as any opioid prescription within 1 to 90 days after surgery, and any opioid prescription within 91 to 180 days after surgery. Patients can therefore be reassured that when people receive opioids appropriately to treat acute pain after major surgery, the majority do not experience prolonged use. Our findings therefore help inform patients' and clinicians' understanding of the risks of prolonged opioid use after major surgery, especially since patients' understandable fears about opioid dependence may be an important barrier to achieving adequate acute postsurgical pain relief.

None the less, given the millions of major surgical procedures performed worldwide every year,¹ 3.1% does represent a large absolute number of patients who continue to use opioids for more than three months after surgery. This relatively low individual risk of 3.1% thus still represents a substantial overall public health concern at the population level. It is therefore critical that we elucidate the risk factors, as well as underlying mechanisms, for the development of prolonged postoperative opioid use. Our study identified several such risk factors, including surgical procedure, younger age, lower socioeconomic status, and specific comorbidities or use of specific drugs preoperatively. The underlying mechanisms that might explain the association of these risk factors with prolonged opioid use include development of persistent postsurgical pain, non-pain related factors driving opioid prescription (that is, doctors' prescription practises, geographical location, addiction), and the presence of pre-existing unmet needs for pain before surgery.

The development of persistent postsurgical pain may explain the association of prolonged postoperative opioid use with thoracic surgical procedures, younger age, and drugs used to treat anxiety or depression (that is, benzodiazepines, SSRIs). Approximately 40-80% of patients with a thoracotomy incision develop post-thoracotomy pain syndrome, which in turn impairs activities of daily living, disrupts sleep,^{19 20} and leads to long

term analgesic use.^{20 21} In more than 50% of cases, this pain is neuropathic in origin,^{22 23} presumably due to nerve injury or compression during the surgical procedure.^{23 24} Importantly, such neuropathic pain is poorly responsive to treatment with opioids alone. Such affected patients should instead receive first line drugs for neuropathic pain (for example, anticonvulsants, tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors),²⁵ either alone or combination with opioids.

Previous work has also identified younger biological age as a predictor of subsequent persistent postsurgical pain, which may explain in part the association of younger age with prolonged opioid use in our study.^{26 27} Conversely, the protective characteristic of advanced age for development of persistent postsurgical pain has also been identified in preclinical²⁸ and clinical studies.²⁹ Preoperative fear and anxiety have been shown to be correlated with acute postoperative pain, acute postoperative analgesic consumption,³⁰ and risks of subsequent persistent postsurgical pain.^{31 32} After surgery, depression, psychological vulnerability, and stress are also correlated with the presence of persistent postsurgical pain.³³ Thus, pre-existing anxiety and depression may be underlying mechanisms explaining the association of prolonged opioid use with preoperative use of benzodiazepine and SSRIs.

Several factors unrelated to pain, such as doctors' prescription practises, might also have played a role in the development of prolonged postoperative opioid use in our cohort. For example, we found that patients with heart failure or receiving ACE inhibitors had an increased risk of continuing opioids for more than three months after major surgery. This increased risk might be explained, in part, by doctors' concerns about precipitating decompensated heart failure as a result of non-steroidal anti-inflammatory drugs being administered to patients with known heart failure, thereby leading to a preferential use of opioids for managing postoperative pain. In addition, we found that residence in lower income neighbourhoods was a predictor of prolonged postoperative opioid use, with evidence of a clear dose-response relation between decreasing neighbourhood income and increasing risks for opioid use (table 3). Non-pain related factors have explained this relation, such as unmeasured patient level characteristics, doctors' prescribing practises in lower income neighbourhoods, or greater reluctance among patients on a lower income to question their doctors about the appropriateness of prolonged opioid treatment. Our findings on markers of socioeconomic status are consistent with previous research examining opioid utilisation for non-cancer pain among recipients of social assistance.³⁴ This research found that socioeconomically disadvantaged patients used more opioid drugs more often and at higher prescribed doses. The development of opioid dependence or addiction, although not captured by our data sources, may have also accounted for the development of prolonged opioid use in some patients in our cohort.

Although we tried to exclude people with pre-existing pain disorders from our study cohort, it is possible that some participants still had unmet pain management needs before surgery. Such people may have found that opioids prescribed for acute postoperative pain also helped manage chronic pre-existing pain conditions (for example, osteoarthritis) that were undertreated before surgery. These patients may in turn continue to use opioids persistently after surgery to manage these pre-existing chronic pain conditions, as opposed to pain directly related to surgery. The contribution of this underlying mechanism is supported by the increased risk of prolonged postoperative opioid use in patients with preoperative comorbidities that are known to be associated with unrelieved

chronic pain conditions. For example, patients with heart failure³⁵⁻³⁷ or with chronic obstructive pulmonary disease³⁸ have been shown to have unrelieved pain conditions. In our present study, these same patients also had higher risks of developing prolonged postoperative opioid use.

Implications for future research

Our results help facilitate the appropriate design of future studies of interventions to help mitigate risks of prolonged opioid use. Specifically, such studies should focus on high risk patients, especially since the majority of patients who had not used opioids before major surgery in this study did not develop persistent opioid requirements. The risk factors identified in our present study should facilitate identification of these high risk subgroups for participation in such trials. Future research should also include prospective studies with detailed follow-up to confirm our findings and to better understand why people with these risk factors continue to use opioids. Understanding the mechanisms underlying the development of prolonged opioid use is key to developing appropriate interventions to decrease opioid use. For example, interventions that focus exclusively on restricting access to opioids for patients after surgery would not be appropriate if the predominant causal mechanism is development of persistent postsurgical pain. In such a scenario, research into interventions should possibly focus on intervening in high risk patients before or immediately after surgery to help mitigate development of persistent postsurgical pain, potentially by minimising the deleterious immediate and long term effects of noxious perioperative afferent input.³⁹

Limitations of this study

Our study should be interpreted cautiously in light of its limitations. Firstly, our data sources lacked important clinical details such as in-hospital drug use, reasons for opioid prescriptions, and some complications, such as persistent postsurgical pain. We therefore cannot determine whether prolonged postoperative opioid use in individual patients was reflective of persistent postsurgical pain, physiological opioid dependence, addiction, or even opioid diversion. Secondly, our cohort only included patients aged 66 years or older, by virtue of limitations of prescription data available in our administrative databases. Thus, the generalisability of our findings to younger populations is uncertain. Thirdly, patients taking opioids before surgery were excluded from the current study; hence we are unable to extrapolate our findings to opioid dependent patients presenting for major surgery. Fourthly, as our study was observational, it does not prove that all identified associations represented causal relations. Future research should therefore include similar large retrospective studies to assess the replicability of our findings, prospective cohort studies to capture detailed information on pathophysiological mechanisms underlying prolonged postoperative opioid use, and randomised controlled trials to evaluate promising interventions that act on these presumed underlying mechanisms to help prevent prolonged postoperative opioid use.

Conclusions

Within the context of the growing concern of an addiction crisis resulting from doctor prescribed drugs,⁴⁰ major surgery remains a common healthcare scenario where some degree of opioid use is largely unavoidable. This population based multicentre study provides reassurance to both the doctors dealing with patients preoperatively and the patients themselves about the potential risks of opioid use after major surgery. Indeed, our findings

indicate that a simple global restriction of opioids for every patient undergoing major surgery would simply not be appropriate. In addition, we identified several important risk factors for prolonged postoperative opioid use.

Future research should be focused on high risk patients with these predictive factors, both to delineate mechanisms for development of prolonged opioid use and to evaluate preventive interventions. Such research is critical if doctors are to ensure that low risk surgical patients continue to have access to postoperative opioids for effective relief of acute pain, while high risk patients receive the targeted effective interventions needed to mitigate risk of prolonged opioid use.

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Ethical approval: This study was approved by Sunnybrook Health Sciences Centre.

Data sharing: No additional data available.

Transparency: The corresponding author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained. The corresponding author is the study guarantor.

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What is already known on this topic

Although opioids are effective for acute postoperative pain, patients requiring major surgery may be concerned about developing prolonged use from perioperative use of opioids

The risk of developing prolonged postoperative opioid use after major surgery is unclear

What this study adds

Approximately 3.1% of patients who had not used opioids previously continued to use them for more than 90 days after major elective surgery

Although 3.1% risk is low at an individual patient's level, it represents an important public health concern because millions of patients undergo major surgery every year

Factors associated with the development of prolonged postoperative opioid use include younger age, lower income, specific comorbidities, use of specific preoperative drugs, and thoracic surgical procedures

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Tables

Table 1 | Patterns of post-discharge opioid use across different surgical procedures. Values are proportions (%) with exact 95% binomial confidence intervals

Procedures	No of participants (n=39 140)	Duration of opioid use	
		Early post-discharge* % (95% CI)	Prolonged post-discharge† % (95% CI)
Urological surgery‡:			
Radical prostatectomy (open and minimally invasive)	5193	65.2 (63.9 to 66.5)	2.8 (2.4 to 3.2)
Coronary artery bypass graft via sternotomy	9488	53.5 (52.4 to 54.5)	3.3 (2.9 to 3.6)
Intrathoracic surgery:			
Minimally invasive lung resection	720	65.7 (62.1 to 69.2)	6.3 (4.6 to 8.3)
Open lung resection	2423	72.4 (70.6 to 74.2)	8.5 (7.4 to 9.6)
Intra-abdominal surgery:			
Minimally invasive colorectal surgery	3202	44.1 (42.3 to 45.9)	3.2 (2.6 to 3.9)
Open colorectal surgery	8642	38.0 (37.0 to 39.1)	2.8 (2.4 to 3.1)
Gynaecological surgery:			
Minimally invasive hysterectomy	5287	35.7 (34.4 to 37.0)	1.5 (1.2 to 1.8)
Open hysterectomy	4185	47.3 (45.7 to 48.8)	2.5 (2.1 to 3.0)

*≥1 prescriptions for opioids within 1-90 days after surgery.

†≥1 prescriptions for opioids within 1-90 days after surgery, along with ≥1 prescriptions for opioids within 91-180 days after surgery.

‡Subgroup specific results for open versus minimally invasive prostatectomy not reported owing to privacy regulations on reporting of small numbers of people within subgroups.

Table 2| Proportions of patients with prolonged post-discharge opioid use, according to perioperative characteristics

Characteristics	No of participants (n=39 140)	No (%) with prolonged post-discharge opioid use
Age group (years):		
66-75	26 509	851 (3.2)
76-85	11 398	353 (3.1)
≥86	1233	25 (2.0)
Women	18 753	554 (3.0)
Neighbourhood income fifth:		
First (lowest)	6741	248 (3.7)
Second	8009	283 (3.5)
Third	7776	250 (3.2)
Fourth	8170	222 (2.7)
Fifth (highest)	8444	226 (2.7)
Rural residence	6130	187 (3.1)
Surgical procedure:		
Coronary artery bypass graft	9488	310 (3.3)
Minimally invasive lung resection surgery	720	45 (6.2)
Open lung resection surgery	2423	205 (8.5)
Minimally invasive colorectal surgery	3202	102 (3.2)
Open colorectal surgery	8642	238 (2.8)
Minimally invasive hysterectomy	5287	78 (1.5)
Open hysterectomy	4185	105 (2.5)
Prostatectomy (open and minimally invasive)*	5193	146 (2.8)
Comorbid disease:		
Coronary artery disease	11 735	400 (3.4)
Heart failure	1340	64 (4.8)
Cerebrovascular disease	673	27 (4.0)
Peripheral vascular disease	751	26 (3.5)
Diabetes	10 156	376 (3.7)
Hypertension	28 360	934 (3.3)
Pulmonary disease	1051	70 (6.7)
Renal disease	1190	45 (3.8)
Malignancy:		
Primary	9930	341 (3.4)
Metastatic	354	20 (5.6)
Preoperative drugs:		
Benzodiazepines	4518	188 (4.2)
SSRIs	1556	73 (4.7)
β blockers	12 628	434 (3.4)
Statins	16 565	566 (3.4)
ACE inhibitors	12 568	473 (3.8)
Angiotensin receptor blockers	5425	178 (3.3)

ACE=angiotensin converting enzyme; SSRIs=selective serotonin reuptake inhibitors.

*Subgroup specific results for open versus minimally invasive prostatectomy are not presented owing to privacy regulations on reporting of small numbers of people within subgroups.

Table 3| Adjusted associations of patient level and surgery level factors with prolonged post-discharge opioid use*

Factors	Unadjusted comparison		Adjusted comparison	
	Odds ratio (95% CI)	P value	Odd ratio (95% CI)	P value
Personal characteristics				
Women	0.89 (0.79 to 1.00)	0.04	1.10 (0.96 to 1.27)	0.19
Age groups (years):				
66-75	1.60 (1.07 to 2.40)	0.06	1.63 (1.08 to 2.46)	0.03
76-85	1.54 (1.03 to 2.33)		1.47 (0.97 to 2.22)	
≥86	Reference		Reference	
Income fifth:				
1 (lowest)	Reference	<0.001	Reference	0.005
2	0.96 (0.81 to 1.14)		0.98 (0.82 to 1.16)	
3	0.87 (0.73 to 1.04)		0.90 (0.75 to 1.07)	
4	0.73 (0.61 to 0.88)		0.76 (0.63 to 0.92)	
5 (highest)	0.72 (0.60 to 0.87)		0.77 (0.64 to 0.93)	
Rural residence:				
Urban	Reference	0.66	Reference	0.79
Rural	0.97 (0.83 to 1.13)		0.98 (0.83 to 1.15)	
Surgical procedures				
		<0.001		
Radical prostatectomy:				
Open prostatectomy	Reference		Reference	
Minimally invasive prostatectomy	0.36 (0.13 to 0.98)		0.37 (0.14 to 1.01)	
CABG via sternotomy	1.11 (0.91 to 1.36)		0.95 (0.71 to 1.29)	
Intrathoracic surgery:				
Open lung resection	3.05 (2.45 to 3.80)		2.58 (2.03 to 3.28)	
Minimally invasive lung resection	2.20 (1.56 to 3.10)		1.95 (1.36 to 2.78)	
Intra-abdominal surgery:				
Open colorectal surgery	0.93 (0.76 to 1.15)		0.84 (0.67 to 1.07)	
Minimally invasive colorectal surgery	1.09 (0.84 to 1.40)		1.00 (0.76 to 1.32)	
Total hysterectomy:				
Open hysterectomy	0.85 (0.66 to 1.10)		0.73 (0.55 to 0.98)	
Minimally invasive hysterectomy	0.49 (0.37 to 0.65)		0.45 (0.33 to 0.62)	
Comorbid disease				
Coronary artery disease	1.13 (1.00 to 1.28)	0.05	0.95 (0.75 to 1.21)	0.70
Heart failure	1.58 (1.22 to 2.04)	<0.001	1.32 (1.02 to 1.74)	0.05
Cerebrovascular disease	1.30 (0.88 to 1.91)	0.19	1.06 (0.71 to 1.58)	0.77
Peripheral vascular disease	1.11 (0.75 to 1.65)	0.61	0.85 (0.57 to 1.27)	0.42
Diabetes	1.27 (1.12 to 1.44)	<0.001	1.15 (1.00 to 1.31)	0.04
Hypertension	1.21 (1.06 to 1.38)	0.005	1.06 (0.92 to 1.23)	0.42
Pulmonary disease	2.28 (1.77 to 2.92)	<0.001	1.53 (1.17 to 1.99)	0.002
Renal disease	1.22 (0.90 to 1.65)	0.20	1.01 (0.74 to 1.39)	0.94
Malignancy:				
Primary	1.15 (1.01 to 1.30)	0.03	1.05 (0.91 to 1.21)	0.21
Metastatic	1.93 (1.22 to 3.05)		1.41 (0.88 to 2.25)	
Preoperative drug use†				
Benzodiazepines	1.40 (1.20 to 1.64)	<0.001	1.26 (1.07 to 1.48)	0.005
SSRIs	1.55 (1.22 to 1.98)	<0.001	1.41 (1.10 to 1.80)	0.01
β blockers	1.15 (1.02 to 1.30)	0.02	1.05 (0.92 to 1.21)	0.35
Statins	1.17 (1.04 to 1.31)	0.01	1.00 (0.88 to 1.14)	0.75
ACE inhibitors	1.34 (1.19 to 1.50)	<0.001	1.26 (1.09 to 1.44)	<0.001

Table 3 (continued)

Factors	Unadjusted comparison		Adjusted comparison	
	Odds ratio (95% CI)	P value	Odd ratio (95% CI)	P value
Angiotensin receptor blockers	1.05 (0.90 to 1.24)	0.52	1.08 (0.90 to 1.28)	0.34

ACE=angiotensin converting enzyme; CABG=coronary artery bypass graft; NA=not applicable; SSRIs=selective serotonin reuptake inhibitors.

*Multivariable logistic regression model used for these analyses had good calibration (Hosmer-Lemeshow statistic P=0.59) and modest discrimination (C statistic 0.64).

†Outpatient prescription within 90 days before index surgery.