Post-Surgical Prescriptions for Opioid-Naïve Patients and the Association with Overdose and Abuse

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Post-Surgical Prescriptions for Opioid-Naïve Patients and the Association with Overdose and Abuse: A Retrospective Cohort Study

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ABSTRACT

Importance: Rates of non-fatal opioid overdose have risen by more than 50% over 10 years. Most cases originate from an initial medical prescription. Post-surgical patients are nearly four times more likely to receive post-discharge opioids as their non-surgical counterparts. Because existing guidelines do not adequately address post-discharge dispensation, surgical providers face a dilemma with each prescription refill.

Objective: We quantified the effects of varying opioid prescribing patterns after surgery on dependence, overdose, or abuse in an opioid-naïve population.

Design: Retrospective cohort study.

Setting: Surgical claims were extracted from a linked medical and pharmacy administrative database of 37,651,619 commercially insured patients between 2008 and 2016.

Population: Opioid-naïve patients undergoing surgery

Interventions: N/A

Main Outcomes/Measures: Oral opioid exposure after discharge as defined by refills and total dosage and duration. The primary outcome was a composite outcome of *misuse* identified by a diagnostic code of opioid dependence, abuse, or overdose.

Results: 568,612 (56%) patients received post-operative opioids, and a misuse code was identified in 5,906 patients (0.6%, 183 per 100,000 person-years). Total opioid duration was the strongest predictor of misuse, with each refill and additional week of opioid exposure associated with an adjusted increase in the rate of misuse of 51.6% (CI 47.7 to 55.6%, p<0.001) and 20.0% (CI 18.5 to 21.1%, p<0.001), respectively.

Conclusions: The total duration of opioid prescription after surgery is more predictive of opioid misuse than dosage. Each refill dramatically increases the rate of misuse. With the complementary forces of opioid duration and dose, our analysis quantifies the association of prescribing choices on opioid misuse and identifies levers for possible impact.

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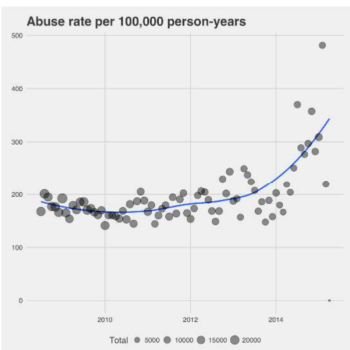
PRINT ABSTRACT:



Study Question: We quantified the effects of varying opioid prescribing patterns after surgery on dependence, overdose, or abuse in an opioid-naïve population.

Methods: A retrospective cohort study was undertaken of surgical claims extracted from a linked medical and pharmacy administrative database of 37,651,619 commercially insured patients between 2008 and 2016. The primary outcome was a composite of *misuse* identified by a diagnostic code of opioid dependence, abuse, or overdose. Post-discharge refills, duration, and dosage of filled oral opioid prescriptions were compared with rates of misuse.

Study Answer and Limitations: Total opioid duration was the strongest predictor of misuse, with each refill and additional week of opioid exposure associated with an adjusted increase in the rate of misuse of 51.6% (CI 47.7 to 55.6%, p<0.001) and 20.0% (CI 18.5 to 21.1%, p<0.001), respectively. These results represent claims-based characteristics for commercially insured patients; effects may be different in the elderly and non-insured populations.

What This Study Adds: Each refill and week of opioid prescription is associated with a large increase in opioid misuse among opioid-naïve patients. Our data suggests that duration of the prescription rather than dosage is more strongly associated with ultimate misuse in the early post-surgical period.

Funding, Competing Interests, Data Sharing: There is no declared funding or competing interest for this study. Data was donated by Aetna Inc.

WHAT THIS PAPER ADDS

What is already known:

- Opioid misuse is rising rapidly in the US and internationally.
- Surgical patients are four times more likely to get opioids at discharge than their non-surgical counterparts.
- It is unknown how opioid prescribing habits by clinicians are related to rates of misuse.

What this study adds:

- Each refill and week of opioid prescription is associated with a large increase in opioid misuse among opioid-naïve patients.
- Our data suggests that duration of the prescription rather than dosage is more strongly associated with ultimate misuse in the early post-surgical period.

INTRODUCTION

In the last fifteen years, age-adjusted opioid overdose rates have tripled and now rank as the leading cause of unintentional injury-related death.[1,2] Prescription medications are implicated in the majority of the cases, as rates of opioid prescription quadrupled [3,4] and were paralleled by rising rates of overdose deaths. Non-fatal overdose events from prescription opioids account for 7-11 times more episodes than fatal overdoses[2,5] and have similarly risen by more than 50% over 10 years. [6] Most striking is the fact that the majority of these non-fatal overdose episodes take place in patients identified as non-chronic (<90 days) opioid users.

Over-prescription of opioids is thought to be a major contributor,[7] where two thirds of opioid misuse can be attributed to opioids obtained through a single physician.[2] Overprescribing enables opioid diversion and increases the potential for addiction. [8,9] Surgical patients are nearly 4 times more likely to get post-discharge opioids as their non-surgical counterparts. Orthopedic surgeons alone were responsible for 7.7% of all opioid prescriptions in 2009.[10,11] Despite these numbers, surgeons have yet to find the right balance of opioid prescriptions: between 3 and 10% of opioid-naïve patients become chronic users, while emerging research suggests that the remaining group of patients leave as many as 80% of all prescribed pills unused.[12]

The lack of guidance around post-surgical opioid prescribing[13,14] is partially a result of the fact that little is known about the effect of longer and larger regimens of post-discharge opioids. More directly, we do not know how prescription refills affect long-term likelihood of misusing opioids. Prominent authors have called for study into this question[6,15,16] to underpin future guidelines.[17] Furthermore, there is evidence that any post-discharge exposure is a risk factor for multiple refills[18] independent of the specific prescription.[19] In this study, we examine the association between opioid prescription refills after surgery and misuse in an opioid-naïve population.

METHODS

Data Source

Surgical patients with medical and pharmacy insurance were drawn from a de-identified administrative database at Aetna Inc., a commercial managed healthcare company. This database includes 37,651,619 million members with Aetna health and pharmacy insurance coverage between 2008 and early 2016. Members were defined by a unique numerical identifier. Data included all medical claims during the study period.

Patient Involvement

Patients were not involved in the design of this study. Surgical providers were consulted extensively during the initial design and will be involved in dissemination of study results.

Sample Cohort

For this retrospective cohort study, the study cohort consisted of members who underwent surgery and had at least 6 months of medical and 3 months of pharmacy insurance before surgery, as well as 90 days of pharmacy and 1 year of medical coverage[16] after surgery. The index surgery for each member was chosen as the first surgery in the database that met criteria and after which no further surgery claims were filed for 90 days. Members were followed until they experienced an opioid-related event or their last month of enrollment in the database.

A member was considered opioid naïve and eligible for inclusion if total opioid exposure in the 60 days before surgery was 7 days or less.[20] Post-surgical opioid exposure was measured if the member filled a prescription for an included opioid within 30 days of discharge. Exposure was considered concluded when either 30 days elapsed without a filled opioid prescription or a misuse diagnosis was observed.

We excluded patients who had pre-surgical evidence of opioid or other non-specific forms of misuse in the 6 months prior to surgery (see Supplemental eTable 1 for a list of pre-surgical exclusion codes). Finally, we excluded a small subset of patients with missing data for any variable. The protocol and sample derivation is summarized in Supplemental eFigure 1.

Outcome Measures

Surgical claims were identified by a comprehensive list of Current Procedural Terminology (CPT) codes associated with inpatient and outpatient surgery and specialty released by the National Surgical Quality Improvement Program (NSQIP) of the American College of Surgeons in 2015.[21] Organ-based categories were derived from top-level CPT headers (e.g.10030-19499 for surgeries of the integumentary system).

The primary outcome was an International Classification of Disease (ICD) diagnosis code of opioid dependence, abuse, or overdose (see Supplemental eTable 1). Opioid misuse was defined as the presence of at least one of these ICD codes after discharge. This term encompasses a composite of a wide range of forms of misuse. Only diagnosis codes related specifically to prescription opioids were included.

Opioid Use

Opioids were identified in the database as narcotic analgesics or narcotic analgesic combinations by therapeutic category from Cerner's Multum Lexicon Drug Database.[22] Only non-injected drugs associated with the following primary ingredients were used: codeine, hydrocodone, hydromorphone, morphine, oxycodone, oxymorphone, or tramadol. Other less common opioids were excluded for low numbers or association with palliative care or dependence treatment. We determined the morphine milligram equivalent (MME) dosage for each opioid prescription, using standard conversions.[23] In order to decrease the influence of extreme outliers while respecting variation seen in the literature, daily dose was truncated at 350 MME/day.[24] Length of exposure was truncated at 90 plus 1 days, and number of refills was truncated at 5.

Refill Identification

A medication refill is a physical event with varying lengths. Like the initial prescription, there is no standard refill dosage or duration. Thus, identification of the event is a somewhat artificial threshold marking continuation of the opioid exposure. Because it requires a patient to approach their care provider for further medication, the event is also relevant. In this vein, we chose to identify refills in two ways. First, the number of physical prescriptions filled were counted after the initial exposure. The first post-discharge prescription was counted as the initial exposure and all subsequent prescriptions with less than a 30-day gap between prescriptions were included.

Second, we identified total post-discharge exposure by duration and dosage. Post-discharge opioid exposure duration was determined to be the total number of calendar days covered by a prescription for an opioid after discharge from the index surgical procedure. This identified the “cabinet supply” of opioids acquired by a patient as outlined by Mosher.[25] We also used a well-described method[26] to consider overlapping prescriptions as part of the same episode and an indication of a completed previous prescription at a higher dose. Accounting for overlapping prescriptions consisted of defining exposure as the total days of accumulated prescriptions minus overlap.

When a single discharge date was listed on all medical claims associated with the index surgery date, this was used as the official discharge date. When multiple discharge dates were present, the last date was used. If no discharge date was associated with any medical claim on the index surgery date, the surgery date was used as discharge date.

Statistical Analysis

We analyzed the time until misuse event over the entire study period. Raw rates of opioid misuse were computed as total number of misuse events divided by total follow-up time and are reported as cases per 100,000 person-years (cases/100,000). Weighted linear regression (WLS) was used for unadjusted analysis of log-transformed weekly rates of misuse, where each week was weighted according to sample size. Cox proportional hazards models were used for adjusted analysis of time until misuse event. Adjusted models included either refills or duration, as well as daily dose (MME/day), age, sex, state of residence, surgery type by CPT top-level grouping, surgery year, concurrent benzodiazepine use, and binary indicators of pre-surgical diagnoses potentially related to misuse. A single surgery might be associated with multiple surgery types, if multiple CPT codes were assigned.

Pre-surgical diagnoses of interest were determined using penalized logistic regression.[27] All 590 ICD codes assigned to at least 0.5% of patients in the 6 months prior to surgery were included in the model, as well as age, sex, and surgery type. In total, 65 pre-surgical diagnosis codes were selected (see Supplemental eTable 2).

WLS effects are reported as multiplicative percent increases in rate, and Cox effects as multiplicative percent increases in hazard or equivalently hazard ratios (HRs). Two-sided p-values and 95% confidence intervals (CIs) are reported throughout. All analyses were conducted using R 3.2.2 (R Core Team).

We performed sensitivity analyses restricted to (i) one year post-surgery and to (ii) members with no additional surgeries during follow-up to ensure that the effect we observed was driven by the initial opioid exposure and not downstream unidentified factors. For misuse events within one year, we used logistic regression to adjust for covariates.

We considered two additional sensitivity analyses to detect if structural factors due to changing trends over time (year of surgery) or geography were influencing our estimates. We considered a Cox model including an interaction between duration and an indicator for year and another model including an interaction between duration and state of residence. Further sensitivity analysis attempted to mimic an unobserved confounder by creating a synthetic binary variable that was associated with both duration and opioid misuse. A Cox model was fit including this synthetic confounder to see the degree to which strong unobserved confounding might explain the observed association.

The de-identified data in this study was exempt from Institutional Review Board review as confirmed by the Harvard Medical School IRB committee.

RESULTS

Cohort Characteristics

The study sample included 1,015,116 members who met study criteria and underwent an index surgery. Members were followed for a median of 2.67 years. After the index surgery, 568,612 (56%) filled a post-operative opioid prescription. Ninety percent of prescriptions were filled within 3 days of discharge. In the subsequent follow-up period, misuse was identified in 5,906 members (0.6%, 183 cases/100,000), with 1,857 occurring within one year after surgery (0.2%).

Characteristics of the cohort followed national trends (Table 1). Surgeries were more prevalent among older age groups, and younger groups had higher rates of opioid usage. The most common surgery types were those of the musculoskeletal system (367,317 surgeries; 2,448 misuse events; 206 cases/100,000), digestive system (293,905 surgeries; 1,825 misuse events; 198 cases/100,000), and integumentary system (106,914 surgeries; 533 misuse events; 161 cases/100,000). Rates of misuse by age group followed national patterns with higher rates among younger adult males (Figure 1A) and increasing rates over the study period (Figure 1B).

The study period saw notable changes in opioid prescription characteristics and rates of misuse, as demonstrated in Table 1. Post-surgical incidence of misuse increased from 183 cases/100,000 (2009) to 269 cases/100,000 (2014), while opioid prescription fill rates plateaued and began to fall in the later years of the study (also see Figure 1C). Median duration and median dose prescribed remained stable throughout the study period at about 5 days and 50 MME/day, respectively. These stable numbers masked a change in opioid prescription characteristics during the study period: fewer short-course and increased numbers of longer duration prescriptions as well as a trend toward lower doses by episode (see Figures 2D and 2E). Similar prescribing changes were detected in all surgery types. See Supplemental eFigure 2 for further detail.

Rates of Misuse by Opioid Exposure

The number of post-discharge prescriptions best predicted eventual misuse. Overall rates of misuse were low, but rates grew rapidly with increasing exposure. The rate of misuse more than doubled among those with one refill (86,654 [15.2%]; 293 cases/100,000) versus those with no refills (434,273 [76.2%] patients; 145 cases/100,000). In total, each additional refill increased the rate of misuse by 70.7% (CI 54.6-88.4%) before adjustment and increased the hazard of misuse by 44.0% (CI 40.8-47.2%, $p<0.001$) after adjusting for covariates.

The relationship between number of refills and misuse was further supported by evaluation of the number of days of opioid exposure post-discharge. In the aggregate, each additional week of opioid exposure was associated with an average increase in the rate of misuse of 34.2% (CI 26.4-42.6%, p-value < 0.001, see Figure 2A). Adjusting for covariates, each additional week of exposure to opioids was associated with a 19.9% increase in hazard (CI 18.5-21.4%, p-value < 0.001). For both refills and duration, Figure 2A shows that the risk of misuse initially follows the trend-line and begins to taper at higher levels of exposure >11 weeks of duration.

In comparison to duration of exposure, the dosage prescribed was a weaker predictor of misuse (Figure 2C), and dose became important only at extended duration (Figure 2E). Each additional 10 MME/day were associated with only a 0.8% increase in hazard of misuse (HR 1.008, CI 1.003-1.013, p-value = 0.001). Even high doses (>150 MME/day) were associated with only mild increases in risk when duration was short (Figure 2E). For example, when post-discharge prescription duration was less than 2 weeks, similar rates of misuse were found for lower (40-50 MME/day) vs. higher (100-150 MME/day) opioid dose. Conversely, members receiving greater than 9 weeks of opioids at a higher dose had dramatically increasing rates of misuse: 476 cases/100,000 (at <20 MME/day, n=422) to 2398 cases/100,000 (at 50-60 MME/day, n=430) to 5689 cases/100,000 (at >150 MME/day, n=237). *For short-term opioid use <90 days, higher doses of opioids had smaller effects on the rate of misuse than additional weeks of exposure.*

Additional Risk Factors of Misuse

After adjusting for covariates, other risk factors (detailed in Supplemental eTable 2), including benzodiazepines (HR 1.77, CI 1.64-1.93) as well as regimens initiated with hydromorphone (HR 1.76, CI 1.37-2.26) and oxycodone (HR 1.24, CI 1.03-1.48) had significant association with opioid misuse. The adjusted effect of surgery was greatly attenuated after controlling for the strongly associated pre-surgical diagnoses. Notable pre-surgical diagnoses included bariatric surgery status (V45.86, HR 2.19, CI 1.77-2.72), tobacco use disorder (305.1, HR 2.16, CI 1.97-

2.36), other chronic pain (338.29, HR 2.02, CI 1.68-2.42), and major depressive disorder (311, HR 1.60, CI 1.44-1.78).

Sensitivity Analyses

As part of a sensitivity analysis, we constructed models that removed potential sequential confounders. We found no difference in effect, with similar results for misuse events within one year of surgery (Supplemental eFigure 3) and among patients with no additional surgery during follow-up (Supplemental eFigure 4). To ensure that our outcome analysis was not biased by a specific ICD9 code, we removed 304.00 opioid dependence, the most common code, leaving only specific abuse and overdose codes. The findings of the model were virtually unchanged with this smaller subset: each additional refill was associated with an increased risk of 70.9% vs. 70.7% in the comprehensive model.

We also verified that the observed association was not affected by geography or biased by changing conditions across the study period. We compared the association between duration and misuse over different years (see Figure 3) and at the state level; results were statistically indistinguishable from a model with aggregated duration effect (likelihood ratio test p-value 0.26 and 0.99, respectively). Figure 3A shows that surgeons reduced the mean dosage within their specialty during the study period. Typical reductions ranged from 3 to 18 MME/day (4 to 24%) over the duration of the study. While dosage fell, mean duration of exposure during the years of the study remained relatively stable (Figure 3B). Despite changing clinician behavior over time, the relationship between duration of exposure and misuse was persistent (see Figure 3C). Such stability is further evidence of the robustness of this effect.

Finally, we assessed the potential effect of unobserved confounding by generating a synthetic binary variable strongly associated with both length of exposure (OR 2.7) and misuse (HR 5.0) and inserted it into the model. An example of such a confounder could be an undiagnosed risk factor for post-surgical misuse, such as pre-surgical alcohol dependence. Even in the presence of this artificial explanatory confounder, which has an unrealistically strong relationship to misuse, each week of exposure was still associated with a 13% increase in hazard of misuse.

DISCUSSION

Principle Findings

Physicians struggle to appropriately prescribe and dose post-operative opioids while addressing the very real needs of operative acute pain. [28,29] This is the first study to quantify the strong relationship between number and duration of refills of prescribed opioid pain medication and subsequent opioid misuse in the surgical population. We focused on typical surgical patients without previous misuse history or ongoing opioid use. We estimated an adjusted 44% increase in misuse for every refill fulfilled or 20% increase for every week of prescription. This association remained significant in multiple sensitivity analyses and using both time until any event and events within one year of surgery. While rates of misuse were low, the large number of surgeries performed every year increases the importance of these numbers.

Our adjusted models suggest that the effect of duration is not explained by temporal changes in physician behavior or patient population. During the later parts of the study period, surgeons appear to have reduced the number of patients receiving opioids and the number of patients with short prescriptions (<7 days). They increased rates of longer prescriptions for a subset of patients (see figure 2D). In the face of these changes, overall rates of opioid misuse have continued to increase (Figure 1B), demonstrating that this epidemic is multi-factorial and is not only driven by duration of exposure on an aggregate level. But despite the worsening crisis and these temporal changes, we specifically found that the effect of duration was stable across the study years and was unchanged by the changing misuse and prescribing rates in the population. The stable relationship shown in Figure 3 is suggestive of an independent effect.

A second finding was that duration of treatment rather than dosage of equivalent opioids was more strongly associated with subsequent misuse for acute post-discharge prescriptions. This builds on Miller's and Edlund's[30,31] finding of the importance of prescription duration. Each week of opioid exposure was associated with a 20% increase in misuse; short-term dosage carried a small (~10%) incremental impact per 100 MME on misuse and became noteworthy only at longer durations of administration. While this seems discordant with other studies that have found 2-9 fold increases in the rates of misuse for doses >100 MME/day,[5,7,24,31] our work differs from previous studies—which focused on chronic users—by examining a general surgical population who typically receive fewer than 2 weeks of opioids. Patients with chronic opioid usage may exhibit different misuse risk profiles.

Comparison with Other Studies

Our data was remarkably consistent with previous literature: the rate of refills[32] and the misuse event rate of 0.2% within one year[33] was similar to that identified in other studies. These striking numbers build on recent literature about the broad effect of post-discharge prescriptions on subsequent opioid use. Patients who received even one post-discharge prescription were three times more likely to be taking opioids at one year[18]. This finding extended across specialties, where surgical and non-surgical patients had similar rates of opioid refills. Several studies in surgical patients have also shown that early opioid administration after surgery is associated with subsequent long-term usage.[31,34] Irrespective of the direction of causality, our data suggest that patients who require subsequent refills of opioid medications are significantly more likely to have a misuse episode, even years after the index surgery. Whether driven by the patient's underlying need or the clinician's tendency to prescribe opioids, this relationship further holds when examining refills as individual weeks of exposure.

Our findings suggest that opioid-naïve patients who receive low to moderately high doses of pain medications for short durations have small associated increases in their overall rates of misuse. Many studies have shown that pain is often poorly managed after surgery. [35–39] Higher doses (to a point) may better saturate mu receptors, while under treatment of acute pain increases the risk of pseudo-addiction, chronic pain, and, potentially, overdose.[40,41] These findings suggest a more nuanced understanding of the relationship between duration and dosage with a focus on early appropriate treatment of pain (including higher doses) for a limited time. Such findings suggest that optimal post-operative prescribing, which maximizes analgesia and minimizes the risk of misuse, may be achieved with moderate to high opioid dosages at shorter durations, a combination that merits further investigation in population-based and clinical studies.[41]

Limitations

We recognize that administrative data has inherent biases that may affect our results. First, our dataset fails to exclude patients with undocumented pre-surgical misuse or opioid usage. Similarly, we may not detect post-operative misuse in members who leave the cohort because they lose or change coverage. Miscoding claims is possible but less likely as coding of opioid abuse has been found to be accurate 85% of the time. [42] Alternatively, increased recognition of the problem of opioid misuse may lead to overcoding in later years or undercoding in earlier years. This could be one explanation for the rising rates of misuse observed in later years, but recent national studies by other authors have also shown similar trends.[1] Finally, measurement of opioid exposure is complicated by the possibility that patients might fill a prescription and modify the course or dosing of the drug.[43] Our cabinet method of measuring exposure attempts to conservatively overestimate usage.

As for the problem of confounding, we controlled for disease burden by adjusting for surgery type and examined the full space of pre-surgical diagnosis codes, but these are, at best, partial measures of disease state at the time of surgery. Notably, we are unable to control for the extent of pain or the vagaries of surgical techniques. In the presence of uncontrolled confounding, we cannot be certain of the magnitude of the effect that we see. Those patients with higher likelihood for developing misuse may be requesting augmented treatment.[44] The consistency of our findings, despite extensive sensitivity analyses, suggest there may yet be a causal component to our analysis. This is further supported by evidence tying a majority of patients who present to addiction centers to an initial prescribed opioid for pain.[45]

As a final point, the generalizability of this study is limited to insured adults in the US, as several studies have shown increased rates of misuse in Medicaid, Medicare, and veteran populations.[25,46,47]

Conclusions and Policy Implications

In this study, we quantified the strong association between short-term post-surgical refills and ultimate misuse. A single refill increased the potential of misuse by more than 50%, and the duration of exposure appeared to be the most prominent predictor of misuse. Our findings are significant as they offer a potential lever for intervention and behavior change after surgery. Given that surgical and non-surgical patients receive similar numbers of refills, these findings have the potential to extend beyond surgery. Surgeons and non-surgeons are changing their opioid prescription characteristics, but rates of misuse continue to rise. They are trapped between guidelines that recommend shorter duration and smaller dosing of opioid medication and a subset of patients who request or require opioids beyond the initial prescription. With these seemingly conflicting forces at play, our analysis provides a broad evidentiary framework to inform clinician behavior and promote protocol development. Further research of this relationship is needed to determine how initial treatment regimens can minimize abuse and addiction.

AUTHORSHIP

GB, DA, and MB designed the study. CMW, DK, and KF contributed data assets. GB and DA wrote the manuscript. GB, DA, AB, and NP performed the analysis. MH contributed critical analytical tools for the analysis. CMW, DK, KF, MB, IK, and BY contributed citations, evaluated and edited the manuscript.

The lead author (the manuscript's guarantor) affirms that the 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.

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No additional data available.

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DECLARATION OF INTERESTS

Drs. Brat, Agniel, Beam, Yorkgitis, Homer, Bicket, Knecht, Walraven, Fox, Palmer, and Kohane have nothing to disclose.

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Tables and Figure Legends

Tables and Figures
Table 1: Demographic and Unadjusted Data
Figure 1: Age and Gender Breakdown
Figure 2: Misuse by Dose and Duration
Figure 3: Temporal Effects and Sensitivity Analysis

Supplemental Material
eTable1: Table of ICD9 Codes of Pre-Operative Misuse and Post-Operative Misuse
eTable2: All Events Cox Model
eFigure1: CONSORT Flow Diagram
eFigure2: Prescribing Changes by Gender, Group, Surgery Category
eFigure3: Sensitivity Analysis with One-Year Events and No Intervening Surgery

Table 1: Baseline Demographic Information and Unadjusted Associations

Category	Type	Total	Abuse/ Overdose Events	Opioid Prescription Filled (%)	Median Duration (days)	Median MME/day	Median Follow-up (years)	Median Time to Abuse (years)	Cases/ 100,000 Pt-Yrs
Entire Sample		1,015,116	5,906	56	5	50	2.67	1.74	183.2
Gender	F	563,170	3,166	54.3	5	50	2.67	1.82	176.3
	M	451,946	2,740	58.2	5	50	2.66	1.67	191.8
Birth Year	<15	54,098	118	46	5	30	2.74	2.39	66.7
	15-24	92,458	1,160	62.9	5	54.2	2.51	1.47	420.6
	25-34	97,856	666	60.6	5	50	2.41	1.68	226
	35-44	175,969	1,086	58.9	5	50	2.69	1.9	190.7
	45-54	238,154	1,284	57.9	5	50	2.78	1.95	164
	55-64	211,308	989	56.1	5	50	2.55	1.64	152.4
	65+	145,273	603	45.5	5	45	2.93	2.07	126.9
Surgery Year	2008	142,332	1,031	47.5	5	50	3.3	2.76	183.1
	2009	205,618	1,374	53	5	50	3.62	2.51	169.5
	2010	157,640	982	61.1	5	50	3.66	2.28	168.9
	2011	137,648	780	62.8	5	50	3.52	1.72	171.6
	2012	130,096	705	57.6	5	50	3.2	1.38	193
	2013	113,841	505	63.9	5	50	2.39	1.29	195
	2014	110,392	461	49.1	5	50	1.52	0.76	268.7

Please see following page for continuation of table.

Table 1 Continued: Baseline Demographic Information and Unadjusted Associations

Category	Type	Total	Abuse/ Overdose Events	Opioid Prescription Filled (%)	Median Duration (days)	Median MME/day	Median Follow-up (years)	Median Time to Abuse (years)	Cases/ 100,000 Pt-Yrs
Surgery Type	Musculoskeletal System	367,317	2,448	60.3	6	57.7	2.71	1.86	206.2
	Digestive System	293,905	1,825	63.2	5	50	2.63	1.68	198.1
	Integumentary System	106,914	533	39.3	5	45	2.61	1.75	160.8
	Female Genital System	98,444	449	56.7	5	46.9	2.69	1.85	142.3
	Cardiovascular System	57,715	241	33.3	6	44.4	2.65	1.52	134.4
	Nervous System	38,698	374	61.1	8	56.2	2.6	1.52	306.5
	Urinary System	30,274	121	49.8	5	45	2.71	1.52	125.8
	Male Genital System	26,524	76	59.3	5	41.2	2.73	1.98	89.6
	Endocrine System	19,622	110	49.2	4	45	2.72	1.6	172
	Hernia and Lymphatic Systems	11,836	56	62.6	5	50	2.6	1.52	153.9
	Auditory System	10,250	37	30.1	5	41.7	2.62	1.76	114.6
	Respiratory System	6,280	50	59.5	8	50	2.44	0.85	270.2
	Maternity Care and Delivery	2,692	13	67.4	4	46.9	2.42	2.28	162.2
	Mediastinum and Diaphragm	1,186	13	62	6	67.5	2.74	2.52	344.1
	Reproductive System	10	0	30	5	30	1.51	-	0
Drug	Hydrocodone	275,292	1,695	-	5	45	2.83	1.95	187.5
	Oxycodone	205,559	1,432	-	5	62.5	2.7	1.68	219
	Codeine	35,041	148	-	4	27	2.84	2.45	127.6
	Mixed	30,803	324	-	9	60	2.62	1.52	339.7
	Tramadol	11,721	70	-	8	30	2.21	1.53	221.1
	Hydromorphone	9,600	123	-	5	66.7	2.47	1.45	427.6

Supplemental Tables and Figures

eTable 1: ICD Code Tables Used in the Study

1A: All Observed Outcome Codes

ICD	LONG DESCRIPTION	N in sample
304.00	Opioid type dependence, unspecified	2,203
304.01	Opioid type dependence, continuous	1,311
305.50	Opioid abuse, unspecified	484
965.09	Poisoning by other opiates and related narcotics	409
E935.2	Other opiates and related narcotics causing adverse effects in therapeutic use	384
965.00	Poisoning by opium (alkaloids), unspecified	190
304.70	Combinations of opioid type drug with any other drug dependence, unspecified	113
305.51	Opioid abuse, continuous	77
304.71	Combinations of opioid type drug with any other drug dependence, continuous	72
E850.2	Accidental poisoning by other opiates and related narcotics	63
304.02	Opioid type dependence, episodic	39
305.53	Opioid abuse, in remission	35
305.52	Opioid abuse, episodic	30
304.72	Combinations of opioid type drug with any other drug dependence, episodic	11

1B: All Abuse Codes Used for Exclusion Criteria

ICD	LONG DESCRIPTION	N in sample
304.00	Opioid type dependence, unspecified	2,240
305.90	Other, mixed, or unspecified drug abuse, unspecified	1,625
304.01	Opioid type dependence, continuous	1,486
304.90	Unspecified drug dependence, unspecified	1,417
977.9	Poisoning by unspecified drug or medicinal substance	1,076
292.0	Drug withdrawal	956
305.50	Opioid abuse, unspecified	589
304.03	Opioid type dependence, in remission	283

E935.2	Other opiates and related narcotics causing adverse effects in therapeutic use	256
965.09	Poisoning by other opiates and related narcotics	229
304.91	Unspecified drug dependence, continuous	226
977.8	Poisoning by other specified drugs and medicinal substances	222
304.70	Combinations of opioid type drug with any other drug dependence, unspecified	177
305.93	Other, mixed, or unspecified drug abuse, in remission	160
965.00	Poisoning by opium (alkaloids), unspecified	145
305.51	Opioid abuse, continuous	134
304.71	Combinations of opioid type drug with any other drug dependence, continuous	121
305.91	Other, mixed, or unspecified drug abuse, continuous	120
305.53	Opioid abuse, in remission	90
305.53	Opioid abuse, in remission	90
304.02	Opioid type dependence, episodic	67
E980.0	Poisoning by analgesics, antipyretics, and antirheumatics, undetermined whether accidentally or purposely inflicted	48
304.93	Unspecified drug dependence, in remission	47
E850.2	Accidental poisoning by other opiates and related narcotics	44
965.01	Poisoning by heroin	43
305.92	Other, mixed, or unspecified drug abuse, episodic	42
305.52	Opioid abuse, episodic	36
304.73	Combinations of opioid type drug with any other drug dependence, in remission	32
965.02	Poisoning by methadone	25
292.12	Drug-induced psychotic disorder with hallucinations	24
304.72	Combinations of opioid type drug with any other drug dependence, episodic	18
304.92	Unspecified drug dependence, episodic	14

E850.0	Accidental poisoning by heroin	10
292.11	Drug-induced psychotic disorder with delusions	7
E850.1	Accidental poisoning by methadone	4
E935.0	Heroin causing adverse effects in therapeutic use	3

eTable 2: Comprehensive Adjusted Cox Regression Effects Model.

Covariate	Hazard ratio	Confidence interval, low	Confidence interval, high	p-value
Duration in weeks	1.199	1.185	1.214	< 1e-04
Dose in 10 MME/day	1.008	1.003	1.013	0.00126
Age 15-25 vs. <15	5.149	3.904	6.791	< 1e-04
Age 25-35 vs. <15	2.434	1.829	3.24	< 1e-04
Age 35-45 vs. <15	1.89	1.425	2.506	< 1e-04
Age 45-55 vs. <15	1.512	1.141	2.004	0.00404
Age 55-65 vs. <15	1.331	1.001	1.77	0.04908
Age 65+ vs. <15	1.179	0.877	1.586	0.27438
Benzodiazepine use	1.774	1.635	1.926	< 1e-04
Male	1.293	1.203	1.391	< 1e-04
Hydrocodone vs. Codeine	1.067	0.894	1.274	0.47152
Hydromorphone vs. Codeine	1.76	1.37	2.26	< 1e-04
Mixed types vs. Codeine	1.468	1.198	1.799	0.00022
Morphine vs. Codeine	2.247	1.38	3.658	0.00113
Oxycodone vs. Codeine	1.236	1.034	1.477	0.01965
Oxymorphone vs. Codeine	2.039	0.281	14.8	0.48121
Tramadol vs. Codeine	0.956	0.713	1.281	0.76216
State: AK	0.827	0.5	1.367	0.45767
State: AL	0.827	0.494	1.384	0.46909
State: AR	0.725	0.453	1.16	0.18023
State: AZ	1.004	0.77	1.309	0.97464
State: CA	0.901	0.717	1.133	0.37235
State: CO	0.936	0.688	1.273	0.67416
State: CT	0.968	0.752	1.246	0.80141
State: DC	0.907	0.556	1.481	0.69672
State: DE	0.749	0.42	1.334	0.32578
State: FL	0.86	0.683	1.083	0.19980
State: GA	0.844	0.64	1.111	0.22664
State: HI	0	0	1.224e+259	0.97004
State: IA	0.487	0.214	1.109	0.08659
State: ID	1.18	0.744	1.872	0.48210
State: IL	0.684	0.506	0.924	0.01326

State: IN	0.686	0.457	1.031	0.07004
State: KS	0.433	0.256	0.734	0.00186
State: KY	0.896	0.593	1.353	0.60011
State: LA	1.09	0.797	1.489	0.58992
State: MA	0.831	0.561	1.231	0.35659
State: MD	0.898	0.698	1.156	0.40474
State: ME	0.788	0.559	1.111	0.17471
State: MI	0.58	0.409	0.821	0.00215
State: MN	0.875	0.517	1.482	0.61963
State: MO	0.628	0.434	0.909	0.01376
State: MS	1.457	1.017	2.087	0.04002
State: MT	0.505	0.16	1.592	0.24366
State: NC	0.501	0.336	0.749	0.00075
State: ND	0.358	0.05	2.566	0.30650
State: NE	0.516	0.251	1.059	0.07142
State: NH	0.941	0.546	1.622	0.82753
State: NJ	1.016	0.81	1.275	0.89146
State: NM	1.384	0.607	3.153	0.43927
State: NV	1.531	1.116	2.102	0.00838
State: NY	1.206	0.96	1.515	0.10790
State: OH	0.674	0.519	0.877	0.00323
State: OK	1.125	0.843	1.503	0.42380
State: OR	0.835	0.531	1.312	0.43430
State: PA	0.871	0.691	1.099	0.24500
State: RI	1.356	0.66	2.788	0.40689
State: SC	0.717	0.453	1.137	0.15719
State: SD	1.256	0.31	5.092	0.74962
State: TN	1.176	0.863	1.602	0.30351
State: TX	0.966	0.781	1.196	0.75417
State: UT	1.008	0.712	1.428	0.96332
State: VA	0.571	0.434	0.751	< 1e-04
State: VT	1.393	0.567	3.42	0.46966
State: WA	1.198	0.929	1.545	0.16375
State: WI	0.674	0.429	1.059	0.08735
State: WV	0.618	0.331	1.151	0.12920

State: WY	1.783	0.566	5.624	0.32350
Surgery year: 2009	1.041	0.933	1.16	0.47499
Surgery year: 2010	1.082	0.964	1.214	0.17946
Surgery year: 2011	1.077	0.952	1.218	0.23670
Surgery year: 2012	1.258	1.106	1.431	0.00048
Surgery year: 2013	1.273	1.107	1.465	0.00072
Surgery year: 2014	1.795	1.536	2.097	< 1e-04
Surgery year: 2015	2.464	1.744	3.48	< 1e-04
Surgery type: Auditory.system	1.109	0.662	1.857	0.69404
Surgery type: Cardiovascular.system	0.979	0.775	1.237	0.85951
Surgery type: Digestive.system	1.059	0.911	1.23	0.45481
Surgery type: Endocrine.system	1.281	0.968	1.696	0.08331
Surgery type: Female.genital.system	1.084	0.911	1.29	0.36224
Surgery type: Hernic.and.lymphatic.systems	1.032	0.756	1.409	0.84401
Surgery type: Integumentary.system	1.109	0.936	1.313	0.23051
Surgery type: Male.genital.system	0.831	0.618	1.118	0.22145
Surgery type: Maternity.care.and.delivery	1.048	0.555	1.978	0.88447
Surgery type: Mediastinum.and.diaphragm	1.675	0.923	3.042	0.08989
Surgery type: Musculoskeletal.system	1.099	0.951	1.271	0.20134
Surgery type: Nervous.system	0.717	0.607	0.848	0.00010
Surgery type: Reproductive.system	0	0	Inf	0.99714
Surgery type: Respiratory.system	0.901	0.622	1.304	0.57901
Surgery type: Urinary.system	0.875	0.671	1.142	0.32593
038.9: Septicemia NOS	1.481	1.073	2.044	0.01701
276.51: Dehydration	1.076	0.876	1.322	0.48577
276.8: Hypopotassemia	1.148	0.942	1.4	0.17161
296.32: Major depressive disorder, recurrent episode, moderate degree	1.505	1.218	1.86	0.00015
300.00: Anxiety state unspecified	1.47	1.319	1.637	< 1e-04

300.02: Generalized anxiety disorder	1.119	0.936	1.339	0.21656
300.4: Dysthymic disorder	1.489	1.265	1.751	< 1e-04
305.1: Tobacco use disorder	2.157	1.973	2.359	< 1e-04
309.28: Adjustment disorder with mixed anxiety and depressed mood	1.32	1.049	1.662	0.01779
311: Depressive disorder NEC	1.601	1.439	1.781	< 1e-04
314.00: Attention deficit disorder of childhood without mention of hyperactivity	1.516	1.221	1.883	0.00017
314.01: Attention deficit disorder of childhood with hyperactivity	1.504	1.207	1.873	0.00027
338.29: Other chronic pain	2.017	1.682	2.418	< 1e-04
346.90: Migraine, unspecified, without mention of intractable migraine without mention of status migrainosus	1.326	1.121	1.57	0.00101
356.9: Unspecified idiopathic peripheral neuropathy	1.343	1.017	1.773	0.03776
462: Acute pharyngitis	1.153	1.024	1.298	0.01905
466.0: Acute bronchitis	1.258	1.101	1.436	0.00072
473.9: Chronic sinusitis NOS	1.103	0.922	1.318	0.28329
493.90: Asthma, unspecified type, without mention of status asthmaticus	1.217	1.089	1.36	0.00052
518.81: Acute respiratory failure	1.08	0.813	1.433	0.59610
535.10: Atrophic gastritis, without mention of hemorrhage	1.135	0.894	1.44	0.29861
535.40: Other specified gastritis, without mention of hemorrhage	1.23	0.967	1.565	0.09174
535.50: Unspecified gastritis and gastroduodenitis, without mention of hemorrhage	1.067	0.888	1.283	0.48863
558.9: Other and unspecified noninfectious gastroenteritis and colitis	1.095	0.907	1.321	0.34494
564.00: Constipation NOS	1.229	1.049	1.438	0.01047
682.6: Cellulitis and abscess of leg,	1.475	1.102	1.974	0.00892

except foot				
714.0: Rheumatoid arthritis	1.417	1.104	1.819	0.00613
721.3: Lumbosacral spondylosis without myelopathy	1.339	1.129	1.588	0.00082
722.4: Degeneration of cervical intervertebral disc	1.269	1.043	1.545	0.01747
722.52: Degeneration of lumbar or lumbosacral intervertebral disc	1.055	0.896	1.242	0.52376
723.1: Cervicalgia	1.079	0.95	1.226	0.24348
723.4: Brachial neuritis or radiculitis NOS	1.178	0.977	1.421	0.08622
724.2: Lumbago	1.287	1.154	1.436	< 1e-04
724.4: Thoracic or lumbosacral neuritis or radiculitis, unspecified	1.364	1.172	1.587	< 1e-04
724.5: Backache unspecified	1.265	1.118	1.43	0.00018
724.8: Other symptoms referable to back	1.04	0.787	1.374	0.78263
729.1: Myalgia and myositis unspecified	1.164	1.014	1.336	0.03083
780.52: Insomnia, unspecified	1.661	1.441	1.914	< 1e-04
780.53: Hypersomnia with sleep apnea, unspecified	1.131	0.9	1.419	0.29070
780.79: Other malaise and fatigue	1.252	1.139	1.375	< 1e-04
780.97: Altered mental status	1.271	0.923	1.749	0.14119
783.21: Loss of weight	1.252	0.999	1.569	0.05132
784.0: Headache	1.157	1.028	1.302	0.01537
785.0: Tachycardia NOS	1.022	0.823	1.27	0.84102
786.09: Other dyspnea and respiratory abnormality	1.081	0.942	1.241	0.26638
786.2: Cough	1.035	0.919	1.166	0.56788
786.50: Unspecified chest pain	1.034	0.932	1.148	0.52593
787.01: Nausea with vomiting	1.173	1.02	1.349	0.02515
787.03: Vomiting alone	1.349	1.126	1.616	0.00118
787.3: Flatulence, eructation, and gas pain	1.142	0.915	1.425	0.24016
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unspecified site				
789.07: Abdominal pain, generalized	1.288	1.124	1.476	0.00026
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V45.86: Bariatric surgery status	2.195	1.77	2.724	< 1e-04
V58.81: Encounter for fitting and adjustment of vascular catheter	1.046	0.847	1.294	0.67452
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V70.0: Routine general medical examination at a health care facility	0.769	0.691	0.855	< 1e-04
V71.89: Observation for other specified suspected conditions	1.191	0.902	1.573	0.21687
V76.12: Other screening mammogram	0.928	0.813	1.059	0.26826
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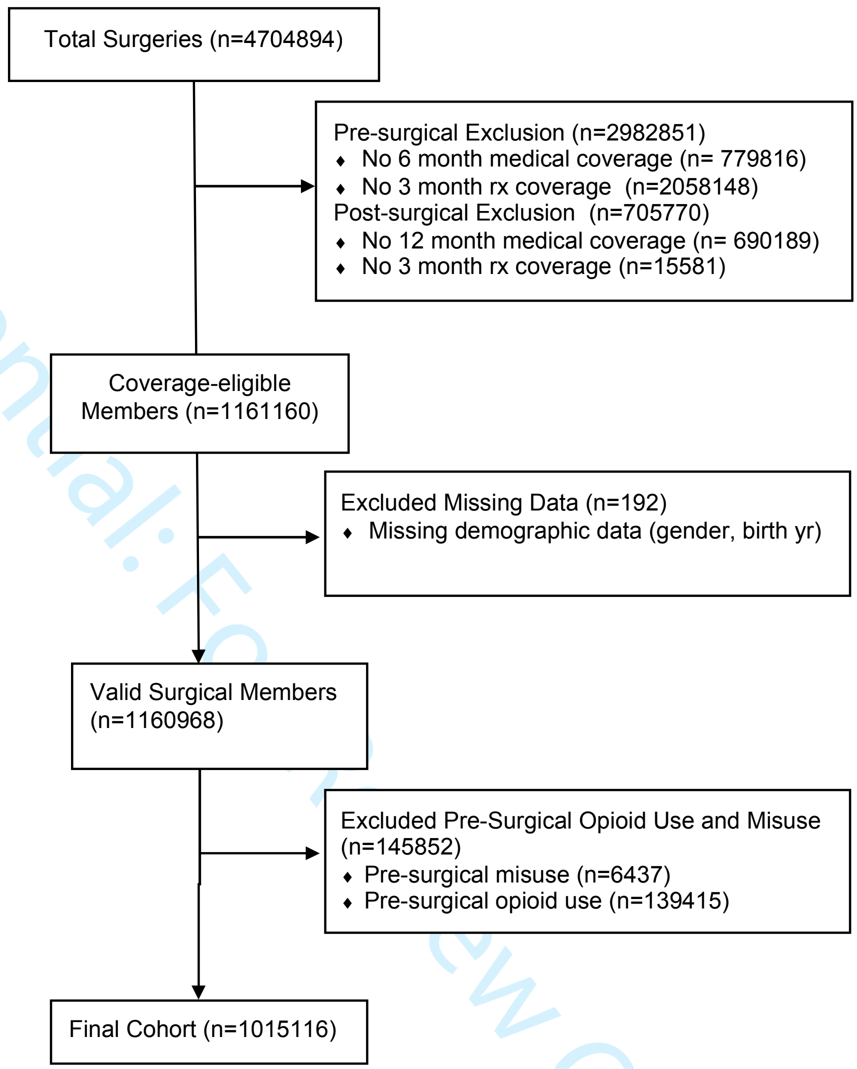
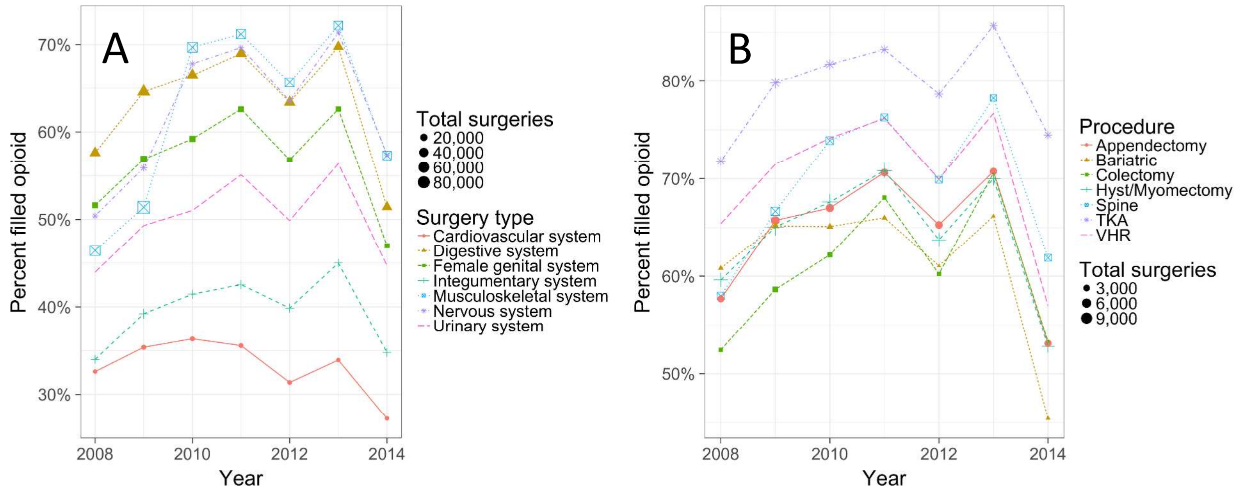
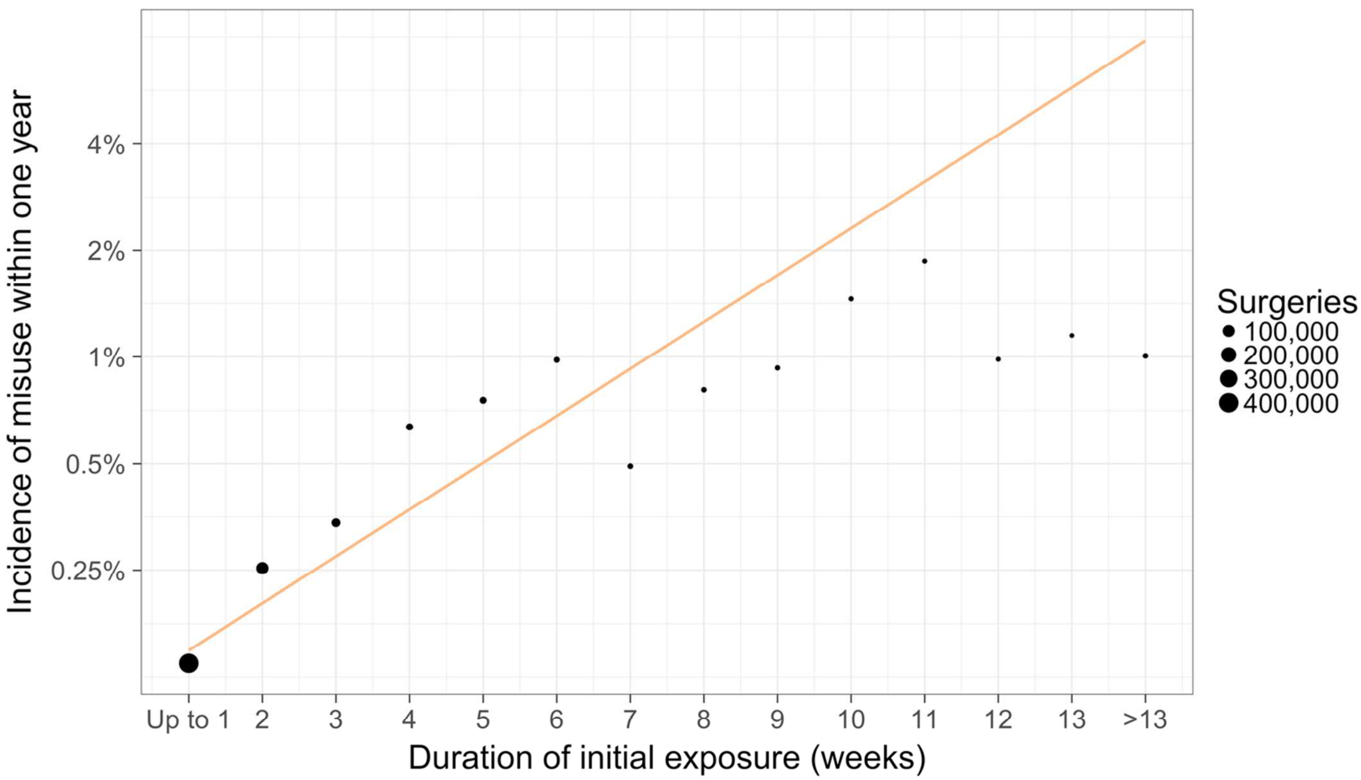


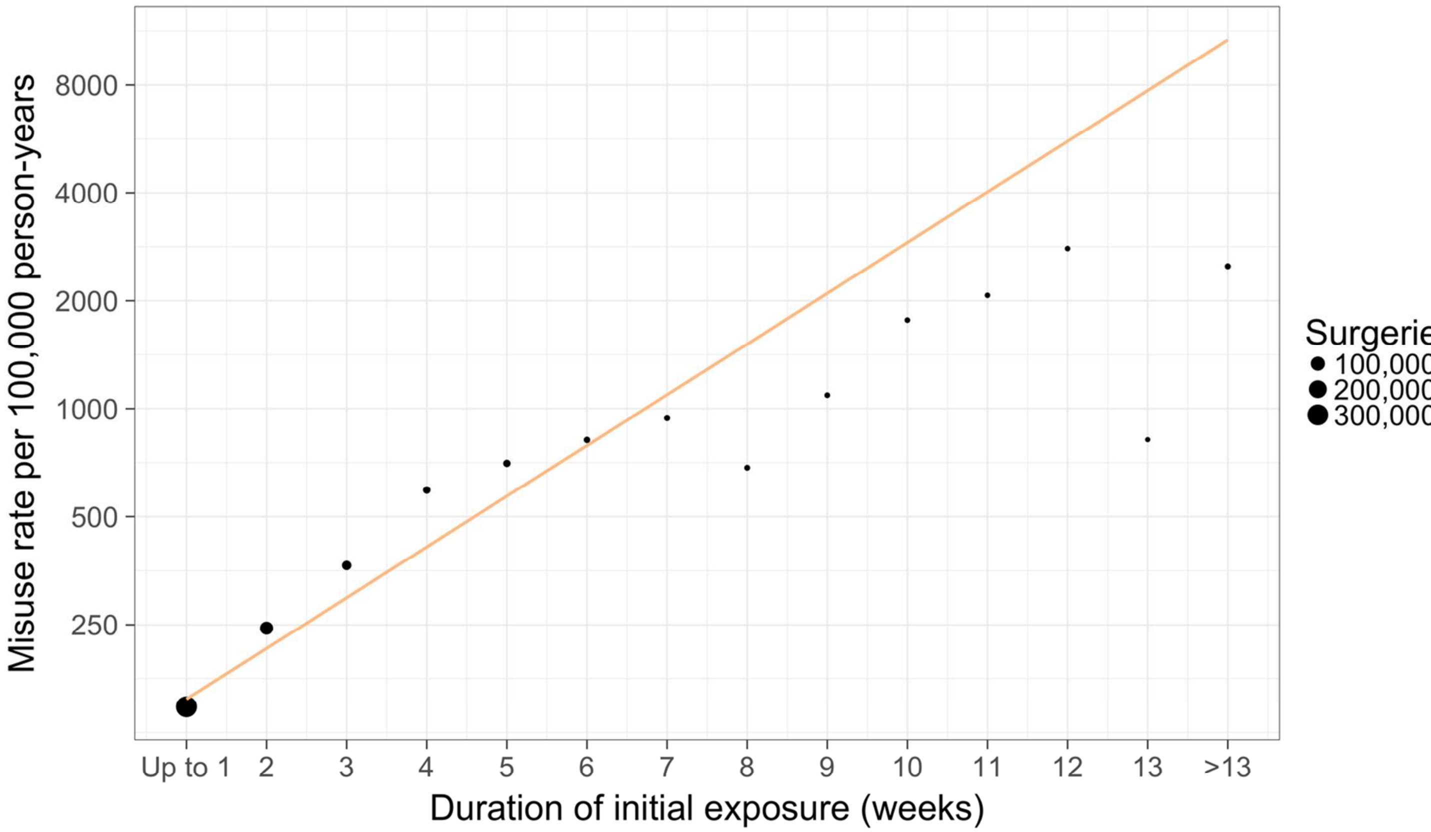
eFigure 1: CONSORT Diagram of Cohort Derivation.



eFigure 2: Rate of Post-Discharge Opioid Prescriptions During the Years of the Study. The graphs are arranged by (A) surgery type and (B) select representative surgeries. The size of each data point represents the number of surgical events.



eFigure 3: Incidence of Opioid Abuse and Overdose Within One Year After Surgery by Week of Exposure. The relationship between rates of opioid abuse and weeks of post-surgical opioid prescription. The size of each data point represents the number of surgical events. Y axis is represented on a log scale.



eFigure 4: Rate of Opioid Abuse and Overdose Among Those with No Subsequent Surgery by Week of Exposure. The relationship between rates of overdose and weeks of post-surgical opioid prescription duration for patients who did not have subsequent surgeries after the index surgery. The size of each data point represents the number of surgical events. Y axis is represented on a log scale.

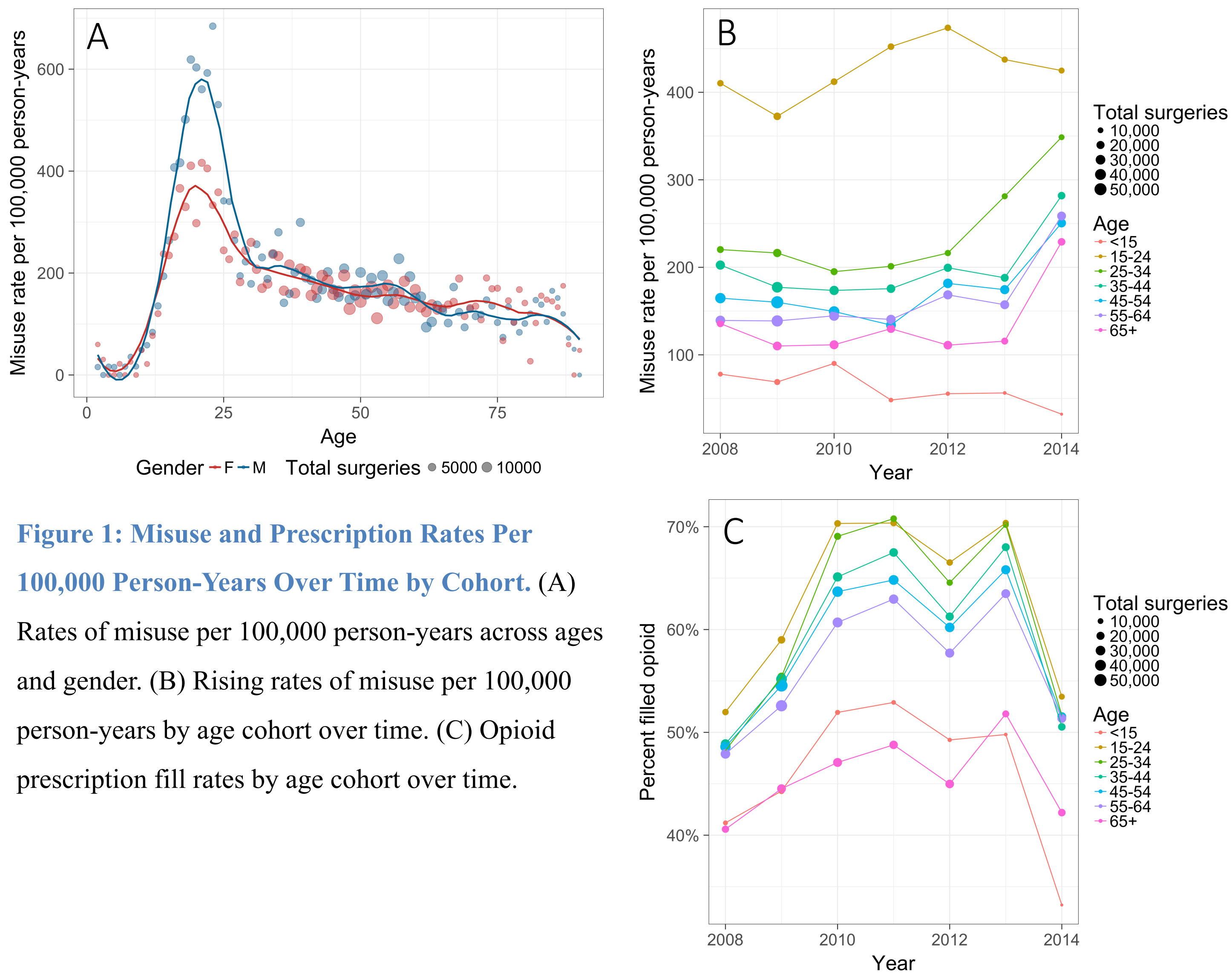


Figure 1: Misuse and Prescription Rates Per 100,000 Person-Years Over Time by Cohort. (A) Rates of misuse per 100,000 person-years across ages and gender. (B) Rising rates of misuse per 100,000 person-years by age cohort over time. (C) Opioid prescription fill rates by age cohort over time.

Supplemental Tables and Figures

eTable 1: ICD Code Tables Used in the Study

1A: All Observed Outcome Codes

ICD	LONG DESCRIPTION	N in sample
304.00	Opioid type dependence, unspecified	2,203
304.01	Opioid type dependence, continuous	1,311
305.50	Opioid abuse, unspecified	484
965.09	Poisoning by other opiates and related narcotics	409
E935.2	Other opiates and related narcotics causing adverse effects in therapeutic use	384
965.00	Poisoning by opium (alkaloids), unspecified	190
304.70	Combinations of opioid type drug with any other drug dependence, unspecified	113
305.51	Opioid abuse, continuous	77
304.71	Combinations of opioid type drug with any other drug dependence, continuous	72
E850.2	Accidental poisoning by other opiates and related narcotics	63
304.02	Opioid type dependence, episodic	39
305.53	Opioid abuse, in remission	35
305.52	Opioid abuse, episodic	30
304.72	Combinations of opioid type drug with any other drug dependence, episodic	11

1B: All Abuse Codes Used for Exclusion Criteria

ICD	LONG DESCRIPTION	N in sample
304.00	Opioid type dependence, unspecified	2,240
305.90	Other, mixed, or unspecified drug abuse, unspecified	1,625
304.01	Opioid type dependence, continuous	1,486
304.90	Unspecified drug dependence, unspecified	1,417
977.9	Poisoning by unspecified drug or medicinal substance	1,076
292.0	Drug withdrawal	956
305.50	Opioid abuse, unspecified	589
304.03	Opioid type dependence, in remission	283

E935.2	Other opiates and related narcotics causing adverse effects in therapeutic use	256
965.09	Poisoning by other opiates and related narcotics	229
304.91	Unspecified drug dependence, continuous	226
977.8	Poisoning by other specified drugs and medicinal substances	222
304.70	Combinations of opioid type drug with any other drug dependence, unspecified	177
305.93	Other, mixed, or unspecified drug abuse, in remission	160
965.00	Poisoning by opium (alkaloids), unspecified	145
305.51	Opioid abuse, continuous	134
304.71	Combinations of opioid type drug with any other drug dependence, continuous	121
305.91	Other, mixed, or unspecified drug abuse, continuous	120
305.53	Opioid abuse, in remission	90
305.53	Opioid abuse, in remission	90
304.02	Opioid type dependence, episodic	67
E980.0	Poisoning by analgesics, antipyretics, and antirheumatics, undetermined whether accidentally or purposely inflicted	48
304.93	Unspecified drug dependence, in remission	47
E850.2	Accidental poisoning by other opiates and related narcotics	44
965.01	Poisoning by heroin	43
305.92	Other, mixed, or unspecified drug abuse, episodic	42
305.52	Opioid abuse, episodic	36
304.73	Combinations of opioid type drug with any other drug dependence, in remission	32
965.02	Poisoning by methadone	25
292.12	Drug-induced psychotic disorder with hallucinations	24
304.72	Combinations of opioid type drug with any other drug dependence, episodic	18
304.92	Unspecified drug dependence, episodic	14

E850.0	Accidental poisoning by heroin	10
292.11	Drug-induced psychotic disorder with delusions	7
E850.1	Accidental poisoning by methadone	4
E935.0	Heroin causing adverse effects in therapeutic use	3

eTable 2: Comprehensive Adjusted Cox Regression Effects Model.

Covariate	Hazard ratio	Confidence interval, low	Confidence interval, high	p-value
Duration in weeks	1.199	1.185	1.214	< 1e-04
Dose in 10 MME/day	1.008	1.003	1.013	0.00126
Age 15-25 vs. <15	5.149	3.904	6.791	< 1e-04
Age 25-35 vs. <15	2.434	1.829	3.24	< 1e-04
Age 35-45 vs. <15	1.89	1.425	2.506	< 1e-04
Age 45-55 vs. <15	1.512	1.141	2.004	0.00404
Age 55-65 vs. <15	1.331	1.001	1.77	0.04908
Age 65+ vs. <15	1.179	0.877	1.586	0.27438
Benzodiazepine use	1.774	1.635	1.926	< 1e-04
Male	1.293	1.203	1.391	< 1e-04
Hydrocodone vs. Codeine	1.067	0.894	1.274	0.47152
Hydromorphone vs. Codeine	1.76	1.37	2.26	< 1e-04
Mixed types vs. Codeine	1.468	1.198	1.799	0.00022
Morphine vs. Codeine	2.247	1.38	3.658	0.00113
Oxycodone vs. Codeine	1.236	1.034	1.477	0.01965
Oxymorphone vs. Codeine	2.039	0.281	14.8	0.48121
Tramadol vs. Codeine	0.956	0.713	1.281	0.76216
State: AK	0.827	0.5	1.367	0.45767
State: AL	0.827	0.494	1.384	0.46909
State: AR	0.725	0.453	1.16	0.18023
State: AZ	1.004	0.77	1.309	0.97464
State: CA	0.901	0.717	1.133	0.37235
State: CO	0.936	0.688	1.273	0.67416
State: CT	0.968	0.752	1.246	0.80141
State: DC	0.907	0.556	1.481	0.69672
State: DE	0.749	0.42	1.334	0.32578
State: FL	0.86	0.683	1.083	0.19980
State: GA	0.844	0.64	1.111	0.22664
State: HI	0	0	1.224e+259	0.97004
State: IA	0.487	0.214	1.109	0.08659
State: ID	1.18	0.744	1.872	0.48210
State: IL	0.684	0.506	0.924	0.01326

State: IN	0.686	0.457	1.031	0.07004
State: KS	0.433	0.256	0.734	0.00186
State: KY	0.896	0.593	1.353	0.60011
State: LA	1.09	0.797	1.489	0.58992
State: MA	0.831	0.561	1.231	0.35659
State: MD	0.898	0.698	1.156	0.40474
State: ME	0.788	0.559	1.111	0.17471
State: MI	0.58	0.409	0.821	0.00215
State: MN	0.875	0.517	1.482	0.61963
State: MO	0.628	0.434	0.909	0.01376
State: MS	1.457	1.017	2.087	0.04002
State: MT	0.505	0.16	1.592	0.24366
State: NC	0.501	0.336	0.749	0.00075
State: ND	0.358	0.05	2.566	0.30650
State: NE	0.516	0.251	1.059	0.07142
State: NH	0.941	0.546	1.622	0.82753
State: NJ	1.016	0.81	1.275	0.89146
State: NM	1.384	0.607	3.153	0.43927
State: NV	1.531	1.116	2.102	0.00838
State: NY	1.206	0.96	1.515	0.10790
State: OH	0.674	0.519	0.877	0.00323
State: OK	1.125	0.843	1.503	0.42380
State: OR	0.835	0.531	1.312	0.43430
State: PA	0.871	0.691	1.099	0.24500
State: RI	1.356	0.66	2.788	0.40689
State: SC	0.717	0.453	1.137	0.15719
State: SD	1.256	0.31	5.092	0.74962
State: TN	1.176	0.863	1.602	0.30351
State: TX	0.966	0.781	1.196	0.75417
State: UT	1.008	0.712	1.428	0.96332
State: VA	0.571	0.434	0.751	< 1e-04
State: VT	1.393	0.567	3.42	0.46966
State: WA	1.198	0.929	1.545	0.16375
State: WI	0.674	0.429	1.059	0.08735
State: WV	0.618	0.331	1.151	0.12920

State: WY	1.783	0.566	5.624	0.32350
Surgery year: 2009	1.041	0.933	1.16	0.47499
Surgery year: 2010	1.082	0.964	1.214	0.17946
Surgery year: 2011	1.077	0.952	1.218	0.23670
Surgery year: 2012	1.258	1.106	1.431	0.00048
Surgery year: 2013	1.273	1.107	1.465	0.00072
Surgery year: 2014	1.795	1.536	2.097	< 1e-04
Surgery year: 2015	2.464	1.744	3.48	< 1e-04
Surgery type: Auditory.system	1.109	0.662	1.857	0.69404
Surgery type: Cardiovascular.system	0.979	0.775	1.237	0.85951
Surgery type: Digestive.system	1.059	0.911	1.23	0.45481
Surgery type: Endocrine.system	1.281	0.968	1.696	0.08331
Surgery type: Female.genital.system	1.084	0.911	1.29	0.36224
Surgery type: Hernic.and.lymphatic.systems	1.032	0.756	1.409	0.84401
Surgery type: Integumentary.system	1.109	0.936	1.313	0.23051
Surgery type: Male.genital.system	0.831	0.618	1.118	0.22145
Surgery type: Maternity.care.and.delivery	1.048	0.555	1.978	0.88447
Surgery type: Mediastinum.and.diaphragm	1.675	0.923	3.042	0.08989
Surgery type: Musculoskeletal.system	1.099	0.951	1.271	0.20134
Surgery type: Nervous.system	0.717	0.607	0.848	0.00010
Surgery type: Reproductive.system	0	0	Inf	0.99714
Surgery type: Respiratory.system	0.901	0.622	1.304	0.57901
Surgery type: Urinary.system	0.875	0.671	1.142	0.32593
038.9: Septicemia NOS	1.481	1.073	2.044	0.01701
276.51: Dehydration	1.076	0.876	1.322	0.48577
276.8: Hypopotassemia	1.148	0.942	1.4	0.17161
296.32: Major depressive disorder, recurrent episode, moderate degree	1.505	1.218	1.86	0.00015
300.00: Anxiety state unspecified	1.47	1.319	1.637	< 1e-04

300.02: Generalized anxiety disorder	1.119	0.936	1.339	0.21656
300.4: Dysthymic disorder	1.489	1.265	1.751	< 1e-04
305.1: Tobacco use disorder	2.157	1.973	2.359	< 1e-04
309.28: Adjustment disorder with mixed anxiety and depressed mood	1.32	1.049	1.662	0.01779
311: Depressive disorder NEC	1.601	1.439	1.781	< 1e-04
314.00: Attention deficit disorder of childhood without mention of hyperactivity	1.516	1.221	1.883	0.00017
314.01: Attention deficit disorder of childhood with hyperactivity	1.504	1.207	1.873	0.00027
338.29: Other chronic pain	2.017	1.682	2.418	< 1e-04
346.90: Migraine, unspecified, without mention of intractable migraine without mention of status migrainosus	1.326	1.121	1.57	0.00101
356.9: Unspecified idiopathic peripheral neuropathy	1.343	1.017	1.773	0.03776
462: Acute pharyngitis	1.153	1.024	1.298	0.01905
466.0: Acute bronchitis	1.258	1.101	1.436	0.00072
473.9: Chronic sinusitis NOS	1.103	0.922	1.318	0.28329
493.90: Asthma, unspecified type, without mention of status asthmaticus	1.217	1.089	1.36	0.00052
518.81: Acute respiratory failure	1.08	0.813	1.433	0.59610
535.10: Atrophic gastritis, without mention of hemorrhage	1.135	0.894	1.44	0.29861
535.40: Other specified gastritis, without mention of hemorrhage	1.23	0.967	1.565	0.09174
535.50: Unspecified gastritis and gastroduodenitis, without mention of hemorrhage	1.067	0.888	1.283	0.48863
558.9: Other and unspecified noninfectious gastroenteritis and colitis	1.095	0.907	1.321	0.34494
564.00: Constipation NOS	1.229	1.049	1.438	0.01047
682.6: Cellulitis and abscess of leg,	1.475	1.102	1.974	0.00892

except foot				
714.0: Rheumatoid arthritis	1.417	1.104	1.819	0.00613
721.3: Lumbosacral spondylosis without myelopathy	1.339	1.129	1.588	0.00082
722.4: Degeneration of cervical intervertebral disc	1.269	1.043	1.545	0.01747
722.52: Degeneration of lumbar or lumbosacral intervertebral disc	1.055	0.896	1.242	0.52376
723.1: Cervicalgia	1.079	0.95	1.226	0.24348
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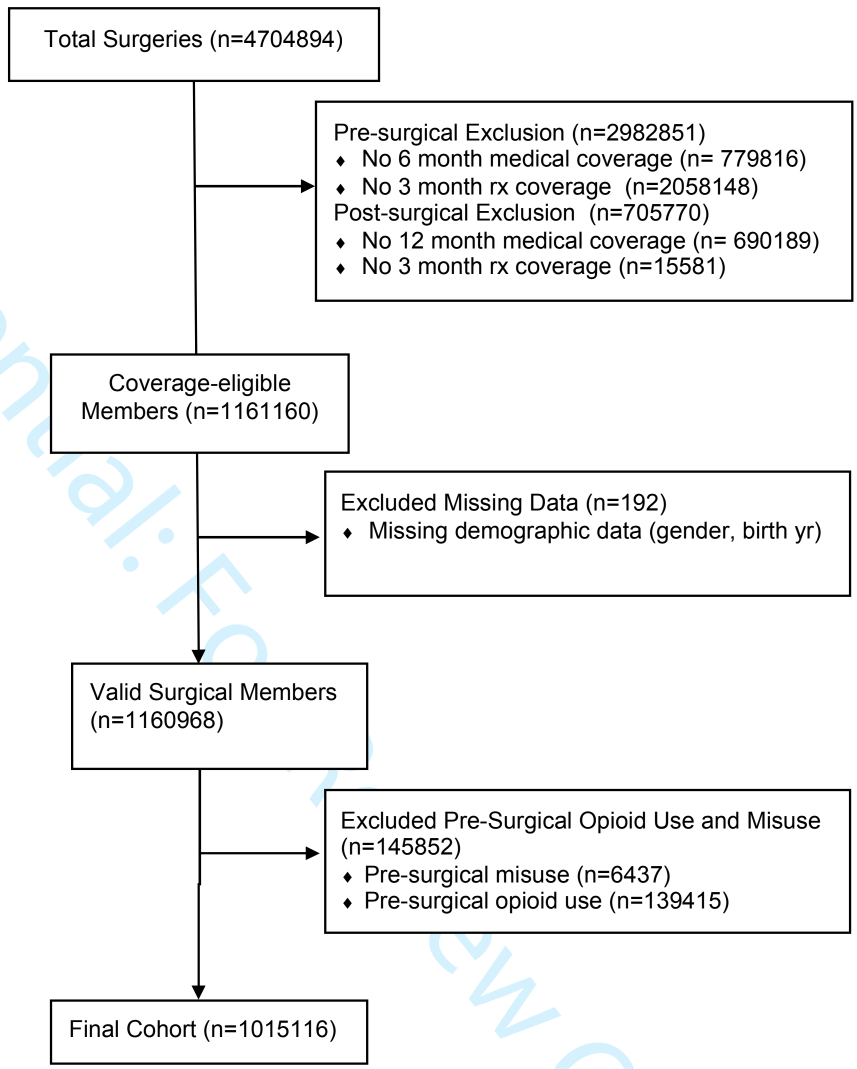

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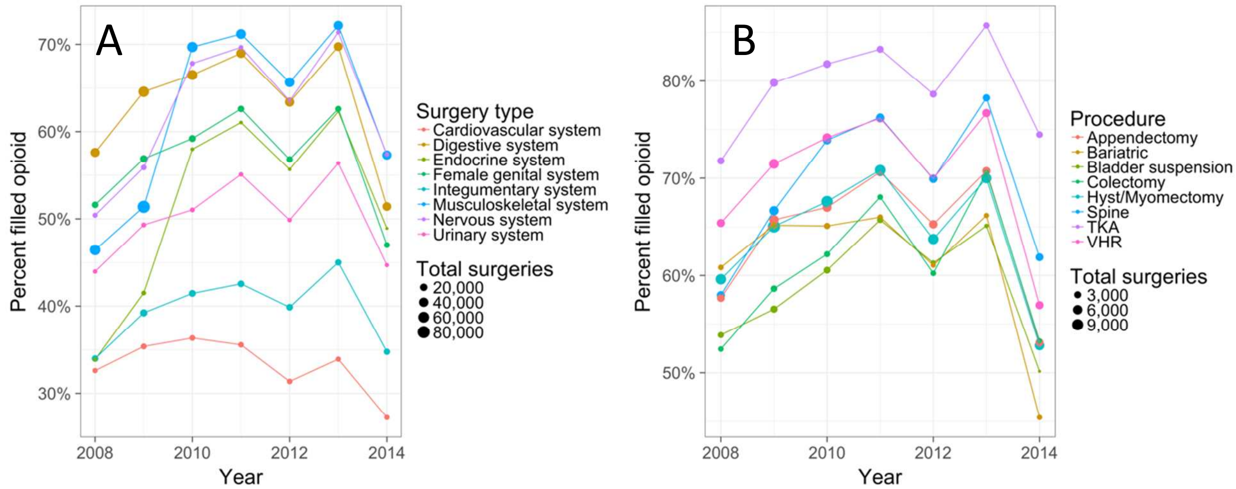
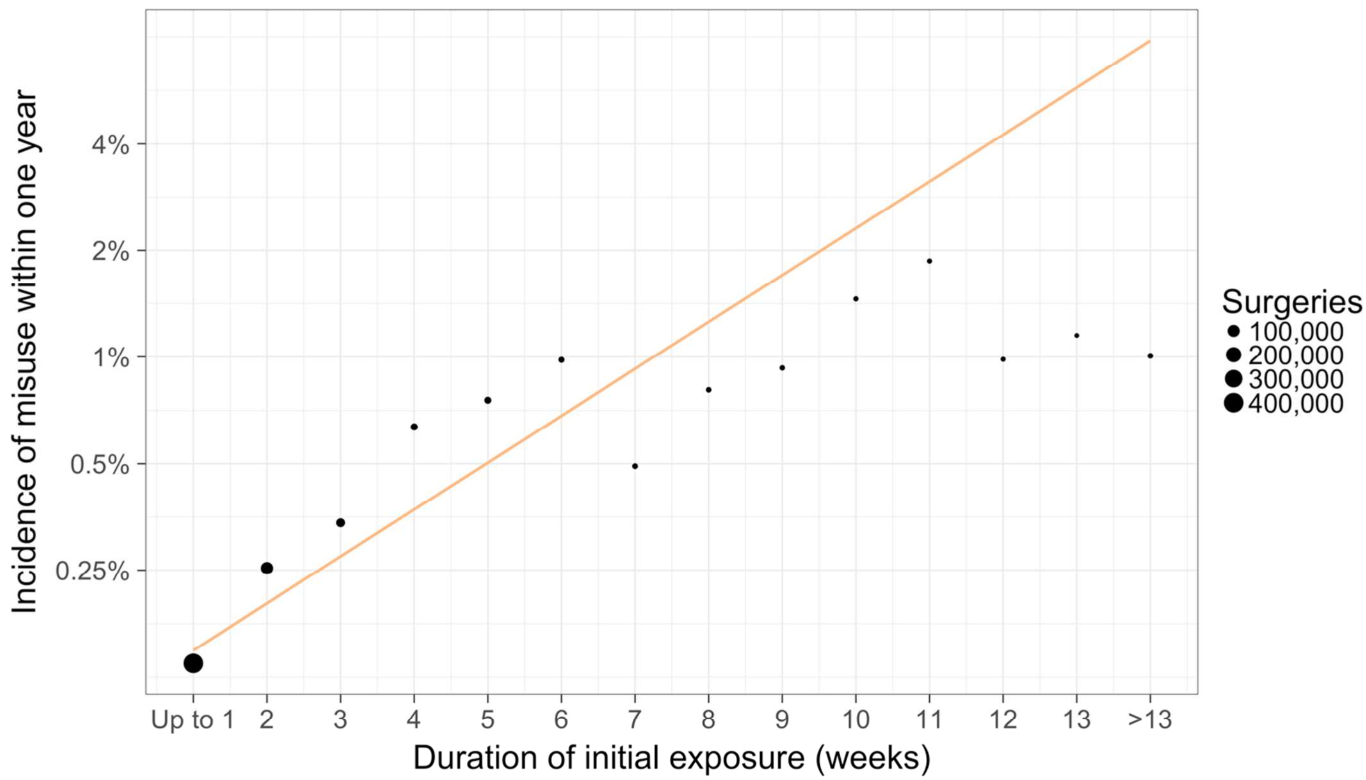
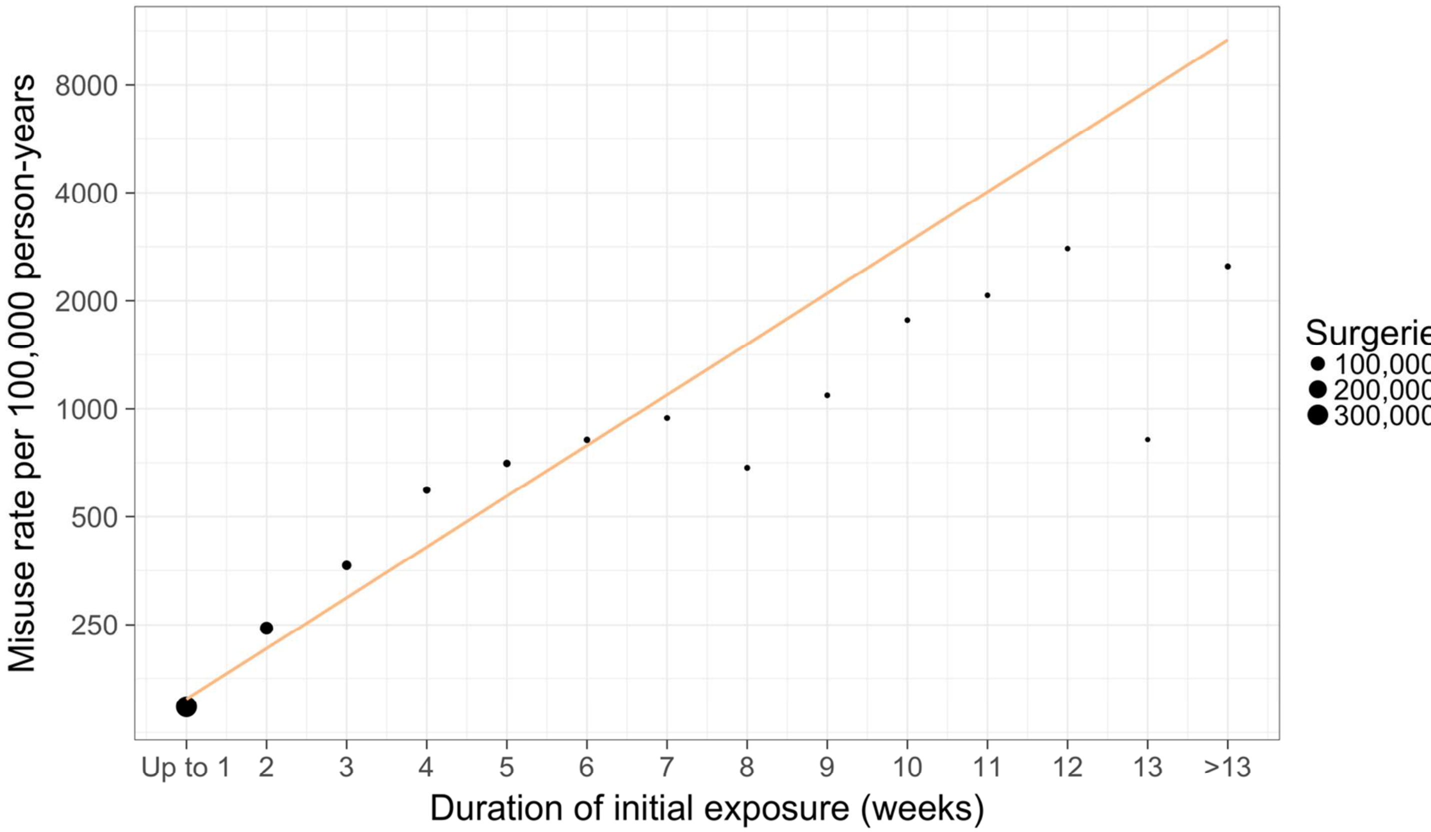


eFigure 2: Rate of Opioid Prescription Within 7 Days of Discharge During the Years of the Study. The graphs are arranged by (A) surgery type and (B) select representative surgeries. The size of each data point represents the number of surgical events.



eFigure 3: Incidence of Opioid Abuse and Overdose Within One Year After Surgery by Week of Exposure. The relationship between rates of opioid abuse and weeks of post-surgical opioid prescription. The size of each data point represents the number of surgical events. Y axis is represented on a log scale.



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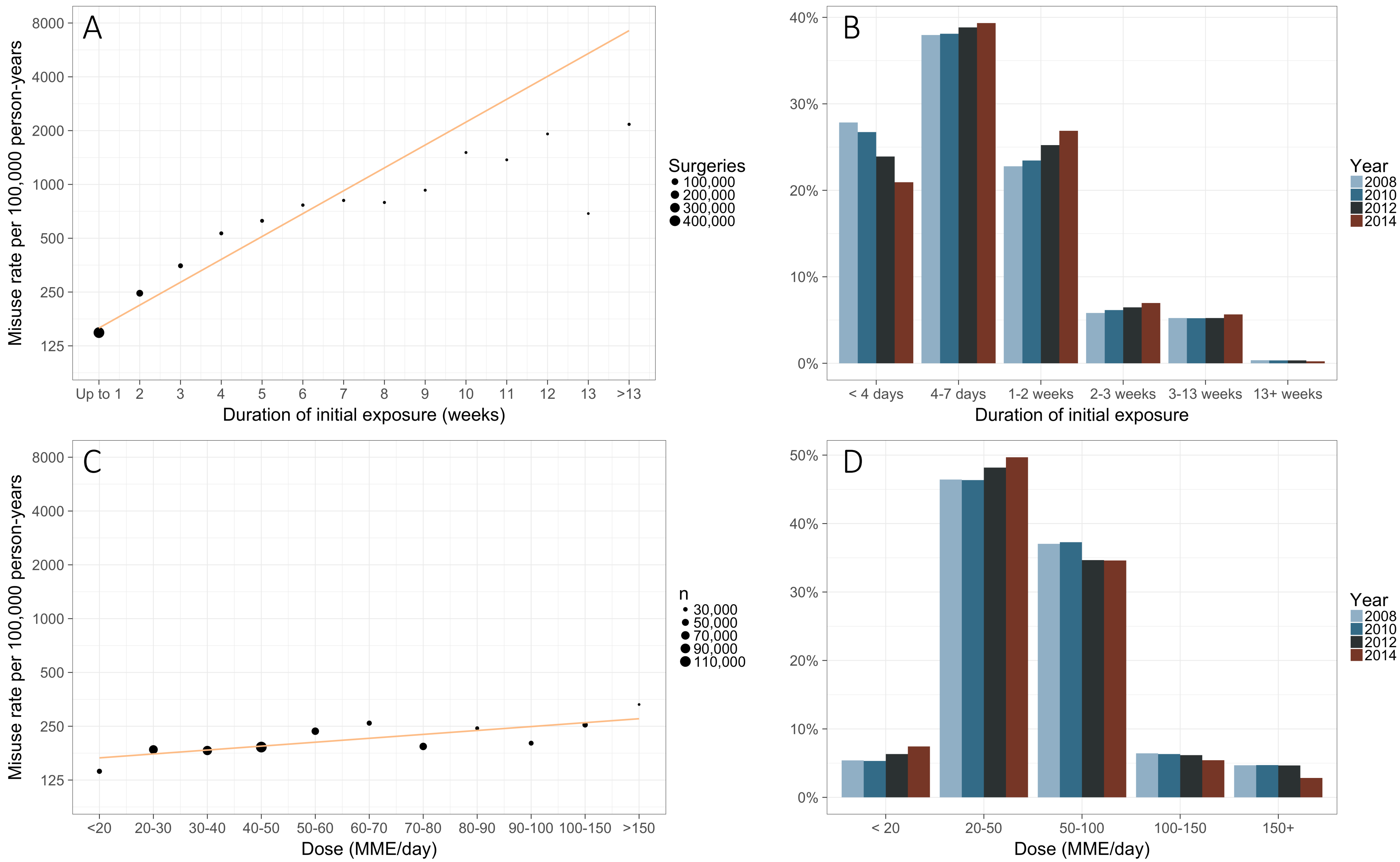

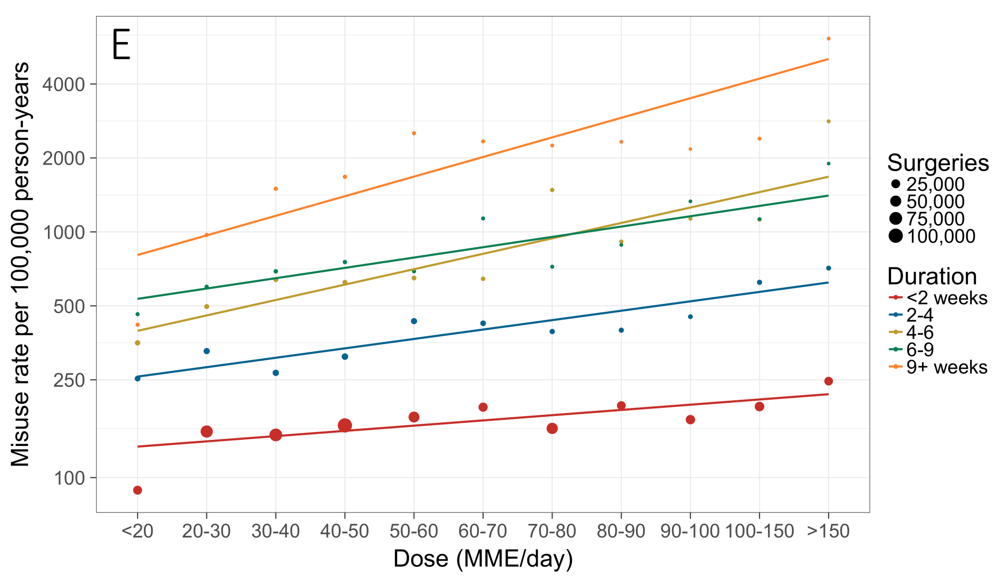

Figure 2: Post-Surgical Rates of Abuse by Dosage and Duration of Opioid Prescription. (A) Rates of opioid misuse per 100,000 person-years by week of exposure (y-axis is on log-scale). (B) Changing rates of duration of exposure during the study. (C) Rates of opioid misuse per 100,000 person-years by dose in MME/day (y-axis is on log-scale). (D) Changing dosage during the study by year. (E) Rates of opioid misuse per 100,000 person-years by dose, grouped by duration of exposure (y-axis is on log-scale).

Post-Surgical Prescriptions for Opioid-Naïve Patients and the Association with Overdose and Abuse

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ABSTRACT

Importance: Rates of non-fatal opioid overdose have risen by more than 50% over 10 years. Most cases originate from an initial medical prescription. Post-surgical patients are nearly four times more likely to receive post-discharge opioids as their non-surgical counterparts. Because existing guidelines do not adequately address post-discharge dispensation, surgical providers face a dilemma with each prescription refill.

Objective: We quantified the effects of varying opioid prescribing patterns after surgery on dependence, overdose, or abuse in an opioid-naïve population.

Design: Retrospective cohort study.

Setting: Surgical claims were extracted from a linked medical and pharmacy administrative database of 37,651,619 commercially insured patients between 2008 and 2016.

Population: Opioid-naïve patients undergoing surgery

Interventions: N/A

Main Outcomes/Measures: Oral opioid exposure after discharge as defined by refills and total dosage and duration. The primary outcome was a composite outcome of *misuse* identified by a diagnostic code of opioid dependence, abuse, or overdose.

Results: 568,612 (56%) patients received post-operative opioids, and a misuse code was identified in 5,906 patients (0.6%, 183 per 100,000 person-years). Total opioid duration was the strongest predictor of misuse, with each refill and additional week of opioid exposure associated with an adjusted increase in the rate of misuse of 51.6% (CI 47.7 to 55.6%, $p<0.001$) and 20.0% (CI 18.5 to 21.1%, $p<0.001$), respectively.

Conclusions: The total duration of opioid prescription after surgery is more predictive of opioid misuse than dosage. Each refill dramatically increases the rate of misuse. With the complementary forces of opioid duration and dose, our analysis quantifies the association of prescribing choices on opioid misuse and identifies levers for possible impact.

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WHAT THIS PAPER ADDS

What is already known:

- Opioid misuse is rising rapidly in the US and internationally.
- Surgical patients are four times more likely to get opioids at discharge than their non-surgical counterparts.
- It is unknown how opioid prescribing habits by clinicians are related to rates of misuse.

What this study adds:

- Each refill and week of opioid prescription is associated with a large increase in opioid misuse among opioid-naïve patients.
- Our data suggests that duration of the prescription rather than dosage is more strongly associated with ultimate misuse in the early post-surgical period.

INTRODUCTION

In the last fifteen years, age-adjusted opioid overdose rates have tripled and now rank as the leading cause of unintentional injury-related death.[1,2] Prescription medications are implicated in the majority of the cases, as rates of opioid prescription quadrupled [3,4] and were paralleled by rising rates of overdose deaths. Non-fatal overdose events from prescription opioids account for 7-11 times more episodes than fatal overdoses[2,5] and have similarly risen by more than 50% over 10 years. [6] Most striking is the fact that the majority of these non-fatal overdose episodes take place in patients identified as non-chronic (<90 days) opioid users.

Over-prescription of opioids is thought to be a major contributor,[7] where two thirds of opioid misuse can be attributed to opioids obtained through a single physician.[2] Overprescribing enables opioid diversion and increases the potential for addiction. [8,9] Surgical patients are nearly 4 times more likely to get post-discharge opioids as their non-surgical counterparts. Orthopedic surgeons alone were responsible for 7.7% of all opioid prescriptions in 2009.[10,11] Despite these numbers, surgeons have yet to find the right balance of opioid prescriptions: between 3 and 10% of opioid-naïve patients become chronic users, while emerging research suggests that the remaining group of patients leave as many as 80% of all prescribed pills unused.[12]

The lack of guidance around post-surgical opioid prescribing[13,14] is partially a result of the fact that little is known about the effect of longer and larger regimens of post-discharge opioids. More directly, we do not know how prescription refills affect long-term likelihood of misusing opioids. Prominent authors have called for study into this question[6,15,16] to underpin future guidelines.[17] Furthermore, there is evidence that any post-discharge exposure is a risk factor for multiple refills[18] independent of the specific prescription.[19] In this study, we examine the association between opioid prescription refills after surgery and misuse in an opioid-naïve population.

METHODS

Data Source

Surgical patients with medical and pharmacy insurance were drawn from a de-identified administrative database at Aetna Inc., a commercial managed healthcare company. This database includes 37,651,619 million members with Aetna health and pharmacy insurance coverage between 2008 and early 2016. Members were defined by a unique numerical identifier. Data included all medical claims during the study period.

Patient Involvement

Patients were not involved in the design of this study. Surgical providers were consulted extensively during the initial design and will be involved in dissemination of study results.

Sample Cohort

For this retrospective cohort study, the study cohort consisted of members who underwent surgery and had at least 6 months of medical and 3 months of pharmacy insurance before surgery, as well as 90 days of pharmacy and 1 year of medical coverage[16] after surgery. The index surgery for each member was chosen as the first surgery in the database that met criteria and after which no further surgery claims were filed for 90 days. Members were followed until they experienced an opioid-related event or their last month of enrollment in the database.

A member was considered opioid naïve and eligible for inclusion if total opioid exposure in the 60 days before surgery was 7 days or less.[20] Post-surgical opioid exposure was measured if the member filled a prescription for an included opioid within 30 days of discharge. Exposure was considered concluded when either 30 days elapsed without a filled opioid prescription or a misuse diagnosis was observed.

We excluded patients who had pre-surgical evidence of opioid or other non-specific forms of misuse in the 6 months prior to surgery (see Supplemental eTable 1 for a list of pre-surgical exclusion codes). Finally, we excluded a small subset of patients with missing data for any variable. The protocol and sample derivation is summarized in Supplemental eFigure 1.

Outcome Measures

Surgical claims were identified by a comprehensive list of Current Procedural Terminology (CPT) codes associated with inpatient and outpatient surgery and specialty released by the National Surgical Quality Improvement Program (NSQIP) of the American College of Surgeons in 2015.[21] Organ-based categories were derived from top-level CPT headers (e.g.10030-19499 for surgeries of the integumentary system).

The primary outcome was an International Classification of Disease (ICD) diagnosis code of opioid dependence, abuse, or overdose (see Supplemental eTable 1). Opioid misuse was defined as the presence of at least one of these ICD codes after discharge. This term encompasses a composite of a wide range of forms of misuse. Only diagnosis codes related specifically to prescription opioids were included.

Opioid Use

Opioids were identified in the database as narcotic analgesics or narcotic analgesic combinations by therapeutic category from Cerner's Multum Lexicon Drug Database.[22] Only non-injected drugs associated with the following primary ingredients were used: codeine, hydrocodone, hydromorphone, morphine, oxycodone, oxymorphone, or tramadol. Other less common opioids were excluded for low numbers or association with palliative care or dependence treatment. We determined the morphine milligram equivalent (MME) dosage for each opioid prescription, using standard conversions.[23] In order to decrease the influence of extreme outliers while respecting variation seen in the literature, daily dose was truncated at 350 MME/day.[24] Length of exposure was truncated at 90 plus 1 days, and number of refills was truncated at 5.

Refill Identification

A medication refill is a physical event with varying lengths. Like the initial prescription, there is no standard refill dosage or duration. Thus, identification of the event is a somewhat artificial threshold marking continuation of the opioid exposure. Because it requires a patient to approach their care provider for further medication, the event is also relevant. In this vein, we chose to identify refills in two ways. First, the number of physical prescriptions filled were counted after the initial exposure. The first post-discharge prescription was counted as the initial exposure and all subsequent prescriptions with less than a 30-day gap between prescriptions were included.

Second, we identified total post-discharge exposure by duration and dosage. Post-discharge opioid exposure duration was determined to be the total number of calendar days covered by a prescription for an opioid after discharge from the index surgical procedure. This identified the "cabinet supply" of opioids acquired by a patient as outlined by Mosher.[25] We also used a well-described method[26] to consider overlapping prescriptions as part of the same episode and an indication of a completed previous prescription at a higher dose. Accounting for overlapping prescriptions consisted of defining exposure as the total days of accumulated prescriptions minus overlap.

When a single discharge date was listed on all medical claims associated with the index surgery date, this was used as the official discharge date. When multiple discharge dates were present, the last date was used. If no discharge date was associated with any medical claim on the index surgery date, the surgery date was used as discharge date.

Statistical Analysis

We analyzed the time until misuse event over the entire study period. Raw rates of opioid misuse were computed as total number of misuse events divided by total follow-up time and are reported as cases per 100,000 person-years (cases/100,000). Weighted linear regression (WLS) was used for unadjusted analysis of log-transformed weekly rates of misuse, where each week was weighted according to sample size. Cox proportional hazards models were used for adjusted analysis of time until misuse event. Adjusted models included either refills or duration, as well as daily dose (MME/day), age, sex, state of residence, surgery type by CPT top-level grouping, surgery year, concurrent benzodiazepine use, and binary indicators of pre-surgical diagnoses potentially related to misuse. A single surgery might be associated with multiple surgery types, if multiple CPT codes were assigned.

Pre-surgical diagnoses of interest were determined using penalized logistic regression.[27] All 590 ICD codes assigned to at least 0.5% of patients in the 6 months prior to surgery were included in the model, as well as age, sex, and surgery type. In total, 65 pre-surgical diagnosis codes were selected (see Supplemental eTable 2).

WLS effects are reported as multiplicative percent increases in rate, and Cox effects as multiplicative percent increases in hazard or equivalently hazard ratios (HRs). Two-sided p-values and 95% confidence intervals (CIs) are reported throughout. All analyses were conducted using R 3.2.2 (R Core Team).

We performed sensitivity analyses restricted to (i) one year post-surgery and to (ii) members with no additional surgeries during follow-up to ensure that the effect we observed was driven by the initial opioid exposure and not downstream unidentified factors. For misuse events within one year, we used logistic regression to adjust for covariates.

We considered two additional sensitivity analyses to detect if structural factors due to changing trends over time (year of surgery) or geography were influencing our estimates. We considered a Cox model including an interaction between duration and an indicator for year and another model including an interaction between duration and state of residence. Further sensitivity analysis attempted to mimic an unobserved confounder by creating a synthetic binary variable that was associated with both duration and opioid misuse. A Cox model was fit including this synthetic confounder to see the degree to which strong unobserved confounding might explain the observed association.

The de-identified data in this study was exempt from Institutional Review Board review as confirmed by the Harvard Medical School IRB committee.

RESULTS

Cohort Characteristics

The study sample included 1,015,116 members who met study criteria and underwent an index surgery. Members were followed for a median of 2.67 years. After the index surgery, 568,612 (56%) filled a post-operative opioid prescription. Ninety percent of prescriptions were filled within 3 days of discharge. In the subsequent follow-up period, misuse was identified in 5,906 members (0.6%, 183 cases/100,000), with 1,857 occurring within one year after surgery (0.2%).

Characteristics of the cohort followed national trends (Table 1). Surgeries were more prevalent among older age groups, and younger groups had higher rates of opioid usage. The most common surgery types were those of the musculoskeletal system (367,317 surgeries; 2,448 misuse events; 206 cases/100,000), digestive system (293,905 surgeries; 1,825 misuse events; 198 cases/100,000), and integumentary system (106,914 surgeries; 533 misuse events; 161 cases/100,000). Rates of misuse by age group followed national patterns with higher rates among younger adult males (Figure 1A) and increasing rates over the study period (Figure 1B).

The study period saw notable changes in opioid prescription characteristics and rates of misuse, as demonstrated in Table 1. Post-surgical incidence of misuse increased from 183 cases/100,000 (2009) to 269 cases/100,000 (2014), while opioid prescription fill rates plateaued and began to fall in the later years of the study (also see Figure 1C). Median duration and median dose prescribed remained stable throughout the study period at about 5 days and 50 MME/day, respectively. These stable numbers masked a change in opioid prescription characteristics during the study period: fewer short-course and increased numbers of longer duration prescriptions as well as a trend toward lower doses by episode (see Figures 2D and 2E). Similar prescribing changes were detected in all surgery types. See Supplemental eFigure 2 for further detail.

Rates of Misuse by Opioid Exposure

The number of post-discharge prescriptions best predicted eventual misuse. Overall rates of misuse were low, but rates grew rapidly with increasing exposure. The rate of misuse more than doubled among those with one refill (86,654 [15.2%]; 293 cases/100,000) versus those with no refills (434,273 [76.2%] patients; 145 cases/100,000). In total, each additional refill increased the rate of misuse by 70.7% (CI 54.6-88.4%) before adjustment and increased the hazard of misuse by 44.0% (CI 40.8-47.2%, $p<0.001$) after adjusting for covariates.

The relationship between number of refills and misuse was further supported by evaluation of the number of days of opioid exposure post-discharge. In the aggregate, each additional week of opioid exposure was associated with an average increase in the rate of misuse of 34.2% (CI 26.4-42.6%, p-value < 0.001, see Figure 2A). Adjusting for covariates, each additional week of exposure to opioids was associated with a 19.9% increase in hazard (CI 18.5-21.4%, p-value < 0.001). For both refills and duration, Figure 2A shows that the risk of misuse initially follows the trend-line and begins to taper at higher levels of exposure >11 weeks of duration.

In comparison to duration of exposure, the dosage prescribed was a weaker predictor of misuse (Figure 2C), and dose became important only at extended duration (Figure 2E). Each additional 10 MME/day were associated with only a 0.8% increase in hazard of misuse (HR 1.008, CI 1.003-1.013, p-value = 0.001). Even high doses (>150 MME/day) were associated with only mild increases in risk when duration was short (Figure 2E). For example, when post-discharge prescription duration was less than 2 weeks, similar rates of misuse were found for lower (40-50 MME/day) vs. higher (100-150 MME/day) opioid dose. Conversely, members receiving greater than 9 weeks of opioids at a higher dose had dramatically increasing rates of misuse: 476 cases/100,000 (at <20 MME/day, n=422) to 2398 cases/100,000 (at 50-60 MME/day, n=430) to 5689 cases/100,000 (at >150 MME/day, n=237). *For short-term opioid use <90 days, higher doses of opioids had smaller effects on the rate of misuse than additional weeks of exposure.*

Additional Risk Factors of Misuse

After adjusting for covariates, other risk factors (detailed in Supplemental eTable 2), including benzodiazepines (HR 1.77, CI 1.64-1.93) as well as regimens initiated with hydromorphone (HR 1.76, CI 1.37-2.26) and oxycodone (HR 1.24, CI 1.03-1.48) had significant association with opioid misuse. The adjusted effect of surgery was greatly attenuated after controlling for the strongly associated pre-surgical diagnoses. Notable pre-surgical diagnoses included bariatric surgery status (V45.86, HR 2.19, CI 1.77-2.72), tobacco use disorder (305.1, HR 2.16, CI 1.97-

2.36), other chronic pain (338.29, HR 2.02, CI 1.68-2.42), and major depressive disorder (311, HR 1.60, CI 1.44-1.78).

Sensitivity Analyses

As part of a sensitivity analysis, we constructed models that removed potential sequential confounders. We found no difference in effect, with similar results for misuse events within one year of surgery (Supplemental eFigure 3) and among patients with no additional surgery during follow-up (Supplemental eFigure 4). To ensure that our outcome analysis was not biased by a specific ICD9 code, we removed 304.00 opioid dependence, the most common code, leaving only specific abuse and overdose codes. The findings of the model were virtually unchanged with this smaller subset: each additional refill was associated with an increased risk of 70.9% vs. 70.7% in the comprehensive model.

We also verified that the observed association was not affected by geography or biased by changing conditions across the study period. We compared the association between duration and misuse over different years (see Figure 3) and at the state level; results were statistically indistinguishable from a model with aggregated duration effect (likelihood ratio test p-value 0.26 and 0.99, respectively). Figure 3A shows that surgeons reduced the mean dosage within their specialty during the study period. Typical reductions ranged from 3 to 18 MME/day (4 to 24%) over the duration of the study. While dosage fell, mean duration of exposure during the years of the study remained relatively stable (Figure 3B). Despite changing clinician behavior over time, the relationship between duration of exposure and misuse was persistent (see Figure 3C). Such stability is further evidence of the robustness of this effect.

Finally, we assessed the potential effect of unobserved confounding by generating a synthetic binary variable strongly associated with both length of exposure (OR 2.7) and misuse (HR 5.0) and inserted it into the model. An example of such a confounder could be an undiagnosed risk factor for post-surgical misuse, such as pre-surgical alcohol dependence. Even in the presence of this artificial explanatory confounder, which has an unrealistically strong relationship to misuse, each week of exposure was still associated with a 13% increase in hazard of misuse.

DISCUSSION

Physicians struggle to appropriately prescribe and dose post-operative opioids while addressing the very real needs of operative acute pain. [28,29] This is the first study to quantify the strong relationship between number and duration of refills of prescribed opioid pain medication and subsequent opioid misuse in the surgical population. We focused on typical surgical patients without previous misuse history or ongoing opioid use. We estimated an adjusted 44% increase in misuse for every refill fulfilled or 20% increase for every week of prescription. This association remained significant in multiple sensitivity analyses and using both time until any event and events within one year of surgery. Further, our data was remarkably consistent with previous literature: the rate of refills[30] and the misuse event rate of 0.2% within one year[31] was similar to that identified in other studies. While rates of misuse were low, the large number of surgeries performed every year increases the importance of these numbers.

These striking numbers build on recent literature about the broad effect of post-discharge prescriptions on subsequent opioid use. Patients who received even one post-discharge prescription were three times more likely to be taking opioids at one year[18]. This finding extended across specialties, where surgical and non-surgical patients had similar rates of opioid refills. Several studies in surgical patients have also shown that early opioid administration after surgery is associated with subsequent long-term usage.[32,33] Irrespective of the direction of causality, our data suggest that patients who require subsequent refills of opioid medications are significantly more likely to have a misuse episode, even years after the index surgery. Whether driven by the patient's underlying need or the clinician's tendency to prescribe opioids, this relationship further holds when examining refills as individual weeks of exposure.

Furthermore, our adjusted models suggest that the effect of duration is not explained by temporal changes in physician behavior or patient population. During the later parts of the study period, surgeons appear to have reduced the number of patients receiving opioids and the number of patients with short prescriptions (<7 days). They increased rates of longer prescriptions for a subset of patients (see figure 2D). In the face of these changes, overall rates of opioid misuse have continued to increase (Figure 1B), demonstrating that this epidemic is multi-factorial and is not only driven by duration of exposure on an aggregate level. But despite the worsening crisis and these temporal changes, we specifically found that the effect of duration was stable across the study years and was unchanged by the changing misuse and prescribing rates in the population. The stable relationship shown in Figure 3 is suggestive of an independent effect.

A second finding was that duration of treatment rather than dosage of equivalent opioids was more strongly associated with subsequent misuse for acute post-discharge prescriptions. This builds on Miller's and Edlund's[33,34] finding of the importance of prescription duration. Each week of opioid exposure was associated with a 20% increase in misuse; short-term dosage carried a small (~10%) incremental impact per 100 MME on misuse and became noteworthy only at longer durations of administration. While this seems discordant with other studies that have found 2-9 fold increases in the rates of misuse for doses >100 MME/day,[5,7,24,33] our work differs from previous studies—which focused on chronic users—by examining a general surgical population who typically receive fewer than 2 weeks of opioids. Patients with chronic opioid usage may exhibit different misuse risk profiles.

Our data suggests that opioid-naïve patients who receive low to moderately high doses of pain medications for short durations have small associated increases in their overall rates of misuse. Many studies have shown that pain is often poorly managed after surgery. [35–39] Higher doses (to a point) may better saturate mu receptors, while under treatment of acute pain increases the risk of pseudo-addiction, chronic pain, and, potentially, overdose.[40,41] These findings suggest a more nuanced understanding of the relationship between duration and dosage with a focus on early appropriate treatment of pain (including higher doses) for a limited time. Such findings suggest that optimal post-operative prescribing, which maximizes analgesia and minimizes the risk of misuse, may be achieved with moderate to high opioid dosages at shorter durations, a combination that merits further investigation in population-based and clinical studies.[41]

Limitations

We recognize that administrative data has inherent biases that may affect our results. First, our dataset fails to exclude patients with undocumented pre-surgical misuse or opioid usage. Similarly, we may not detect post-operative misuse in members who leave the cohort because they lose or change coverage. Miscoding claims is possible but less likely as coding of opioid abuse has been found to be accurate 85% of the time. [42] Alternatively, increased recognition of the problem of opioid misuse may lead to overcoding in later years or undercoding in earlier years. This could be one explanation for the rising rates of misuse observed in later years, but recent national studies by other authors have also shown similar trends.[1] Finally, measurement of opioid exposure is complicated by the possibility that patients might fill a prescription and modify the course or dosing of the drug.[43] Our cabinet method of measuring exposure attempts to conservatively overestimate usage.

As for the problem of confounding, we controlled for disease burden by adjusting for surgery type and examined the full space of pre-surgical diagnosis codes, but these are, at best, partial measures of disease state at the time of surgery. Notably, we are unable to control for the extent of pain or the vagaries of surgical techniques. In the presence of uncontrolled confounding, we cannot be certain of the magnitude of the effect that we see. Those patients with higher likelihood for developing misuse may be requesting augmented treatment.[44] The consistency of our findings, despite extensive sensitivity analyses, suggest there may yet be a causal component to our analysis. This is further supported by evidence tying a majority of patients who present to addiction centers to an initial prescribed opioid for pain.[45]

As a final point, the generalizability of this study is limited to insured adults in the US, as several studies have shown increased rates of misuse in Medicaid, Medicare, and veteran populations. [25,46,47]

CONCLUSION

In this study, we quantified the strong association between short-term post-surgical refills and ultimate misuse. A single refill increased the potential of misuse by more than 50%, and the duration of exposure appeared to be the most prominent predictor of misuse. Our findings are significant as they offer a potential lever for intervention and behavior change after surgery. Given that surgical and non-surgical patients receive similar numbers of refills, these findings have the potential to extend beyond surgery. Surgeons and non-surgeons are changing their opioid prescription characteristics, but rates of misuse continue to rise. They are trapped between guidelines that recommend shorter duration and smaller dosing of opioid medication and a subset of patients who request or require opioids beyond the initial prescription. With these seemingly conflicting forces at play, our analysis provides a broad evidentiary framework to inform clinician behavior and promote protocol development. Further research of this relationship is needed to determine how initial treatment regimens can minimize abuse and addiction.

AUTHORSHIP

GB, DA, and MB designed the study. CMW, DK, and KF contributed data assets. GB and DA wrote the manuscript. GB, DA, AB, and NP performed the analysis. MH contributed critical analytical tools for the analysis. CMW, DK, KF, MB, IK, and BY contributed citations, evaluated and edited the manuscript.

The lead author (the manuscript's guarantor) affirms that the 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.

All authors have completed the [Unified Competing Interest form] (available on request from the corresponding author) and declare: no support from any organization for the submitted work [or describe if any]; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

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DECLARATION OF INTERESTS

Drs. Brat, Agniel, Beam, Yorkgitis, Homer, Bicket, Knecht, Walraven, Fox, Palmer, and Kohane have nothing to disclose.

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Tables and Figure Legends

Table 1: Baseline Demographic Information and Unadjusted Associations

Category	Type	Total	Abuse/ Overdose Events	Opioid Prescription Filled (%)	Median Duration (days)	Median MME/day	Median Follow-up (years)	Median Time to Abuse (years)	Cases/ 100,000 Pt-Yrs
Entire Sample		1,015,116	5,906	56	5	50	2.67	1.74	183.2
Gender	F	563,170	3,166	54.3	5	50	2.67	1.82	176.3
	M	451,946	2,740	58.2	5	50	2.66	1.67	191.8
Birth Year	<15	54,098	118	46	5	30	2.74	2.39	66.7
	15-24	92,458	1,160	62.9	5	54.2	2.51	1.47	420.6
	25-34	97,856	666	60.6	5	50	2.41	1.68	226
	35-44	175,969	1,086	58.9	5	50	2.69	1.9	190.7
	45-54	238,154	1,284	57.9	5	50	2.78	1.95	164
	55-64	211,308	989	56.1	5	50	2.55	1.64	152.4
	65+	145,273	603	45.5	5	45	2.93	2.07	126.9
Surgery Year	2008	142,332	1,031	47.5	5	50	3.3	2.76	183.1
	2009	205,618	1,374	53	5	50	3.62	2.51	169.5
	2010	157,640	982	61.1	5	50	3.66	2.28	168.9
	2011	137,648	780	62.8	5	50	3.52	1.72	171.6
	2012	130,096	705	57.6	5	50	3.2	1.38	193
	2013	113,841	505	63.9	5	50	2.39	1.29	195
	2014	110,392	461	49.1	5	50	1.52	0.76	268.7

Please see following page for continuation of table.

Table 1 Continued: Baseline Demographic Information and Unadjusted Associations

Category	Type	Total	Abuse/ Overdose Events	Opioid Prescription Filled (%)	Median Duration (days)	Median MME/day	Median Follow-up (years)	Median Time to Abuse (years)	Cases/ 100,000 Pt-Yrs
Surgery Type	Musculoskeletal System	367,317	2,448	60.3	6	57.7	2.71	1.86	206.2
	Digestive System	293,905	1,825	63.2	5	50	2.63	1.68	198.1
	Integumentary System	106,914	533	39.3	5	45	2.61	1.75	160.8
	Female Genital System	98,444	449	56.7	5	46.9	2.69	1.85	142.3
	Cardiovascular System	57,715	241	33.3	6	44.4	2.65	1.52	134.4
	Nervous System	38,698	374	61.1	8	56.2	2.6	1.52	306.5
	Urinary System	30,274	121	49.8	5	45	2.71	1.52	125.8
	Male Genital System	26,524	76	59.3	5	41.2	2.73	1.98	89.6
	Endocrine System	19,622	110	49.2	4	45	2.72	1.6	172
	Hernia and Lymphatic Systems	11,836	56	62.6	5	50	2.6	1.52	153.9
	Auditory System	10,250	37	30.1	5	41.7	2.62	1.76	114.6
	Respiratory System	6,280	50	59.5	8	50	2.44	0.85	270.2
	Maternity Care and Delivery	2,692	13	67.4	4	46.9	2.42	2.28	162.2
	Mediastinum and Diaphragm	1,186	13	62	6	67.5	2.74	2.52	344.1
	Reproductive System	10	0	30	5	30	1.51	-	0
Drug	Hydrocodone	275,292	1,695	-	5	45	2.83	1.95	187.5
	Oxycodone	205,559	1,432	-	5	62.5	2.7	1.68	219
	Codeine	35,041	148	-	4	27	2.84	2.45	127.6
	Mixed	30,803	324	-	9	60	2.62	1.52	339.7
	Tramadol	11,721	70	-	8	30	2.21	1.53	221.1
	Hydromorphone	9,600	123	-	5	66.7	2.47	1.45	427.6

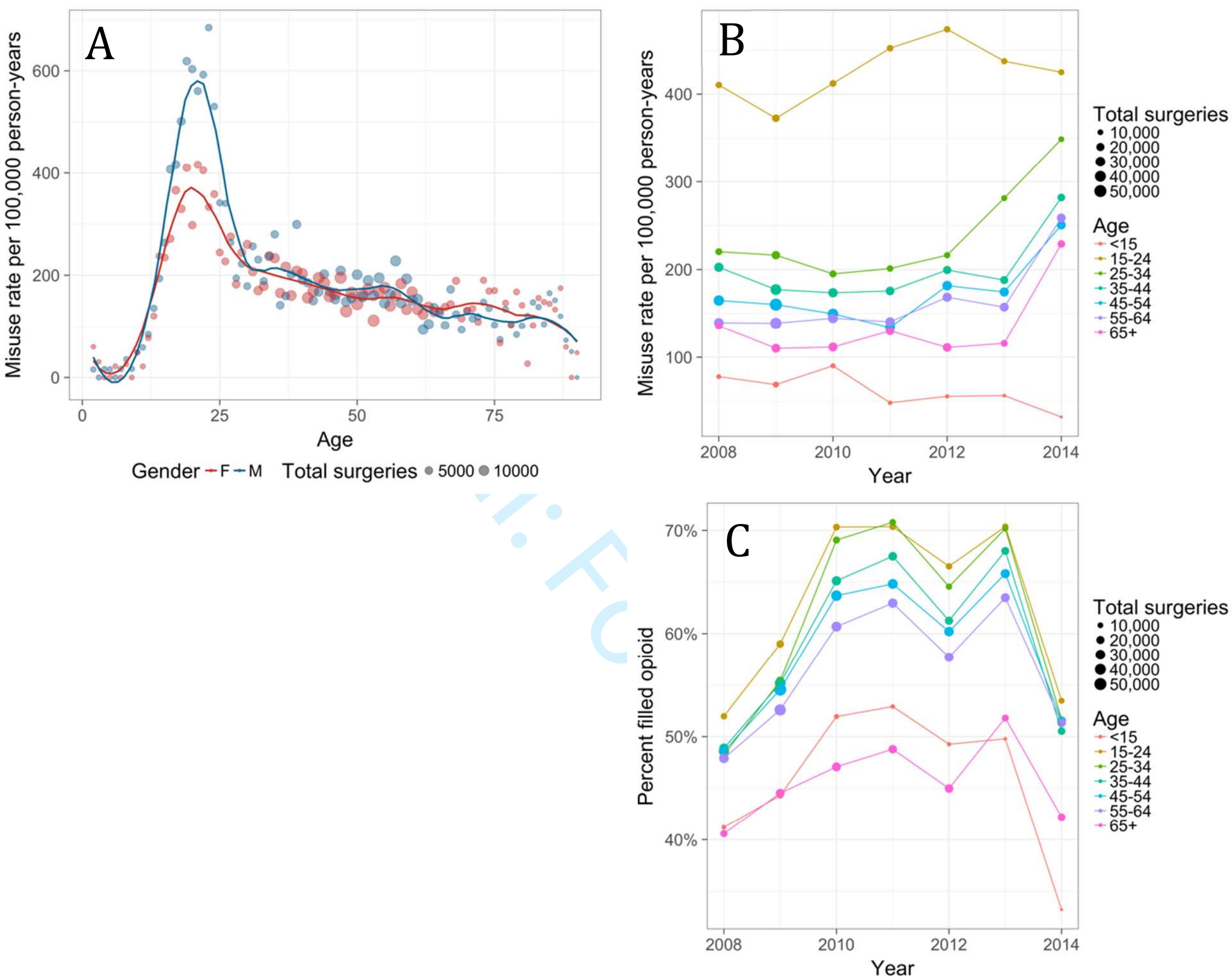


Figure 1: Misuse and Prescription Rates Per 100,000 Person-Years Over Time by Cohort. (A) Rates of misuse per 100,000 person-years across ages and gender. (B) Rising rates of misuse per 100,000 person-years by age cohort over time. (C) Opioid prescription fill rates by age cohort over time.

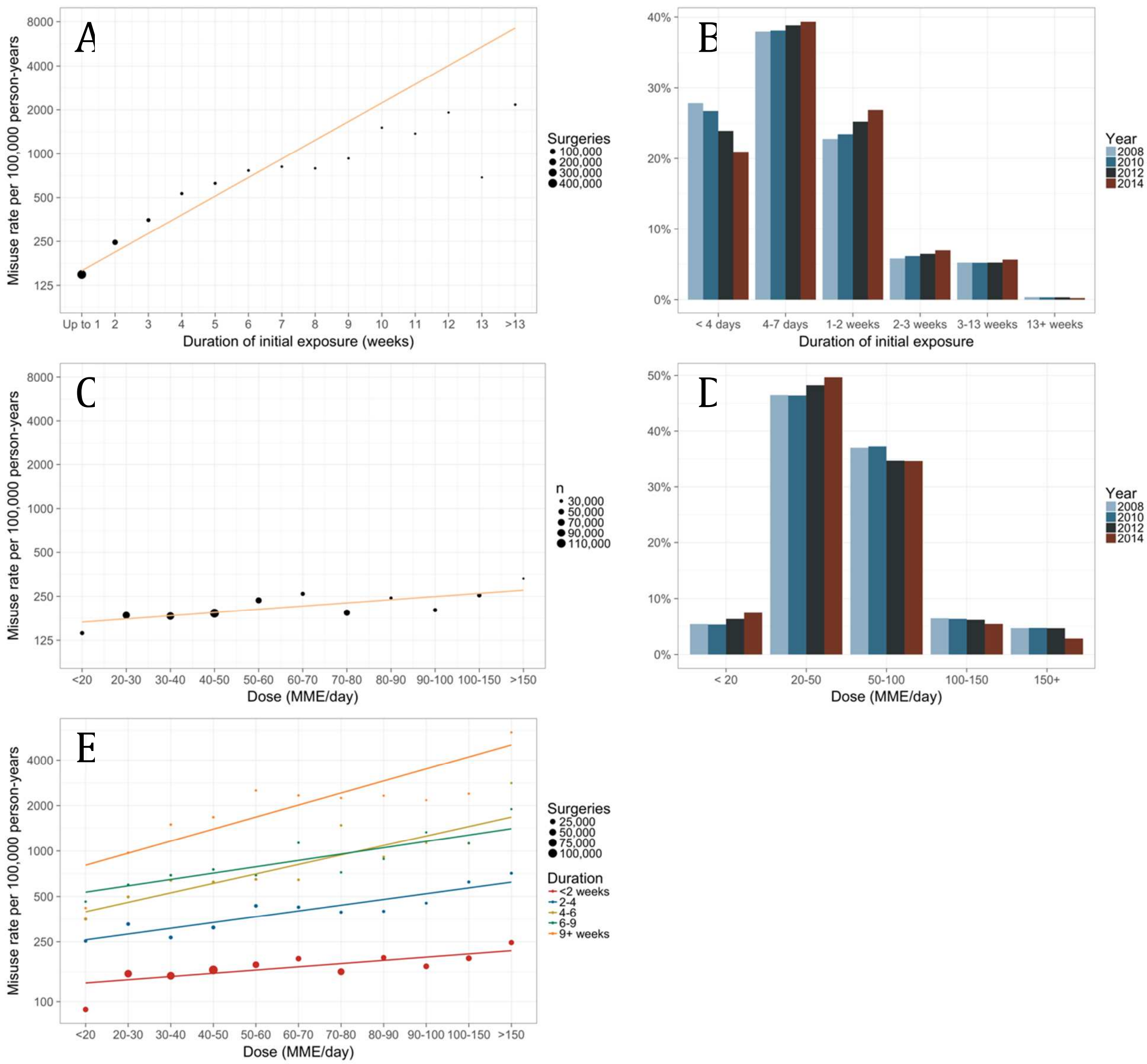


Figure 2: Post-Surgical Rates of Abuse by Dosage and Duration of Opioid Prescription. (A) Rates of opioid misuse per 100,000 person-years by week of exposure (y-axis is on log-scale). (B) Changing rates of duration of exposure during the study. (C) Rates of opioid misuse per 100,000 person-years by dose in MME/day (y-axis is on log-scale). (D) Changing dosage during the study by year. (E) Rates of opioid misuse per 100,000 person-years by dose, grouped by duration of exposure (y-axis is on log-scale).

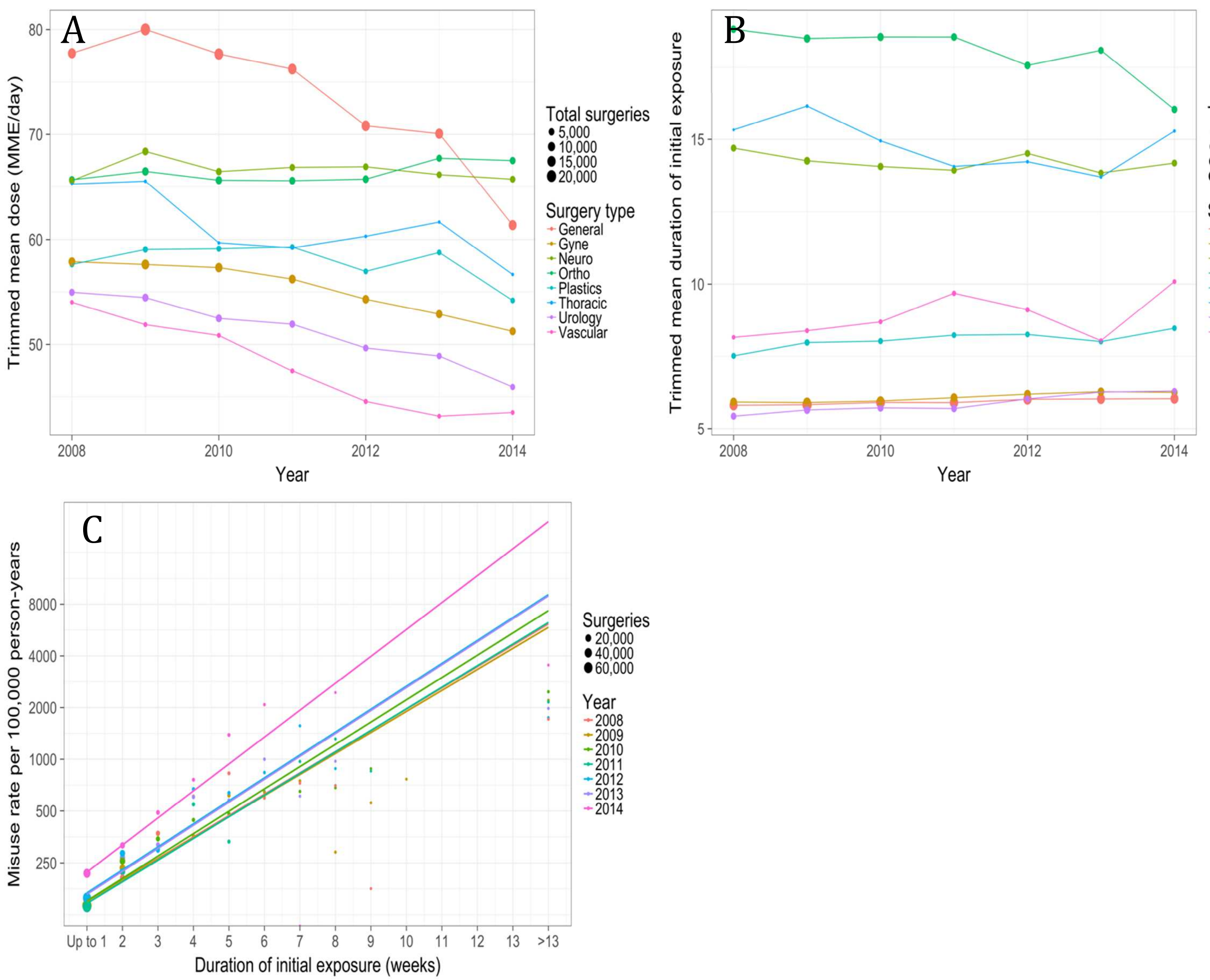
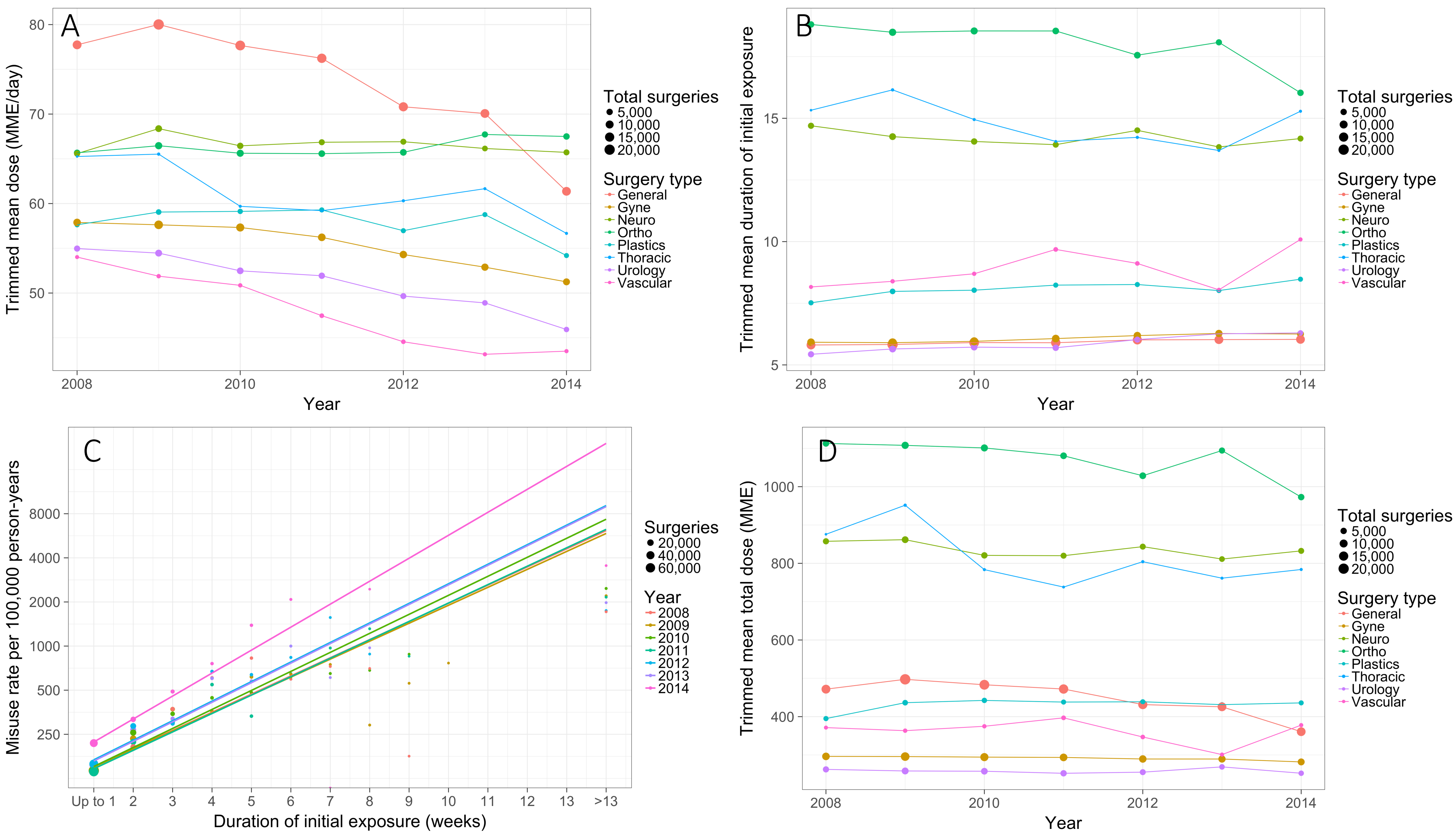


Figure 3: Temporal Changes in Opioid Exposure. (A) Decreasing mean dosage (MME/day) by surgical specialty during the years of the study, while (B) mean length of exposure (days) by surgical specialty remains relatively stable. (C) Rates of misuse per 100,000 person-years by duration of exposure in each year of the study (y-axis is on log-scale). The relationship is stable with similar trend lines. Only weeks with greater than 100 surgeries were included.



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