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Drug Enforcement Agency 2014 Hydrocodone Rescheduling Rule and Opioid Dispensing after Surgery

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Hydrocodone is a commonly prescribed but also commonly misused analgesic
- The rescheduling of hydrocodone from Schedule III to Schedule II by the U.S. Drug Enforcement Agency in 2014 was intended to reduce unnecessary hydrocodone use

What This Article Tells Us That Is New

- Data derived from a large insurance database for a group of 10 common ambulatory orthopedic surgeries suggested that hydrocodone dispensing increased after rescheduling for the 30-day period after surgery
- Data from the same source showed no difference in hydrocodone prescribing from 90 to 180 days after surgery

ABSTRACT

Background: In 2014, the U.S. Drug Enforcement Agency reclassified hydrocodone from Schedule III to Schedule II of the Controlled Substances Act, resulting in new restrictions on refills. The authors hypothesized that hydrocodone rescheduling led to decreases in total opioid dispensing within 30 days of surgery and reduced new long-term opioid dispensing among surgical patients.

Methods: The authors studied privately insured, opioid-naïve adults undergoing 10 general or orthopedic surgeries between 2011 and 2015. The authors conducted a differences-in-differences analysis that compared overall opioid dispensing before *versus* after the rescheduling rule for patients treated by surgeons who frequently prescribed hydrocodone before rescheduling (*i.e.*, patients who were functionally exposed to rescheduling's impact) while adjusting for secular trends *via* a comparison group of patients treated by surgeons who rarely prescribed hydrocodone (*i.e.*, unexposed patients). The primary outcome was any filled opioid prescription between 90 and 180 days after surgery; secondary outcomes included the 30-day refill rate and the amount of opioids dispensed initially and at 30 days postoperatively.

Results: The sample included 65,136 patients. The percentage of patients filling a prescription beyond 90 days was similar after *versus* before rescheduling (absolute risk difference, −1.1%; 95% CI, −2.3% to 0.1%; $P = 0.084$). The authors estimated the rescheduling rule to be associated with a 45.4-mg oral morphine equivalent increase (difference-in-differences estimate; 95% CI, 34.2–56.7 mg; $P < 0.001$) in initial opioid dispensing, a 4.1% absolute decrease (95% CI, −5.5% to −2.7%; $P < 0.001$) in refills within 30 days, and a 37.7-mg oral morphine equivalent increase (95% CI, 20.6–54.8 mg; $P = 0.008$) in opioids dispensed within 30 days.

Conclusions: Among patients treated by surgeons who frequently prescribed hydrocodone before the Drug Enforcement Agency 2014 hydrocodone rescheduling rule, rescheduling did not impact long-term opioid receipt, although it was associated with an increase in opioid dispensing within 30 days of surgery.

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In October 2014, the U.S. Drug Enforcement Agency (Springfield, Virginia) reclassified hydrocodone from Schedule III to Schedule II of the Controlled Substances Act,[1] prohibiting refills from being written in individual hydrocodone prescriptions. At a population level, rescheduling was associated with decreases in dispensing of hydrocodone[2,3] specifically and opioids overall.[4] However, its impact on postoperative opioid dispensing remains unclear; one analysis found rescheduling to have unintentionally increased opioid dispensing immediately after

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surgery,[5] whereas another observed no difference in opioid dispensing after *versus* before rescheduling.[6] Both analyses were limited by not having accounted for secular trends in opioid dispensing and neither examined rescheduling's impact on distal outcomes such as new long-term opioid receipt among previously opioid-naïve individuals.

Understanding rescheduling's impact on postoperative opioid dispensing has importance for health policy. Multiple policy interventions have targeted excess opioid dispensing for acute indications,[7,8] and limiting acute prescribing has been theorized to prevent development of new long-term opioid use.[9–14] Hydrocodone rescheduling may have altered short-term postoperative opioid dispensing by limiting refills or by unintentionally encouraging larger initial prescriptions; therefore, rescheduling provides an opportunity to examine the impact of changes in short-term postoperative opioid dispensing on new long-term opioid receipt.

We tested the impact of hydrocodone rescheduling on overall opioid dispensing (*i.e.*, dispensing of hydrocodone or another opioid analgesic) in a sample of commercially insured U.S. adults undergoing 10 general or orthopedic surgeries. To account for secular prescribing trends, we used a "difference-in-differences"[15] approach that compared dispensing outcomes after *versus* before rescheduling across groups of patients who were more *versus* less likely to have been impacted by the policy change based on their surgeon's tendency to prescribe hydrocodone before the schedule change. We hypothesized that rescheduling was associated with a decrease in opioid dispensing within 30 days after surgery (owing to a decrease in refills) and, consequently, with a decrease in the rate of opioid dispensing beyond 90 days after surgery.

Materials and Methods

Policy Context

The Drug Enforcement Agency's final rule regarding hydrocodone rescheduling was published on August 21, 2014 and took effect on October 6, 2014.[1] After this date, initial hydrocodone prescriptions could no longer include refills and could not be called in by phone to pharmacies, aligning with rules applicable to most other opioids.

Overview of Study Design

A data analysis and statistical plan was written and posted on a publicly accessible server (arxiv.org) after the data were accessed (Supplemental Digital Content, http://links.lww.com/ALN/C262).[16] Briefly, we designed a difference-in-differences analysis that divided patients into exposed and unexposed groups based on the relative impact that we anticipated rescheduling would have on their care. Because medication selection tends to be stable over time within prescribers,[17–19] we reasoned that opioid dispensing would be unlikely to vary as a direct consequence of the rescheduling rule for patients treated by surgeons who rarely prescribed hydrocodone before rescheduling. Conversely, we reasoned that hydrocodone rescheduling could impact care received by patients whose surgeons frequently prescribed hydrocodone before rescheduling. We estimated the impact of hydrocodone rescheduling by comparing opioid prescribing patterns after *versus* before rescheduling among patients treated by clinicians who frequently prescribed hydrocodone prior to rescheduling (*i.e.*, those functionally exposed to the policy effect of the rule) *versus* those treated by clinicians who rarely prescribed hydrocodone (unexposed patients).

Data

We used data from the 2004 to 2016 Optum deidentifed Clinformatics Data Mart Database, a U.S. health insurance database that includes approximately 17 to 19 million annual covered lives and comprises both commercial and Medicare Advantage health plan data. The population is geographically diverse, spanning all 50 states, and includes medical and pharmacy claims and tables with member eligibility and inpatient confinement data. Information on filled opioid prescriptions was obtained from pharmacy claims files within the Optum database; the database did not include information on prescriptions that were issued but not filled.

Characterizing Provider Prescribing before Rescheduling

Using uniform provider identifiers in the study database, we identified all individual surgeons or medical group practices submitting five or more claims between August 22, 2011 and August 21, 2014 for any of 10 common ambulatory or short-stay orthopedic or general surgeries among patients who filled an opioid prescription within 7 days after the procedure. Relevant opioids included oral analgesic formulations of codeine, hydrocodone, hydromorphone, levorphanol, meperidine, morphine, oxycodone, oxymorphone, pentazocine, tramadol, fentanyl, and tapentadol. Eligible procedures included laparoscopic cholecystectomy, open cholecystectomy, inguinal hernia repair, laparoscopic appendectomy, open appendectomy, breast excision, carpal tunnel release, knee arthroscopy, total knee replacement, and total hip replacement, as identified by Current Procedural Terminology codes (appendix 1). For each provider, we calculated the proportion of filled initial postoperative opioid prescriptions accounted for by hydrocodone products. Providers for whom hydrocodone products represented at least 75% of initial filled prescriptions were classified as hydrocodone prescribers; providers for whom hydrocodone accounted for 25% or fewer of initial filled prescriptions were classified as hydrocodone nonprescribers.

Defining the Study Sample

To permit a sufficient window of observation to confirm the absence of a notable trend in key outcome measures

before the policy change,[20,21] we defined the 3 yr before the final rule date (August 22, 2011 through August 21, 2014) as the preimplementation period. We defined the year after the effective date (October 6, 2014 through October 5, 2015) as the postimplementation period. We included patients aged 18 yr or older who had any of the above surgical procedures during the pre- or postimplementation period based on the procedure or hospital discharge date, whichever came later. We restricted our sample to patients treated by hydrocodone prescribers and hydrocodone nonprescribers as defined above. Patients treated by hydrocodone prescribers were classified as exposed; patients treated by hydrocodone nonprescribers were classified as unexposed. Patients treated by clinicians prescribing hydrocodone products for between 25% and 75% of cases were excluded because we could not attribute changes in dispensing for these patients to the impact of rescheduling *versus* other factors.

For patients with more than one eligible surgery, we used the first available claim. To permit uniform windows for assessment of patient characteristics and outcomes, we restricted the sample to patients who had at least 90 days of continuous enrollment before the procedure or admission date (whichever came first) and at least 180 days of enrollment after the procedure or discharge date (whichever came last). Because we aimed to examine the impact of rescheduling on the incidence of new long-term opioid dispensing, we restricted the sample to individuals with no filled opioid prescriptions in the 90 days before surgery (*i.e.*, opioid-naïve individuals). Finally, after confirming in preliminary analyses that the rate of any filled opioid prescription within 7 days after surgery was similar after *versus* before rescheduling for exposed *versus* unexposed patients, we restricted our sample to patients who filled at least one opioid prescription within 7 days of their procedure.

Outcome

Our primary outcome was a filled prescription for any of the 12 above-listed opioids between 90 and 180 days after surgery.[12,22,23] In separate work (publication pending), our group evaluated the sensitivity and specificity of 24 measures of long-term opioid dispensing for predicting opioid-related adverse events in the year after surgery; we found this measure to have similarly high sensitivity (sensitivity: 95%) with a higher degree of specificity than most other measures (sensitivity: 12%). Secondary outcomes included (1) the total amount of opioid dispensed in the first postoperative prescription filled within 7 days of surgery or discharge as measured in milligram (mg) oral morphine equivalents,[24] (2) filling of a refill prescription for any opioid refill in the first 30 days after surgery, and (3) the total amount of opioids dispensed across all filled prescriptions within the first 30 days after surgery or discharge in mg oral morphine equivalent.

Covariates

We obtained demographic data from registration files. We defined baseline comorbidities using pharmacy claims and International Classification of Disease 9–Clinical Modification diagnosis codes listed from inpatient and outpatient encounters during the 90 days before surgery.[25,26] We created variables for surgery type, length of hospital stay, and whether the provider submitting the claim for the index procedure was an individual practitioner or a group practice.

Statistical Analysis

Initial analyses compared baseline characteristics and outcomes of exposed *versus* unexposed patients using chi-squared tests and two-sample t-tests. We explored changes in outcomes before *versus* after rescheduling by plotting each outcome for exposed *versus* unexposed patients in the pre- and postimplementation periods.

We next carried out our difference-in-differences analysis. This analysis estimated changes in opioid dispensing among exposed patients (those treated by hydrocodone prescribers) between the postimplementation and preimplementation periods, and quantified outcome differences between exposed and unexposed patients (those treated by hydrocodone nonprescribers). This approach allowed us to account for other contemporaneous influences on opioid dispensing, which would be reflected in trends among unexposed patients.[15,27]

Specifically, we fit multivariable linear regression models to predict each study outcome; analyses of binary outcomes were confirmed using logistic regression. Robust standard errors were used to account for clustering of observations within providers.[28] As we anticipated low rates of missing data for key outcomes or covariates, our models handled missing data *via* complete case analysis (*i.e.*, individuals with missing data on any covariate were excluded from study models). All models included an interaction term between exposure status (exposed *vs.* unexposed) and period (pre- *vs.* postimplementation), which allowed us to estimate how adjusted outcomes varied between exposed and unexposed patients after *versus* before rescheduling. To adjust for confounding due to patent, procedure, and provider characteristics that could differ between exposed patients, all models also adjusted for demographics, comorbidities, surgery type, length of stay, and provider type (individual *vs.* group practice). Age and length of stay were entered into the model as continuous variables without transformation. The difference-in-differences estimate represents the effect of hydrocodone rescheduling on exposed patients, accounting for secular trends and the above-named covariates.[15,27] No formal statistical power calculations were conducted; all analyses were based on the available data.

Supplementary Analyses. Because postoperative opioid selection could differ for ambulatory surgery patients *versus*

inpatients, we conducted subgroup analyses restricted to ambulatory surgery patients. As reported in the technical preprint,[16] we assessed whether patients in the exposed *versus* unexposed groups had parallel preimplementation outcome trends using standard methods.[15] These analyses found no evidence for violations of the parallel trends assumption for three of four study outcomes but did find a small but statistically significant difference across study groups in trends over time for the total amount of opioid dispensed in the initial filled postoperative prescription. As such, we confirmed all findings in supplemental differences-in-differences regressions that formally modeled differential trends between exposed and unexposed groups over time (see additional methods in appendix 2).[29] Finally, to assess the robustness of our findings to alternate definitions of exposed *versus* unexposed groups, we repeated our analyses using more restrictive and more inclusive thresholds for categorizing surgeons as hydrocodone prescribers or nonprescribers.

Analysis of the complete study database began only after publication of our technical preprint on June 10, 2019 and used SAS version 9.4 (SAS Institute, USA). All hypothesis tests were two-tailed; we considered $P < 0.05$ to indicate statistical significance.

Results

A total of 65,136 patients met study inclusion criteria, including 41,712 exposed patients (33,319 preimplementation; 8,393 postimplementation) treated by 4,620 hydrocodone prescribers and 23,424 unexposed patients (18,808 preimplementation; 4,616 postimplementation; fig. 1) treated by 2,798 hydrocodone nonprescribers. By design, all patients included in the sample filled at least one opioid prescription within 7 days after surgery; over the full period, the first filled opioid prescription was for hydrocodone in 35,746 of 41,712 (85.7%) exposed patients *versus* 2,941 of 23,424 (12.6%) unexposed patients. Compared with unexposed patients, exposed patients were more often treated on an outpatient basis and more often underwent carpal tunnel release and knee arthroscopy. Total joint replacement occurred more commonly among unexposed *versus* exposed patients (table 1; additional data available in appendix 3).

Figure 2 depicts outcome trends for exposed *versus* unexposed patients. Rates of filled opioid prescriptions beyond 90 days were similar over time in both groups (exposed: 12.0% preimplementation [3,982 of 33,319] *versus* 10.5% postimplementation [883 of 8,393], $P < 0.001$; unexposed: 11.1% preimplementation [2,088 of 18,808] *versus* 10.8% postimplementation [498 of 4,616], $P = 0.548$). The mean oral morphine equivalent dispensed to exposed patients in the initial filled postoperative prescription was 259 mg (SD, 200.4 mg) preimplementation *versus* 295 mg (SD, 250 mg; $P < 0.001$) postimplementation compared with 382 mg (SD, 310.7 mg) *versus* 366 mg (SD, 280.9 mg; $P = 0.026$) for unexposed patients. The rate of refills within 30 days after surgery among exposed patients was 20.5% (6,830 of 33,319) before implementation *versus* 15.8% 1,323 of 8,393) after implementation ($P < 0.001$), compared with 22.7% (4,266 of 18,808) *versus* 21.2% (977 of 4,616) among unexposed patients ($P = 0.062$). The total oral morphine equivalent dispensed within 30 days increased between the preimplementation to postimplementation period for exposed patients from 329 mg (SD, 370.1 mg) to 355 mg (SD, 391.5 mg; $P < 0.001$) while decreasing among control patients from 492 mg (537.7 mg) to 468 mg (504.6 mg; $P = 0.049$). Among exposed patients, the percentage receiving hydrocodone as the first filled opioid prescription after surgery decreased from 89.9% (29,931 of 33,319) to 69.3% (5,815 of 8,393) before *versus* after rescheduling ($P < 0.001$); among unexposed patients, the percentage receiving hydrocodone increased from 11.5% (2,158 of 18,808) to 17.0% (783 of 4,616) across periods ($P < 0.001$).

We included 65,125 patients with complete study data (>99.9% of the full sample) in our adjusted difference-in-differences analysis (table 2); 11 patients were excluded because of missing data on sex. The incidence of filled opioid prescriptions between 90 and 180 days was similar after *versus* before rescheduling for exposed *versus* unexposed patients (difference-in-differences estimate: −1.1%; 95% CI, −2.3% to 0.1%; $P = 0.084$). Rescheduling was associated with a 45.4 mg (95% CI, 34.2–56.7 mg; $P < 0.001$) adjusted increase in oral morphine equivalent dispensed at 7 days after surgery among exposed *versus* unexposed patients, a 4.1% percentage point decrease (95% CI, −5.5% to −2.7%; $P < 0.001$) in refills within 30 days of surgery, and a net increase of 37.7 mg (95% CI: 20.6 mg, 54.8 mg, $P = 0.008$) in total oral morphine equivalent dispensed within 30 days. We observed similar results using logistic models for binary endpoints (appendix 4), in a subgroup analysis restricted to ambulatory surgery patients (appendix 5), in models with controls for preimplementation trends (appendix 6), and in models using alternate thresholds for categorizing surgeons as hydrocodone prescribers or nonprescribers (appendices 7 and 8).

Discussion

Among 65,136 opioid-naïve individuals undergoing 10 general or orthopedic surgeries, we estimated the Drug Enforcement Agency's 2014 hydrocodone rescheduling to have resulted in a 4% absolute decrease in opioid refills within 30 days of surgery among patients treated by clinicians who frequently prescribed hydrocodone before rescheduling (*i.e.*, those functionally exposed to the policy effect of the rule) *versus* those treated by clinicians who rarely prescribed hydrocodone (unexposed patients); this change was in accordance with the specific goals of the rescheduling rule, which explicitly prevented prescribers from issuing refill prescriptions at the time of an initial opioid prescription. However, we also found rescheduling to

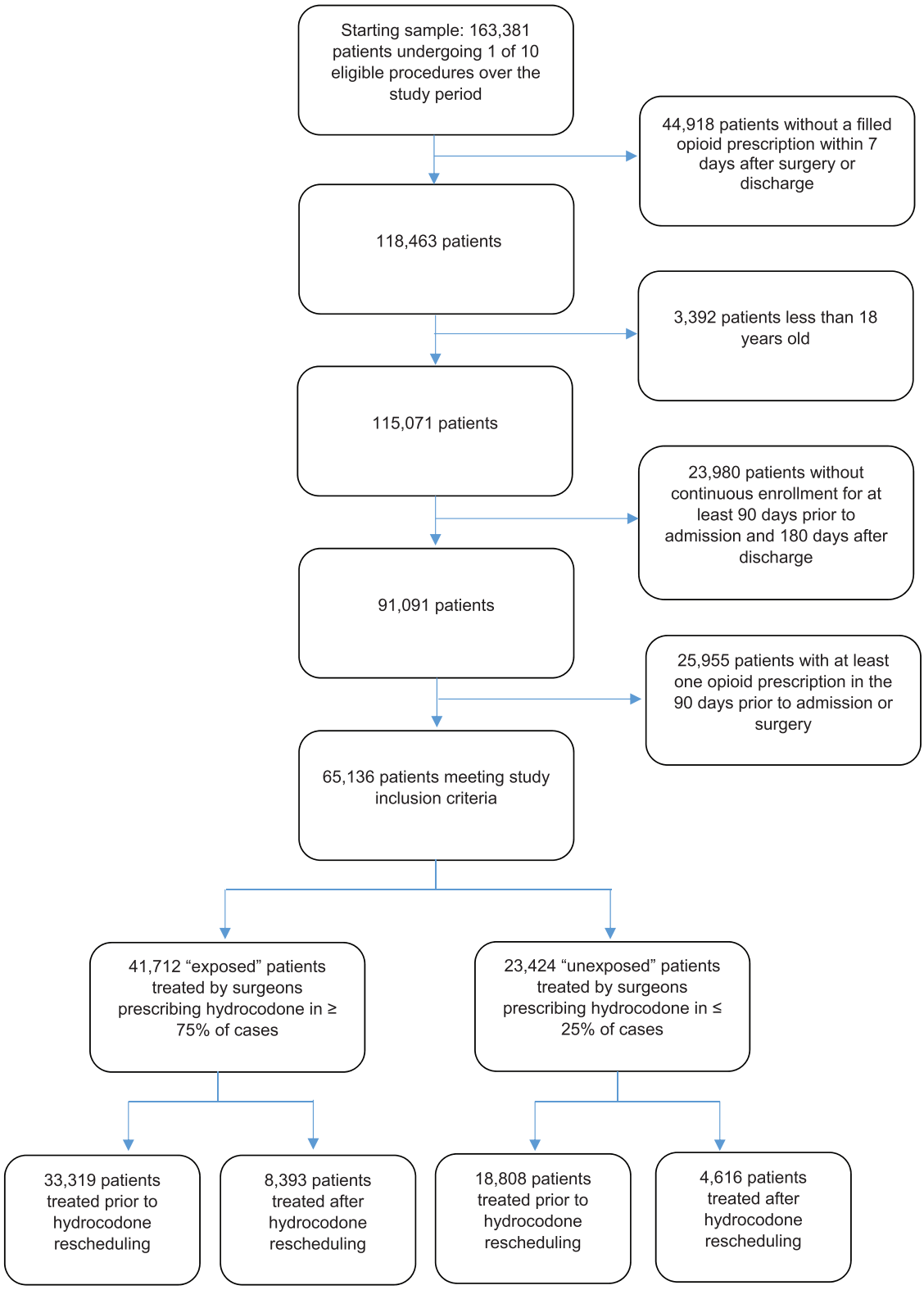

Fig. 1. Development of the study sample.

Table 1. Characteristics of Patients Included in the Study Sample

Variable	Exposed Patients (N = 41,712)	Unexposed Patients (N = 23,424)	*P* Value
Age, median (IQR)	52 (40–62)	54 (42–64)	< 0.001
Sex, N (%)			0.222
Male	19,120 (45.8)	10,852 (46.3)	
Female	22,587 (54.2)	12,566 (53.7)	
Provider type, N (%)			< 0.001
Individual	26,526 (63.6)	15,717 (67.1)	
Group practice	15,186 (36.4)	7,707 (32.9)	
Length of stay, N (%)			< 0.001
0 days	33,511 (80.3)	15,686 (67.0)	
1 or 2 days	3,995 (9.6)	3,980 (17.0)	
3 or more days	4,206 (10.1)	3,758 (16.0)	
Procedure type, N (%)			
Laparoscopic cholecystectomy	10,506 (25.2)	5,366 (22.9)	< 0.001
Open cholecystectomy	219 (0.5)	127 (0.5)	0.773
Laparoscopic appendectomy	3,630 (8.7)	2,058 (8.8)	0.718
Open appendectomy	276 (0.7)	203 (0.9)	0.003
Inguinal hernia repair	4,643 (11.1)	2,846 (12.1)	< 0.001
Carpal tunnel release	4,686 (11.2)	1,344 (5.7)	< 0.001
Knee arthroscopy	9,318 (22.3)	3,918 (16.7)	< 0.001
Total knee replacement	3,268 (7.8)	3,688 (15.7)	< 0.001
Total hip replacement	1,430 (3.4)	2,009 (8.6)	< 0.001
Breast excision	3,736 (9.0)	1,865 (8.0)	< 0.001
Comorbidities, N (%)			
Congestive heart failure	749 (1.8)	504 (2.2)	0.002
Cardiac arrhythmia	3,503 (8.4)	2,179 (9.3)	< 0.001
Cardiac valve disease	1,403 (3.4)	1,090 (4.7)	< 0.001
Peripheral vascular disorders	1,175 (2.8)	730 (3.1)	0.030
Hypertension, uncomplicated	15,255 (36.6)	9,302 (39.7)	< 0.001
Hypertension, complicated	1,111 (2.7)	771 (3.3)	< 0.001
Other neurologic disorders	614 (1.5)	373 (1.6)	0.227
Chronic pulmonary disease	4,515 (10.8)	2,919 (12.5)	< 0.001
Diabetes, uncomplicated	4,987 (12.0)	2,905 (12.4)	0.094
Diabetes, complicated	1,070 (2.6)	594 (2.5)	0.820
Hypothyroidism	4,986 (12.0)	3,013 (12.9)	< 0.001
Renal failure	1,012 (2.4)	653 (2.8)	0.005
Liver disease	2,956 (7.1)	1,572 (6.7)	0.071
Solid tumor without metastasis	3,334 (8.0)	1,932 (8.2)	0.252
Rheumatoid arthritis	1,136 (2.7)	731 (3.1)	0.004
Coagulopathy	512 (1.2)	411 (1.8)	< 0.001
Obesity	5,497 (13.2)	3,651 (15.6)	< 0.001
Fluid and electrolyte disorders	1,979 (4.7)	1,342 (5.7)	< 0.001
Iron deficiency anemia	882 (2.1)	631 (2.7)	< 0.001
Depression	4,200 (10.1)	2,599 (11.1)	< 0.001
Antidepressant receipt in last 90 days	6,424 (15.4)	3,398 (14.5)	0.002

Exposed patients are those treated by surgeons prescribing hydrocodone in at least 75% of cases before rescheduling; unexposed patients are those treated by surgeons prescribing hydrocodone in no more than 25% of cases before rescheduling.

have been associated with a 38-mg increase in oral morphine equivalent dispensed within 30 days of surgery, likely owing to larger initial prescriptions written in response to new restrictions on refills that came with rescheduling. We found no evidence that these changes in short-term opioid dispensing impacted long-term opioid receipt after surgery as measured between 90 and 180 days either in our full sample or in a subgroup of ambulatory surgery patients.

This work extends previous evaluations of hydrocodone rescheduling's impact on postoperative opioid dispensing. Using data from one U.S. academic center, Tan *et al.*[6] used interrupted time series analysis and found no difference in the average amount of opioid initially dispensed after surgery after *versus* before rescheduling. Using data from 75 Michigan hospitals, Habbouche *et al.*[5] applied similar methods and observed a 5% decrease in refills and an increase in the amount of opioid initially dispensed after surgery, but no change in total oral morphine equivalent dispensed at 30 days after surgery after *versus* before rescheduling.

Neither of these previous studies accounted for secular changes in opioid dispensing that could confound estimates of rescheduling's impact. In contrast, our difference-in-differences

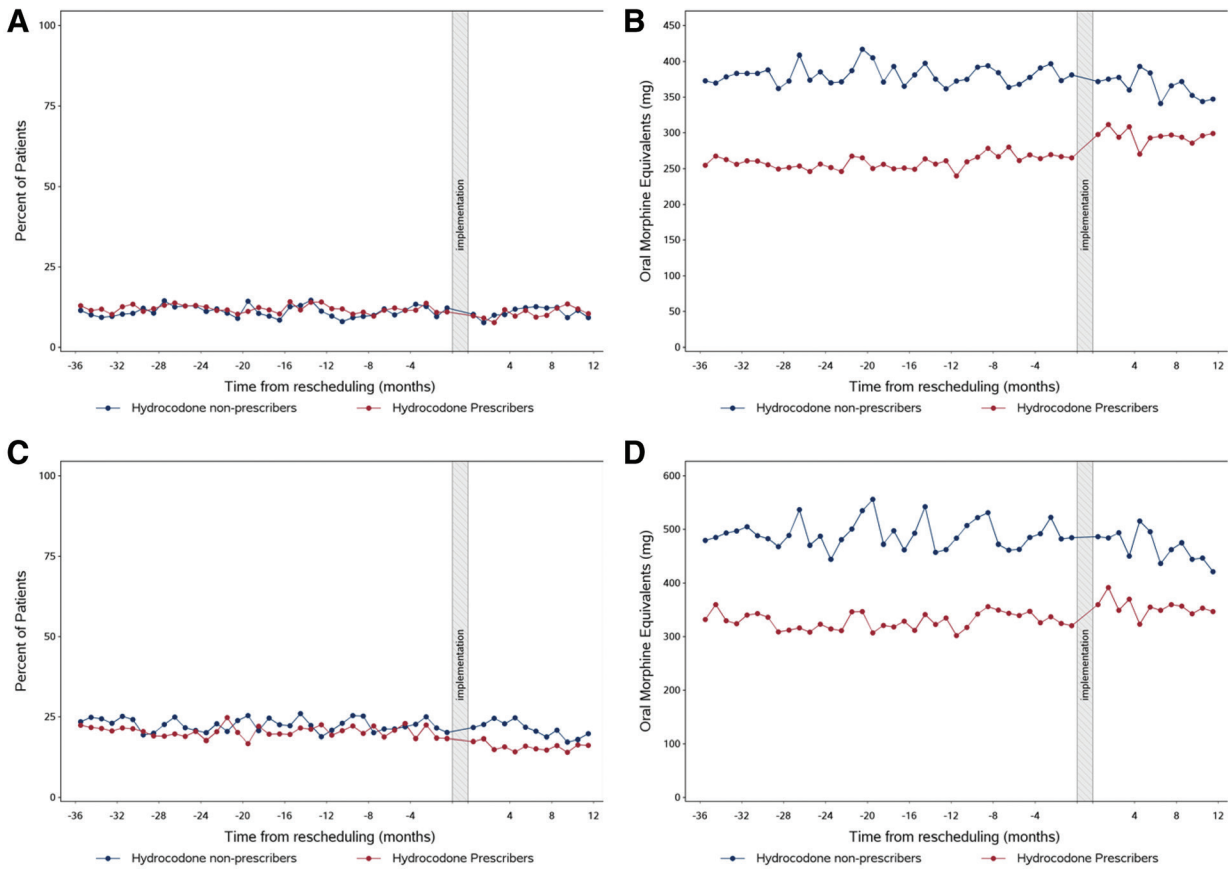

Fig. 2. Pre- and postimplementation study outcomes by exposure group. (*A*) Percentage filling any opioid prescription between 90 and 180 days. (*B*) Total amount of opioid dispensed in oral morphine equivalents (OME) in milligrams (mg) at 7 days. (*C*) Percentage obtaining an opioid refill within 30 days of surgery. (*D*) Total OME dispensed at 30 days, in mg. *Blue lines* correspond to patients treated by surgeons prescribing hydrocodone in no more than 25% of cases (unexposed patients); *red lines* correspond to patients treated by surgeons prescribing hydrocodone in at least 75% of cases (exposed patients).

design allows us to separate the impact of the rescheduling rule from other secular changes in opioid dispensing.[15] Moreover, we extend the generalizability of previous analyses through use of a national claims database and go beyond previous work in examining rescheduling's impact on filled opioid prescriptions beyond 90 days after surgery. As an incidental finding, we observed a modest decrease in oral morphine equivalent dispensed within 30 days after surgery among patients treated by hydrocodone nonprescribers over the 12 months after rescheduling. We observe this change occurring at an earlier date than most changes in postoperative opioid dispensing have been described, highlighting opportunities for future research to more broadly characterize trends in postoperative opioid dispensing over time.

This work has limitations. Although our statistical models adjusted for a variety of potential confounders, our results could have been affected by residual confounding if the study database failed to capture important differences between patients treated by hydrocodone prescribers *versus* nonprescribers, or between patients treated after *versus* before rescheduling. Because of limitations of the study dataset, we were unable to control for provider-level differences in experience or training that may have influenced opioid prescribing habits and responses to hydrocodone rescheduling. Because the rate of hydrocodone prescribing was greater than zero in our unexposed (control) group before rescheduling, it is possible that the rule change may have had some effects on opioid dispensing outcomes for this group; therefore, our findings may underestimate the true impact of rescheduling. Finally, our observation of differences in 7-day oral morphine equivalent dispensing trends for exposed *versus* nonexposed groups over the 3 yr before rescheduling could raise concern that our findings may not be solely attributable to the impact of hydrocodone rescheduling. This concern is mitigated by our confirmation of our main findings in regression models that adjusted for differences in

Table 2. Adjusted Study Outcomes

Outcome	Adjusted Change, after *versus* before Hydrocodone Rescheduling		Difference-in-Differences Estimate (95% CI)*
	Exposed Patients (95% CI)*	Unexposed Patients (95% CI)*	
Oral morphine equivalents			
Oral morphine equivalents dispensed in initial postoperative prescription, up to day 7	26.9 mg (20.8–33.0 mg)	−18.5 mg (−27.9 to −9.1 mg)	45.4 mg (34.2–56.7 mg)
Oral morphine equivalents dispensed within first 30 days after surgery	10.3 mg (2.8–17.9 mg)	−27.4 mg (−42.7 to −12.0 mg)	37.7 mg (20.6–54.8 mg)
Percentage points			
Percent with any opioid refill within first 30 days after surgery	−5.6% (−6.5% to −4.8%)	−1.6% (−2.7% to −0.4%)	−4.1% (−5.5% to −2.7%)
Percent with any opioid prescription between 90 and 180 days after surgery	−1.6% (−2.4% to −0.9%)	−0.5% (−1.5% to 0.5%)	−1.1% (−2.3% to 0.1%)

*Results obtained from linear models that included an interaction term between patient exposure status (exposed *vs.* unexposed) and period (pre- *vs.* postimplementation), and were adjusted for sex, individual provider *versus* group practice, age, length of stay, surgery type, peripheral vascular disorders, hypertension (uncomplicated), hypertension (complicated), neurologic disorders, chronic pulmonary disease, diabetes (uncomplicated), diabetes (complicated), hypothyroidism, renal failure, liver disease, solid tumor without metastasis, rheumatoid arthritis, coagulopathy, obesity, fluid and electrolyte disorders, iron deficiency anemia, depression, antidepressant receipt in last 90 days, congestive heart failure, cardiac arrhythmia, and cardiac valve disease.

preimplementation trends, the fact that the identified difference in preimplementation trends was small in magnitude and likely to be clinically insignificant, and our finding of no difference in preimplementation trends for our three other study outcomes. Because we focus exclusively on opioid dispensing outcomes among surgical patients, our analysis is limited in its ability to assess the net benefit or harm to public health attributable to hydrocodone rescheduling.

Despite these limitations, the present work has important implications for clinical practice and health policy. We find a modest increase in postoperative opioid dispensing attributable to rescheduling. Because the stated intent of the hydrocodone rescheduling rule was to limit, rather than to encourage, additional opioid dispensing, this finding highlights the potential for unintended consequences to arise from interventions that affect one aspect of postoperative prescribing, such as the ability to issue refills in the initial postoperative prescription, in isolation. Although we cannot comment based on this analysis on the specific benefits or harms of hydrocodone rescheduling at the level of the individual patient, the increase we observe in 30-day opioid dispensing may have had negative consequences at the level of the population if it increased the volume of unused opioids available for diversion or misuse. At the same time, we find that, despite an increase in 30-day opioid dispensing, patients experienced no consequent increase in the risk of new long-term opioid receipt, arguing against negative effects of the hydrocodone rescheduling act with regard to population-level patterns of new long-term opioid use. Although further work is required to fully understand the association between the extent of short-term opioid dispensing, refill rates, and the development of new long-term use,[13,30] our findings argue against a link between modest variations in the amount of opioids dispensed in the first 30 days after surgery and greater rates of new opioid receipt beyond 90 days.

In conclusion, among patients treated by surgeons who frequently prescribed hydrocodone before the Drug Enforcement Agency's 2014 hydrocodone schedule change, rescheduling was associated with a modest net increase in opioids dispensed within 30 days of surgery, but was not associated with changes in the incidence of new opioid receipt beyond 90 days. These findings suggest that hydrocodone rescheduling may have had limited unintended consequences if it increased the volume of unused opioids available for diversion or misuse, but was unlikely to have impacted patterns of new long-term opioid use after surgery.

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Competing Interests

Dr. Bateman is an investigator on grants to his institution from Baxalta (Westlake Village, California), Eli Lilly and Co. (Indianapolis, Indiana), GlaxoSmithKline (Brentford, United Kingdom), Pfizer (New York, New York), and Pacira (Parsippany, New Jersey) for unrelated studies and is a consultant to the Alosa Foundation (Boston, Massachusetts) and Aetion, Inc. (New York, New York). Dr. Hennessey has consulted for Braeburn Pharmaceuticals, Inc. (Princeton, New Jersey), Daiichi Sankyo, Inc. (Tokyo, Japan), Egalet Corporation (Wayne, Pennsylvania), Esteve Pharmaceuticals, LLC (Barcelona, Spain), Indivior, Inc. (Richmond, Virginia),

Inspiron Delivery Sciences, LLC (Morristown, New Jersey), Nektar Therapeutics Inc. (San Francisco, California), and Purdue Pharma, LP (Stamford, Connecticut). The other authors declare no competing interests.

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Appendix 1. Additional Information on Regression Adjustment for Nonparallel Preintervention Trends

Our principal difference-in-differences models assume the following form:

$$Y = b_0 + b_1 T + b_2 post + a(T \times post) + dX + e$$

Where Y corresponds to the outcome for each patient i; T corresponds to the indicator of exposure group such that $T = 0$ for unexposed patients and $T = 1$ for exposed patients; *post* corresponds to the indicator of time period such that $post = 0$ for patients undergoing surgery in the preimplementation period and $post = 1$ for patients undergoing surgery in the postimplementation period; and X represents a vector of patient and provider characteristics.

As noted elsewhere,[15,29] a key assumption of difference-in-difference analysis is that trends in outcomes for exposed and unexposed groups would have been the same in the absence of the intervention or policy change under evaluation. Although this parallel trends assumption cannot be fully tested (because we do not know what the exposed group's outcomes would have been in the postintervention period had the intervention counterfactually not taken place), we can test the assumption's plausibility by testing whether the exposed group and unexposed group trends are parallel in the preintervention period. The technical preprint that accompanies this article[16] presents a preliminary analysis that assessed potential violations of this parallel trends assumption by examining the trends for all outcomes among exposed *versus* unexposed patients over the 3 yr before the publication of the final rule for hydrocodone rescheduling in August 2014 (*i.e.*, the preimplementation period). These analyses did not find evidence for violations of the parallel trends assumption for three of four outcomes (receipt of any opioid between 90 and 180 days after surgery [primary outcome], total oral morphine equivalents dispensed in the first 30 days after surgery, and receipt of any refill within 30 days); however, we did observe small but statistically significant differences across study groups in trends over time in total oral morphine equivalents received within 7 days after surgery. As such, we carried out additional secondary analyses in the present work using estimators that accounted for differences in preimplementation trends by formally modeling differential trends between exposed and unexposed groups over time as follows:

$$Y = b_0 + b_1 T + b_2 post + b_3 time + \psi(T \times time) + \alpha(T \times post) + \delta X + \varepsilon$$

Where *time* corresponds to a vector of indicator variables for calendar month, with all other terms defined as above.

Appendix 2. Procedures Included in the Study Sample

Procedure	Current Procedural Terminology (CPT) Code
1. Carpal tunnel release	64721; 29848
2. Laparoscopic cholecystectomy	47562; 47563; 47564
3. Open cholecystectomy	47600; 47605; 47610
4. Inguinal hernia repair	49505; 49507; 49520; 49521; 49525
5. Knee arthroscopy—meniscectomy & other	29881; 29880; 29877; 29875; 29876; 29870
6. Total knee replacement	27446;27447; 27486; 27487
7. Total hip replacement	27130; 27132*
8. Laparoscopic appendectomy	44970
9. Open appendectomy	44950; 44960
10. Breast excision	19301, 19302, 19120

*Excluding any patient with an International Classification of Diseases 9th Revision, Clinical Modification diagnosis code indicating hip fracture (820.00-820.9)

Appendix 3. Characteristics of Patients Included in the Study Sample, by Exposure Period

	Patients Treated by Surgeons Prescribing Hydrocodone in No More than 25% of Eligible Cases (N = 23,424)		Patients Treated by Surgeons Prescribing Hydrocodone in at Least 75% of Cases (N = 41,712)	
Covariate	**Preimplementation**	**Postimplementation**	**Preimplementation**	**Postimplementation**
Age, median (IQR)	54 (42–64)	55 (43–64)	52 (40–62.0)	52 (40–62)
Sex, N (%)				
Male	8,700 (46.3%)	2,152 (46.6%)	15,221 (45.7%)	3,899 (46.5%)
Female	10,102 (53.7%)	2,464 (53.4%)	18,094 (54.3%)	4,493 (53.5%)
Provider type, N (%)				
Individual	12,894 (68.6%)	2,823 (61.2%)	21,508 (64.6%)	5,018 (59.8%)
Group practice	5,914 (31.4%)	1,793 (38.8%)	11,811 (35.4%)	3,375 (40.2%)
Length of stay, N (%)				
0 days	12,502 (66.5%)	3,184 (69.0%)	26,709 (80.2%)	6,802 (81.0%)
1 or 2 days	3,131 (16.6%)	849 (18.4%)	3,112 (9.3%)	883 (10.5%)
3 or more days	3,175 (16.9%)	583 (12.6%)	3,498 (10.5%)	708 (8.4%)
Procedure type, N (%)				
Laparoscopic cholecystectomy	4,308 (22.9%)	1,058 (22.9%)	8,433 (25.3%)	2,073 (24.7%)
Open cholecystectomy	106 (0.6%)	21 (0.5%)	189 (0.6%)	30 (0.4%)
Laparoscopic appendectomy	1,646 (8.8%)	412 (8.9%)	2,866 (8.6%)	764 (9.1%)
Open appendectomy	175 (0.9%)	28 (0.6%)	234 (0.7%)	42 (0.5%)
Inguinal hernia repair	2,360 (12.5%)	486 (10.5%)	3,772 (11.3%)	871 (10.4%)
Carpal tunnel release	1,049 (5.6%)	295 (6.4%)	3,814 (11.4%)	872 (10.4%)
Knee arthroscopy	3,114 (16.6%)	804 (17.4%)	7,420 (22.3%)	1,898 (22.6%)
Total knee replacement	2,937 (15.6%)	751 (16.3%)	2,518 (7.6%)	750 (8.9%)
Total hip replacement	1,615 (8.6%)	394 (8.5%)	1,094 (3.3%)	336 (4.0%)
Breast excision	1,498 (8.0%)	367 (8.0%)	2,979 (8.9%)	757 (9.0%)
Comorbidities, N (%)				
Congestive heart failure	400 (2.1%)	104 (2.3%)	592 (1.8%)	157 (1.9%)
Cardiac arrhythmia	1,706 (9.1%)	473 (10.2%)	2,810 (8.4%)	693 (8.3%)
Cardiac valve disease	862 (4.6%)	228 (4.9%)	1,165 (3.5%)	238 (2.8%)
Peripheral vascular disorders	566 (3.0%)	164 (3.6%)	927 (2.8%)	248 (3.0%)
Hypertension, uncomplicated	7,416 (39.4%)	1,886 (40.9%)	12,227 (36.7%)	3,028 (36.1%)
Hypertension, complicated	601 (3.2%)	170 (3.7%)	883 (2.7%)	228 (2.7%)
Other neurologic disorders	306 (1.6%)	67 (1.5%)	498 (1.5%)	116 (1.4%)
Chronic pulmonary disease	2,338 (12.4%)	581 (12.6%)	3,587 (10.8%)	928 (11.1%)
Diabetes, uncomplicated	2,289 (12.2%)	616 (13.3%)	3,983 (12.0%)	1,004 (12.0%)
Diabetes, complicated	455 (2.4%)	139 (3.0%)	844 (2.5%)	226 (2.7%)
Hypothyroidism	2,367 (12.6%)	646 (14.0%)	3,932 (11.8%)	1,054 (12.6%)
Renal Failure	499 (2.7%)	154 (3.3%)	790 (2.4%)	222 (2.6%)
Liver disease	1,239 (6.6%)	333 (7.2%)	2,316 (7.0%)	640 (7.6%)
Solid tumor without metastasis	1,545 (8.2%)	387 (8.4%)	2,642 (7.9%)	692 (8.2%)
Rheumatoid arthritis	584 (3.1%)	147 (3.2%)	879 (2.6%)	257 (3.1%)
Coagulopathy	320 (1.7%)	91 (2.0%)	411 (1.2%)	101 (1.2%)
Obesity	2,781 (14.8%)	870 (18.8%)	4,191 (12.6%)	1,306 (15.6%)
Fluid and electrolyte disorders	1,077 (5.7%)	265 (5.7%)	1,566 (4.7%)	413 (4.9%)
Iron deficiency anemia	518 (2.8%)	113 (2.4%)	696 (2.1%)	186 (2.2%)
Depression	2,089 (11.1%)	510 (11.0%)	3,309 (9.9%)	891 (10.6%)
Antidepressant receipt in last 90 days	2,716 (14.4%)	682 (14.8%)	5,128 (15.4%)	1,296 (15.4%)

IQR, interquartile range.

Appendix 4. Adjusted Odds Ratios (OR) for Selected Study Outcomes for the Postimplementation Period *versus* Preimplementation Period among Exposed and Unexposed Patients

	Exposed Patients (95% CI)*	Unexposed Patients (95% CI)*	Exposed *versus* Unexposed Patients (95% CI)
OR for any opioid refill within first 30 days after surgery	0.62 (0.58, 0.67)	0.89 (0.81, 0.98)	0.70 (0.62, 0.79)
OR for any opioid prescription between 90 and 180 days after surgery	0.85 (0.78, 0.91)	0.95 (0.85, 1.05)	0.89 (0.78, 1.02)

*Results obtained from logistic models that included an interaction term between patient exposure status (exposed *vs.* unexposed) and period (pre- *vs.* postimplementation), and were adjusted for sex, individual provider *versus* group practice, age, length of stay, surgery type, peripheral vascular disorders, hypertension (uncomplicated), hypertension (complicated), neurologic disorders, chronic pulmonary disease, diabetes (uncomplicated), diabetes (complicated), hypothyroidism, renal failure, liver disease, solid tumor without metastasis, rheumatoid arthritis, coagulopathy, obesity, fluid and electrolyte disorders, iron deficiency anemia, depression, antidepressant receipt in last 90 days, congestive heart failure, cardiac arrhythmia, and cardiac valve disease.

Appendix 5. Adjusted Study Outcomes (Ambulatory Surgery Patients Only)

Outcome	Adjusted Change, after *versus* before Hydrocodone Rescheduling		Difference-in-Differences Estimate (95% CI)*
	Exposed Patients (95% CI)*	Unexposed Patients (95% CI)*	
Oral morphine equivalents			
Oral morphine equivalents dispensed in initial postoperative prescription, up to day 7	15.2 mg (10.7–19.8 mg)	−10.4 mg (−18.0 to −2.7 mg)	25.6 mg (16.8–34.4 mg)
Oral morphine equivalents dispensed within first 30 days after surgery	5.2 mg (−0.3–10.8 mg)	−14.7 mg (−24.4 to −4.9 mg)	19.9 mg (8.7–31.1 mg)
Percentage points			
Percent with any opioid refill within first 30 days after surgery	−5.1% (−6.0% to −4.3%)	−1.5% (−2.7% to −0.3%)	−3.6% (−5.1% to −2.2%)
Percent with any opioid prescription between 90 and 180 days after surgery	−1.6% (−2.4% to −0.8%)	−0.4% (−1.6% to 0.8%)	−1.2% (−2.7% to 0.2%)

*Results obtained from linear models that included an interaction term between patient exposure status (exposed *vs.* unexposed) and period (pre- *vs.* postimplementation), and were adjusted for sex, individual provider *versus* group practice, age, length of stay, surgery type, peripheral vascular disorders, hypertension (uncomplicated), hypertension (complicated), neurologic disorders, chronic pulmonary disease, diabetes (uncomplicated), diabetes (complicated), hypothyroidism, renal failure, liver disease, solid tumor without metastasis, rheumatoid arthritis, coagulopathy, obesity, fluid and electrolyte disorders, iron deficiency anemia, depression, antidepressant receipt in last 90 days, congestive heart failure, cardiac arrhythmia, and cardiac valve disease.

Appendix 6. Adjusted Study Outcomes Controlling for Preintervention Trends

Outcome	Adjusted Change, after *versus* before Hydrocodone Rescheduling		Difference-in-Differences Estimate (95% CI)*
	Exposed Patients (95% CI)*	Unexposed Patients (95% CI)*	
Oral morphine equivalents			
Oral morphine equivalents dispensed in initial postoperative prescription, up to day 7	24.2 mg (16.9 to 31.5 mg)	−11.5 mg (−23.9 to 1.0 mg)	35.6 mg (21.2 to 50.0 mg)
Oral morphine equivalents dispensed within first 30 days after surgery	16.0 mg (5.6 to 26.3 mg)	−13.5 mg (−34.5 to 7.4 mg)	29.5 mg (6.1 to 52.9 mg)
Percentage points			
Percent with any opioid refill within first 30 days after surgery	−4.7% (−6.0% to −3.5%)	0.1% (−1.6% to 1.8%)	−4.8% (−6.9% to −2.7%)
Percent with any opioid prescription between 90 and 180 days after surgery	−1.0% (−2.2% to 0.1%)	−0.5% (−2.0% to 1.0%)	−0.5% (−2.4% to 1.4%)

*Results obtained from linear models that included interaction terms between (1) patient exposure status (exposed *vs.* unexposed) and period (pre- *vs.* postimplementation) and (2) patient exposure status (exposed *vs.* unexposed) and calendar month. Models were adjusted for sex, individual provider *versus* group practice, age, length of stay, surgery type, peripheral vascular disorders, hypertension (uncomplicated), hypertension (complicated), neurologic disorders, chronic pulmonary disease, diabetes (uncomplicated), diabetes (complicated), hypothyroidism, renal failure, liver disease, solid tumor without metastasis, rheumatoid arthritis, coagulopathy, obesity, fluid and electrolyte disorders, iron deficiency anemia, depression, antidepressant receipt in last 90 days, congestive heart failure, cardiac arrhythmia, and cardiac valve disease.

Appendix 7. Adjusted Study Outcomes Using More Restrictive Thresholds for Defining Exposed *versus* Unexposed Patients

In the original analysis, exposed patients were defined as individuals treated by providers for whom hydrocodone products represented at least 75% of initial filled prescriptions before the 2014 schedule change. Unexposed patients were those treated by providers for whom hydrocodone accounted for 25% or fewer of initial filled prescriptions prior to rescheduling. The below table shows results from models using samples of exposed patients (N = 13,607) and unexposed patients (N = 25,657) that we created using alternate cut points of 85% and 15% for classifying provider tendency to prescribe hydrocodone prior to rescheduling.

Outcome	Adjusted Change, after *versus* before Hydrocodone Rescheduling		Difference-in-Differences Estimate (95% CI)*
	Exposed Patients (95% CI)*	Unexposed Patients (95% CI)*	
Oral morphine equivalents			
Oral morphine equivalents dispensed in initial postoperative prescription, up to day 7	26.0 mg (18.2 to 33.8 mg)	–13.6 mg (–26.0 to –1.2 mg)	39.6 mg (24.8 to 54.3 mg)
Oral morphine equivalents dispensed within first 30 days after surgery	11.2 mg (1.6 to 20.8 mg)	–21.6 mg (–41.2 to –2.1 mg)	32.9 mg (11.1 to 54.7 mg)
Percentage points			
Percent with any opioid refill within first 30 days after surgery	–5.7% (–6.8% to –4.6%)	–1.5% (–3.0% to –0.0%)	–4.2% (–6.0% to –2.3%)
Percent with any opioid prescription between 90 and 180 days after surgery	–1.3% (–2.1% to –0.4%)	–0.9% (–2.1% to 0.4%)	–0.4% (–2.0% to 1.1%)

*Results obtained from linear models that included an interaction term between patient exposure status (exposed *vs.* unexposed) and period (pre- *vs.* postimplementation), and were adjusted for sex, individual provider *versus* group practice, age, length of stay, surgery type, peripheral vascular disorders, hypertension (uncomplicated), hypertension (complicated), neurologic disorders, chronic pulmonary disease, diabetes (uncomplicated), diabetes (complicated), hypothyroidism, renal failure, liver disease, solid tumor without metastasis, rheumatoid arthritis, coagulopathy, obesity, fluid and electrolyte disorders, iron deficiency anemia, depression, antidepressant receipt in last 90 days, congestive heart failure, cardiac arrhythmia, and cardiac valve disease.

Appendix 8. Adjusted Study Outcomes Using Less Restrictive Thresholds for Defining Exposed *versus* Unexposed Patients

In the original analysis, exposed patients were defined as individuals treated by providers for whom hydrocodone products represented at least 75% of initial filled prescriptions before the 2014 schedule change. Unexposed patients were those treated by providers for whom hydrocodone accounted for 25% or fewer of initial filled prescriptions before rescheduling. The below table shows results from models using samples of exposed patients (N = 62,468) and unexposed patients (N = 39,757) that we created using alternate cut points of 60% and 40% for classifying provider tendency to prescribe hydrocodone prior to rescheduling. Appendix 3. Characteristics of Patients Included in the Study Sample, by Exposure Period

Outcome	Adjusted Change, after *versus* before Hydrocodone Rescheduling		Difference-in-Differences Estimate (95% CI)*
	Exposed Patients (95% CI)*	Unexposed Patients (95% CI)*	
Oral morphine equivalent			
Oral morphine equivalents dispensed in initial postoperative prescription, up to day 7	22.8 mg (17.9 to 27.7 mg)	–10.9 mg (–17.9 to –3.9 mg)	33.7 mg (25.1 to 42.3 mg)
Oral morphine equivalents dispensed within first 30 days after surgery	10.2 mg (3.7 to 16.7 mg)	–19.6 mg (–30.9 to –8.3 mg)	29.8 mg (16.8 to 42.8 mg)
Percentage points			
Percent with any opioid refill within first 30 days after surgery	–5.1% (–5.8% to –4.4%)	–2.1% (–2.9% to –1.2%)	–3.0% (–4.2% to –1.9%)
Percent with any opioid prescription between 90 and 180 days after surgery	–1.3% (–1.9% to –0.6%)	–0.8% (–1.6% to –0.0%)	–0.4% (–1.4% to 0.6%)

*Results obtained from linear models that included an interaction term between patient exposure status (exposed *vs.* unexposed) and period (pre- *vs.* postimplementation), and were adjusted for sex, individual provider *versus* group practice, age, length of stay, surgery type, peripheral vascular disorders, hypertension (uncomplicated), hypertension (complicated), neurologic disorders, chronic pulmonary disease, diabetes (uncomplicated), diabetes (complicated), hypothyroidism, renal failure, liver disease, solid tumor without metastasis, rheumatoid arthritis, coagulopathy, obesity, fluid and electrolyte disorders, iron deficiency anemia, depression, antidepressant receipt in last 90 days, congestive heart failure, cardiac arrhythmia, and cardiac valve disease.

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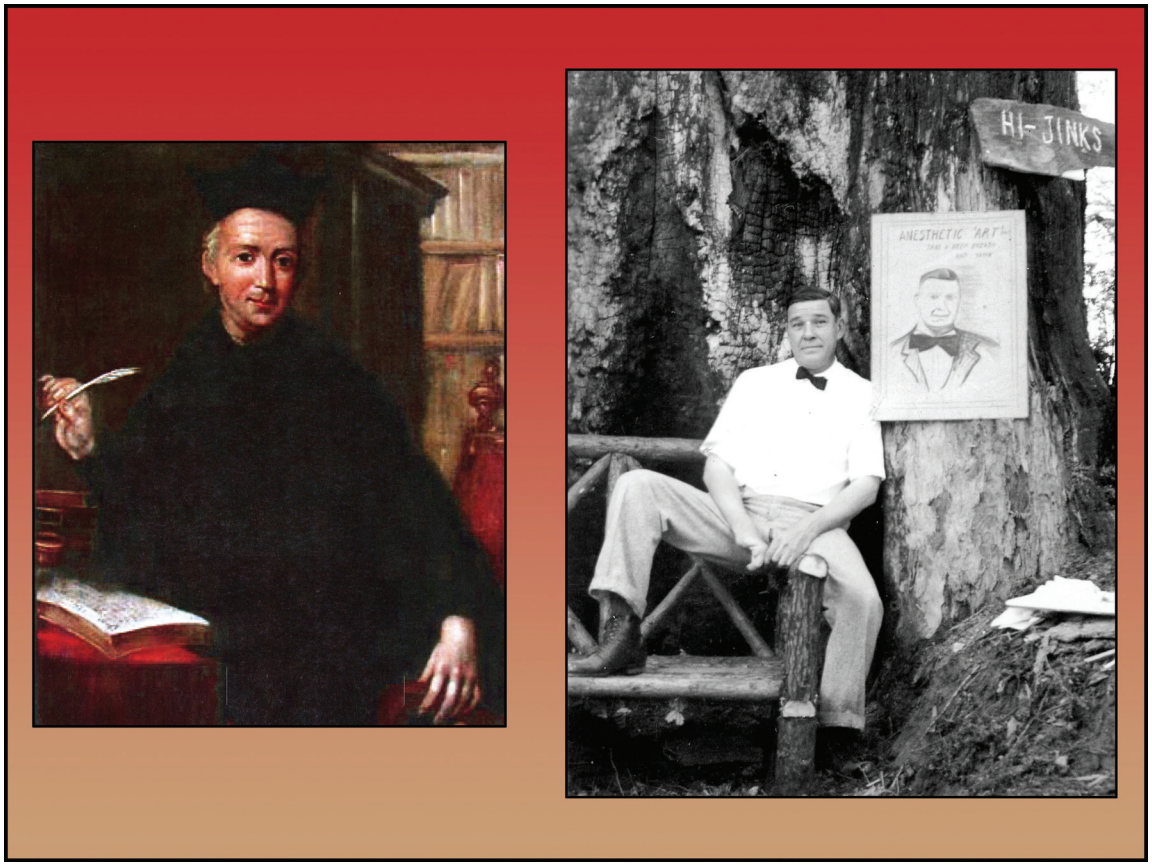
Art Guedel and *The Art of Worldly Wisdom*



The Art of Worldly Wisdom: A Pocket Oracle (1647), a wondrous text by Spanish priest Baltasar Gracián (1601 to 1658, *left*), graced the homes of several forefathers of American anesthesiology. Dr. Arthur "Art" Guedel (1883 to 1956, *right*), a Los Angeles–based devotee of *The Art*, was so taken by the little book that he shared it freely with friends in anesthesiology like Drs. Ralph Waters, Emery Rovenstine, Paul Wood, Henry Ruth, and Ralph Tovell. Gracián, a theologian who had examined the lives of aristocrats to glean secrets of success, had deftly crafted *The Art*—a collection of 300 witty aphorisms—in minimalistic prose. Art Guedel, a man of action and candor, marveled at *The Art*, a model of discernment and discretion. Although their styles differed, Art and *The Art* both prized virtue and friendship, which enhanced the book's appeal. Guedel popularized Gracián's *Art* as a guide for pioneering anesthesiologists, many of whom contended with external and internal rivalries to establish anesthesiology as an independent American specialty. (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology.)

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