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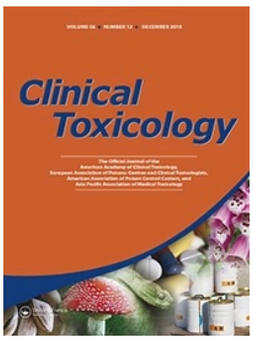

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POISON CENTRE RESEARCH

Trends in hydrocodone combination product exposures reported to California Poison Control System (CPCS) following DEA rescheduling

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ABSTRACT

Context: On October 6, 2014, the United States Drug Enforcement Administration (DEA) implemented a regulatory change for hydrocodone combination products (HCPs), moving them from Schedule III to II, in an effort to decrease drug overdoses. Existing research suggests this regulatory action reduced HCP prescribing and dispensing; however, there is limited research assessing its possible effects on overdoses and accidental exposures.

Objective: To analyze the changes in opioid exposures reported to the California Poison Control System (CPCS) before and after DEA rescheduling of HCPs.

Methods: We collected monthly exposure data reported to CPCS from 2012 to 2019 and conducted interrupted time series analyses to assess changes in exposures after rescheduling for HCPs, tramadol, oxycodone, morphine, codeine, fentanyl, and heroin. Additional analyses were done to assess any changes in exposures resulting in severe outcomes (moderate or major health effects). For HCPs, we also conducted logistic regressions to identify characteristics of exposures resulting in severe outcomes before and after rescheduling.

Results: Overall monthly opioid exposures reported to CPCS decreased after DEA rescheduling of HCPs. These decreases were significant for HCP, tramadol, and morphine ($p < 0.001$). Exposures significantly increased for heroin and fentanyl ($p < 0.001$). There were no significant changes in the share of severe outcomes attributed to HCP exposures after rescheduling.

Discussion: The DEA rescheduling of HCPs was associated with a significant decrease in HCP exposures and prescription opioid exposures overall, but was associated with increased fentanyl and heroin exposures. While other initiatives may have contributed to this decrease, our findings suggest that rescheduling may be a useful regulatory strategy to reduce drug exposures.

Conclusion: DEA rescheduling of HCPs was associated with a significant reduction in prescription opioid exposures, suggesting that rescheduling high-risk drugs may be an effective strategy to improve public health.

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Hydrocodone; analgesics; opioid; drug overdose; public health; drug and narcotic control

Introduction

From 2010 to 2014 drug overdose deaths in the United States (US) increased by 23% [1]. The Drug Enforcement Administration (DEA) classifies controlled drugs into five different schedules depending on the abuse or dependence potential, with Schedule V representing the lowest potential and Schedule I the highest [2]. Six of the top 10 drugs involved in overdose deaths from 2010 to 2014 were opioid analgesics [1]. Of these, hydrocodone, available in hydrocodone combination products (HCPs), was the only opioid analgesic classified as Schedule III until late 2014 [3]. Other drugs in this class, including oxycodone, methadone, morphine and heroin were classified as Schedule I or II [2]. Hydrocodone overdose-related deaths accounted for around 3000 deaths annually from 2010 to 2014, approximately 7% of the total [1].

To address growing concern about HCP overdoses, the DEA increased regulation of HCPs by reclassifying them as Schedule II on October 6, 2014 [3,4]. This ruling affected the accessibility of prescribed HCPs because Schedule II medications are more strictly regulated. Unlike Schedule III–V medications, prescriptions for Schedule II medications in all states cannot be called, faxed into the pharmacy, or refilled[5] .Additionally, prescriptions for Schedule II medications must be either written on a hard-copy prescription pad with enhanced security features or electronically prescribed [5].

Several regional retrospective studies in the US were conducted following the rescheduling of HCPs. Opioid prescription rates at 14 Texas pharmacies were analyzed to determine the effects of rescheduling and showed a decrease in prescription rates and quantity [6]. In Massachusetts, opioid prescription claims and pill counts after rescheduling analyzed using Medicaid data showed a similar decrease [4]. Data obtained from pharmacies in Texas calculated the number of opioid pills dispensed, showing an overall decrease after policy enactment [7]. Studies performed in Ohio and South

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Supplemental data for this article can be accessed here.

Dakota based on data from prescription drug monitoring programs showed comparable declines [8,9]. A national study of physician opioid prescribing rates also found a decrease in prescriptions after rescheduling, although results varied across states [10].

These previous studies primarily focused on analyzing trends in prescription rates and prescriber behavior following the rescheduling of HCPs rather than changes in exposures, including overdoses [11]. Calls made to poison control centers, in contrast, offer a way to assess exposures before and after rescheduling. In 2016, Texas Poison Center Network (TPCN) data covering the period six months before and after HCP rescheduling showed a decrease in HCP exposures, but an increase in exposures to alternative opioids, specifically codeine and tramadol [12]. These findings suggest the need for additional research to determine whether the observed decrease and possible substitution effects persisted beyond the first six months and occurred outside a single state [12].

The Office of National Drug Control Policy has implemented recommendations in the National Drug Control Strategy, which include increased education for both patients and providers, controlled substance monitoring programs, and further recognition of avenues for diversion [13]. These initiatives appear to have reduced opioid misuse, however continued deaths suggest the need for further policy interventions [13]. Federal legislative efforts such as rescheduling may play an additional role in curbing opioid misuse.

Our study aim was to analyze exposures to opioids reported to the California Poison Control System (CPCS) before and after the 2014 rescheduling of HCPs. We hypothesized that HCP exposures would decrease following rescheduling. In addition, we analyzed exposures to alternative prescription opioids and heroin to assess possible substitution trends.

Methods

This observational, retrospective study analyzed trends in exposures to HCPs and alternative opioids reported to the CPCS before and after the rescheduling of HCPs. De-identified data was obtained from CPCS for all cases from January 1, 2012 to December 31, 2019, two years before and five years after implementation.

Cases analyzed in this study met the following inclusion criteria: calls made to CPCS from within California reporting exposures to hydrocodone, HCPs, tramadol, oxycodone, morphine, codeine, fentanyl, or heroin. These included both single-substance and multiple-substance (both opioid and non-opioid) exposures. Exposures were defined based on the American Association of Poison Control Centers (AAPCC) definition of exposure as someone to have "had contact with the substance in some way; for example, ingested, inhaled, or absorbed a substance by the skin or eyes." [14] Hydrocodone alone is only available as an extended release formulation under the brand names Hysingla® ER, Zohydro® ER [15], and Vantrela® ER [16]. These products, however, are not widely used [15] and the majority of hydrocodone exposures involve HCPs. In addition to hydrocodone and HCPs, we reviewed exposures to tramadol, oxycodone, morphine, codeine, fentanyl, and heroin, as these agents (with the exception of heroin) were commonly prescribed alternatives to HCPs. For hydrocodone, codeine, tramadol, and oxycodone, exposures included combination and single-drug products. Exclusion criteria encompassed calls made into the CPCS from outside of California or labeled as location unknown.

Variables extracted from each CPCS record included patient age, gender, reason for exposure, and medical outcome. Patients were grouped by age as minors ($<$18 years old) and adults ($\geq$18 years old). Exposures were coded by CPCS based on the following AAPCC defined reasons: intentional use, unintentional use, adverse reaction to therapeutic use, other (malicious and contamination/tampering), and unknown reason [17]. CPCS clinicians coded the known AAPCC defined medical outcome of each exposure as no effect, minor (minimally bothersome symptoms), moderate (pronounced, prolonged symptoms), major (life-threatening symptoms), or death [17]. We defined non-severe medical outcomes as those that resulted in no effect or minor effects and severe medical outcomes as those that resulted in moderate effects, major effects, or death.

We conducted interrupted time series analyses (ITSA) of exposure counts using the "itsa" plugin for Stata® (version 15) [18]. Our outcome variables were counts of the total monthly exposures for each drug and the intervention was rescheduling. Because rescheduling was implemented on October 6, 2014, any subsequent exposures were characterized as post-intervention. For each drug and for a composite of all prescription opioids of interest, the data was plotted by time (in months) versus count of exposures along with predicted probabilities and trendlines.

Secondary outcome measures included (1) the number of exposures per drug with severe medical outcomes using ITSA, (2) odds ratios between individual-level variables and severe medical outcomes for HCP exposures, and (3) HCP exposures stratified by age (minors and adults) using ITSA. All secondary outcome measures analyzed exposures before and after rescheduling of HCPs. For (2) we calculated odds ratios using logistic regression in Stata to determine association between patient variables (minors, female, reasons for exposure of unintentional, intentional, and adverse effect) and severe medical outcomes for HCP exposures. For (1) and (2), exposures with unknown medical outcomes were excluded.

Our analysis involved multiple statistical testing, raising the risk of type I identification errors [19]. A conservative strategy to address this risk is the use of Bonferroni corrections, however this is not advised in cases where individual test outcomes are critical, where it is important to avoid the risk of type II errors, and where there are a small number of planned comparisons [19]. As these standards applied to our analysis, we assessed significance at the 0.05 level for differences in trendlines before and after intervention.

The University of California, San Francisco Institutional Review Board approved this study as exempt on February 7, 2020 (#19-29546).

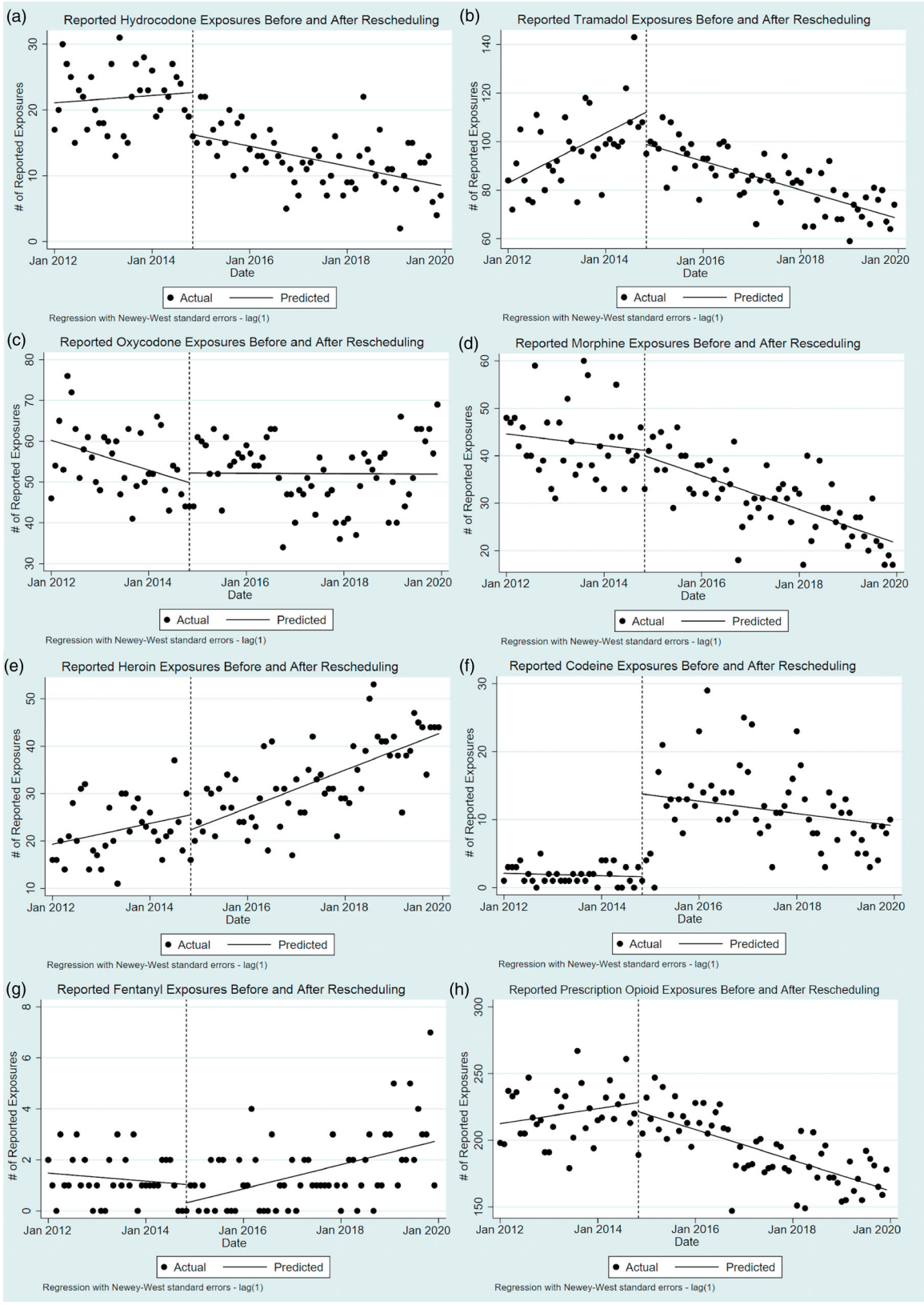

Figure 1. Interrupted time series analysis of exposures from January 2012 to December 2019. The intervention time point is the month following implementation of rescheduling. Figures show exposures over time for the following drugs of interest: (a) hydrocodone (decrease; $p < 0.001$); (b) tramadol (decrease; $p < 0.001$); (c) oxycodone (no significant change; $p = 0.95$); (d) morphine (decrease; $p < 0.001$); (e) heroin (increase; $p < 0.001$); (f) codeine (no significant change; $p = 0.15$); (g) fentanyl (increase; $p < 0.001$); (h) all prescription opioids (decrease; $p < 0.001$).

Results

We identified 8040 exposure cases in the two years prior to HCP rescheduling, and 14,131 exposure cases in the five years following the change, for a total of 22,171 exposure cases. Hydrocodone ($n = 38$) and HCP ($n = 1474$) exposures accounted for 7% of the total opioid exposure cases. In the entire sample, exposures to tramadol were most common

(38%), followed by oxycodone (23%), morphine (15%), heroin (13%), codeine (4%), and fentanyl (1%). The changes in these percentages before and after rescheduling are shown in Supplemental Table 1. After rescheduling, average monthly exposures declined for the most common exposures: hydrocodone, tramadol, oxycodone, and morphine, and increased for the least common: codeine, fentanyl, and heroin.

Following rescheduling, exposures decreased significantly (Figure 1, Table 1) for hydrocodone and HCPs, tramadol and morphine. In contrast, exposure counts increased significantly after rescheduling for heroin and fentanyl. There were no significant changes in exposures over time for oxycodone or codeine. Despite differences for individual drugs, we observed a statistically significant decline in exposures over time for all prescription opioids (all drugs of interest except heroin) combined.

For severe outcomes (Figure 2, Table 1) across all prescription opioids combined, there was no significant difference in exposures after rescheduling. Exposures to morphine resulting in severe medical outcomes decreased significantly following rescheduling. There was no change in severe medical outcomes after rescheduling for hydrocodone, tramadol or codeine. However severe medical outcomes significantly increased after rescheduling for oxycodone, heroin and fentanyl. The increase in severe outcomes for heroin and fentanyl mirrored their increase in overall exposures. However, despite a lack of significant change in overall exposures for oxycodone, exposures resulting in severe outcomes increased (Supplemental Table 2).

We reviewed the characteristics associated with severe medical outcomes for hydrocodone and HCP exposures using logistic regression and assessed whether these changed after rescheduling (Table 2). Before rescheduling, the only statistically significant association for severe outcomes was unintentional exposure [OR = 0.13; CI: 0.03,0.51]; unintentional exposures were less likely to be severe. After rescheduling, there were additional associations with severe outcomes; those who were under 18 [OR = 0.27; CI: 0.11,0.67], unintentionally exposed [OR = 0.04; CI: 0.01,0.12], intentionally exposed [OR = 0.31; CI: 0.11,0.83], or were calling to report an adverse effect after exposure [OR = 0.04; CI; 0.01,0.26] were significantly less likely to experience severe medical outcomes. A similar analysis was completed for oxycodone (Supplemental Table 3).

The third outcome examined differences in exposures for minors and adults (Figure 3). An ITSA showed that monthly exposure counts decreased significantly following rescheduling for both minors and adults. However minors were involved in significantly fewer monthly exposure cases than adults (−19.14 [CI: −22.47, −15.82]).

Additional analyses performed to determine if other factors were associated with changes in exposures can be found in the Supplement.

Discussion

Our analysis of CPCS data reviewed the counts of monthly exposures to HCPs and other opioids between 2012 and 2019 to analyze the effects of the 2014 DEA rescheduling of HCPs. We found that exposures decreased significantly after rescheduling, consistent with the intent of this regulatory change. The identified decrease in HCP exposures after rescheduling parallels findings from previous studies, which relied on a shorter follow-up period [12].

Tramadol and morphine exposures also decreased following rescheduling. Studies on prescribing patterns and Texas poison control data found an increase in both tramadol prescription rates and exposures after rescheduling [6,12]. However, our study showed a steady decrease in exposures immediately following the rescheduling, suggesting that trends may vary by state. Morphine was classified as Schedule II[2] so we cannot attribute these results to rescheduling.

Despite a decrease in HCP exposures, those of heroin and fentanyl increased. This unintended effect associated with rescheduling has been observed in previous research [20,21]. It is possible that decreased availability of prescription hydrocodone contributed to the increased use of illicit opioids.

Table 1. Slope and confidence intervals for drug exposure trend lines before and after rescheduling*.

	Before		After		
Drug	Slope	Confidence Interval	Slope	Confidence Interval	*p*-Value (Δ in trendline)
Exposures leading to all outcomes					
Hydrocodone*	0.05	−0.11, 0.20	−0.12	−0.18, −0.07	<0.001
Tramadol	0.85	0.41, 1.31	−0.49	−0.57, −0.41	<0.001
Oxycodone	−0.31	−0.62, 0.01	−0.004	−0.14, 0.13	0.95
Morphine	−0.10	−0.29, 0.09	−0.30	−0.36, −0.24	<0.001
Codeine	−0.15	−0.06, 0.03	−0.08	−0.19, 0.13	0.15
Fentanyl	−0.13	−0.05, 0.02	0.04	0.02, 0.06	<0.001
Heroin	0.18	−0.19, 0.38	0.33	0.25, 0.42	<0.001
All prescription opioids	0.47	−0.17, 1.10	−0.96	−1.19, −0.73	<0.001
Exposures leading to severe outcomes					
Hydrocodone*	−0.08	−0.18, 0.32	−0.03	−0.07, 0.0003	0.05
Tramadol	0.20	0.04, 0.35	−0.01	−0.09, 0.06	0.69
Oxycodone	−0.19	−0.33, −0.06	0.11	0.03, 0.20	0.008
Morphine	0.05	−0.07, 0.17	−0.05	−0.10, −0.01	0.02
Codeine	0.01	−0.03, 0.04	−0.01	−0.02, 0.01	0.45
Fentanyl	−0.02	−0.04, 0.13	0.02	0.01, 0.04	0.001
Heroin	0.01	−0.11, 0.12	0.12	0.06, 0.17	<0.001
All prescription opioids	−0.02	−0.28, 0.24	0.03	−0.11, 0.17	0.69

*The intervention time point was October 6, 2014.

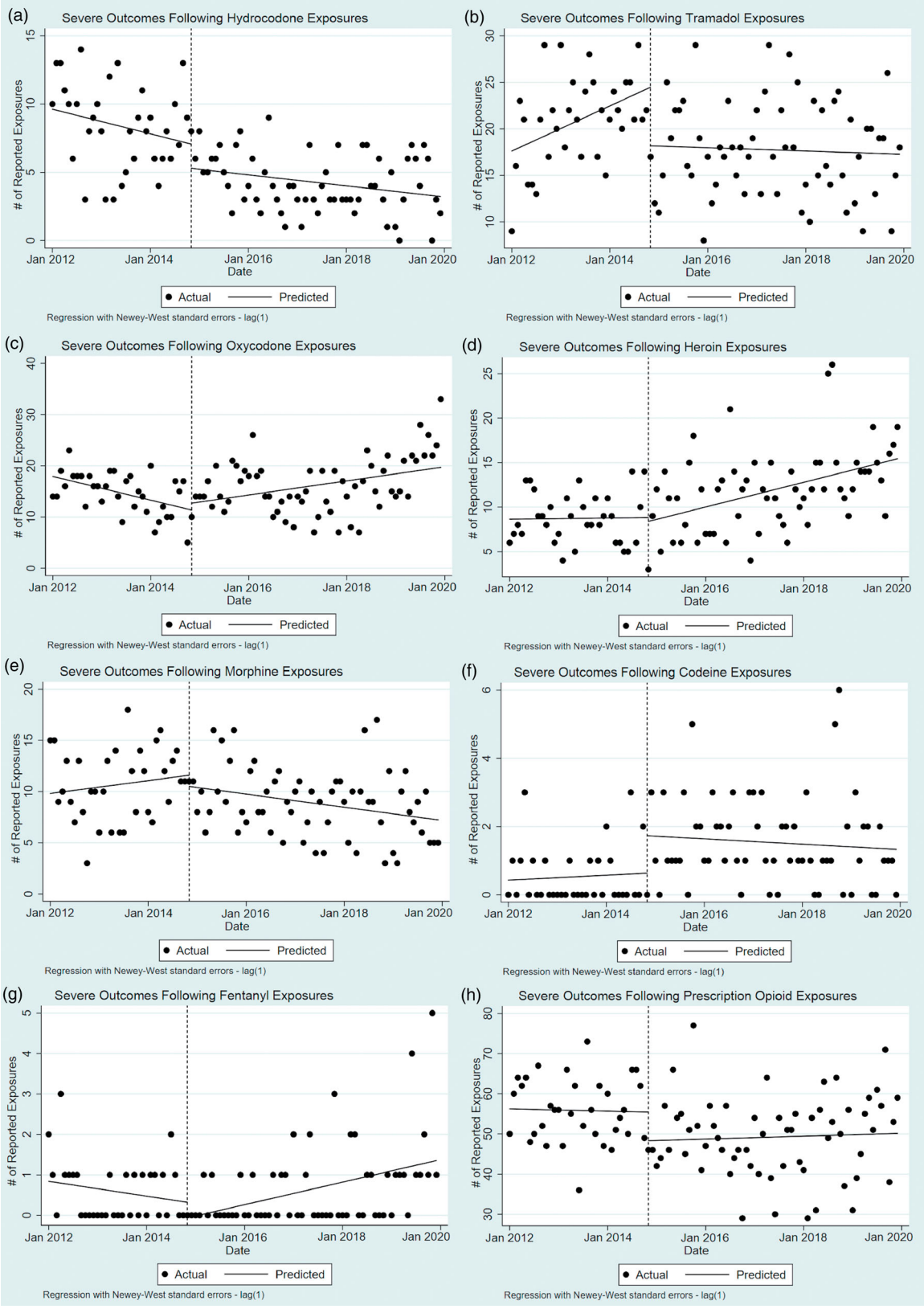

Figure 2. Interrupted time series analyses of exposures resulting in severe outcomes from January 2012 to December 2019. The intervention time point is the month following implementation of rescheduling. Figures show exposures over time for the following drugs of interest: (a) hydrocodone (no significant change; $p = 0.05$); (b) tramadol (no significant change; $p = 0.69$); (c) oxycodone (increase; $p = 0.008$); (d) heroin (increase; $p < 0.00l$); (e) morphine (decrease; $p = 0.02$); (f) codeine (no significant change = 0.45); (g) fentanyl (increase; $p = 0.001$); (h) all prescription opioids (no significant change; $p = 0.69$).

Heroin and fentanyl were increasingly available illicitly beginning in 2014 [21], which may also have contributed to increased exposures.

There were no significant changes in oxycodone and codeine exposures after rescheduling. Immediately after rescheduling, we observed a short-term increase in

Table 2. Analyzing different variables' effect on severe outcomes from HCP exposure.

	Before rescheduling			After rescheduling		
Variables	Odds ratio	Confidence interval	*p*-Value	Odds ratio	Confidence interval	*p*-Value
Minor	0.71	0.33, 1.55	0.39	0.27**	0.11, 0.67	0.01
Female	1.04	0.76, 1.43	0.81	0.92	0.67, 1.26	0.62
Reason for exposure: unintentional	0.13**	0.03, 0.51	0.003	0.04**	0.01, 0.12	<0.001
Reason for exposure: intentional	0.94	0.28, 3.13	0.93	0.31*	0.11, 0.83	0.02
Reason for exposure: adverse effects	0.27	0.06, 1.20	0.09	0.04**	0.01, 0.26	0.001

Odds ratios determined from logistic regressions demonstrating the likelihood of various risk factors contributing to exposures. Significance of odds ratio determined by $^{*}p < 0.05$ and $^{**}p < 0.01$. Other comparison groups not included in "Reason for exposure" include "unknown" and "other."

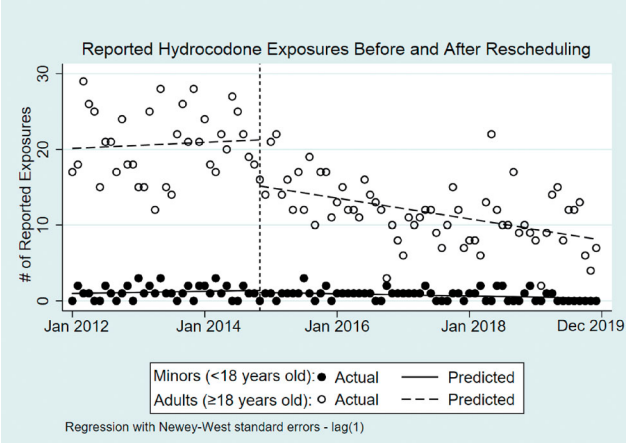

Figure 3. Interrupted times series analysis of hydrocodone exposures before and after rescheduling for minors and adults. The time period was from January 1, 2012 to December 31, 2019. The intervention time point was the implementation of the rescheduling (October 6, 2014). The statistical significance of the slopes before and after rescheduling were determined by calculating the *p*-value. The *p*-value for minors and adults was 0.02 and <0.001, respectively.

exposures to codeine, consistent with previous research [12]. Although average monthly exposures increased following rescheduling (likely due to an increase in codeine prescriptions [6]) we observed a downward trend in codeine exposures over time.

In addition to overall opioid exposures, we examined severe outcomes to provide more insight about the public health impact of rescheduling. Our findings were not consistent across all alternatives; there was a significant decrease in morphine exposures and no changes for HCPs, tramadol, and codeine. Oxycodone, heroin, and fentanyl all showed significant increases in severe exposures. Previous research has identified an increase in illicit sales of these more potent opioids following rescheduling [20]. All prescription opioids analyzed together as a group showed no significant changes for severe outcomes.

Despite HCPs constituting only 7% of all exposures (Supplemental Table 1), they represented 36% of all severe outcomes over the entire period (Supplemental Table 4). We considered factors that were associated with HCP exposures leading to severe outcomes and found that after rescheduling, severe outcomes were less likely for minors, those unintentionally exposed, those intentionally exposed, and those whose exposure was an adverse effect of therapeutic use. These findings suggest that severe outcomes, including intentional overdoses, became less problematic for certain groups, such as minors and those intentionally exposed, both of which demonstrated the largest changes in odds ratios post-intervention. One possible explanation for this finding is that rescheduling may have decreased accessibility to HCPs by prohibiting refills, making it more difficult to obtain large quantities of pills.

Finally, we examined the effect of rescheduling on HCP exposures in different age groups: minors and adults, finding that exposures significantly decreased for both minors and adults. Because rescheduling is intended to decrease access by reducing circulation of HCPs, it is possible that minors may have had less access from adults (family members or friends). Overall, rescheduling appears to have been beneficial, as it was associated with decreased HCP exposures for both age groups.

Overall our findings suggest that short follow-up periods in previous studies may have hidden the effects of rescheduling. We considered all five years after policy implementation and found that HCP exposures continued to decline, as did exposures from all opioid alternatives together, suggesting that the policy was associated with decreased exposures through prolonged impact.

Our study has limitations. Data were drawn from the poison control system of only one state, California, which limited the sample size and may affect generalizability at the national level. Like all poison control data, the number of observed exposures does not represent actual exposures because data came only from individuals who called CPCS. Additionally, reported exposures are rarely confirmed through laboratory follow-up. Although we found an association between rescheduling and decreased exposures, these findings are not necessarily causal, given that other national (Prevention for States) and statewide (Statewide Opioid Safety Workgroup, Naloxone Grant Program) initiatives intended to reduce overdoses have been implemented since 2014 [22] and may have contributed to the decrease in exposures. Because both single-substance and multiple-substance exposures were analyzed, the drug contributing most to outcome severity could not be identified. Our analysis of severe medical outcomes could only identify associations and more detailed review may be necessary to determine specific drugs responsible for severe outcomes. Despite these limitations, we found that rescheduling was associated with reduced exposures, suggesting it may be a useful strategy in efforts to reduce overdoses.

Conclusions

Rescheduling hydrocodone-containing products was associated with a decrease in exposures to prescription opioids

reported to CPCS. Despite recent efforts to curb the increasing numbers of opioid-related deaths, the opioid crisis has continued to claim lives [23]. Our findings suggest that rescheduling may contribute to reducing prescription opioid exposures. Future research could investigate associations between this regulatory change and severe outcomes and whether the same effect was observed in other states that did implement other interventions.

Implications

We found that changing HCPs from Schedule III to II was associated with reduced exposures. However, the continuing high rates of opioid misuse and increase in fentanyl and heroin exposures suggest that further interventions are needed to decrease exposures. Our results suggest that rescheduling may be a policy intervention worth investigating if policymakers seek to decrease exposures to other drugs with overdose potential; one example is benzodiazepines (Schedule IV), which were involved in 10,724 overdose deaths in 2018, 85% of which involved concomitant opioid use [23]. Overall, our results suggest rescheduling was associated with its intended outcomes, although further interventions may be needed to further reduce overdoses.

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Disclosure statement

The authors declare they have no actual or potential competing financial interests.

Author contributions

All authors worked together to design the study, analyze the data, interpret the results, and revise the manuscript. KN, CP, MQ, and AW drafted the manuscript, JL collected CPCS data, DA conducted interrupted time series analysis, and AW prepared the figures.

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Data availability statement

Data for replication can be obtained by recruiting a collaborator employed by California Poison Control System (CPCS) and submitting a Data Request Form to the CPCS.

References

[1] Warner M, Trinidad JP, Bastian BA, et al. Drugs most frequently involved in drug overdose deaths: United States, 2010–2014. Natl Vital Stat Rep. 2016;65(10):1–15.
[2] Drug Scheduling. [cited 2020 May 11]. Available from: https://www.dea.gov/drug-scheduling
[3] DEA To Publish Final Rule Rescheduling Hydrocodone Combination Products. [cited 2020 May 11]. Available from: https://www.dea.gov/press-releases/2014/08/21/dea-publish-final-rule-rescheduling-hydrocodone-combination-products
[4] Tran S, Lavitas P, Stevens K, et al. The effect of a federal controlled substance act schedule change on hydrocodone combination products claims in a medicaid population. JMCP. 2017;23(5):532–539.
[5] DEA Final Rule Rescheduling Hydrocodone Combination Products; 2014. Available from: https://www.asahq.org/-/media/sites/asahq/files/public/advocacy/federal-activities/regulatory-activities/pain-medicine/rescheduling-hydrocodone-products.pdf.
[6] Seago S, Hayek A, Pruszynski J, et al. Change in prescription habits after federal rescheduling of hydrocodone combination products. Proc (Bayl Univ Med Cent). 2016;29(3):268–270.
[7] Shumway JW, Ran R, McClusky J, et al. Impact of rescheduling hydrocodone-combination products in an urban Texas county healthcare system. J Opioid Manag. 2018;14(4):257–264.
[8] Liu Y, Baker O, Schuur JD, et al. Effects of rescheduling hydrocodone on opioid prescribing in Ohio. Pain Med. 2019. DOI:10.1093/pm/pnz210
[9] Kuschel LM, Mort JM. Impact of the hydrocodone schedule change on opioid prescription patterns in South Dakota. S D Med. 2017;70(10):449–455.
[10] Raji MA, Kuo Y-F, Adhikari D, et al. Decline in opioid prescribing after federal rescheduling of hydrocodone products. Pharmacoepidemiol Drug Saf. 2018;27(5):513–519.
[11] Harrison ML, Walsh TL. The effect of a more strict 2014 DEA schedule designation for hydrocodone products on opioid prescription rates in the United States. Clin Toxicol (Phila). 2019;57(11):1064–1072.
[12] Haynes A, Kleinschmidt K, Forrester MB, et al. Trends in analgesic exposures reported to Texas Poison Centers following increased regulation of hydrocodone. Clin Toxicol (Phila). 2016;54(5):434–440.
[13] Brady KT, McCauley JL, Back SE. Prescription opioid misuse, abuse, and treatment in the United States: an update. Am J Psychiatry. 2016;173(1):18–26.
[14] American Association of Poison Control Centers (AAPCC) - Notes About Poison Control Data. [cited 2020 May 11]. Available from: https://aapcc.org/datainfo
[15] Critical appraisal of extended-release hydrocodone for chronic pain: patient considerations. [cited 2020 May 11]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4622415/
[16] Choy M. Pharmaceutical approval update. Pharm Ther. 2017;42(4):235–255. [cited 2020 May 11]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5358679/
[17] American Association of Poison Control Centers. 2019. National Poison Data System (NDPS) Coding User's Manual Version 4.1 (April 16). Available from: https://bezoar.georgiapoisoncenter.org/wp-content/uploads/2014/07/NPDS-2019.pdf
[18] Linden A. Conducting interrupted time-series analysis for single- and multiple-group comparisons. Stata J. 2015;15(2):480–500.
[19] Armstrong RA. When to use the Bonferroni correction. Ophthalmic Physiol Opt. 2014;34(5):502–508.
[20] Martin J, Cunliffe J, Décary-Hétu D, et al. Effect of restricting the legal supply of prescription opioids on buying through online illicit marketplaces: interrupted time series analysis. BMJ. 2018;361:k2270.
[21] Beletsky L, Davis CS. Today's fentanyl crisis: Prohibition's Iron Law, revisited. Int J Drug Policy. 2017;46:156–159.
[22] California's Activities. [cited 2020 May 11]. Available from: https://www.cdph.ca.gov/Programs/CCDPHP/DCDIC/SACB/Pages/CaliforniasStrategiesAndActivities.aspx
[23] National Institute on Drug Abuse. Overdose Death Rates. [Published 2020 Mar 10; cited 2020 May 11]. Available from: https://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates