Chronic and Sustained High-Dose Opioid Use in an Integrated Health System

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Introduction: The Centers for Disease Control and Prevention Guideline for Prescribing Opioids for Chronic Pain released in 2016 had led to decreases in opioid prescribing. This study sought to examine chronic and sustained high-dose prescription opioid use in an integrated health system.

Methods: A serial cross-sectional study was conducted in 2021 to estimate the annual age-adjusted prevalence and incidence of chronic and high-dose opioid use among demographically diverse non-cancer adults in an integrated health system in Southern California during 2013–2020. Interrupted time-series analysis with segmented regression was conducted to estimate changes in the trends in annual rates before (2013–2015) and after (2017–2020) the 2016 guideline, treating 2016 as a wash-out period.

Results: Prevalence and incidence of chronic use and sustained high-dose use had started to decrease after a health system intervention program before the 2016 Centers for Disease Control and Prevention guideline release and continued to decline after the guideline. Among those with sustained high-dose use, there was a substantial decrease in persons with an average daily dosage ≥90 morphine milligram equivalent and concurrent benzodiazepine use. An accelerated decrease in prevalent chronic use after the guideline was observed (slope change: −11.1 [95% CI= −20.3, −1.9] users/10,000 person-years, p=0.03). The incidence of chronic use and sustained high-dose use continued to decrease after the guideline release but at a slower pace.

Conclusions: Implementing evidence-based prescribing guidelines was associated with a decrease in chronic and sustained high-dose prescription opioid use.

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INTRODUCTION

Although opioid analgesics are effective for alleviating pain in the short term,1,2 the effectiveness of opioids for chronic noncancer pain (i.e., pain lasting longer than 3–6 months) remains controversial.3–5 Some patients using opioids in the long term may continue to have moderate-to-severe pain and diminished quality of life.4,6 In addition, the development of opioid tolerance that leads to dose escalation in long-term opioid therapy might cause opioid-induced hyperalgesia, resulting in exacerbation of pain sensation rather than relief.7–9 The long-term use of opioid for chronic noncancer pain has been associated with increases in aberrant drug behavior (misuse, drug diversion, dependence, and addiction) and opioid overdoses.10–12 After a steady increase in the national opioid dispensing rate starting in 2006, the total number of prescriptions dispensed peaked in 2012; total opioid
prescriptions have decreased by 44.4% between 2011 and 2020, including a 6.9% decrease from 2019 to 2020. In recent years, the substance use crisis in the U.S. has rapidly evolved, with increasing overdose deaths associated primarily with synthetic opioids and intensifying poly-substance use.14,15

The ongoing opioid epidemic in the U.S. has raised concerns among clinicians and healthcare systems regarding the benefit of long-term opioid use for chronic pain versus serious risks of opioid use disorder and overdose—particularly associated with high opioid dosages12 and concurrent use of sedatives—hypnotics, including benzodiazepines.16,17 The Centers for Disease Control and Prevention (CDC) released the Guideline for Prescribing Opioids for Chronic Pain in March 2016 (referred to as CDC 2016 guideline in the remaining parts of this paper). This guideline cautions against daily dosages above 50 morphine milligram equivalents (MMEs) and advises avoidance of daily dosages ≥90 MME and concurrent sedative–hypnotic prescription for patients taking long-term opioids.18 Several studies found a significant decrease in days’ supply and high dosage (≥50 MME) in the initial prescriptions for chronic pain after CDC 2016 guideline release19,20 and decreased opioid dosage in the first prescription after general and orthopedic surgical procedures.21 However, these studies focused on changes in healthcare provider prescribing behavior without directly measuring the pharmacy dispensing record to estimate patient-level changes in chronic and sustained high-dose opioids use.

Many health systems have taken steps to help clinicians better manage patients with noncancer chronic pain to reduce potential adverse consequences from long-term opioid therapy. From 2010 through 2015, the Safe and Appropriate Opioid Prescribing Program, a comprehensive clinically driven system-level intervention targeting chronic and high-dose opioid therapy across multiple care settings, was introduced in Kaiser Permanente Southern California (KPSC), a Region of the Kaiser Permanente system, a large integrated health system. The details of the multipronged intervention and the short-term outcomes of opioid prescribing practice were reported by Losby et al.22 In mid-2016 after CDC 2016 guideline release, the stepwise intervention further incorporated an ongoing opioid and pain management clinician education program, a prescriber-guided tapering plan and tapering guide, a quality peer review process for high-dose opioid prescribing, and clinician approved opioid prescribing practice recommendations.

This study sought to evaluate the impact of the KPSC’s system-level intervention and the integration of CDC 2016 guidelines by examining the trends in chronic and sustained high-dose prescription opioid use among adults treated for noncancer pain. The findings from the real-world data may inform future policy and guidelines for addressing the opioid epidemic.

METHODS

Study Population

A serial cross-sectional analysis was conducted to assess the annual prevalence and incidence of chronic and sustained high-dose opioids use among adults in KPSC from 2013 to 2020 using comprehensive electronic health record databases. KPSC provides integrated preventive and medical care to >4.7 million members enrolled in commercial health plans as well as through Medicare and Medicaid and State health insurance programs for low-income populations. Data indicate that Kaiser Permanente members are demographically diverse and very similar to the local and statewide population, with slight under-representation of those in lower and higher income and education categories.23

Adults (aged ≥18 years) with at least 1-day health plan coverage in each calendar year were included. Those with a cancer diagnosis and in hospice or palliative care before January 1 were excluded from each year’s analysis, and observation was censored at the earliest date of a cancer diagnosis, receipt of hospice or palliative care, death, or membership disenrollment. This method excludes patients with a history of cancer who may have been using opioids for noncancer pain as well as patients using opioids for cancer pain. Buprenorphine and naltrexone combination products and opioids not dispensed as tablets, capsules, or transdermal patches were excluded to minimize the capture of cough syrups and other products not indicated for pain.

Measures

KPSC electronic health record databases include information on age, sex, race/ethnicity, pharmacy files, and medical encounter data for all covered services, including services provided directly by the health plan and outside utilization billed through claims. The pharmacy files contain dispense records, including generic drug name, strength, directions for use, date dispensed, quantity dispensed, days’ supply, prescriber identification number, and the National Drug Code (NDC) identification number.

To account for multiple consecutive prescriptions, continuous opioid therapy episodes were constructed using medication sold dates and days’ supply documented in the pharmacy database. Gaps in supply ≤15 days between prescriptions were considered part of the same episode. Medication overlaps because of prescriptions filled early were added to the end of the following prescription. Patients were defined as chronic opioid users if they had at least 1 continuous opioid therapy episode with ≥90 days’ supply.24,25 Among chronic users, those who newly met the criteria for chronic opioid use (i.e., without a history of chronic use) were considered incident chronic opioid users.

The average daily morphine-equivalent dose for each therapy episode was calculated using CDC oral MME conversion factors on the basis of the drug’s NDC.26,27 Specifically, opioid dosage strength was obtained by referencing the NDC and CDC Oral MME Conversion File provided. Prescriptions with a missing
NDC number were identified in the Food and Drug Administration’s NDC Directory and assigned a conversion factor equal to an exact medication match from the CDC conversion file. Differential conversion factors according to the dose of the medication were used for methadone. An as-prescribed approach was used to convert the drug dosage to a daily MME dosage defined as daily MME= MME Conversion x dosage x (quantity dispensed/days supplied).

The duration of 183 days was chosen to account for autocorrelation was performed to evaluate the users.

Interrupted time-series analysis with segmented regression was performed to evaluate the impact of integration of the CDC 2016 guideline on the trend changes. Owing to expected lag in implementing the 2016 CDC guideline in clinical practice, the change in slope of annual rates before and after 2016 (2013–2015 versus 2017–2020) were compared, treating 2016 as a wash-out period.

Among patients with chronic opioid use, a subset of sustained
high-dose opioid users was defined as those who consistently had a daily dose ≥50 MME for ≥183 days. This cut off value of 50 MME for defining high-dose opioid use was derived from the CDC 2016 guideline. The duration of 183 days was chosen to define sustained use on the basis of the authors’ clinical experience. Patients who remain on high-dose for 6 months are considered at substantial risk for developing dependency and should be prioritized for dose reduction. Among patients with incident sustained high-dose opioid use (i.e., without a previous history of sustained high-dose use), concurrent use of sedative–hypnotics was evaluated, including benzodiazepines, gabapentinoids, muscle relaxants, and sleep aids (Appendix Table 1, available online), defined as a cumulative duration of overlap ≥30 days of these medications with prescription opioids.

Statistical Analysis
Age-adjusted annual prevalence and incidence of chronic opioid use and sustained high-dose use per 10,000 person-years and 95% CI were calculated by direct standardization using the 2010 U.S. Census population. Because national surveillance data showed that annual average prescription pain reliever misuse differed by sex and race/ethnicity during 2015–2019, this study also assessed the trends stratified by sex and race/ethnicity. The distribution of average daily MME and concurrent use of sedative–hypnotics were examined among incident sustained high-dose opioid users.

Interrupted time-series analysis with segmented regression accounting for autocorrelation was performed to evaluate the impact of integration of the CDC 2016 guideline on the trend changes. Owing to expected lag in implementing the 2016 CDC guideline in clinical practice, the change in slope of annual rates before and after 2016 (2013–2015 versus 2017–2020) were compared, treating 2016 as a wash-out period.

RESULTS
Between 2013 and 2020, there were 88,552 adults with chronic opioid use (57.7% female) among 5,862,950 adult enrollees (50.4% female). Prevalent chronic opioid users increased each year slightly between 2013 and 2016, followed by a steady decline after 2016. The number of incident chronic opioid users declined by 72.6%, from 11,821 in 2013 to 3,239 in 2020 (Figure 1). The proportion of sustained high-dose opioid users among chronic opioid users decreased from 34% in 2013 to 18% in 2020. This decreasing trend was more prominent in the proportion of incident sustained high-dose users (36% in 2013 vs 9% in 2020).

The age-adjusted prevalence and incidence of chronic opioid use both declined steadily (Figure 2). The prevalence declined by 40.6%, from 162.3 (95% CI=160.7, 164.0) to 96.4 (95% CI=95.3, 97.5) users per 10,000 person-years; the incidence declined by 79.3%, from 50.8 (95% CI=49.9, 51.8) to 10.5 (95% CI=10.2, 10.9) users per 10,000 person-years. Profound decreases were observed in age-adjusted prevalence and incidence of sustained high-dose opioid use (Figure 3), with the prevalence declining by 68.2% from 54.4 (95% CI=53.5, 55.4) to 17.3 (95% CI=16.9, 17.8) per 10,000 person-years and the incidence declining by 95.0% from 18.1 (95% CI=17.5, 18.6) to 0.9 (95% CI=0.8, 1.0) users per 10,000 person-years. The declining trends in the incidence of chronic opioid use were similar in females and males (Appendix Table 2, available online). By the end of 2020, the incidence of sustained high-dose opioid use was approximately the same for males and females. Non-Hispanic White patients had the highest prevalence and incidence of chronic opioid use as well as of sustained high-dose opioid use, followed by non-Hispanic

Table 1. Interrupted Time-Series Analysis on the Change in Trends Among Opioid Users Between 2013–2015 and 2017–2020

<table>
<thead>
<tr>
<th>Opioid users</th>
<th>Average annual rates change, users per 10,000 person-years (95% CI)</th>
<th>Difference in slope change, Users per 10,000 person-years (95% CI)</th>
<th>p-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalent chronic opioid users</td>
<td>−3.1 (−10.9, 4.63)</td>
<td>−11.1 (−20.3, −1.9)</td>
<td>0.03</td>
</tr>
<tr>
<td>Incident chronic opioid users</td>
<td>−5.8 (−8.3, −3.3)</td>
<td>1.3 (−1.6, 4.3)</td>
<td>0.2</td>
</tr>
<tr>
<td>Prevalent sustained high-dose opioid users</td>
<td>−4.7 (−7.3, −2.1)</td>
<td>−1.4 (−4.5, 1.7)</td>
<td>0.3</td>
</tr>
<tr>
<td>Incident sustained high-dose opioid users</td>
<td>−4.6 (−6.3, −2.9)</td>
<td>3.5 (1.4, 5.5)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Note: Boldface indicates statistical significance (p<0.05).
Figure 1. Number of prevalent and incident chronic opioid users and proportion of patients with sustained high-dose use, 2013–2020.

Note: Chronic opioid users are defined as those who have taken opioids continuously for >90 days. Sustained high-dose opioid users are a subgroup of chronic users who have taken a daily dose ≥50 MME for a continuous opioid therapy episode of 183 days or longer. The percentage refers to the proportion of sustained high-dose opioid users among chronic opioid users.

MME, morphine milligram equivalent.

Figure 2. Trends in age-adjusted prevalence and incidence of chronic opioid users by race/ethnicity, 2013–2020.

Note: Chronic opioid users are defined as those who have taken opioids continuously for >90 days. Incident chronic opioid users are defined as those who have taken opioids continuously for >90 days and with no history of chronic prescription opioid use.
Black and Hispanic patients, and Asian patients had the lowest prevalence and incidence (Figures 2 and 3). The prevalence and incidence of chronic opioid use and sustained high-dose opioid use declined in all race/ethnicity groups, with the steepest decline among non-Hispanic White patients. Of note, the differences in the incidences by race/ethnicity were substantially diminished in 2020 compared with that in 2013.

Among incident sustained high-dose opioid users, the proportion of older adults and those with Medicaid coverage increased over time, which was likely because of the Affordable Care Act expansion in 2014. The race/ethnicity distribution remained largely stable over time, with the majority being non-Hispanic White (Appendix Table 3, available online). The proportion of those receiving a daily dosage ≥90 MME declined by more than half between 2013 and 2020, with a more prominent reduction in those with a daily dosage ≥150 MME (Appendix Table 3, available online). Concurrent use of benzodiazepines also decreased from 38.1% in 2013 to 12.9% in 2020 among the incident sustained high-dose opioid users. However, concurrent use of gabapentinoids had an over twofold increase from 17.3% to 42.0%. Concurrent use of muscle relaxants increased slightly from 29.2% to 34.0%, and concurrent use of sleep aids decreased from 10.7% to 3.5%.

The decreasing trend in the prevalence of chronic opioid use started before 2016 in the study period, with an average annual change of $-3.1 (95\% \text{ CI} = -10.9, 4.63)/10,000 \text{ person-years during 2013} - 2015$, whereas the decline accelerated considerably after the CDC 2016 guideline release, with an average annual change of $-14.2 (95\% \text{ CI} = -19.1, -9.3)/10,000 \text{ person-years during 2017} - 2020$ (Table 1). In the interrupted time-series analysis, there was a statistically significant slope change for the trend in the prevalence of chronic opioid use between the pre and postguideline periods (slope change: $-11.1 [95\% \text{ CI} = -20.3, -1.9] \text{ users/10,000 person-years per year, } p=0.03$) (Table 1). A similar accelerated decline in the prevalence of sustained high-dose opioid use was observed; however, the slope change was not statistically significant ($p=0.3$). Although both the incidence of chronic opioid use and sustained high-dose opioid use decreased steadily over time, there was no evidence of accelerated decline during the postguideline period.

**DISCUSSION**

Both the prevalence and incidence of chronic and sustained high-dose opioid use declined steadily between 2013 and 2020. The decrease before CDC 2016 guideline
release was expected after the comprehensive KPSC system-level interventions to reduce long-term high-dose opioid therapy for noncancer pain. The declining trends in the number of chronic and sustained high-dose opioid users and age-adjusted prevalence and incidence likely reflect the efforts in tapering existing high-dose chronic opioid use, tapering opioids in patients on concurrent opioids and sedatives– hypnotics, as well as prescribing behavior changes in treating new patients. It is notable that the decline in the prevalence and incidence of sustained high-dose use was even steeper, and the proportion of patients receiving very high dosage and concurrent benzodiazepines also decreased substantially over time. These findings are consistent with the U.S. trends in opioid dose tapering among patients prescribed long-term higher doses of opioids and changes in the number of opioid prescriptions and prescribing patterns observed in other settings. Although a recent cohort study of commercially insured adults without cancer or hospice care found an accelerated decreasing trend in high-dose opioid prescribing after the CDC 2016 guideline release, there was no accelerated decline in incident chronic opioids use or sustained high-dose use in this study population.

Racial/ethnic differences were observed in both chronic opioid use and sustained high-dose opioid use in this integrated health system. Non-Hispanic White patients bear the highest burden of chronic opioid use and sustained high-dose opioid use than patients of other races/ethnicities. This finding is consistent with those of previous studies that reported that racial minorities were less likely to receive prescription opioids for chronic pain than non-Hispanic White patients. Furthermore, recent data from a national sample of patients in 310 health systems indicated that non-Hispanic White patients received markedly more morphine-equivalent opioid doses than non-Hispanic Black patients. Although both the prevalence and incidence of chronic opioid use remained the highest among non-Hispanic White patients across the study period, the most profound declines in both prevalence and incidence were also observed among non-Hispanic White patients. By the end of 2020, the racial/ethnic differences in the incidence of chronic opioid use, particularly in sustained high-dose use, were diminished substantially. These findings suggest that the risk of unsafe prescription opioid use and associated adverse consequences by race/ethnicity may be mitigated over time.

Moreover, there was also a substantial decreasing trend in daily dosage ≥90 MME and concurrent use of benzodiazepines among patients with sustained high-dose opioid use. These findings were consistent with the CDC 2016 guideline regarding the avoidance of high opioid dosage and concurrent prescription of sedative– hypnotic medications in long-term opioid users. The current findings are similar to those from a study using national pharmacy data to evaluate the reduction in high-dosage opioid therapy and overlapping prescription of benzodiazepines after 2016. The observed increase in concurrent use of gabapentinoids and muscle relaxants may reflect a trend in replacing opioids with these medications in pain management, especially when there are more restrictions on high-dose opioid prescribing and aggressive titration of opioids.

Decreased dosage of prescription opioids and decline in benzodiazepines coprescription are intended to decrease overdose risk. However, there is emerging evidence suggesting that patients are at increased risk of opioid overdose, substance use disorder, or suicide after discontinuation of opioid treatment and that the risk increases with the length of opioid treatment before discontinuation. Although these findings raise questions about the potential harms of tapering, interpretation is limited by the observational study design. The associations observed in previous studies cannot be assumed to be causal because the context in which opioid prescriptions were discontinued might contribute to risk and was not investigated. Future cohort studies with information on the context of opioid dose reduction and measures of function may help to delineate the causal relationship between rapid tapering or discontinuation of prescription opioid use and patient-reported outcomes. Future studies need to focus on unintended adverse effects on pain management and function, quality of life, and the likelihood of synthetic opioids and other illicit drug substitution and associated harms.

Limitations
This observational study is subject to several limitations. First, pharmacy dispensing records were used to estimate the duration of opioid use and calculate morphine-equivalent dosage assuming that medications were taken as prescribed without measures of actual opioid ingested, opioids were obtained through other means, or chronic use was initiated before the membership enrollment. Therefore, opioid therapy episodes could be misclassified, and dosage might be overestimated or underestimated. Second, prescriptions received outside of the health system may be missed if claims were not filed. Although most patients are on pre-paid health plans and are financially incentivized to use the pharmacies within the health system and file claims for health services received elsewhere, it is possible some patients may obtain prescription opioids through another insurance or family members and friends or may opt to pay cash...
for prescriptions without the claims process—potentially leading to an underestimate of chronic opioid use and dosage. Third, because data on the type of pain and comorbidity were not collected in this analysis, therefore stratified analysis by pain type or comorbidities that may affect the risk of substance use disorder such as depression was not conducted. Fourth, this study examined chronic opioid use among insured patients in a large integrated health system, thus generalizability to other systems or patients without insurance may be limited. Finally, federal regulatory agencies (such as the Centers for Medicare & Medicaid Services) and pharmacy quality rating agencies (including National Committee for Quality Assurance and Pharmacy Quality Alliance) created care quality metrics after the 2016 CDC guideline was released. Other statewide policies targeting the prescription of controlled substances might have also influenced prescribing behavior during the study period. Effective from October 2, 2018, California’s Prescription Drug Monitoring Program set forth the mandatory requirements for healthcare practitioners to consult the California Controlled Substance Utilization Review and Evaluation System before prescribing, ordering, administering, or furnishing a Schedules II–IV controlled substance for a patient. These regulatory actions in the U.S. and the State of California may have helped to reinforce the intervention effect on reducing excessive opioid prescriptions.

CONCLUSIONS

Chronic prescription opioid use and particularly sustained high-dose opioid use declined steadily after the implementation of a comprehensive system-level intervention for safer opioid prescribing, and the declining trend accelerated in the prevalence of chronic opioid use after the integration of the CDC 2016 guideline. Implementing evidence-based local policies and adopting national guidelines can lead to a sustained decline in chronic and sustained high-dose opioid use and has the potential to reduce opioid-related harm.

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SUPPLEMENTAL MATERIAL

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REFERENCES


