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High-risk opioid prescribing trends in the outpatient setting prior to issuance of federal guidance

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ABSTRACT

Co-prescription of opioid and benzodiazepine products increases the risk of overdose-related mortality four-fold due to respiratory depression. Accordingly, prevention of high-risk opioid prescribing (HROP) has become a focus over the past two decades and was the subject of a black-box warning (BBW) issued by the U.S. Food and Drug Administration (FDA) on August 31, 2016. Because older patients are at increased risk for these outcomes, we compared rates of HROP for older (aged ≥65 years) and younger (aged 18–64 years) adults using a repeated cross-sectional cohort design. Data from the National Ambulatory Medical Care Survey of U.S. office-based physician visits were accessed for 2006–2016 August. From 2006 to 2016, the opioid-prescribing rate increased by 40% among those aged 18–64 years and by 54% among those aged ≥65 years. From 2012–2013 to 2014–2016, the HROP rate, expressed as a proportion of all opioid-prescribing visits, increased to 26.6% among those aged 18–64 years but declined to 21.0% among those aged ≥65 years, primarily because of changes for patients aged ≥75 years. Prior to the FDA-issued BBW, the HROP prescribing rate trended upward for all adults, except in 2014–2016 when it began to decline among older adults.

1. Introduction

Prevention of opioid overdose-related mortality has become a key target of public health promotion in the past two decades due to rapid increases in use and misuse of both prescribed and/or illicit opioids (Centers for Disease Control and Prevention, 2018; Guy et al., 2017; Kanouse and Compton, 2015). The rate of opioid overdose-related mortality increases up to 4-fold with co-prescribed benzodiazepines, primarily because the risk of respiratory depression, which is independently associated with each medication, is compounded when the two are co-administered (Jones and McAninch, 2015; Park et al., 2015; Sun et al., 2017). Given this risk, on August 31, 2016, the U.S. Food and Drug Administration (FDA) announced requirements for a "black box" warning. This warning is included in the prescribing information for all benzodiazepine- or opioid-containing products to alert prescribers of the serious risk of respiratory depression and death from opioid-benzodiazepine co-prescription. The warning suggests prescribing this combination only if necessary, for a limited duration, at a limited dose, only if alternative treatment options are unavailable, and with close monitoring (U.S. Food and Drug Administration, 2016).

Even before the FDA warning was issued, trends in opioid-benzodiazepine co-prescription may have begun to decline, but evidence on this point is inconsistent. One analysis of office visits made by adults aged ≥20 years for pain-related conditions found that the rate of opioid co-prescription in patients using benzodiazepines, measured per 1000 persons, increased by 86% from 189 in 2005 to 351 in 2010, and declined thereafter to 172 in 2015 (Ladapo et al., 2018). However, another study using the same data source and measuring opioid-benzodiazepine co-prescription in adults aged 18–64 years making an office visit for pain-related conditions found a relatively steady rate of increase from 9.8 per 10,000 visits in 1993 to 62.5 per 10,000 visits in 2014 (Hirschtritt et al., 2018).

Whether this difference in findings reflects the inclusion of older adults in the study by Ladapo et al. but not that of Hirschtritt et al. is an important question, because the morbidity and mortality risks associated with opioid-benzodiazepine co-prescription are elevated in patients aged ≥65 years. In one study of emergency visits made for co-prescribed opioid-benzodiazepine from 2005 to 2011, patients aged ≥65 years had the highest predicted risk of hospital admission or death compared with patients in younger age groups (Substance Abuse and

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Mental Health Services Administration, 2014). Opioid-benzodiazepine combined misuse also increases the risk of suicidal ideation in older adults (Schepis et al., 2019). Because of these risks, the generally limited base of evidence about the prevalence and predictors of opioid-benzodiazepine misuse by older adults has been identified as an important gap in the literature (Maree et al., 2016), and our more recent search of the literature on medication use by older adults supports this viewpoint (Hirschtritt et al., 2018; Ladapo et al., 2018).

In addition to addressing this gap in information about older adults, the present study was conducted to expand the surveillance of high-risk opioid prescribing (HROP) in two ways. First, the study included barbiturates and hypnotics in the definition of HROP because opioid-related respiratory depression risk may be increased by central nervous system depressants other than benzodiazepines (Paulozzi et al., 2012; National Institute on Drug Abuse, 2018). Second, all opioid-treated patients, rather than only those with pain-related diagnoses, were included in the present study sample to inform prevention initiatives by providing information about population-level prevalence and predictors of HROP. The study examined trends in opioid and HROP over the ten-year period beginning in 2006, comparing rates of use in cohorts of patients aged 18–64 years and ≥65 years. Additionally, the study assessed predictors of HROP in 2014 through the first 8 months of 2016, the 32-month time period preceding the FDA black-box warning.

2. Materials and methods

2.1. Data source

Study data were obtained from the National Ambulatory Medical Care Survey (NAMCS), a nationally representative assessment of care provided in office visits made to non-federally employed U.S. physicians, which is conducted annually by the National Center for Health Statistics (NCHS). NAMCS data are widely used in published research on use of medications, including controlled substances (Hirschtritt et al., 2018; Fairman et al., 2017; Gerlach et al., 2017; Olfson et al., 2013).

Details of the NAMCS sampling strategy and data collection methods are described in detail elsewhere (National Center for Health Statistics, 2015a). Briefly, the NCHS uses a complex, multistage sampling design that includes stratification by physician specialty, cluster sampling by physician, random selection of one of 52 weeks each year, and random sampling of visits within the chosen week. Prior to 2012, cluster sampling by geographic area was also employed. For each sampled office visit, U.S. Bureau of the Census field representatives abstract data elements from the medical record using an automated laptop-based survey instrument (National Center for Health Statistics, 2015b).

Data collected by the NCHS include diagnoses (up to three until 2013, up to five beginning in 2014); treatments, services, and laboratory tests ordered or provided at the visit; and prescribed medications that were either initiated or continued by the treating provider. Although up to 30 drugs are currently recorded in NAMCS, the present study is based on the first eight listed drugs through 2011, the maximum recorded in that time frame, and the first ten listed drugs thereafter. Additionally, data collectors record conditions that are clinically important but may not have prompted the extant office visit. Examples include diabetes, hypertension, and hyperlipidemia.

2.2. Design and sample

Choice of the design, sample, and analytic covariates for the present study were based on a review of the literature on use of opioids and other controlled substances by older adults. We used a repeated cross-sectional cohort design in which office visits were the unit of analysis. The sampling frame comprised all office visits provided to U.S. adults aged 18 years or older on the visit date during the period from 2006 through the first 8 months of 2016. Cohorts were defined based on age: 18–64 years and ≥65 years. To provide additional information about utilization patterns by age group, especially for older adults, age categories for post hoc analyses of time trends and for logistic regression analyses were based on those of Hirschtritt et al. (2018), with added categories representing adults aged 65–74 and ≥75 years. Another post hoc trend analysis examined trends for patients with chronic noncancer pain or substance use disorder because opioid use in these groups has been a target of public health initiatives (Dowell et al., 2016).

2.3. Study measures

To identify drugs for study, Multum Lexicon generic drug codes provided by the NCHS were matched to drug names, which were classified into therapy categories for analysis (Appendix 1). Drug-related measures included the prescribing of at least one opioid at the visit, alone or with a barbiturate, benzodiazepine, or hypnotic (i.e., HROP). Medical conditions and comorbidities were identified using condition/comorbidity indicators and diagnoses, measured as International Classification of Diseases, Ninth Revision (ICD-9) codes in 2014–2015 and ICD-10 codes in 2016 (Appendix 2).

2.4. Statistical analyses

Use prevalence rates for each drug or drug combination were defined as the number of visits at which the drug was newly prescribed or continued, divided by the total number of visits. HROP prevalence rates were calculated as total number of HROP visits expressed as a proportion of all visits at which an opioid was prescribed. Longitudinal analysis examined these rates over time, grouping data into multiyear time periods as advised by the NCHS to increase statistical reliability, a commonly used technique in analyses of this dataset (Fairman et al., 2017; Hsiao, 2010; Myrick, n.d.; Olfson et al., 2013).

For the most recent time period included in the study, 2014 through the first 8 months of 2016, patient characteristics—including sex, cardiovascular risk factors and diagnosed cardiovascular disease, chronic pain, psychiatric conditions, and substance use disorder—were measured as prevalence rates (total number of visits in which the diagnosis or condition was reported, divided by total number of visits). In bivariate analyses of high-risk opioid users, these calculations were performed separately for each of the two age groups. Characteristics included in these analyses were chosen from literature review, specifically based on (a) those reported by Hirschtritt et al. as significant predictors of opioid-benzodiazepine use compared with opioid use alone, such as substance use disorder, anxiety, and depression, plus (b) risk factors (e.g., diabetes, hypertension) and diagnoses for cardiovascular or respiratory diseases, which are often chronically comorbid with substance use disorders (Wu et al., 2018).

To assess the independent associations of each demographic and clinical characteristic with high-risk opioid use, a binary logistic regression of high-risk opioid use on demographic and clinical predictors was performed. To increase statistical power for this analysis, the list of cardiovascular risk factors was recoded to categories of 1, 2, or ≥3, compared with no (0) risk factors as the reference category. Additionally, predictors that were insignificant in both the work of Hirschtritt et al. (2018) and in the bivariate analysis were not included in the logistic regression analysis, with the exception that chronic pain was included because of the focus on patients with this condition in previous work (Hirschtritt et al., 2018; Ladapo et al., 2018). The logistic regression analysis was limited to patients without cancer due to the high rate of opioid use within this population.

2.5. Statistical reliability and calculation of nationally representative estimates

For each office visit record, the NCHS provides (1) a weight that adjusts for the sampling design and nonresponse and (2) sample design

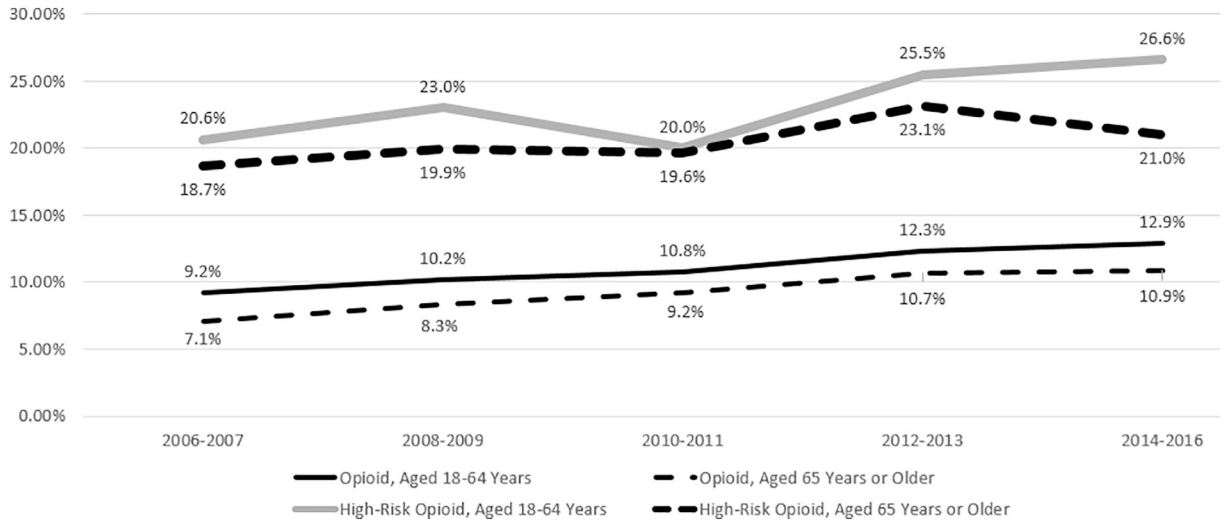


Fig. 1. Rates of opioid and high-risk opioid prescribing, [a]2006–2016, [6]adults, by age category.
[a]Rates represent > 1 prescription newly initiated or continued. Opioid prescribing is calculated as a percentage of all office visits. High-risk opioid prescribing (i.e. opioid + benzodiazepine, barbiturate, or hypnotic) is calculated as a percentage of visits in which ≥1 opioid was initiated or continued. [b]Through August, prior to the warning regarding co-prescription of opioids with benzodiazepines, which was issued on August 31, 2016.

weights that reflect the clustered and stratified design. Using these weights, procedures for complex samples produce nationally representative estimates and sampling variance measures that have been adjusted for sampling design. For the present study, the SPSS (IBM SPSS, Armonk, NY) v25.0 complex samples procedure was used. Estimates were assessed for statistical reliability using the standard recommended by the NCHS of ≥30 records and ratio of standard error to the estimate < 30% (National Center for Health Statistics, 2015b).

3. Results

From 2006 to 2007 to 2014–2016 August, opioid prescribing rates in office visits made by adults increased by 40% (from 9.2% to 12.9%) among those aged 18–64 years and by 54% (from 7.1% to 10.9%) among those aged ≥65 years (Fig. 1). For both age groups, about one-fifth of visits in which opioids were prescribed in 2006–2007 included a concomitant high-risk drug (barbiturate, benzodiazepine, or hypnotic). Through 2012–2013, both age groups displayed similar patterns of increase in HROP rates, expressed as a proportion of opioid-prescribing visits. In 2014–2016 August, HROP rates continued to increase to 26.6% among those aged 18–64 years, while declining to 21.0% among those aged ≥65 years, resulting in a very slight decline from 24.8% in 2012–2013 to 24.6% in 2014–2016 for adults overall (results for all adults not shown in Fig. 1).

A post-hoc analysis with separate trends for those aged 50–64 years, 65–74 years, and ≥75 years showed a decline in opioid use by those aged ≥75 years (Fig. 2, Panel A) and a leveling off of HROP among patients aged 65–74 years who were prescribed opioids, from 22.9% in 2012–2013 to 22.7% in 2014–2016 August (Fig. 2, Panel B). Among patients aged ≥75 years who were prescribed opioids, trends in HROP fluctuated over time, declining to 18.5% in 2014–2016 August (Fig. 2, Panel B). Sensitivity analyses of patients with chronic noncancer pain or substance use disorder produced similar results, although the number of older adults with substance use disorder was insufficient for analysis

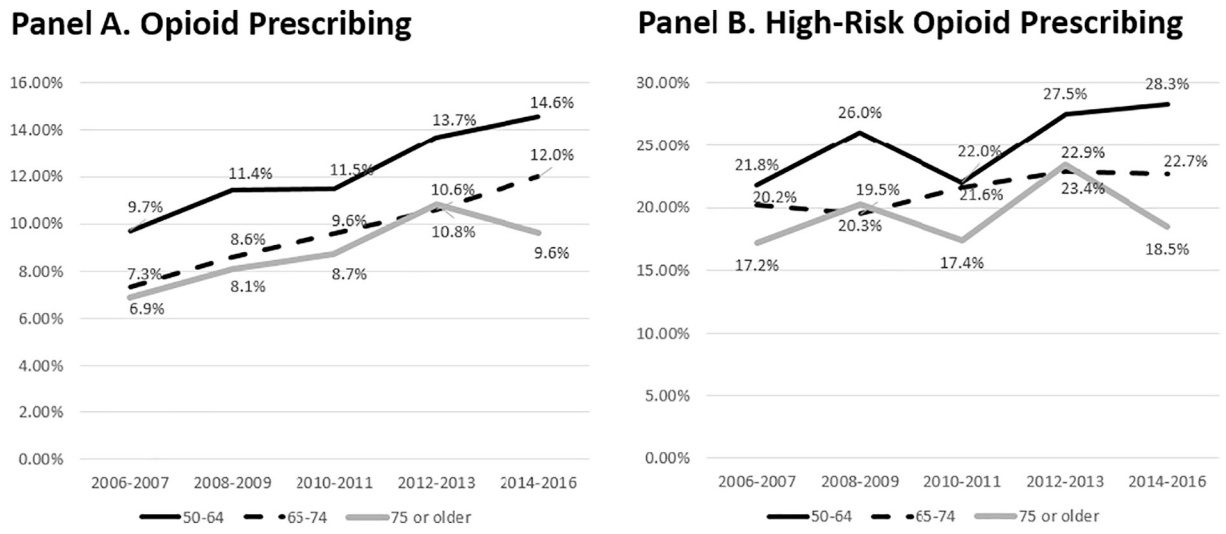


Fig. 2. Rates of opioid and high-risk opioid prescribing, [a]2006–2016, [6]older adults, by age category.
[a]Rates represent > 1 prescription newly initiated or continued. Opioid prescribing is calculated as a percentage of all office visits. High-risk opioid prescribing (i.e. opioid + benzodiazepine, barbiturate, or hypnotic) is calculated as a percentage of visits in which ≥1 opioid was initiated or continued. [b]Through August, prior to the warning regarding co-prescription of opioids with benzodiazepines, which was issued on August 31, 2016.

Table 1
Characteristics (%) by age group, patients prescribed ≥1 high-risk opioid combination (opioids + barbiturate, benzodiazepine, or hypnotic), 2014–2016 August[a].

	Aged 18–64 years	Aged > 65 years	All
Unweighted N	1416	598	2014
Weighted N, annualized	46,322,848	16,851,254	63,174,102
Female	59.3%	59.2%	59.3%
Race			
White	86.7%	86.3%	86.6%
Nonwhite	13.3%	NR	13.4%
Comorbid cardiac risk factors			
Diabetes**	13.7%	26.5%	17.1%
Hyperlipidemia**	22.7%	44.2%	28.5%
Hypertension**	34.2%	63.8%	42.1%
Obesity	12.3%	8.7%	11.4%
Obstructive sleep apnea	3.9%	6.2%	4.5%
Tobacco use**	37.7%	19.8%	32.7%
Cancer[b]	3.0%	NR	3.5%
Cardiovascular disease[c] (any)**	7.1%	27.5%	12.5%
Atrial fibrillation/ arrhythmia[b,**]	NR	6.2%	2.0%
Cerebrovascular disease	NR	2.5%	1.8%
Coronary artery disease**	4.4%	20.0%	8.6%
Pain (chronic)[b]	52.4%	44.2%	50.2%
Psychiatric comorbidities			
Anxiety[b]	17.8%	NR	17.0%
Depression*	26.8%	19.7%	24.9%
Renal disease[d,**]	NR	16.3%	5.9%
Respiratory disease[e]	11.9%	16.7%	13.2%
Substance use disorder[f,**]	13.9%	5.0%^	11.6%
Alcohol (diagnosis or code/ recommendation)	2.7%^	NR	2.4%
Substance use disorder[f] *or* long-term drug use code with controlled substance**	17.2%	7.0%	14.4%

BMI = body mass index; COPD = chronic obstructive pulmonary disease; ICD = international classification of diseases; kg = kilograms; m^2 = body surface area in squared meters; MI = myocardial infarction; NEC = not elsewhere classified; NR = not statistically reliable (standard error exceeds 30% of the estimate). Pearson chi-square test $^{*}P < 0.05$; $^{**}P < 0.01$. ^ Indicates that $N \geq 20$, $N < 30$, and ratio of standard error to the estimate meets standards for statistical reliability.

[a] Through August 2016, prior to the US Food and Drug Administration black-box warning.

[b] Coded by diagnosis (ICD-9 in 2014–2015, ICD-10 in 2016); see codes in Appendix 2. Hepatic impairment estimates are not shown because they did not meet statistical reliability standards.

[c] Condition code of coronary artery disease, cerebrovascular disease, or congestive heart failure, or diagnosis of angina, atrial fibrillation/arrhythmia, cardiomegaly, cardiomyopathy, hypertensive heart disease, "old" (history) MI, or peripheral arterial disease. ICD codes in Appendix 2.

[d] Condition code for chronic kidney disease or end-stage renal disease.

[e] Condition code for asthma or condition code for COPD or any of the following: cystic fibrosis, chronic bronchitis, emphysema, bronchiectasis, extrinsic allergic alveolitis, chronic airway obstruction NEC; see ICD codes in Appendix 2.

[f] Condition code for substance abuse or alcohol abuse, or provided/recommended education on substance abuse or alcohol abuse, or reason for visit is drug- or alcohol-related, or any diagnosis for addiction/abuse of alcohol, opioids, hypnotics/anxiolytics, stimulants, or other/unspecified substances; see codes in Appendix 2.

Table 2
Predictive model of high-risk opioid prescribing, patients without cancer, 2014–2016 August[a].

	Exponentiated beta (odds ratio)	95% Confidence interval lower limit	95% Confidence interval upper limit
Age (years)			
18–34	**0.528**	**0.378**	**0.738**
35 to 49	Ref	Ref	Ref
50 to 64[b]	1.060	0.824	1.364
65 to 74[b]	0.841	0.602	1.173
75 or older[b]	**0.552**	**0.360**	**0.844**
Anxiety[c]	**3.521**	**2.290**	**5.412**
Depression[b,c]	**1.765**	**1.254**	**2.486**
Chronic pain[c]	**3.673**	**2.906**	**4.642**
Current tobacco user[c]	**2.266**	**1.794**	**2.861**
Substance use disorder[c,d]	**2.324**	**1.626**	**3.323**
Comorbid cardiac risk factors[e]			
None	Ref	Ref	Ref
One[b]	**1.600**	**1.206**	**2.122**
Two[b]	**1.441**	**1.049**	**1.978**
Three or more[b]	**1.789**	**1.194**	**2.683**

N of cases = 53,928 unweighted; Nagelkerke R square = 0.140; C-statistic = 0.719.
Bold font denotes statistical significance.

[a] Through August 2016, prior to the US Food and Drug Administration black-box warning.

[b] Relative standard error > 30%; result should be interpreted cautiously.

[c] For diagnoses and medical conditions, reference category includes those without the disorder shown in the row label.

[d] Condition code for substance abuse or alcohol abuse, or provided/recommended education on substance abuse or alcohol abuse, or reason for visit is drug- or alcohol-related, or any diagnosis for addiction/abuse of alcohol, opioids, hypnotics/anxiolytics, stimulants, or other/unspecified substances; or code for long-term drug use in patients with a controlled substance prescription; see codes in Appendix 2.

[e] Diabetes, hyperlipidemia, hypertension, obesity, and obstructive sleep apnea.

until 2012–2013 (Appendix 3).

In 2014–2016 August, approximately 63 million office visits made by US adults resulted in the initiation or continuation of a high-risk opioid combination (Table 1). In these visits, commonly recorded diagnoses or conditions included chronic pain (50%), hypertension (42%), and depression (25%).

As expected, rates of cardiovascular risk factors were significantly higher for older than younger adults; and 28% of older adults, compared with 7% of younger adults, had a diagnosis of cardiovascular disease. Conversely, younger adults were more likely than older adults to have a diagnosis of chronic pain (52% vs. 44%, respectively), depression (27% vs. 20%), or substance use disorder (14% vs. 5%, respectively), and were much more likely to use tobacco (38% vs. 20%, respectively). Anxiety was also common among younger adults (18%). In bivariate analysis of predictors, these factors were strongly predictive of high-risk opioid use, as were age categories based on the work of Hirschtritt et al. (2018) (Appendix 4).

In the logistic regression analysis, the odds of HROP were multiplied by 3.67 (95% confidence interval [CI] = 2.91–4.64) with a diagnosis of chronic pain; by 3.52 (95% CI = 2.29–5.41) with anxiety; and were more than doubled with current tobacco use or substance use disorder (Table 2). Cardiovascular risk factors were also associated with increased odds of HROP, although to a lesser degree. Compared with the reference group of adults aged 35–49 years, odds of HROP were not significantly different among those 50–64 years or 65–74 years, but were significantly lower for those aged 18–34 years (odds ratio = 0.53, 95% CI = 0.38–0.74) and those aged ≥75 years (odds ratio = 0.55, 95% CI = 0.36–0.84).

4. Discussion

In physician office visits made by patients aged ≥65 years, the rate of HROP, which had increased steadily over time from 2006–2007 to 2012–2013, began to decline in 2014–2016 August, primarily because of changes occurring among patients aged ≥75 years and a leveling of

the HROP rate among those aged 65–74 years. Since previous research has found a strong association between use of high-risk opioid combinations and high direct and indirect costs, the decreased rate of HROP may translate to improved patient outcomes, decreased costs, and prevention of opioid-overdose related mortality (Reinhart et al., 2018; Kacara-Mandic et al., 2017).

Although a positive finding because of the elevated risk of respiratory depression in older adults, this result is surprising because our study period preceded the issuance of the new FDA guidance on opioid-benzodiazepine co-prescription. The decline in prescribing rates may have been due to several states implementing more stringent requirements for opioid prescriptions prior to 2016. It is also possible that concern about potential opioid-related risks for the "older-older" has increased (Jaul and Barron, 2017). Our findings are consistent with those of a previous study that reported reduced high-dose opioid use with age ≥75 years (Musich et al., 2019), perhaps because known opioid-related risks, such as cardiovascular events or fractures (Saunders et al., 2010; Solomon et al., 2010) are highly prevalent and clinically serious in this age group (Jaul and Barron, 2017).

In contrast to the findings for older adults, the rate of HROP in patients aged 18–64 years continued to increase in 2014–2016 August. The rate of HROP was multiplied > 3-fold with diagnoses of either chronic pain or anxiety, and doubled with a diagnosis of tobacco or substance use disorder. The continued increase of HROP overlaid with these diagnoses may result in unintended harm, such as increased risk of opioid-overdose related mortality.

Among all study patients, there was a slight decline in HROP from 2012–2013 to 2014–2016. This finding aligns with that of Ladapo et al. (2018), who found an overall reduction in HROP prevalence over time. This reduction was not apparent in the study by Hirschtritt et al. (2018), likely due to the exclusion of patients aged ≥65 years from their sample. Despite the present study's finding of improvement in HROP rates among patients aged ≥65 years, it should be noted that rates for both age groups remain elevated above those from 2006 to 2007. Additionally, despite the decline in HROP rates, rates of opioid prescribing overall continued to increase among older adults from 2012–2013 to 2014–2016 August, highlighting the importance of public health prevention strategies for opioid use reduction. In concert with the recommendations of the FDA, the Centers for Disease Control and Prevention (CDC) released Guidelines for Prescribing Opioids for Chronic Pain in 2016 that suggest non-pharmacological and non-opioid treatment modalities when managing chronic pain (U.S. Food and Drug Administration, 2016; Dowell et al., 2016). As interest in the risks associated with increased controlled substance use and misuse by older adults continues to grow (Han et al., 2019; Huang et al., 2018; McCabe et al., 2019), continued monitoring of trends in HROP in this age group is warranted. Additional research to clarify sociocultural predictors of high-risk drug use, such as family history, criminality, or socioeconomic status, may be helpful to providers who wish to identify older adults who are at elevated risk (Ranapurwala et al., 2018; Webster, 2017).

4.1. Limitations

Several limitations of the study should be noted. First, the NAMCS does not measure medication strength, prescribed duration or dosage, or patient adherence. Second, each NAMCS record represents a single physician office visit. Other than the medical condition codes (e.g., hypertension, diabetes), the NAMCS record does not provide information on patient history. Third, although the NAMCS record does include medications prescribed by another physician and continued by the sampled physician, it does not capture illicit drugs, prescriptions intentionally concealed by patients (e.g., in "doctor shopping"), or medication that was discontinued in the sampled office visit. Fourth, the study sample represents care delivered in physician office visits, not in emergency departments or inpatient hospital settings.

5. Conclusion

While prescribing rates of high-risk opioid use declined in older adults prior to the FDA Black Box Warning regarding opioid-benzodiazepine co-prescription, these rates continued to trend upwards through the first 8 months of 2016 in adults aged 18–64 years. Future studies are needed to assess the impact of the FDA Black Box Warning and CDC Chronic Pain Guideline from 2016 on the rates of HROP.

Declaration of Competing Interest

The authors declare there is no conflict of interest.

Appendix 1

Appendix 1
Unweighted counts of drugs by therapy class, office visits made by adults, all years and 2014–2016 August[a].

	2006–2016	2014–2016
Barbiturates[b]	1521	376
Butalbital	1292	337
Mephobarbital	3	1
Phenobarbital	230	38
Benzodiazepines[b]	23,771	5683
Alprazolam	8240	2054
Chlordiazepoxide	331	76
Clobazam	16	11
Clonazepam	5427	1253
Clorazepate	186	19
Diazepam	2912	757
Estazolam	38	11
Flurazepam	75	13
Lorazepam	5625	1334
Midazolam	466	128
Oxazepam	95	17
Temazepam	1270	243
Triazolam	148	19
Opioids[b]	34,688	8353
Buprenorphine	1125	339
Butorphanol	39	3
Codeine	2438	676

(continued on next page)

Appendix 1 (*continued*)

	2006–2016	2014–2016
Dihydrocodeine	5	1
Fentanyl	1224	296
Hydrocodone	15,939	3722
Hydromorphone	662	160
Mepiridine	272	38
Methadone	780	114
Morphine	1226	280
Nalbuphine	37	0
Opium	15	3
Oxycodone	7415	2031
Oxymorphone	124	41
Pentazocine	25	4
Propoxyphene	1270	13
Tapentadol	105	31
Tramadol (became a controlled substance in July 2014)	5878	1570
Z hypnotics/other hypnotics[b]	7371	1476
Eszopiclone	864	129
Sodium oxybate	14	3
Suvorexant	6	6
Zaleplon	156	28
Zolpidem	6394	1319

[a] Across all drugs prescribed in the visit; 8 drugs maximum through 2011 and 10 drugs maximum thereafter. Measured through August 2016, prior to the US Food and Drug Administration black-box warning.

[b] Indicates use of one or more of the drugs shown in the rows below. Individual drug counts may not sum to therapy class total because patients could use more than one drug.

Appendix 2

Appendix 2
Medical claims codes for diagnoses.

Diagnosis	ICD-9 codes	ICD-10 codes
Abuse/addiction or condition codes as shown in table shell; note that these codes did not become available until 2014.	291 Alcohol-induced mental disorders 292 Drug-induced mental disorders 303.xx Alcohol dependence syndrome 304.xx Drug dependence 305.xx Nondependent abuse of drugs 965.0 Poisoning by opiates and related narcotics 967 Poisoning by sedatives and hypnotics 969.1, 969.2, 969.4, 969.5, 969.6, 969.7 Poisoning by tranquilizers, hallucinogens, or psychostimulants 970 Poisoning by central nervous system stimulants E850.0 Accidental poisoning by heroin E850.1 Accidental poisoning by methadone E850.2 Accidental poisoning by other opiates and related narcotics E851 Accidental poisoning by barbiturates E852 Accidental poisoning by other sedatives and hypnotics E853 Accidental poisoning by tranquilizers E854.1 Accidental poisoning by psychodysleptics [hallucinogens] E854.2 Accidental poisoning by psychostimulants E854.3 Accidental poisoning by central nervous system stimulants	F10 Alcohol related disorders F11 Opioid related disorders F12 Cannabis related disorders F13 Sedative, hypnotic, or anxiolytic related disorders F14 Cocaine related disorders F15 Other stimulant related disorders F16 Hallucinogen related disorders F18 Inhalant related disorders F19 Other psychoactive substance related disorders T40 Poisoning by and adverse effects of narcotics and psychodysleptics (excluding codes for underdosing) T42.3x, T42.4x, T42.6x, T42.7x poisoning by and adverse effects of barbiturates, benzodiazepines, other/unspecified antiepileptic and sedative-hypnotic drugs (excluding codes for underdosing) T43.6x Poisoning by and adverse effects of psychostimulants (excluding codes for underdosing) Underdosing is indicated by a code of "6" in the sixth position. K70 Alcoholic liver disease
Angina	413 Angina pectoris	I20 Angina pectoris
Anxiety	300 Anxiety, dissociative and somatoform disorders	F40 Phobic anxiety disorders F41 Other anxiety disorders F42 Obsessive compulsive disorder F44 Dissociative and conversion disorders F45 Somatoform disorders

(*continued on next page*)

Appendix 2 (*continued*)

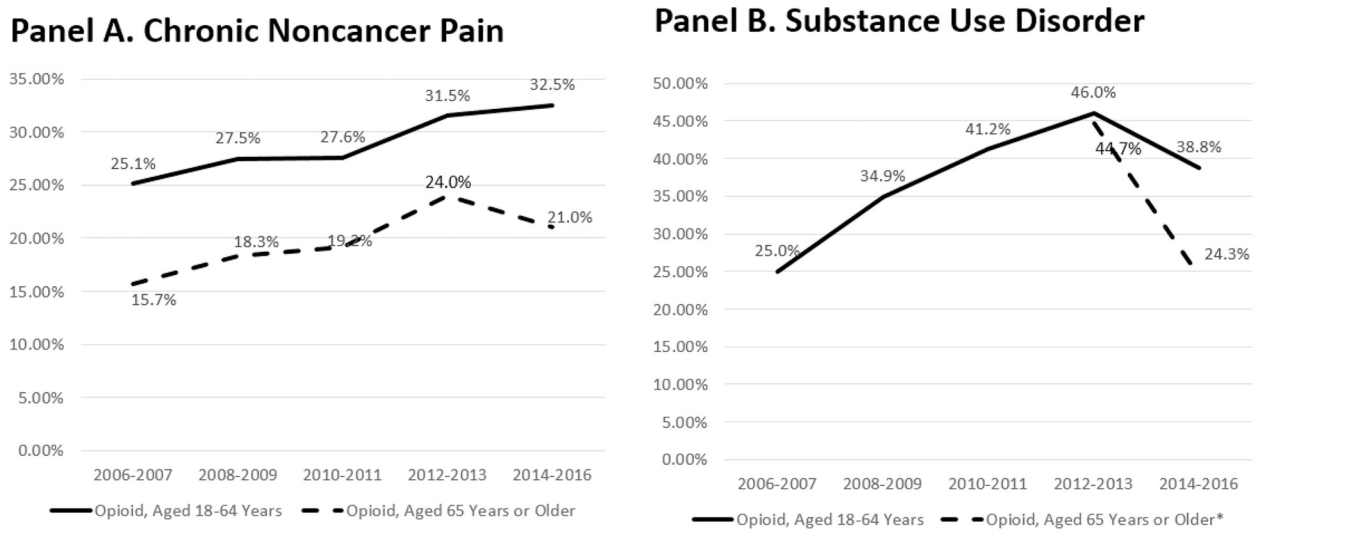
Diagnosis	ICD-9 codes	ICD-10 codes
Arrhythmia	426 Conduction disorders	I44 Atrioventricular and left bundle-branch block
	427 Cardiac dysrhythmias	I45 Other conduction disorders
	V45.0 Cardiac device in situ; unspecified, pacemaker, automatic implantable defibrillator, or other	I48 Atrial fibrillation and flutter
		I49 Other cardiac arrhythmias
		Z95.0 Presence of cardiac pacemaker
		Z95.81 Presence of defibrillator, heart assist device, artificial heart, cardiac implant
Cancer	140–149 Malignant neoplasm of lip, oral cavity, and pharynx	C00-C14 Malignant neoplasms of lip, oral cavity and pharynx
		C15-C26 Malignant neoplasms of digestive organs
	150–159 Malignant neoplasm of digestive organs and peritoneum	C30-C39 Malignant neoplasms of respiratory and intrathoracic organs
		C40-C41 Malignant neoplasms of bone and articular cartilage
	160–165 Malignant neoplasm of respiratory and intrathoracic organs	C43-C44 Melanoma and other malignant neoplasms of skin
		C45-C49 Malignant neoplasms of mesothelial and soft tissue
	170 Malignant neoplasm of bone and articular cartilage	C50-C50 Malignant neoplasms of breast
		C51-C58 Malignant neoplasms of female genital organs
	171 Malignant neoplasm of connective and other soft tissue	C60-C63 Malignant neoplasms of male genital organs
		C64-C68 Malignant neoplasms of urinary tract
	172 Malignant melanoma of skin	C69-C72 Malignant neoplasms of eye, brain and other parts of central nervous system
	174 Malignant neoplasm of female breast	
	175 Malignant neoplasm of male breast	C73-C75 Malignant neoplasms of thyroid and other endocrine glands
	176 Kaposi's sarcoma	C76-C80 Malignant neoplasms of ill-defined, other secondary and unspecified sites
	179–189 Malignant neoplasm of genitourinary organs	C7A-C7A Malignant neuroendocrine tumors
		C7B-C7B Secondary neuroendocrine tumors
	190–199 Malignant neoplasm of other and unspecified sites	C81-C96 Malignant neoplasms of lymphoid, hematopoietic and related tissue
	200–209 Malignant neoplasm of lymphatic and hematopoietic tissue	
Cardiomegaly (LVH)	429.3 Cardiomegaly	I51.7 Cardiomegaly
Cardiomyopathy	425 Cardiomyopathy	I42 Cardiomyopathy
		I43 Cardiomyopathy in diseases classified elsewhere
Congenital heart anomalies	745 Bulbus cordis anomalies and anomalies of cardiac septal closure	Q20 Congenital malformations of cardiac chambers and connections
		Q21 Congenital malformations of cardiac septa
	746 Other congenital anomalies of heart	Q22 Congenital malformations of pulmonary and tricuspid valves
	747 Other congenital anomalies of circulatory system	Q23 Congenital malformations of aortic and mitral valves
		Q24 Other congenital malformations of heart
		Q25 Congenital malformations of great arteries
		Q26 Congenital malformations of great veins
		Q27 Other congenital malformations of peripheral vascular system
		Q28 Other congenital malformations of circulatory system
Hepatic impairment	070 Viral hepatitis	B15 Acute hepatitis A
	570 Acute and subacute necrosis of liver	B16 Acute hepatitis B
	571 Chronic liver disease and cirrhosis	B17 Other acute viral hepatitis
	572 Liver abscess and sequelae of chronic liver disease	B18 Chronic viral hepatitis
		B19 Unspecified viral hepatitis
	573 Other disorders of liver	K70 Alcoholic liver disease
		K71 Toxic liver disease
		K72 Hepatic failure, not elsewhere classified
		K73 Chronic hepatitis, not elsewhere classified
		K74 Fibrosis and cirrhosis of liver
		K75 Other inflammatory liver diseases
		K76 Other diseases of liver
		K77 Liver disorders in diseases classified elsewhere
Hypertensive heart disease	402 Hypertensive heart disease	I11 Hypertensive heart disease
	404 Hypertensive heart and chronic kidney disease	I13 Hypertensive heart and chronic kidney disease
Long-term drug use	V58.69 Long-term (current) use of other medications	Z79.891 Long-term use of opiate analgesic
"Old" MI	411.0 Postmyocardial infarction syndrome	I24.1 Dressler's syndrome
	412 Old myocardial infarction	I25.2 Old myocardial infarction
"Old" stent	V45.81 Aortocoronary bypass status	Z95.1 Presence of aortocoronary bypass graft
	V45.82 PTCA status	Z95.5 Presence of coronary angioplasty implant and graft
		Z98.6 Angioplasty status
Pain (chronic)	250.6x Diabetes with neurological manifestations	E08.4 Diabetes mellitus due to underlying condition with neurological complications
	338.2x Chronic pain	E10.4 Type 1 diabetes mellitus with neurological complications
	338.4x Chronic pain syndrome	E11.4 Type 2 diabetes mellitus with neurological complications
	353 Nerve root and plexus disorders	E13.4 Other specified diabetes mellitus with neurological complications
	354 Mononeuritis of upper limb and mononeuritis multiplex	G89.2 Chronic pain, not elsewhere classified
		G89.4 Chronic pain syndrome
	355 Mononeuritis of lower limb and unspecified site	G50-G59 Nerve, nerve root and plexus disorders
		G60-G65 Polyneuropathies and other disorders of the peripheral nervous system
	356 Hereditary and idiopathic peripheral neuropathy	G89 Pain, not elsewhere classified
	357 Inflammatory and toxic neuropathy	L89 Pressure ulcer

(*continued on next page*)

Appendix 2 (*continued*)

Diagnosis	ICD-9 codes	ICD-10 codes
	707 Chronic ulcer of skin	M00-M02 Infectious arthropathies
	710.xx-719.xx Arthropathies and related disorders	M04-M04 Autoinflammatory syndromes
	720.xx-724.xx Dorsopathies	M05-M14 Inflammatory polyarthropathies
	725.xx-729.xx Rheumatism, excluding the back	M15-M19 Osteoarthritis
	730.xx-739.xx Osteopathies, chondropathies, and acquired musculoskeletal deformities	M20-M25 Other joint disorders
	V66.7 Encounter for palliative care	M30-M36 Systemic connective tissue disorders
		M40-M43 Deforming dorsopathies
		M45-M49 Spondylopathies
		M50-M54 Other dorsopathies
		M60-M63 Disorders of muscles
		M65-M67 Disorders of synovium and tendon
		M70-M79 Other soft tissue disorders
		M80-M85 Disorders of bone density and structure
		M86-M90 Other osteopathies
		M91-M95 Chondropathies and other disorders of musculoskeletal system
		M96-M97 Postoperative complications and periprosthetic fracture
		Z51.5 Encounter for palliative care
Peripheral arterial disease	443.9 Peripheral artery disease, unspecified	I73.9 Peripheral vascular disease, unspecified
Respiratory disease (chronic) or condition codes as shown in table shell	277.0 Cystic fibrosis	E84 Cystic fibrosis
	491 Chronic bronchitis	J41 Simple and mucopurulent chronic bronchitis
	492 Emphysema	J42 Unspecified chronic bronchitis
	494 Bronchiectasis	J43 Emphysema
	495 Extrinsic allergic alveolitis	J44 Other chronic obstructive pulmonary disease
	496 Chronic airway obstruction, not elsewhere classified	J47 Bronchiectasis
Valvular disorders	397.0 Diseases of tricuspid valve	I34 Nonrheumatic mitral valve disorders
	424.0 Mitral valve disorders	I35 Nonrheumatic aortic valve disorders
	424.1 Aortic valve disorders	I36 Nonrheumatic tricuspid valve disorders
	424.2 Tricuspid valve disorders, specified as nonrheumatic	I37 Nonrheumatic pulmonary valve disorders
	424.3 Pulmonary valve disorders	I38 Endocarditis, valve unspecified
	424.9 Endocarditis valve unspecified	I39 Endocarditis and heart valve disorders in diseases classified elsewhere

Appendix 3



[a] Rates represent ≥1 prescription newly initiated or continued. Opioid prescribing is calculated as a percentage of all office visits. [b] Through August, prior to the warning regarding co-prescription of opioids with benzodiazepines, which was issued on August 31, 2016. *Results for 2006-2011 are not shown because they did not meet statistical reliability standards.

Appendix 3. Rates of opioid and high-risk opioid prescribing,[a] 2006–2016,[6] adults diagnosed with chronic noncancer pain or substance use disorder, by age category.

Appendix 4

Appendix 4
Rate of high-risk combination (opioids + barbiturate, benzodiazepine, or hypnotic) use by sample subgroups, patients without cancer, 2014–2016 August[a].

Characteristic	Rate[b]
Sex	
Female	2.9
Male	3.1
Race	
White	3.2
Nonwhite	2.3
Age group (years)**	
18 to 34	1.7
35 to 49	3.7
50 to 64	4.1
65 to 74	2.7
75 or older	1.8
Comorbid cardiac risk factors** (sum of condition codes for diabetes, hyperlipidemia, hypertension, obesity, sleep apnea, max = 5, truncated at 3 or more)	
None	2.4
One	3.9
Two	3.2
Three or more	3.8
Individual comorbidities	
Diabetes	3.2
Hyperlipidemia*	3.7
Hypertension**	3.7
Obesity*	3.8
Obstructive sleep apnea	3.9
Tobacco use**	7.4
Cardiovascular disease[c,d] (any)	3.1
Cerebrovascular disease	2.6
Congestive heart failure	2.3
Coronary artery disease	3.5
Other diagnoses and conditions	
Pain (chronic)[d],**	7.2
Psychiatric comorbidities	
Anxiety[d], **	10.4
Depression**	6.4
Respiratory disease[d,e] **	4.2
Substance use disorder[d,f] **	9.1
Alcohol (dx or code/recommendation)**	5.8
Substance use disorder *or* long-term drug use code with controlled substance[d,f] **	10.6

BMI = body mass index; COPD = chronic obstructive pulmonary disease; ICD = international classification of diseases; kg = kilograms; m^2 = body surface area in squared meters; MI = myocardial infarction; NEC = not elsewhere classified; NR = not statistically reliable (standard error exceeds 30% of the estimate). Pearson chi-square test $^{*}P < 0.05$; $^{**}P < 0.01$. ^ Indicates that N ≥ 20, $N < 30$, and ratio of standard error to the estimate meets standards for statistical reliability.

[a] Through August 2016, prior to U.S. Food and Drug Administration black-box warning.

[b] Number of those in subgroup with high-risk opioid use, divided by total number in subgroup.

[c] Condition code of coronary artery disease, cerebrovascular disease, or congestive heart failure, or diagnosis of angina, atrial fibrillation/arrhythmia, cardiomegaly, cardiomyopathy, hypertensive heart disease, "old" (history) MI, or peripheral arterial disease.

[d] ICD codes in Appendix 2.

[e] Condition code for asthma or condition code for COPD or any of the following: cystic fibrosis, chronic bronchitis, emphysema, bronchiectasis, extrinsic allergic alveolitis, chronic airway obstruction NEC.

[f] Condition code for substance abuse or alcohol abuse, or provided/recommended education on substance abuse or alcohol abuse, or reason for visit is drug- or alcohol-related, or any diagnosis for addiction/abuse of alcohol, opioids, hypnotics/anxiolytics, stimulants, or other/unspecified substances.

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