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

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\textbf{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 \(\geq 65\) 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 \(\geq 65\) 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 \(\geq 65\) years, primarily because of changes for patients aged \(\geq 75\) 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 of 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 \(\geq 20\) 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 \(\geq 65\) years. In one study of emergency visits made for co-prescribed opioid-benzodiazepine from 2005 to 2011, patients aged \(\geq 65\) years had the highest predicted risk of hospital admission or death compared with patients in younger age groups (Substance Abuse and...
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 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.

2.3. 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 weights that adjust for the sampling design and nonresponse.
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.
Table 1
Characteristics (%) by age group, patients prescribed ≥1 high-risk opioid combination (opioids + barbiturate, benzodiazepine, or hypnotic), 2014–2016 August.

|                          | Aged 18–64 years | Aged ≥ 65 years | All                           |
|--------------------------|------------------|----------------|-------------------------------|
| Unweighted N             | 1,416            | 598            | 2,014                         |
| 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%            | NR             | 20.5% (26.8%)                 |
| Hypertension**           | 34.2%            | 63.8%          | 42.2%                         |
| Obesity                  | 12.3%            | 8.7%           | 11.4%                         |
| Obstructive sleep apnea  | 3.9%             | 6.2%           | 4.5%                          |
| Tobacco use**            | 37.7%            | 19.8%          | 23.7%                         |
| Cancer*                  | 3.0%             | NR             | 3.5%                          |
| Cardiovascular disease (any)** | 7.1%        | 27.5%          | 12.5%                         |
| Atypical fibrillation/ arhythmia** | NR | 6.2%          | 2.0%                          |
| Cerebrovascular disease  | 37.3%            | 10.0%          | 21.1%                         |
| Coronary artery disease** | 4.4%           | 20.0%          | 8.7%                          |
| Pain (chronic)**         | 52.4%            | 44.2%          | 50.2%                         |
| Psychiatric comorbidities|                  |                |                               |
| Anxiety**                | 16.6%            | 23.3%          | 18.7%                         |
| Depression**             | 20.3%            | 23.8%          | 21.8%                         |
| Renal disease**          | 26.8%            | NR             | 12.1% (16.3%)                 |
| Respiratory disease**    | 11.9%            | 16.7%          | 13.2%                         |
| Substance use disorder** | 13.9%            | 5.0%           | 11.6%                         |
| Alcohol (diagnosis or code/recommendation) | 2.7%   | NR             | 2.4%                          |
| Substance use disorder 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; m² = body surface area in squared meters; MI = myocardial infarction; NEC = not elsewhere classified; NR = not statistically reliable (standard error exceeds 30% of the estimate). *p < 0.05; **p < 0.001. Indicates that N ≥ 20, N < 30, and ratio of standard error to the estimate meets standards for statistical reliability.

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

** 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.

† Condition code of coronary artery disease, cerebrovascular disease, or congestive heart failure, or diagnosis of angina, atrial fibrillation/arhythmia, cardiomegaly, cardiomyopathy, hypertensive heart disease, “old” (history) MI, or peripheral arterial disease. ICD codes in Appendix 2.

‡ Condition code for chronic kidney disease or end-stage renal disease.

§ 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.

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

|                          | 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                 | 1.060                           | 0.824                             | 1.364                             |
| 65 to 74                 | 0.841                           | 0.602                             | 1.173                             |
| 75 or older              | 0.552                           | 0.360                             | 0.844                             |
| Anxiety                  | 3.521                           | 2.290                             | 5.412                             |
| Depression**             | 1.765                           | 1.254                             | 2.486                             |
| Chronic pain†            | 3.673                           | 2.906                             | 4.642                             |
| Current tobacco use†     | 2.266                           | 1.794                             | 2.861                             |
| Substance use disorder†  | 2.324                           | 1.626                             | 3.323                             |
| Comorbid cardiac risk factors† |                      |                                   |                                   |
| None                     | Ref                             | Ref                               | Ref                               |
| One†                     | 1.600                           | 1.206                             | 2.122                             |
| Two†                     | 1.441                           | 1.049                             | 1.978                             |
| Three or more†           | 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.

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.

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

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Appendix 1 (continued)

| Drug                | 2006–2016 | 2014–2016 |
|---------------------|-----------|-----------|
| Dihydrocodeine      | 5         | 1         |
| Fentanyl            | 1224      | 296       |
| Hydrocodone         | 15,939    | 3722      |
| Hydromorphone       | 662       | 160       |
| Meperidine          | 272       | 38        |
| Methadone           | 780       | 114       |
| Morphine            | 1226      | 280       |
| Naltrexone          | 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 hypnoticsb | 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

Medical claims codes for diagnoses.

| Diagnosis                         | ICD-9 codes | ICD-10 codes |
|-----------------------------------|-------------|--------------|
| Abuse/addiction or condition codes as shown in table; note that these codes did not become available until 2014. |             |              |
| Alcohol-induced mental disorders  | F10 Alcohol related disorders | F11 Opioid related disorders |
| Drug dependence syndrome          | F12 Cannabis related disorders | F13 Sedative, hypnotic, or anxiolytic related disorders |
| Drug dependence                   | F14 Cocaine related disorders | F15 Other stimulant related disorders |
| Nondependent abuse of drugs       | F16 Hallucinogen related disorders | F18 Inhalant related disorders |
| Poisoning by opiates and related narcotics | F19 Other psychoactive substance related disorders | T40 Poisoning by and adverse effects of narcotics and psychostimulants (excluding codes for underdosing) |
| 967.0 Poisoning by sedatives and hypnotics | 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) |
| 969.1, 969.2, 969.4, 969.5, 969.6, 969.7 | Underdosing is indicated by a code of “6” in the sixth position. | K70 Alcoholic liver disease |
| Poisoning by tranquilizers, hallucinogens, or psychostimulants |             |              |
| 970 Poisoning by central nervous system stimulants |             |              |
| EB50.0 Accidental poisoning by heroin |             |              |
| EB50.1 Accidental poisoning by methadone |             |              |
| EB50.2 Accidental poisoning by other opiates and related narcotics |             |              |
| EB851 Accidental poisoning by barbiturates |             |              |
| EB852 Accidental poisoning by other sedatives and hypnotics |             |              |
| EB853 Accidental poisoning by tranquilizers |             |              |
| EB854.1 Accidental poisoning by psychostimulants [hallucinogens] |             |              |
| EB854.2 Accidental poisoning by psychostimulants |             |              |
| EB854.3 Accidental poisoning by central nervous system stimulants |             |              |
| Angina                            | 413 Angina pectoris | I20 Angina pectoris |
| Anxiety                           | 300 Anxiety, dissociative and somatoform disorders | F40 Phobic anxiety disorders |

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### Appendix 2 (continued)

| Diagnosis | ICD-9 codes | ICD-10 codes |
|-----------|-------------|--------------|
| Arhythmia | 426 Conduction disorders | 144 Atrioventricular and left bundle-branch block |
|          | 427 Cardiac dysrhythmias | 145 Other conduction disorders |
|          | V45.0 Cardiac device in situ; unspecified, pacemaker, automatic implantable defibrillator, or other | 148 Atrial fibrillation and flutter |
|          | 149 Other cardiac arrhythmias | 295.0 Presence of cardiac pacemaker |
|          |                          | 295.81 Presence of defibrillator, heart assist device, artificial heart, cardiac implant |
| Cancer   | 140–149 Malignant neoplasm of lip, oral cavity, and pharynx | 140–149 Malignant neoplasms of lip, oral cavity and pharynx |
|          | 150–159 Malignant neoplasm of digestive organs and peritonium | 150–159 Malignant neoplasms of digestive organs and peritonium |
|          | 160–165 Malignant neoplasm of respiratory and intrathoracic organs | 160–165 Malignant neoplasms of respiratory and intrathoracic organs |
|          | 170 Malignant neoplasm of bone and articular cartilage | 170 Malignant neoplasms of bone and articular cartilage |
|          | 171 Malignant neoplasm of connective and other soft tissue | 171 Malignant neoplasms of connective and other soft tissue |
|          | 172 Malignant melanoma of skin | 172 Malignant melanoma of skin |
|          | 174 Malignant neoplasm of female breast | 174 Malignant neoplasms of female breast |
|          | 175 Malignant neoplasm of male breast | 175 Malignant neoplasms of male breast |
|          | 190–199 Malignant neoplasm of other and unspecified sites | 190–199 Malignant neoplasms of other and unspecified sites |
|          | 200–209 Malignant neoplasm of lymphatic and hematopoietic tissue | 200–209 Malignant neoplasms of lymphatic and hematopoietic tissue |
| Cardiomegaly (LVH) | 429.3 Cardiomegaly | 151.7 Cardiomegaly |
|          | 425 Cardiomyopathy | 142 Cardiomyopathy |
| Congenital heart anomalies | 745 Bulbus cordis anomalies and anomalies of cardiac septal closure | 210 Congenital malformations of cardiac septa |
|          | 746 Other congenital anomalies of heart | 222 Congenital malformations of pulmonary and tricuspid valves |
|          | 747 Other congenital anomalies of circulatory system | 223 Congenital malformations of aortic and mitral valves |
|          | 787 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 |
|          | 573 Other disorders of liver | B19 Unspecified viral hepatitis |
|          | 574 Other unspecified sites | K70 Alcoholic liver disease |
|          | 744 Other diseases classified elsewhere | K71 Toxic liver disease |
|          | 745 Other hepatobiliary diseases | K72 Hepatic failure, not elsewhere classified |
|          | 746 Other viral hepatitis | K73 Chronic hepatitis, not elsewhere classified |
|          | 747 Other liver diseases and cirrhosis | K74 Fibrosis and cirrhosis of liver |
|          | 748 Other diseases of liver | K75 Other inflammatory liver diseases |
|          | 749 Other specified liver diseases | K76 Other diseases of liver |
|          | 750 Liver disorders in diseases classified elsewhere | K77 Liver disorders in diseases classified elsewhere |
|          | 751 Other unspecified liver diseases | K78 Other unspecified liver diseases |
| Hypertensive heart disease | 402 Hypertensive heart disease | 111 Hypertensive heart disease |
|          | 403 Hypertensive heart and chronic kidney disease | 113 Hypertensive heart and chronic kidney disease |
|          | 404 Hypertensive heart and chronic kidney disease | 114 Hypertensive heart and chronic kidney disease |
|          | 405 Hypertensive heart disease and hypertension | Z79.891 Long-term use of opiate analgesics |
|          | 406 Hypertensive heart disease and chronic kidney disease | Z79.891 Long-term use of opiate analgesics |
| Long-term drug use | 58.69 Long-term (current) use of other medications | Z79.891 Long-term use of opiate analgesics |
|          | 411.9 Postmyocardial infarction syndrome | I24.1 Dressler's syndrome |
|          | 412 Old myocardial infarction | I25.3 Old myocardial infarction |
| “Old” MI | V45.81 Aortocoronary bypass status | 295.1 Presence of aortocoronary bypass graft |
|          | V45.82 PTCA status | 295.5 Presence of coronary angioplasty implant and graft |
|          | 354 Mononeuropathies of upper limb and mononeuropathies multiplex | Z98.6 Angioplasty status |
|          | 355 Mononeuropathies of lower limb and unspecified site | Z98.6 Angioplasty status |
|          | 356 Hereditary and idiopathic peripheral neuropathy | 114 Hereditary and idiopathic peripheral neuropathy |
|          | 357 Inflammatory and toxic neuropathy | 115 Inflammatory and toxic neuropathy |

(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      |
| M00-M02 Infectious arthropathies                |                        | M40-M42 Deforming dorsopathies                    |
| M04-M04 Autoinflammatory syndromes             |                        | M43-M49 Spondylopathies                           |
| M05-M14 Inflammatory polyarthropathies         |                        | M50-M54 Other dorsopathies                        |
| M15-M19 Osteoarthritis                         |                        | M60-M63 Disorders of muscles                      |
| M20-M25 Other joint disorders                  |                        | M65-M67 Disorders of synovium and tendon          |
| M30-M36 Systemic connective tissue disorders    |                        | M70-M79 Other soft tissue disorders               |
| M40-M42 Deforming dorsopathies                 |                        | M80-M85 Disorders of bone density and structure   |
| M43-M49 Spondylopathies                        |                        | M86-M90 Other osteopathies                        |
| M50-M54 Other dorsopathies                     |                        | M91-M95 Chondropathies and other disorders of musculoskeletal system |
| M60-M63 Disorders of muscles                   |                        | M96-M97 Postoperative complications and periprosthetic fracture |
| 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

Panel A. Chronic Noncancer Pain

Panel B. Substance Use Disorder

Rates represent ≥1 prescription newly initiated or continued. Opioid prescribing is calculated as a percentage of all office visits. 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, 2006–2016, adults diagnosed with chronic noncancer pain or substance use disorder, by age category.
## 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)**$^c$ |         |
| 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**$^d$ (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$^e$ | 3.7     |
| Hypertension$^f$ | 3.7     |
| Obesity$^g$    | 3.8     |
| Obstructive sleep apnea | 3.9   |
| Tobacco use$^h$ | 7.4     |
| Cardiovascular disease$^i$ (any) | 3.1     |
| Cerebrovascular disease | 2.6     |
| Congestive heart failure | 2.3     |
| Coronary artery disease | 3.5     |
| **Other diagnoses and conditions** |         |
| Pain (chronic)$^j$ | 7.2     |
| **Psychiatric comorbidities** |         |
| Anxiety$^k$    | 10.4    |
| Depression$^l$ | 6.4     |
| Respiratory disease$^m$ | 4.2     |
| Substance use disorder$^n$ | 9.1     |
| Alcohol (dx or code/recommendation)$^o$ | 5.8     |
| Substance use disorder or long-term drug use code with controlled substance$^p$ | 10.6    |

BMI = body mass index; COPD = chronic obstructive pulmonary disease; ICD = international classification of diseases; kg = kilograms; $m^2$ = body surface area in square 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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