Drug Overdose in a Retrospective Cohort with Non-Cancer Pain Treated with Opioids, Antidepressants, and/or Sedative-Hypnotics: Interactions with Mental Health Disorders

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BACKGROUND: Opioid analgesics and other psychoactive drugs may pose an even greater risk for drug overdose in persons with mental health disorders.

OBJECTIVE: The purpose of this study was to examine interactions of filled prescriptions for opioids, benzodiazepines, antidepressants, and zolpidem with mental health disorders in regard to drug overdose.

DESIGN: The study was a retrospective cohort review.

SUBJECTS: Subjects were national HMO beneficiaries aged 18–64 years, enrolled at least 1 year (01/2009 to 07/2012), who filled at least two prescriptions for Schedule II or III opioids for non-cancer pain.

MAIN MEASURES: The outcome was the first inpatient or outpatient drug overdose after the first filled opioid prescription. Predictors were calculated in 6-month intervals and exactly 6 months before a drug overdose: opioid use (mean daily morphine-equivalent dose), benzodiazepine use (days' supply), antidepressant use (days' supply), zolpidem use (days' supply), mental health disorders (depression, anxiety/PTSD, psychosis), pain-related conditions, and substance use disorders (alcohol, other drug).

KEY RESULTS: A total of 1,385 (0.67 %) subjects experienced a drug overdose (incidence rate 421/100,000 person-years). The adjusted odds ratios (AOR) for overdose among all subjects rose monotonically with daily opioid dose, but highest (AOR=7.06) for persons with depression and a high opioid dose (≥100 mg) versus no depression or opioid use. Longer-term antidepressants (91–180 days) were protective for persons with depression, with 20 % lower AORs for overdose versus short-term (1–30 days) or none. For persons without depression, the AORs of overdose were increased for antidepressant use, but greatest (AOR=1.98) for short-term use versus none. The AORs of overdose increased with the duration of benzodiazepine therapy among all subjects, with over 2.5-fold higher AORs for 91–180 days versus none.

CONCLUSIONS: Opioids and longer-duration benzodiazepines were associated with drug overdose among all subjects, but opioid risk was greatest for persons with depression. Antidepressant use > 90 days reduced the odds of overdose for persons with depression, but all antidepressant use increased the risk for persons without depression.

INTRODUCTION

Between 1999 and 2009, U. S. rates of mortality from accidental pharmaceutical drug overdose rose over fourfold for opioid analgesics and threefold for sedative-hypnotics.[1] Of the more than 22,000 unintentional pharmaceutical overdose deaths nationally in 2010, three-quarters involved opioid analgesics, while benzodiazepines were identified in one-quarter and antidepressants in nearly 20 %.[2] Concurrent use of these drugs appears to carry an even higher risk. The combination of prescribed opioids and benzodiazepines is the most common cause of polysubstance overdose deaths nationally.[1] Persons with mental health disorders are more likely to be treated for chronic pain with high-dose opioid therapy that has also been associated with more co-prescribed sedative-hypnotic therapy.[3] However, we are unaware of studies examining the risk of drug overdose for complex inter-relationships of multiple drugs commonly used by persons with chronic pain and comorbid mental health disorders.

We hypothesized that patients with mental health disorders who take opioids and other psychotherapeutic drugs would have a significantly greater risk for overdose than those who do not. To examine these hypotheses, we analyzed a longitudinal database from a national health maintenance organization (HMO) of persons with non-cancer pain who filled multiple prescriptions for opioid analgesics. This study offers insights into the risks and potential benefits of opioids, benzodiazepines, antidepressants, and/or zolpidem for persons with mental health disorders.

METHODS

Study Setting

The study utilized patient data from the Aetna Health Maintenance Program that provides comprehensive full-service care to approximately 2.1 million persons nationally.

Study data were obtained from enrollment files and claims for services and prescriptions. The study was approved by the Institutional Review Board of the University of Texas Health Science Center at San Antonio.

Study Subjects. The study cohort included persons aged 18 to 64 years with non-cancer pain who filled at least two Schedule II or III prescriptions for non-injectable opioid analgesics from January 2009 through July 2012. Eligible subjects were continuously enrolled at least 12 months in the Aetna plan and had claims for service utilization at least 6 months before the first drug overdose event. The cohort derivation revealed that the most frequent exclusions were due to incomplete opioid prescription data, missing diagnostic data, or a non-basal cell cancer diagnosis (Fig. 1).

Study subjects' medications and clinical conditions were examined for each 6-month interval after the first filled opioid prescription, up to a maximum of seven intervals. Incomplete intervals were excluded. Examples of 6-month interval data for three sample patients are shown in Fig. 2. Subject A had no overdose event; therefore, time-varying covariates were examined for each complete 6 month-interval after the first filled opioid prescription until the subject left the plan or the study time frame ended. Subject B had an overdose within the first 6-month interval. To examine a full 6 months before that event, covariates were based on data from services and medications received before and after the first opioid prescription. For subject C, the overdose occurred in the third 6-month

interval; therefore, time-varying covariates were calculated for 6-month intervals without an event and from the 6 months before the overdose event. Subjects were censored after the first overdose.

Outcome Variable. The study outcome was drug overdose diagnosed from an inpatient or outpatient clinical encounter following the first filled opioid prescription (drug overdose ICD-9-CM codes in Appendix 1). For each subject, this time-varying outcome was measured in each 6-month interval after the first filled opioid prescription until last enrollment or end of the study time frame. For subjects with multiple overdose events in a given 6-month interval, only the first was considered.

Classification of Morphine-Equivalent Dose. Using an approach previously reported by our group,[4] a morphine-equivalent dose (MED) for each Schedule II or III opioid prescription (non-injectable formulations) was calculated from the number of pills dispensed multiplied by strength (in milligrams), then multiplied by a morphine-equivalent conversion factor derived from several sources, including published data,[5,6] conversion tables from Internet sources, and drug information resources (Table 2 in Appendix 2).[7,8] A clinical pharmacist assisted with calculating conversions. We capped the daily dose based on the maximum recommended for that drug.

The total MED was computed by summing the MEDs for all opioid prescriptions within a given 6-month interval. The mean daily MED in a 6-month interval was calculated by dividing the total MED by days' supply for all prescriptions in that interval, excluding overlapping days. We examined five categories for the mean daily MED (i.e., 0, 1–19, 20–49, 50–99, and ≥100 mg), similar to other studies.[9,10] For the first overdose, the mean daily MED was based on data from exactly 6 months before that event (Fig. 2).

Classification of Psychoactive Medications. For each 6-month interval, we summed the days' supply for antidepressants (i.e., SSRIs, SNRIs, and tricyclics), benzodiazepines, and zolpidem. The duration of each drug class or drug was categorized for analysis as follows: 0, 1–30, 31–90, and 91–180 days. Similar to opioid therapy, these time-varying covariates were measured for each 6-month interval, as well as the 6 months before the first overdose event if applicable.

Demographic and Clinical Variables. Study subject demographic data included age as of July 2012, sex, and U.S. region of residence from among four categories as defined by the Centers for Disease Control and Prevention. Time-varying indicators for pain-related conditions were created for each 6-month interval using diagnosis codes for outpatient and hospital encounters, and included the following: back pain, large joint arthritis/other musculoskeletal disorders, neuropathic pain, unspecified chronic pain, and

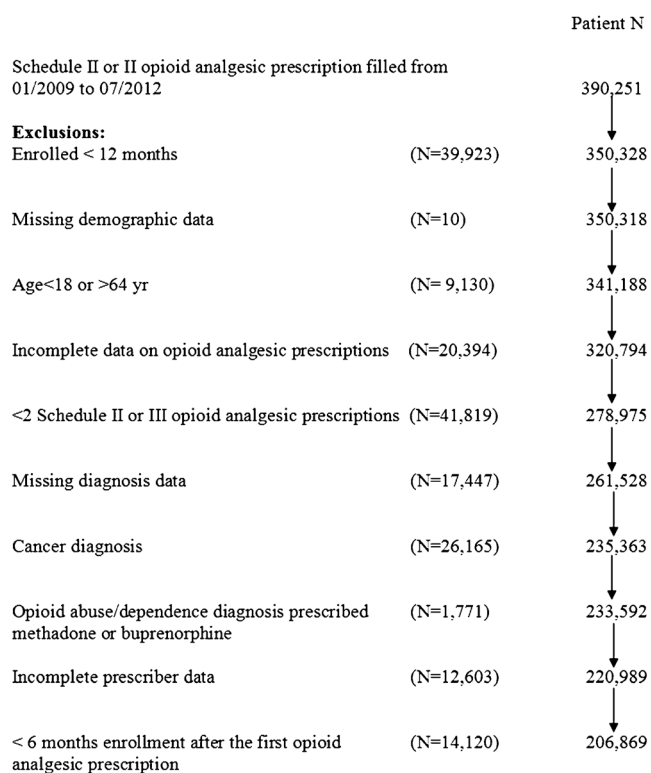|		Patient N
Schedule II or II opioid analgesic prescription filled from 01/2009 to 07/2012		390,251
Exclusions:		
Enrolled < 12 months	(N=39,923)	350,328
Missing demographic data	(N=10)	350,318
Age<18 or >64 yr	(N= 9,130)	341,188
Incomplete data on opioid analgesic prescriptions	(N=20,394)	320,794
<2 Schedule II or III opioid analgesic prescriptions	(N=41,819)	278,975
Missing diagnosis data	(N=17,447)	261,528
Cancer diagnosis	(N=26,165)	235,363
Opioid abuse/dependence diagnosis prescribed methadone or buprenorphine	(N=1,771)	233,592
Incomplete prescriber data	(N=12,603)	220,989
< 6 months enrollment after the first opioid analgesic prescription	(N=14,120)	206,869

Figure 1 Derivation of study cohort of persons filling at least two prescriptions for Schedule II or III opioid analgesics.

Subject	6-Month Interval after First Opioid Prescription†						
	1	2	3	4	5	6	7
A							
B							
C							

Figure 2 Calculation of covariates for persons with an overdose event* and comparison group.* *Dark arrow* shows the date of the overdose event. Persons with an overdose event are censored after the first overdose event. †Date of first opioid prescription indicated by dark line. *A* If no overdose occurred, up to seven 6-month intervals would be observed. Covariates were examined in each observed 6-month interval. *B* Overdose occurred within 6 months of the first opioid prescription, covariates determined from 6 months prior to the overdose date. **Comparison group**: persons with no event in the first interval (such as *A* and *C* in interval 1). *C* Overdose occurred in third 6-month interval, covariates examined from prior 6 months spanning second and third 6-month intervals. **Comparison group**: persons with no event in the third interval (such as *A* in interval 3).

chronic headache (ICD-9-CM codes). Time-varying indicators were also created for mental health/substance use disorders, including anxiety or post-traumatic stress disorder (PTSD), depression, psychosis, drug abuse, and alcohol abuse. Anxiety and PTSD were combined, as the latter was uncommon (<1 %), and these conditions often overlap. Because psychiatric conditions and substance use disorders are usually not transient, once a diagnosis occurred within a 6-month interval, it was considered to persist subsequently. The ICD-9-CM codes used to identify clinical conditions are available upon request.

Analyses. Study cohort characteristics were summarized using descriptive statistics. Differences in characteristics of patients with and without a drug overdose event were examined using the chi-square test for categorical variables and the two-sample t test with an unequal variance assumption for continuous variables. Patterns of treatment with drugs of interest were examined descriptively for each 6-month interval. Using repeated-measures logistic regression with the generalized estimating equations method under an unstructured correlation matrix, we examined the effects of daily opioid dose and duration of filled prescriptions for psychoactive drugs on the odds of overdose, adjusting for time-fixed covariates (i.e., age, sex, and region) as well as time-varying covariates (i.e., chronic pain conditions, mental health, and substance use disorders). Clinical judgment guided a backward model selection procedure. We started with a full model including demographics, clinical conditions, substance use disorders (i.e., drug or alcohol), and medications, as well as all possible interactions of daily opioid dose with each of the three psychoactive drug groups (i.e., benzodiazepines, antidepressants, and zolpidem), and interactions of each of these drugs with mental health conditions (i.e., anxiety/PTSD, depression, and psychotic disorder). The final model included clinically important and/or statistically significant factors. We conducted a post hoc descriptive analysis of combination therapy in each 6-month interval separately for persons diagnosed with depression or anxiety/PTSD. All statistical tests were performed with a two-sided significance level of 0.05 and analyses conducted using SAS software (Version 9.3).

RESULTS

The study cohort comprised over 206,000 subjects; 57 % were women, and the average age was 44 years (Table 1). Nearly half of the cohort resided in southern states, reflecting the distribution of the HMO plan. The most common non-cancer pain-related conditions were musculoskeletal, including large joint arthritis/other musculoskeletal disorders, and back pain-related conditions. With regard to mental health conditions, anxiety/PTSD and depression occurred in 15 and 13 % of the cohort, respectively, while psychosis and alcohol and other substance use disorders were each diagnosed in less than 3 %.

Over the course of 3.5 years, 1,385 of 206,869 (0.67 %) subjects were diagnosed with a drug overdose (Table 1). With the exception of region of residence, persons with an overdose event differed significantly in all observed patient characteristics. Persons who experienced a drug overdose were more likely to be women and of a younger age than those that did not. The greatest clinical differences appeared in patients diagnosed with back pain, chronic pain (unspecified), mental health conditions, and substance use disorders.

Across all 658,280 6-month intervals observed for the cohort, the incidence rate for drug overdose was 421 per 100,000 person-years. The proportion of subjects with a drug overdose was highest (0.06 %) in the first 6-month interval, declining in subsequent intervals from 0.04 to 0.01 %. After the first interval, during which all subjects filled at least one opioid prescription, the proportion receiving opioids subsequently stabilized at 42 to 50 %, with the exception of the last interval, when it

Table 1 Study Cohort Characteristics

Characteristics	Any drug overdose event[*]		Total
	No (*N*=205,484)	Yes (*N*=1385)	(*N*=206,869)
Demographics			
Women, n (%)	116,585 (56.7)	887 (64.0)	117,472 (56.8)
Age, mean (SD)	44.1 (12.0)	42.5 (12.4)	44.1 (12.0)
U.S. Region, n (%)			
Midwest	11,950 (5.8)	78 (5.6)	12,028 (5.8)
Northeast	60,146 (29.3)	421 (30.4)	60,567 (29.3)
South	96,413 (46.9)	659 (47.6)	97,072 (46.9)
West	36,975 (18.0)	227 (16.4)	37,202 (18.0)
Clinical conditions[†], n (%)			
Non-cancer pain conditions			
Large joint arthritis, other musculoskeletal[‡]	101,577 (49.4)	739 (53.4)	102,316 (49.5)
Back pain	79,801 (38.8)	722 (52.1)	80,523 (38.9)
Neuropathy	1762 (0.9)	26 (1.9)	1788 (0.9)
Chronic pain (unspecified)	13,874 (6.8)	337 (24.3)	14,211 (6.9)
Headache	14,460 (7.0)	175 (12.6)	14,635 (7.1)
Mental health and substance use disorders			
Anxiety or post-traumatic stress disorder	30,308 (14.8)	579 (41.8)	30,887 (14.9)
Depression	25,466 (12.4)	757 (54.7)	26,223 (12.7)
Psychosis	5268 (2.6)	335 (24.2)	5603 (2.7)
Alcohol abuse	4283 (2.1)	354 (25.6)	4637 (2.2)
Other substance abuse	4044 (2.0)	376 (27.2)	4420 (2.1)

[*] *P value for comparison of all variables was <0.001 except for region (0.43)*
[†] *Clinical conditions diagnosed at any point in study time frame. ICD-9-CM codes available from authors*
[‡] *Arthritis, arthralgia, fracture, sprains*

was approximately 60 %. In the first interval, over one-third of subjects received higher-daily-dose opioids (≥50 mg), which then declined to about 16 %, except for the last interval, when nearly 30 % received higher-dose opioids.

With regard to psychoactive medications, 19 to 24 % of the cohort filled one or more antidepressant prescriptions in each 6-month interval, with 11 to 16 % filling over 90 days' supply in a given interval. Fifteen to twenty-five percent of the cohort filled at least one benzodiazepine prescription, and 7 to 13 % received more than 90 days' supply. At least one zolpidem prescription was filled by 8 to 12 % of the cohort, with 4 to 7 % filling more than 90 days' supply.

In the fully adjusted model predicting drug overdose, the following significant interactions were observed: opioid therapy with depression (chi(4)=36.53, *p*<0.001); antidepressant therapy with depression (chi(3)=20.20, *p*<0.001); benzodiazepine therapy with anxiety/PTSD (chi(3)=10.36, *p*=0.016) and zolpidem therapy with anxiety/PTSD diagnosis (chi(3)=8.79, *p*=0.03) (Fig. 3; full model-fitting results in Appendix 3). In the interaction between opioid therapy and depression (Fig. 3a), the adjusted odds of overdose were significantly higher for persons with depression than those without this diagnosis, regardless of opioid dose (all *p*<0.001). The adjusted odds of drug overdose were 7.06 (95 % CI: 5.30 to 9.42) for the combined effect of depression and very high opioid dose (≥100 mg) versus no depression or opioid use. Among persons without depression, drug overdose was associated with increasing opioid dose (chi2(4)=161.4, *p*<0.001), but the risk rose gradually with all but a very high daily dose, for which the adjusted odds were 4.34 (95 % CI: 3.37 to 5.57) versus no opioids. Among persons with depression, an increasing opioid

dose monotonically increased the likelihood of drug overdose (chi2(4)=24.20, *p*<0.001), with adjusted odds of 1.78 (95 % CI: 1.39 to 2.29) for a very high opioid dose versus no opioids.

An interaction between antidepressant therapy and depression (Fig. 3b) showed that regardless of antidepressant therapy, the risk of drug overdose was significantly greater for persons diagnosed with depression than for those who were not (all *p*<0.001). For persons with depression, long-term antidepressant therapy (91–180 days) was associated with overdose events (chi2(3)=8.49, *p*=0.037), but this association was protective, with an adjusted odds ratio of 0.79 (95 % CI: 0.66 to 0.95) versus none. On the other hand, shorter-term therapy (≤ 90 days) had no benefit (*p*=0.72 for 1–30 days; *p*=0.133 for 31–90 days). For persons without a diagnosis of depression, antidepressant therapy increased the likelihood of overdose (chi2(3)=28.10, *p*<0.001); this effect was greatest for short-term (1–30 days) antidepressant use, with adjusted odds of 1.98 (95 % CI: 1.48 to 2.65), declining to 1.33 (95 % CI: 1.05 to 1.68, *p*=0.018) for long-term antidepressants (91–180 days) versus none.

Among all subjects, the likelihood of overdose was similarly increased by benzodiazepine therapy, regardless of duration (all *p*>0.06) (Fig. 3c). An interaction showed that duration of benzodiazepine therapy among persons with anxiety/PTSD had a non-monotonic association with drug overdose, but the association was monotonic among persons without anxiety/PTSD. The adjusted odds for drug overdose was highest [OR=2.85 (95 % CI: 2.34 to 3.48)] for persons without anxiety/PTSD who received long-term (91–180 days) benzodiazepine therapy versus none.

Zolpidem use similarly increased the odds of overdose for persons with or without anxiety/PTSD (all *p*>0.10), except for

A Interaction between Opioids and Depression

B Interaction between Antidepressants and Depression

C Interaction between Benzodiazepines and Anxiety/PTSD

D Interaction between Zolpidem and Anxiety/PTSD
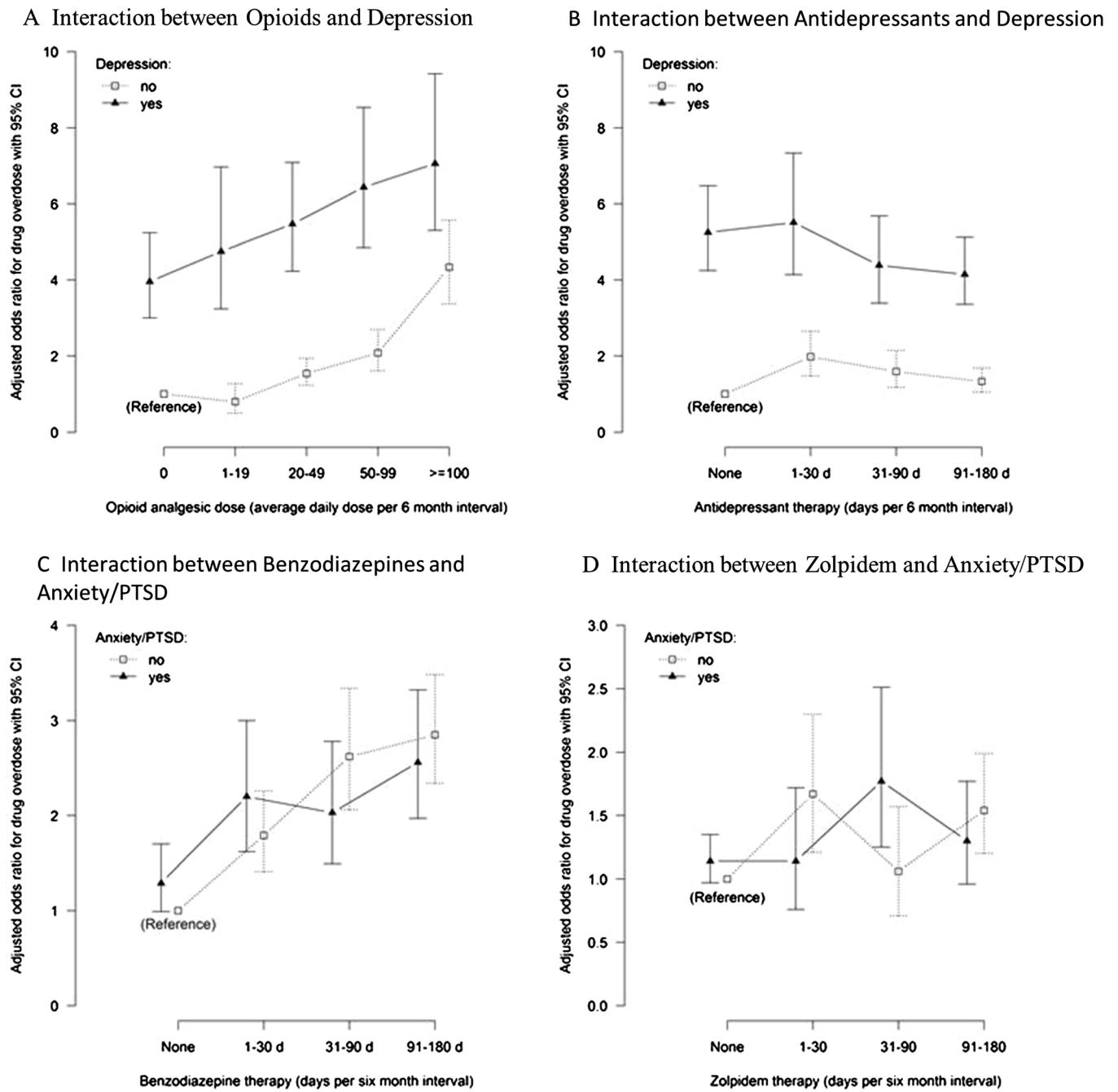

Figure 3 Adjusted odds ratios for drug overdose associated with significant interactions of opioid analgesics and selected psychotherapeutic drugs with mental health conditions. Other variables in the model include: daily morphine-equivalent dose category, time interval, age, gender, region, five chronic non-cancer pain conditions, anxiety/PTSD, depression, psychotic disorder, alcohol abuse, drug abuse, antidepressant therapy, benzodiazepine therapy, and zolpidem per 6-month interval (medications analyzed in four levels: none, 1–30 days, 31–90 days, 91–180 days).

31–90 days (p=0.05). Among persons with anxiety/PTSD, duration of zolpidem use was not associated with drug overdose events (chi2(3)=6.52, p=0.089), but among those without anxiety/PTSD, the association was significant (chi2(3)=18.92, p<0.0001). Among persons without anxiety/PTSD, the adjusted odds of overdose were 1.67 (95 % CI: 1.21 to 2.30) for short-term therapy (1–30 days) versus none, and 1.54 (95 % CI: 1.20 to 1.99) for long-term therapy (91–180 days) versus none. However, the odds of overdose were highest for persons with anxiety/PTSD and 31–90 days of zolpidem therapy

(OR=1.77, 95 % CI: 1.25 to 2.51) versus no anxiety/PTSD and no zolpidem.

A post hoc analysis revealed that among persons diagnosed with depression, treatment with multiple medications was most likely to have occurred in the first 6-month interval, when all subjects filled opioid prescriptions and 69 % also received antidepressants, 45 % received benzodiazepines, and 20 % received zolpidem (Table 5 in Appendix 4). Prescriptions for all four classes of drugs were filled by 5 to 10 % of patients with depression, depending on the 6-month interval. Among

patients with anxiety/PTSD, over half also filled prescriptions for antidepressants or benzodiazepines in the first 6 month-interval, and about 25 % continued both opioids and antidepressants in subsequent intervals, while about 30 % continued both opioids and benzodiazepines.

DISCUSSION

Among over 200,000 HMO beneficiaries with non-cancer pain who filled multiple prescriptions for Schedule II or III opioids, complex interactions with regard to risk of drug overdose appeared between mental health disorders and treatment with opioids or other psychotherapeutic drugs. The adjusted odds of drug overdose in a 6-month interval for high daily morphine-equivalent dose of ≥100 mg increased seven-fold for persons with depression and fourfold for persons without depression. These data are consistent with studies reporting up to a ninefold greater risk of opioid overdose for high-dose opioid therapy (≥100 mg),[10] although our analyses more clearly distinguish the risk for persons with depression.

A novel finding in this study among persons diagnosed with depression was a significant protective effect with regard to drug overdose for longer-term (> 90 days) antidepressant therapy compared to no antidepressant use. Depression is highly prevalent in persons with chronic pain, ranging from 18 to 56 % in a systematic review.[11] A mood disorder may precede or often follows the development of chronic pain and is associated with greater pain severity.[12] Long-term antidepressant therapy can offer dual benefits of improving mood and, as reported in a recent systematic review, improved pain-related outcomes for diverse types of painful conditions.[13]

On the other hand, among persons without depression, antidepressant therapy was associated with significantly greater odds of drug overdose, which was greatest for short-term (1–30 days) therapy. This is unlikely due to suicide attempts after initiating antidepressants, which has primarily been a concern for children and adolescents,[14] or to poisoning by these drugs, as it is relatively rare.[15] Several studies have reported no benefit for short-term antidepressant therapy in the treatment of depression, but less is known about the effects on pain.[16,17] Short-term antidepressant therapy may be an indicator for non-adherence[16] to this medication and increased reliance on riskier medications for pain management. Alternatively, in an analysis of root causes of opioid overdose deaths, Webster and colleagues suggested that antidepressant use could pose risks due to central nervous system depressant effects, and recommended structured care for persons with mental health disorders who are treated with opioids for pain.[18] Unfortunately, psychiatric care is lacking in the management of many chronic pain patients.[19]

Calcaterra and colleagues reported that opioids plus benzodiazepines were the most common cause of polysubstance overdose deaths in a national study from 1999 to 2009, and increased the risk of drug overdose associated with opioids.[1] In our cohort, benzodiazepines significantly increased the risk of overdose but did not disproportionately affect persons with mental health disorders. However, we did find that the odds of overdose progressively rose with longer duration of benzodiazepine therapy. In our national HMO cohort, 45 % of depressed patients were receiving concurrent opioids and benzodiazepines at any one time, and this dangerous combination additively increased the likelihood of overdose. Depending on duration of use, zolpidem increased the odds of overdose by as much as 77 %, and was received by 10 to 20 % of patients with opioids. These data add to the body evidence of risks for zolpidem use along with other frequently misused drugs such as opioids.[20]

This study has several limitations to acknowledge. First, we relied on coded diagnoses to identify mental health disorders that have limited sensitivity, although this misclassification should attenuate our findings, because persons with depression would be included among those without. We also relied on coded diagnoses to identify drug overdose events that miss overdoses occurring out of network or resulting in outpatient death. However, the rate of drug overdose events in this cohort (421/100,000 person-years) in inpatient and outpatient health care settings was predictably higher than the rate of 238.1/100,000 person-years for drug overdose from an analysis of only emergency room visits in North Carolina in 2011.[21] Second, we assumed that patients were taking drugs after they filled prescriptions, but non-adherence for opioids in particular is a major concern.[22,23] In addition, total and average daily opioid dose were computed using days' supply data that may not be reliable. Third, we examined patients' medications and overdose events in 6-month intervals in order to establish a tractable but reasonably long time frame to examine receipt of drugs and this outcome. By design, our analysis only considers prescriptions filled before the overdose event. Reassuringly, our observed associations between opioid use and overdose are similar to those from longitudinal studies of drugs prescribed before an opioid-related overdose death.[24] Fourth, drug overdoses in this cohort may have been due to illicit drug use. According to the CDC, however, opioid painkillers have been involved in the majority of unintentional drug overdose deaths nationally since 2003.[25] Fifth, we were unable to distinguish unintentional overdose from suicide attempts. Sixth, although we adjusted for alcohol and other drug abuse disorders, these conditions likely further complicate observed interactions of opioids and other psychotropic medications with mental health disorders.

This study has several notable strengths. We examined all drug overdose events, instead of only deaths, which represent only a small fraction of these events.

We used data for filled prescriptions instead of prescriptions from an electronic medical record that may or may not have been filled. Our study also has several implications for clinical practice. Among persons with depression, opioid use had a dose–response association with increased odds of drug overdose, and thus dose minimization is essential. Among persons without depression, the odds of overdose rose rapidly for a daily opioid dose of 100 mg or higher. These data reinforce recommendations to use non-pharmacologic pain management approaches such as cognitive behavioral therapy as a means to limit opioid use.[26] We also found that duration of benzodiazepine use was linearly associated with greater overdose risk, but even short-term treatment was positively associated with overdose. Concurrent use of these drugs is common, and represents an important risk. Although the effect of zolpidem was lower, it nonetheless additively increased the risk of overdose. With regard to risk mitigation, our study found a significant protective effect with antidepressant therapy for longer than 90 days among persons diagnosed with depression. Unfortunately, antidepressants appeared to increase the risk of overdose for persons without depression. Overall, these data reinforce the complexities of medication management for chronic pain and support expert recommendations to employ non-drug approaches to pain control while minimizing the risks associated with these drugs.[27]

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APPENDIX 1. ICD-9-CM CODE FOR DIAGNOSIS OF DRUG OVERDOSE

ICD-9-CM code, 965.0, 965.00, 965.02, 965.09, 965.1, 965.4, 965.61, 965.69, 965.8, 965.9, 967.6, 967.8, 967.9, 969.4, 977.9, E850.1-E850.6, E850.8, E850.9, E852.8, E852.9, E853.2, E950.0 or E950.2.

APPENDIX 2

Table 2 Morphine Conversion Factors

gpi_cd	drug_nm	gpi_nm	short_act	max_daily	morph_eqv_fctr	drg_strnth_mg	adj_dose
65991002052020	APAP/CODEINE SOL 120-12/5	Acetaminophen w/ Codeine Soln 120–12 MG/5ML	1	150	0.15	2.4	0.36
65991002051805	CAPITAL/COD SUS 120-12/5	Acetaminophen w/ Codeine Susp 120–12 MG/5ML	1	150	0.15	2.4	0.36
65991002050310	APAP/CODEINE TAB 300-15MG	Acetaminophen w/ Codeine Tab 300–15 MG	1	13	0.15	15	2.25
65991002050315	APAP/CODEINE TAB 300-30MG	Acetaminophen w/ Codeine Tab 300–30 MG	1	12	0.15	30	4.5
65991002050320	APAP/CODEINE TAB 300-60MG	Acetaminophen w/ Codeine Tab 300–60 MG	1	6	0.15	60	9
65991303050120	TREZIX CAP	Acetaminophen-Caffeine-Dihydrocodeine Cap 356.4-30	1	10	0.25	16	4
65991303050340	APAP/CAFF/DI TAB HYDROCOD	Acetaminophen-Caffeine-Dihydrocodeine Tab 712.8-60	1	5	0.25	32	8
65200010100760	BUPRENORPHIN SUB 2MG	Buprenorphine HCl SL Tab 2 MG (Base Equiv)	0	3	75	2	150
65200010100780	BUPRENORPHIN SUB 8MG	Buprenorphine HCl SL Tab 8 MG (Base Equiv)	0	3	75	8	600
65200010208220	SUBOXONE MIS 2-0.5MG	Buprenorphine HCl-Naloxone HCl SL Film 2-0.5 MG (B	0	3	75	2	150
65200010208240	SUBOXONE MIS 8-2MG	Buprenorphine HCl-Naloxone HCl SL Film 8-2 MG (Bas)	0	3	75	8	600
65200010200720	SUBOXONE SUB 2-0.5MG	Buprenorphine HCl-Naloxone HCl SL Tab 2-0.5 MG (Ba)	0	3	75	2	150
65200010200740	SUBOXONE SUB 8-2MG	Buprenorphine HCl-Naloxone HCl SL Tab 8-2 MG (Base)	0	3	75	8	600
65200010008830	BUTRANS DIS 10MCG/HR	Buprenorphine TD Patch Weekly 10 MCG/HR	0	0.286	1800	0.01	18
65200010008840	BUTRANS DIS 20MCG/HR	Buprenorphine TD Patch Weekly 20 MCG/HR	0	0.143	1800	0.02	36
65200010008820	BUTRANS DIS 5MCG/HR	Buprenorphine TD Patch Weekly 5 MCG/HR	0	0.286	1800	0.005	9
65991004100115	BUT/APAP/CAF CAP CODEINE	Butalbital-Acetaminophen-Caff w/ COD Cap 50-325-40	1	6	0.15	30	4.5
65991004300115	ASCOMP/COD CAP 30MG	Butalbital-Aspirin-Caff w/ Codeine Cap 50-325-40-3	1	6	0.15	30	4.5
65100020200305	CODEINE SULF TAB 15MG	Codeine Sulfate Tab 15 MG	1	13	0.15	15	2.25
65100020200310	CODEINE SULF TAB 30MG	Codeine Sulfate Tab 30 MG	1	12	0.15	30	4.5
65100020200315	CODEINE SULF TAB 60MG	Codeine Sulfate Tab 60 MG	1	6	0.15	60	9
65991303100115	SYNALGOS DC CAP	Dihydrocodeine Compound Cap	1	10	0.25	16	4

Table 2. (continued)

gpi_cd	drug_nm	gpi_nm	short_act	max_daily	morph_eqv_fctr	drg_strnth_mg	adj_dose
65100025100310	FENTORA TAB 100MCG	Fentanyl Citrate Buccal Tab 100 MCG (Base Equiv)	1	4	125	0.1	12.5
65100025100320	FENTORA TAB 200MCG	Fentanyl Citrate Buccal Tab 200 MCG (Base Equiv)	1	4	125	0.2	25
65100025100330	FENTORA TAB 400MCG	Fentanyl Citrate Buccal Tab 400 MCG (Base Equiv)	1	4	125	0.4	50
65100025100340	FENTORA TAB 600MCG	Fentanyl Citrate Buccal Tab 600 MCG (Base Equiv)	1	4	125	0.6	75
65100025100350	FENTORA TAB 800MCG	Fentanyl Citrate Buccal Tab 800 MCG (Base Equiv)	1	4	125	0.8	100
65100025108475	FENTANYL OT LOZ 1200MCG	Fentanyl Citrate Lollipop 1200 MCG	1	4	125	1.2	150
65100025108485	FENTANYL OT LOZ 1600MCG	Fentanyl Citrate Lollipop 1600 MCG	1	4	125	1.6	200
65100025108450	FENTANYL OT LOZ 200MCG	Fentanyl Citrate Lollipop 200 MCG	1	4	125	0.2	25
65100025108455	FENTANYL OT LOZ 400MCG	Fentanyl Citrate Lollipop 400 MCG	1	4	125	0.4	50
65100025108460	FENTANYL OT LOZ 600MCG	Fentanyl Citrate Lollipop 600 MCG	1	4	125	0.6	75
65100025108465	FENTANYL OT LOZ 800MCG	Fentanyl Citrate Lollipop 800 MCG	1	4	125	0.8	100
65100025100720	ABSTRAL SUB 200MCG	Fentanyl Citrate SL Tab 200 MCG (Base Equiv)	1	4	125	0.2	25
65100025000910	SUBSYS SPR 100MCG	Fentanyl Sublingual Spray 100 MCG	1	4	125	0.1	12.5
65100025000920	SUBSYS SPR 200MCG	Fentanyl Sublingual Spray 200 MCG	1	4	125	0.2	25
65100025008650	FENTANYL DIS 100MCG/H	Fentanyl TD Patch 72HR 100 MCG/HR	0	1.5	2400	0.1	240
65100025008610	FENTANYL DIS 12MCG/HR	Fentanyl TD Patch 72HR 12 MCG/HR	0	0.5	2400	0.0125	30
65100025008620	FENTANYL DIS 25MCG/HR	Fentanyl TD Patch 72HR 25 MCG/HR	0	0.5	2400	0.025	60
65100025008630	FENTANYL DIS 50MCG/HR	Fentanyl TD Patch 72HR 50 MCG/HR	0	0.5	2400	0.05	120
65100025008640	FENTANYL DIS 75MCG/HR	Fentanyl TD Patch 72HR 75 MCG/HR	0	1	2400	0.075	180
65991702100353	HYDROCO/APAP TAB 10–750MG	HYDROCO/APAP TAB 10–750MG	1	5	1	10	10
65991702100110	STAGESIC CAP 500-5MG	Hydrocodone-Acetaminophen Cap 5–500 MG	1	8	1	5	5
65991702102024	ZOLVIT SOL 10–300MG	Hydrocodone-Acetaminophen Soln 10–300 MG/15ML	1	200	1	0.67	0.67
65991702102025	ZAMICET SOL 10–325MG	Hydrocodone-Acetaminophen Soln 10–325 MG/15ML	1	184.6	1	0.67	0.67
65991702102015	HYCET SOL 7.5–325	Hydrocodone-Acetaminophen Soln 7.5–325 MG/15ML	1	184.6	1	0.5	0.5
65991702102020	HYDROCODONE/ SOL APAP	Hydrocodone-Acetaminophen Soln 7.5–500 MG/15ML	1	120	1	0.5	0.5
65991702100375	XODOL TAB 10–300MG	Hydrocodone-Acetaminophen Tab 10–300 MG	1	13	1	10	10
65991702100305	HYDROCO/APAP TAB 10–325MG	Hydrocodone-Acetaminophen Tab 10–325 MG	1	12	1	10	10

gpi_cd	drug_nm	gpi_nm	short_act	max_daily	morph_eqv_fctr	drg_strnth_mg	adj_dose
65991702100370	ZYDONE TAB 10–400MG	Hydrocodone-Acetaminophen Tab 10–400 MG	1	10	1	10	10
65991702100327	HYDROCO/APAP TAB 10–500MG	Hydrocodone-Acetaminophen Tab 10–500 MG	1	8	1	10	10
65991702100345	HYDROCO/APAP TAB 10–650MG	Hydrocodone-Acetaminophen Tab 10–650 MG	1	6	1	10	10
65991702100346	HYDROCO/APAP TAB 10–660MG	Hydrocodone-Acetaminophen Tab 10–660 MG	1	6	1	10	10
65991702100307	HYDROCO/APAP TAB 2.5–500	Hydrocodone-Acetaminophen Tab 2.5–500 MG	1	8	1	2.5	2.5
65991702100309	HYDROCO/APAP TAB 5–300MG	Hydrocodone-Acetaminophen Tab 5–300 MG	1	13	1	5	5
65991702100356	HYDROCO/APAP TAB 5–325MG	Hydrocodone-Acetaminophen Tab 5–325 MG	1	12	1	5	5
65991702100310	HYDROCO/APAP TAB 5–500MG	Hydrocodone-Acetaminophen Tab 5–500 MG	1	8	1	5	5
65991702100322	XODOL TAB 7.5–300	Hydrocodone-Acetaminophen Tab 7.5–300 MG	1	13	1	7.5	7.5
65991702100358	HYDROCO/APAP TAB 7.5–325	Hydrocodone-Acetaminophen Tab 7.5–325 MG	1	12	1	7.5	7.5
65991702100365	ZYDONE TAB 7.5–400	Hydrocodone-Acetaminophen Tab 7.5–400 MG	1	10	1	7.5	7.5
65991702100325	HYDROCO/APAP TAB 7.5–500	Hydrocodone-Acetaminophen Tab 7.5–500 MG	1	8	1	7.5	7.5
65991702100340	HYDROCO/APAP TAB 7.5–650	Hydrocodone-Acetaminophen Tab 7.5–650 MG	1	6	1	7.5	7.5
65991702100350	HYDROCO/APAP TAB 7.5–750	Hydrocodone-Acetaminophen Tab 7.5–750 MG	1	5	1	7.5	7.5
65991702500330	REPREXAIN TAB 10–200MG	Hydrocodone-Ibuprofen Tab 10–200 MG	1	5	1	10	10
65991702500310	REPREXAIN TAB 2.5–200	Hydrocodone-Ibuprofen Tab 2.5–200 MG	1	5	1	2.5	2.5
65991702500315	HYDROCOD/IBU TAB 5–200MG	Hydrocodone-Ibuprofen Tab 5–200 MG	1	5	1	5	5
65991702500320	HYDROCOD/IBU TAB 7.5–200	Hydrocodone-Ibuprofen Tab 7.5–200 MG	1	5	1	7.5	7.5
65100035100920	HYDROMORPHON LIQ 1MG/ML	Hydromorphone HCl Liqd 1 MG/ML	1	480	4	1	4
65100035105205	HYDROMORPHON SUP 3MG	Hydromorphone HCl Suppos 3 MG	1	12	4	3	12
65100035100310	HYDROMORPHON TAB 2MG	Hydromorphone HCl Tab 2 MG	1	16	4	2	8
65100035100320	HYDROMORPHON TAB 4MG	Hydromorphone HCl Tab 4 MG	1	8	4	4	16
65100035100330	HYDROMORPHON TAB 8MG	Hydromorphone HCl Tab 8 MG	1	4	4	8	32
65100035107530	EXALGO TAB 12MG	Hydromorphone HCl Tab SR 24HR 12 MG	0	2	4	12	48
65100035107540	EXALGO TAB 16MG	Hydromorphone HCl Tab SR 24HR 16 MG	0	2	4	16	64

Table 2. (continued)

gpi_cd	drug_nm	gpi_nm	short_act	max_daily	morph_eqv_fctr	drg_strnth_mg	adj_dose
65100035107555	EXALGO TAB 32MG	Hydromorphone HCl Tab SR 24HR 32 MG	0		4	32	128
65100035107520	EXALGO TAB 8MG	Hydromorphone HCl Tab SR 24HR 8 MG	0	4	4	8	32
65100045102060	MEPERIDINE SOL 50MG/5ML	Meperidine HCl Oral Soln 50 MG/5ML	1	60	0.1	10	1
65100045100310	MEPERITAB TAB 100MG	Meperidine HCl Tab 100 MG	1	6	0.1	100	10
65100045100305	MEPERITAB TAB 50MG	Meperidine HCl Tab 50 MG	1	12	0.1	50	5
65993002200110	MEPROZINE CAP 50-25MG	Meperidine w/ Promethazine Cap 50-25 MG	1	12	0.1	50	5
65100050101310	METHADONE CON 10MG/ML	Methadone HCl Conc 10 MG/ML	1	40	3	10	30
65100050102015	METHADONE SOL 10MG/5ML	Methadone HCl Soln 10 MG/5ML	1	200	3	2	6
65100050102010	METHADONE SOL 5MG/5ML	Methadone HCl Soln 5 MG/5ML	1	400	3	1	3
65100050100310	METHADONE TAB 10MG	Methadone HCl Tab 10 MG	1	40	3	10	30
65100050100305	METHADONE TAB 5MG	Methadone HCl Tab 5 MG	1	80	3	5	15
65100050107320	METHADONE TAB 40MG	Methadone HCl Tab For Oral Susp 40 MG	1	10	3	40	120
65100055107480	MORPHINE SUL TAB 200MG ER	MORPHINE SUL TAB 200MG ER	0		1	200	200
65100055102090	MORPHINE SUL SOL 20MG/ML	Morphine Sulfate (Concentrate) Oral Soln 20 MG/ML	1	36	1	20	20
65100055207050	AVINZA CAP 120MG ER	Morphine Sulfate Beads Cap SR 24HR 120 MG	0	13	1	120	120
65100055207020	AVINZA CAP 30MG	Morphine Sulfate Beads Cap SR 24HR 30 MG	0	1	1	30	30
65100055207025	AVINZA CAP 45MG	Morphine Sulfate Beads Cap SR 24HR 45 MG	0	1	1	45	45
65100055207030	AVINZA CAP 60MG CR	Morphine Sulfate Beads Cap SR 24HR 60 MG	0	1	1	60	60
65100055207035	AVINZA CAP 75MG	Morphine Sulfate Beads Cap SR 24HR 75 MG	0	21	1	75	75
65100055207040	AVINZA CAP 90MG CR	Morphine Sulfate Beads Cap SR 24HR 90 MG	0	17	1	90	90
65100055107010	KADIAN CAP 10MG CR	Morphine Sulfate Cap SR 24HR 10 MG	0	1	1	10	10
65100055107060	KADIAN CAP 100MG CR	Morphine Sulfate Cap SR 24HR 100 MG	0	1	1	100	100
65100055107020	KADIAN CAP 20MG CR	Morphine Sulfate Cap SR 24HR 20 MG	0	2	1	20	20
65100055107030	KADIAN CAP 30MG CR	Morphine Sulfate Cap SR 24HR 30 MG	0	1	1	30	30
65100055107040	KADIAN CAP 50MG CR	Morphine Sulfate Cap SR 24HR 50 MG	0	1	1	50	50
65100055107045	KADIAN CAP 60MG CR	Morphine Sulfate Cap SR 24HR 60 MG	0	1	1	60	60

Table 2. (continued)

gpi_cd	drug_nm	gpi_nm	short_act	max_daily	morph_eqv_fctr	drg_strnth_mg	adj_dose
65100055107050	KADIAN CAP 80MG CR	Morphine Sulfate Cap SR 24HR 80 MG	0	1	1	80	80
65100055102065	MORPHINE SUL SOL 10MG/5ML	Morphine Sulfate Oral Soln 10 MG/5ML	1	480	1	2	2
65100055102070	MORPHINE SUL SOL 20MG/5ML	Morphine Sulfate Oral Soln 20 MG/5ML	1	240	1	4	4
65100055100310	MORPHINE SUL TAB 15MG	Morphine Sulfate Tab 15 MG	1	12	1	15	15
65100055100315	MORPHINE SUL TAB 30MG	Morphine Sulfate Tab 30 MG	1	6	1	30	30
65100055107314	MORPHINE SUL TAB 10MG	Morphine Sulfate Tab Sol 10 MG	1	480	1	10	10
65100055107460	MORPHINE SUL TAB 100MG ER	Morphine Sulfate Tab SR 12HR 100 MG	0	3	1	100	100
65100055107415	MORPHINE SUL TAB 15MG ER	Morphine Sulfate Tab SR 12HR 15 MG	0	3	1	15	15
65100055107430	MORPHINE SUL TAB 30MG CR	Morphine Sulfate Tab SR 12HR 30 MG	0	3	1	30	30
65100055107445	MORPHINE SUL TAB 60MG ER	Morphine Sulfate Tab SR 12HR 60 MG	0	3	1	60	60
65100055700270	EMBEDA CAP 100-4MG	Morphine-Naltrexone Cap CR 100-4 MG	0		1	100	100
65100055700220	EMBEDA CAP 20-0.8MG	Morphine-Naltrexone Cap CR 20-0.8 MG	0	4	1	20	20
65100055700230	EMBEDA CAP 30-1.2MG	Morphine-Naltrexone Cap CR 30-1.2 MG	0	6	1	30	30
65100055700240	EMBEDA CAP 50-2MG	Morphine-Naltrexone Cap CR 50-2 MG	0	2	1	50	50
65100055700250	EMBEDA CAP 60-2.4MG	Morphine-Naltrexone Cap CR 60-2.4 MG	0	4	1	60	60
65100055700260	EMBEDA CAP 80-3.2MG	Morphine-Naltrexone Cap CR 80-3.2 MG	0		1	80	80
65990002200337	NARVOX TAB 10–500MG	NARVOX TAB 10–500MG	1	8	1.5	10	15
65100075100110	OXYIR CAP 5MG	Oxycodone HCl Cap 5 MG	1	18	1.5	5	7.5
65100075101320	ETH-OXYDOSE CON 20MG/ML	Oxycodone HCl Conc 20 MG/ML	1	36	1.5	20	30
65100075102005	OXYCODONE SOL 5MG/5ML	Oxycodone HCl Soln 5 MG/5ML	1	360	1.5	1	1.5
65100075100320	OXYCODONE TAB 10MG	Oxycodone HCl Tab 10 MG	1	12	1.5	10	15
65100075100325	OXYCODONE TAB 15MG	Oxycodone HCl Tab 15 MG	1	12	1.5	15	22.5
65100075100330	OXYCODONE TAB 20MG	Oxycodone HCl Tab 20 MG	1	12	1.5	20	30
65100075100340	OXYCODONE TAB 30MG	Oxycodone HCl Tab 30 MG	1	24	1.5	30	45
65100075100310	OXYCODONE TAB 5MG	Oxycodone HCl Tab 5 MG	1	18	1.5	5	7.5
65100075107410	OXYCONTIN TAB 10MG CR	Oxycodone HCl Tab SR 12HR 10 MG	0	3	1.5	10	15
65100075107415	OXYCONTIN TAB 15MG CR	Oxycodone HCl Tab SR 12HR 15 MG	0	3	1.5	15	22.5
65100075107420	OXYCONTIN TAB 20MG CR	Oxycodone HCl Tab SR 12HR 20 MG	0	3	1.5	20	30
65100075107430	OXYCONTIN TAB 30MG CR	Oxycodone HCl Tab SR 12HR 30 MG	0	3	1.5	30	45
65100075107440	OXYCONTIN TAB 40MG CR	Oxycodone HCl Tab SR 12HR 40 MG	0	3	1.5	40	60
65100075107460	OXYCONTIN TAB 60MG CR	Oxycodone HCl Tab SR 12HR 60 MG	0	3	1.5	60	90
65100075107480	OXYCONTIN TAB 80MG CR	Oxycodone HCl Tab SR 12HR 80 MG	0	8	1.5	80	120
65990002200120	OXYCOD/APAP CAP 5–500MG	Oxycodone w/ Acet-aminophen Cap 5–500 MG	1	8	1.5	5	7.5
65990002202005	ROXICET SOL 5-325/5	Oxycodone w/ Acet-aminophen Soln 5–325 MG/5ML	1	65	1.5	1	1.5

Table 2. (continued)

gpi_cd	drug_nm	gpi_nm	short_act	max_daily	morph_eqv_fctr	drg_strnth_mg	adj_dose
65990002200333	PRIMLEV TAB 10–300MG	Oxycodone w/ Acet-aminophen Tab 10–300 MG	1	13	1.5	10	15
65990002200335	OXYCOD/APAP TAB 10–325MG	Oxycodone w/ Acet-aminophen Tab 10–325 MG	1	12	1.5	10	15
65990002200336	MAGNACET TAB 10–400MG	Oxycodone w/ Acet-aminophen Tab 10–400 MG	1	10	1.5	10	15
65990002200340	OXYCOD/APAP TAB 10–650MG	Oxycodone w/ Acet-aminophen Tab 10–650 MG	1	6	1.5	10	15
65990002200305	OXYCOD/APAP TAB 2.5–325	Oxycodone w/ Acet-aminophen Tab 2.5–325 MG	1	12	1.5	2.5	3.75
65990002200308	PRIMALEV TAB 5–300	Oxycodone w/ Acet-aminophen Tab 5–300 MG	1	12	1.5	5	7.5
65990002200310	OXYCOD/APAP TAB 5–325MG	Oxycodone w/ Acetaminophen Tab 5–325 MG	1	12	1.5	5	7.5
65990002200315	MAGNACET TAB 5–400MG	Oxycodone w/ Acet-aminophen Tab 5–400 MG	1	10	1.5	5	7.5
65990002200325	PRIMALEV TAB 7.5–300	Oxycodone w/ Acet-aminophen Tab 7.5–300 MG	1	13	1.5	7.5	11.25
65990002200327	OXYCOD-APAP TAB 7.5–325	Oxycodone w/ Acet-aminophen Tab 7.5–325 MG	1	12	1.5	7.5	11.25
65990002200328	MAGNACET TAB 7.5–400	Oxycodone w/ Acet-aminophen Tab 7.5–400 MG	1	10	1.5	7.5	11.25
65990002200330	OXYCOD/APAP TAB 7.5–500	Oxycodone w/ Acet-aminophen Tab 7.5–500 MG	1	8	1.5	7.5	11.25
65990002220320	PERCODAN TAB	Oxycodone w/ Aspirin Tab Full Strength	1	12	1.5	4.8355	7.25325
65990002220340	OXYCOD/ASA TAB	Oxycodone-Aspirin Tab 4.8355-325 MG	1	12	1.5	4.8355	7.25325
65990002260320	OXYCOD/IBU TAB 5–400MG	Oxycodone-Ibuprofen Tab 5–400 MG	1	4	1.5	5	7.5
65100080100310	OXYMORPHONE TAB HCL 10MG	Oxymorphone HCl Tab 10 MG	1	24	3	10	30
65100080100305	OXYMORPHONE TAB HCL 5MG	Oxymorphone HCl Tab 5 MG	1	24	3	5	15
65100080107410	OPANA ER TAB 10MG	Oxymorphone HCl Tab SR 12HR 10 MG	0	3	3	10	30
65100080107465	OPANA ER TAB 10MG	Oxymorphone HCl Tab SR 12HR 10 MG (Crush Resistant)	0	3	3	10	30
65100080107415	OPANA ER TAB 15MG	Oxymorphone HCl Tab SR 12HR 15 MG	0	3	3	15	45
65100080107420	OPANA ER TAB 20MG	Oxymorphone HCl Tab SR 12HR 20 MG	0	3	3	20	60
65100080107475	OPANA ER TAB 20MG	Oxymorphone HCl Tab SR 12HR 20 MG (Crush Resistant)	0	3	3	20	60
65100080107430	OPANA ER TAB 30MG	Oxymorphone HCl Tab SR 12HR 30 MG	0	3	3	30	90
65100080107480	OPANA ER TAB 30MG	Oxymorphone HCl Tab SR 12HR 30 MG (Crush Resistant)	0	3	3	30	90

Table 2. (continued)

gpi_cd	drug_nm	gpi_nm	short_act	max_daily	morph_eqv_fctr	drg_strnth_mg	adj_dose
65100080107440	OPANA ER TAB 40MG	Oxymorphone HCl Tab SR 12HR 40 MG	0	6	3	40	120
65100080107485	OPANA ER TAB 40MG	Oxymorphone HCl Tab SR 12HR 40 MG (Crush Resistant)	0	6	3	40	120
65100080107405	OPANA ER TAB 5MG	Oxymorphone HCl Tab SR 12HR 5 MG	0	3	3	5	15
65100080107455	OPANA ER TAB 5MG	Oxymorphone HCl Tab SR 12HR 5 MG (Crush Resistant)	0	3	3	5	15
65100080107407	OXYMORPHONE TAB 7.5MG ER	Oxymorphone HCl Tab SR 12HR 7.5 MG	0	3	3	7.5	22.5
65100091100340	NUCYNTA TAB 100MG	Tapentadol HCl Tab 100 MG	1	6	0.4	100	40
65100091100320	NUCYNTA TAB 50MG	Tapentadol HCl Tab 50 MG	1	12	0.4	50	20
65100091100330	NUCYNTA TAB 75MG	Tapentadol HCl Tab 75 MG	1	8	0.4	75	30
65100091107430	NUCYNTA ER TAB 100MG	Tapentadol HCl Tab SR 12HR 100 MG	0	3	0.4	100	40
65100091107440	NUCYNTA ER TAB 150MG	Tapentadol HCl Tab SR 12HR 150 MG	0	3	0.4	150	60
65100091107450	NUCYNTA ER TAB 200MG	Tapentadol HCl Tab SR 12HR 200 MG	0	2	0.4	200	80
65100091107460	NUCYNTA ER TAB 250MG	Tapentadol HCl Tab SR 12HR 250 MG	0	2	0.4	250	100
65100091107420	NUCYNTA ER TAB 50MG	Tapentadol HCl Tab SR 12HR 50 MG	0	3	0.4	50	20

APPENDIX 3: RESULTS FOR THE FINAL MODEL

Table 3 Type III Sums of Squares Table

Source	DF	Chi-square	Pr > ChiSq
Opioid analgesic dose	4	120.88	<0.0001
Interval	1	2.14	0.1439
Age	1	38.26	<0.0001
Gender	1	8.15	0.0043
U.S. region	3	1.83	0.6076
Back pain	1	0.16	0.6897
Large joint arthritis, other musculoskeletal	1	5.15	0.0233
Neuropathy	1	1.11	0.2921
Chronic pain (unspecified)	1	39.03	<0.0001
Headache	1	0.11	0.7406
Depression	1	102.29	<0.0001
Anxiety or PTSD	1	0.06	0.8135
Psychosis	1	66.59	<0.0001
Alcohol abuse	1	152.28	<0.0001
Other substance abuse	1	122.12	<0.0001
Antidepressant therapy	3	11.77	0.0082
Benzodiazepine therapy	3	127.39	<0.0001
Zolpidem therapy	3	11.2	0.0107
Opioid × Depression	4	36.53	<0.0001
Antidepressant therapy × Depression	3	20.2	0.0002
Benzodiazepine therapy × Anxiety or PTSD	3	10.36	0.0157
Zolpidem therapy × Anxiety or PTSD	3	8.79	0.0300

APPENDIX 3: RESULTS FOR THE FINAL MODEL (CONT.)

Table 4 Adjusted Odds Ratios for Drug Overdose Associated with Significant Interactions of Opioid Analgesics and Selected Psychotherapeutic Drugs with Mental Health Conditions

	Adjusted odds ratio (95 % CI)[*]	
Opioid analgesic dose (average daily dose per 6-month interval)	Depression=no	Depression=yes
0 mg	1	3.96 (3.00, 5.24)
1–19 mg	0.80 (0.50, 1.27)	4.75 (3.24, 6.97)
20–49 mg	1.54 (1.23, 1.94)	5.47 (4.23, 7.09)
50–99 mg	2.08 (1.61, 2.69)	6.44 (4.85, 8.54)
≥100 mg	4.34 (3.37, 5.57)	7.06 (5.30, 9.42)
Antidepressant therapy (days per 6-month interval)	Depression=no	Depression=yes
None	1	5.25 (4.25, 6.48)
1–30 day	1.98 (1.48, 2.65)	5.51 (4.14, 7.34)
31–90 day	1.59 (1.18, 2.15)	4.39 (3.39, 5.68)
91–180 day	1.33 (1.05, 1.68)	4.15 (3.36, 5.12)
Benzodiazepine therapy (days per 6-month interval)	Anxiety/PTSD=no	Anxiety/PTSD=yes
None	1	1.29 (0.99, 1.70)
1–30 day	1.79 (1.41, 2.26)	2.20 (1.62, 3.00)
31–90 day	2.62 (2.06, 3.34)	2.03 (1.49, 2.78)
91–180 day	2.85 (2.34, 3.48)	2.56 (1.97, 3.32)
Zolpidem therapy (days per 6-month interval)	Anxiety/PTSD=no	Anxiety/PTSD=yes
None	1	1.14 (0.97, 1.35)
1–30	1.67 (1.21, 2.3)	1.14 (0.76, 1.72)
31–90	1.06 (0.71, 1.57)	1.77 (1.25, 2.51)
91–180	1.54 (1.2, 1.99)	1.30 (0.96, 1.77)

[*]*Other variables in the model include: opioid daily MED category, time interval, age, gender, region, five chronic non-cancer pain conditions, anxiety/PTSD, depression, psychotic disorder, alcohol abuse, drug abuse, antidepressant therapy, benzodiazepine therapy and zolpidem per 6-month interval (four levels: none, 1–30 days, 31–90 days, 91–180 days)*

APPENDIX 4: COMBINATION DRUGS FILLED BY PERSONS WITH DEPRESSION OR ANXIETY/PTSD BY 6-MONTH INTERVAL

Table 5 Combination Drugs Filled by Persons with Depression or Anxiety/PTSD by 6-Month Interval

Characteristic	1	2	3	4	5	6	7	Total
All subjects, N	206,869	162,706	118,660	80,602	53,562	30,801	5080	658,280
Subjects with depression, N (%)	14,088 (6.8)	15,456 (9.5)	13,813 (11.6)	10,657 (13.2)	7941 (14.8)	5331 (17.3)	1182 (23.3)	68,468 (10.4)
Opioids+Antidepressants, N (%)[*]	9667 (68.6)	6276 (40.6)	5027 (36.4)	3576 (33.6)	2538 (32)	1750 (32.8)	482 (40.8)	29,316 (42.8)
Opioids+Benzodiazepines, N (%)[*]	6329 (44.9)	4547 (29.4)	3733 (27)	2711 (25.4)	1995 (25.1)	1416 (26.6)	431 (36.5)	21,162 (30.9)
Opioids + zolpidem, N (%)[*]	2818 (20.0)	2010 (13.0)	1659 (12.0)	1248 (11.7)	896 (11.3)	645 (12.1)	189 (16.0)	9465 (13.8)
Opioids + Antidepressants+ Benzodiazepines, N (%)[*]	4856 (34.5)	3319 (21.5)	2640 (19.1)	1899 (17.8)	1368 (17.2)	940 (17.6)	286 (24.2)	15,308 (22.4)
Opioids+Benzodiazepines+ Zolpidem, N (%)[*]	1677 (11.9)	1232 (8.0)	1007 (7.3)	749 (7.0)	515 (6.5)	370 (6.9)	108 (9.1)	5658 (8.3)
Opioids +Antidepressants+ Benzodiazepines+ Zolpidem, N (%)[*]	1368 (9.7)	956 (6.2)	782 (5.7)	591 (5.6)	374 (4.7)	266 (5.0)	79 (6.7)	4416 (6.5)
Subjects with anxiety/ PTSD, N (%)	15,532 (7.5)	17,764 (10.9)	16,274 (13.7)	12,933 (16.1)	9626 (18)	6317 (20.5)	1346 (26.5)	79,792 (12.1)

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Table 5. (continued)

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Characteristic	1	2	3	4	5	6	7	Total
All subjects, N	206,869	162,706	118,660	80,602	53,562	30,801	5080	658,280
Opioids+Antidepressants, N (%)[†]	7766 (50)	5204 (29.3)	4298 (26.4)	3127 (24.2)	2265 (23.5)	1542 (24.4)	431 (32)	24,633 (30.9)
Opioids+Benzodiazepines, N (%)[†]	8715 (56.1)	5970 (33.6)	5007 (30.8)	3671 (28.4)	2663 (27.7)	1810 (28.7)	530 (39.4)	28,366 (35.6)
Opioids + Zolpidem, N (%)[*]	2770 (17.8)	1976 (11.1)	1708 (10.5)	1306 (10.1)	939 (9.8)	646 (10.2)	179 (13.3)	9524 (11.9)
Opioids +Antidepressants +Benzodiazepines, N (%)[†]	4922 (31.7)	3295 (18.6)	2685 (16.5)	1947 (15.1)	1414 (14.7)	952 (15.1)	289 (21.5)	15,504 (19.4)
Opioids +Antidepressants+ Benzodiazepines, N (%)[†]	4922 (31.7)	3295 (18.6)	2685 (16.5)	1947 (15.1)	1414 (14.7)	952 (15.1)	289 (21.5)	15,504 (19.4)
Opioids +Benzodiazepines+ Zolpidem, N (%)[†]	1938 (12.5)	1390 (7.8)	1161 (7.1)	859 (6.6)	602 (6.3)	419 (6.6)	116 (8.6)	6485 (8.1)
Opioids +Antidepressants+ Benzodiazepines + Zolpidem, N (%)[†]	1270 (8.2)	877 (4.9)	732 (4.5)	572 (4.4)	357 (3.7)	252 (4)	70 (5.2)	4130 (5.2)

[*]*Entries are N(%) among subjects with depression*
[†]*Entries are N(%) among subjects with anxiety/PTSD*