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Original Reports

Assessing Risk for Drug Overdose in a National Cohort: Role for Both Daily and Total Opioid Dose?

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Abstract: **Current research on the risk of opioid analgesics with drug overdose does not account for the total morphine equivalent dose (MED) of opioids filled by a patient. In this study, time from first opioid prescription until drug overdose was examined for 206,869 privately insured patients aged 18 to 64 with noncancer pain and ≥2 filled prescriptions for Schedule II or III opioids from January 2009 to July 2012. Opioid therapy was examined in 6-month intervals including 6 months before an overdose and categorized as mean daily MED (0, 1–19, 20–49, 50–99, ≥100 mg) and total MED divided at top quartile (0, 1–1,830, >1,830 mg). Survival analysis was used, adjusting for demographics, clinical conditions, and psychoactive drugs. Relative to no opioid therapy, persons at highest risk for overdose (adjusted hazard ratios of 2–3) received a daily MED of ≥100 mg regardless of total dose or a daily MED of 50 to 99 mg with a high total MED (>1,830 mg). The hazard ratio was significantly lower (1.43, 95% confidence interval = 1.15–1.79) for 50 to 99 mg daily MED with a lower total MED (≤1,830 mg), whereas hazard ratios for lower daily MEDs did not differ by total dose. This analysis suggests that clinicians should consider total MED to assess risk of overdose for persons prescribed 50 to 99 mg daily MED.**

Perspective: ***When addressing risks for drug overdose, this analysis supports the need for clinicians, administrators, and policy makers to monitor not only daily opioid dose but also total dose for patients receiving 50 to 99 mg daily MED.***

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Key words: *Analgesics, opioid, overdose, drug, dose response relationship, drug, chronic pain.*

Persons with non–cancer-related pain have an increased risk of fatal and nonfatal drug overdose related to treatment with opioid analgesics.[20] Death from unintentional poisoning due to opioid analgesics increased more than 4-fold nationally from 1999 to 2009.[4] By 2010, opioid analgesics were involved in three-quarters of the 22,134 drug overdose deaths in the United States.[18] The mean daily dose of opioid analgesics has been widely used to assess the risk of overdose death and reported to be greatest for a morphine equivalent dose (MED) at least 100 to 120 mg per day.[2,3,8,12,13,22] However, the total dose of filled opioid prescriptions over a period of time may offer a complementary measure of risk to that provided by the daily MED. The total dose is not necessarily a simple linear transformation of the daily dose because not all patients use opioids every day; instead, it reflects the total amount of opioids available to a patient.

Other studies have computed multiple measures of opioid analgesic utilization, including total dose. Among Medicaid and commercially insured patients taking long-term opioid therapy for chronic noncancer pain, Edlund and colleagues computed the following measures over 1

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year: 1) mean daily dose, in morphine equivalents, 2) total days of opioids supplied in that year, and 3) total dose in morphine equivalents prescribed in that year.[9] In that analysis, the mean daily opioid dose did not increase from 2000 through 2005, but the number of days with opioids prescribed and the total opioid dose increased by approximately 30 to 50%.[9] On the other hand, Gomes and colleagues reported significant increases in the daily dose of oxycodone prescribed for socioeconomically disadvantaged persons in Ontario from 2003 through 2008.[12] In a Norwegian study, persons who continued taking opioids for 5 years doubled their daily dose compared with their initial dose.[11]

To address the hypothesis that daily opioid dose and total dose may offer complementary information for clinicians to distinguish patients at increased risk of drug overdose, we utilized a longitudinal database for a national cohort of beneficiaries in a health maintenance organization (HMO) who filled at least 2 prescriptions for Schedule II or III opioid analgesics for noncancer pain between January 2009 and July 2012. In this large cohort, we examined commonly used categories for mean daily opioid dose[2,8] in combination with categories of the total dose of opioid prescriptions filled within 6-month intervals, including the 6 months *exactly* before a drug overdose event. If risk of drug overdose for daily opioid dose categories differs by total dose, this finding would argue for monitoring both metrics when addressing risks for serious adverse events such as drug overdose.

Methods

Study Sample

The study setting was Aetna's Health Maintenance Program, which provides comprehensive, full service care to approximately 2.1 million persons across the United States. The study cohort was drawn from adults aged 18 to 64 years who were enrolled in the HMO at least 12 months and received full pharmacy benefits. From deidentified data supplied by the HMO, we found 261,528 eligible subjects who filled at least 2 Schedule II or III noninjectable opioid analgesic prescriptions from January 2009 through July 2012 and had complete diagnostic data. We did not consider less potent (Schedule IV) opioids because risks for these drugs are not as great. Subjects were excluded for the following reasons: 1) cancer diagnosis (except basal cell skin cancer) within 6 months before or after an opioid analgesic prescription (n = 26,165); 2) prescription for methadone or buprenorphine-naloxone associated with the diagnosis of opioid dependence (n = 1,771); 3) incomplete prescribing data such as missing days' supply (n = 12,603); and/or 4) incomplete first 6-month interval after the first filled opioid analgesic prescription in the study time frame (n = 14,120). For subjects with an overdose event less than 6 months after the date of the first opioid analgesic prescription, at least 6 months' enrollment with clinical service utilization preceding that event was required. The final sample size was 206,869; details of the derivation of the study sample are provided in Fig 1.

In this longitudinal cohort, we captured the changing nature of clinical conditions and prescription medications using time-varying covariates. In regard to opioid therapy, other researchers computed average daily MED dispensed over 3 months.[8] In our analysis, we selected 6-month intervals, starting with the first opioid prescription, allowing us to examine longer-term total doses received by subjects. For the analysis of persons with an overdose, opioid utilization measures and other covariates were computed using data from exactly 6 months preceding the event. Subjects were followed until the first of the following endpoints: a 6-month interval with an overdose event, end of HMO enrollment, or the end of the study time frame. Incomplete 6-month intervals were excluded.

Outcome Variable

According to the Centers for Disease Control and Prevention, opioids contribute to the majority of drug overdose deaths.[5] Therefore, our study outcome is drug overdose in an inpatient or outpatient clinical encounter after the first filled opioid analgesic prescription (Appendix A). In our survival analysis, time from first opioid prescription to first overdose event was examined.

Primary Independent Variables

To calculate the 2 time-varying opioid therapy measures, all filled Schedule II or III prescriptions for opioid analgesics (excluding injectable formulations) were identified from claims in 6-month intervals starting with the first prescription. The total MED was computed from all opioids dispensed in a 6-month interval multiplied by strength (in milligrams) and then multiplied by a morphine equivalent conversion factor derived from published data,[10,23] conversion tables on the Internet, and drug information resources.[1,15] When opioid prescriptions spanned two 6-month intervals, the total MED was allocated proportionate to the time in each interval. We consulted with a clinical pharmacist to review these calculations. Finally, the total MED was summed for all opioid prescriptions filled in the same interval.

We calculated the mean daily MED for filled opioid prescriptions for each 6-month interval by dividing the total MED by total days' supply covered by all these prescriptions. Based on categories used in other studies,[2,8] the mean daily MED (mg) was examined in 5 categories: 0, 1 to 19, 20 to 49, 50 to 99, and $\geq$100 mg. Because other studies have not examined total dose in relation to the risk of drug overdose, we examined quartiles of nonzero total MED (see Analysis section). When an overdose event occurred in a 6-month interval, both daily MED and total MED were computed from the 6 months exactly preceding that event.

Other Independent Variables

Demographic data for study subjects (time-fixed) included age as of July 2012, sex, and U.S. region in 4 categories defined by the Centers for Disease Control and Prevention. For each subject, time-varying covariates (ie, clinical diagnoses and other medications) were

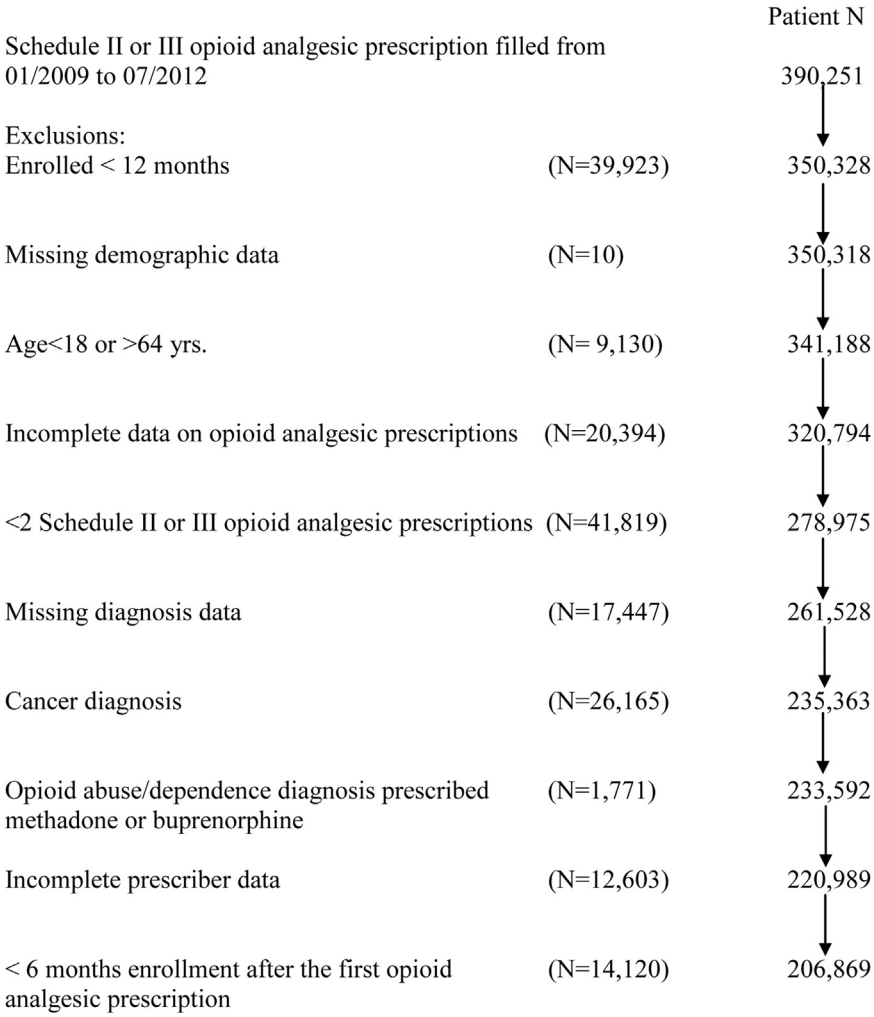

Figure 1. Study sample derivation.

calculated for each 6-month interval after the first opioid prescription or 6-month period prior to an overdose. From diagnosis codes for clinical encounters and hospitalizations in each 6-month interval, we created variables for pain-related conditions (ie, back pain, other musculoskeletal conditions, neuropathic pain, chronic pain unspecified, or chronic headache) (ICD-9-CM codes available from authors). We also created indicators for mental health/substance abuse conditions, including anxiety disorder or posttraumatic stress disorder, depression, psychosis, drug abuse, and alcohol abuse. We combined anxiety disorder and posttraumatic stress disorder for analysis because the latter condition was uncommon (<1%), and these conditions often overlap. For pain-related conditions and psychiatric or substance abuse disorders, once a diagnosis appeared in a 6-month interval, it was considered to persist in subsequent intervals as these conditions are usually not transient.

We also created time-varying indicators for psychoactive medications commonly used by patients with chronic pain and associated with an increased risk of adverse events, including overdose.[4,19] For each 6-month interval, these drugs were categorized by the total days supplied in the 6-month interval as follows: benzodiazepines (0, 1–30, 31–90, 91–180), zolpidem (0, 1–30, 31–90, 91–180), and antidepressants (0, 1–60, 61–180). We examined a longer duration for the second category of the antidepressants use (ie, 1–60 days) because clinical benefit for depressive symptoms can take up to 8 weeks.

Analyses

Descriptive statistics were used to summarize study cohort characteristics. We initially estimated an unadjusted Cox proportional hazards model including 5 total MED categories to examine the risk of overdose for quartiles of total opioid dose within a 6-month interval compared with no opioid therapy. This analysis showed no difference for the 3 lower quartiles of total opioid MED but a significantly higher risk for the highest quartile (Appendix B). Thus, subsequent analyses examined total opioid MED (mg) in the following 3 categories: 0, 1 to 1,830, >1,830. Pearson's correlation coefficient was used to examine the strength of the linear relationship between daily and total MED categories; and Spearman's rank-correlation coefficient was used to measure the extent to which as one measure of opioid dose increases, the other measure tends to increase, without requiring that increase to be represented by a linear relationship. We then combined these total opioid MED categories

Table 1. Study Cohort Characteristics (N = 206,869)

Characteristics	n (%)
Demographics	
Women	117,472 (56.8)
Age, mean (SD)	44.1 (12.0)
U.S. region	
Midwest	12,028 (5.8)
Northeast	60,567 (29.3)
South	97,072 (46.9)
West	37,202 (18.0)
Clinical conditions*	
Noncancer pain conditions	
Back pain–related	80,523 (38.9)
Other musculoskeletal conditions†	102,316 (49.5)
Neuropathy	1,788 (.9)
Chronic pain	14,211 (6.9)
Headache	14,635 (7.1)
Anxiety or posttraumatic stress disorder	30,887 (14.9)
Depression	26,223 (12.7)
Psychosis	5,603 (2.7)
Alcohol abuse	4,637 (2.2)
Substance abuse	4,420 (2.1)

*ICD-9-CM codes available from authors.
†Arthritis, arthralgia, fracture, sprains.

with daily opioid MED categories (ie, 0, 1–19, 20–49, 50–99, and ≥100 mg) to create 9 groups representing all combinations of both measures of opioid utilization. Kaplan-Meier curves of time to the first overdose event were plotted for all subjects and by daily opioid dose categories, total dose categories, and 9 combined daily and total opioid dose treatment groups. Both log-rank test and Wilcoxon/Breslow test were used to test for the equality of daily dose categories, total dose categories, and combined treatment groups in these analyses. In a series of Cox proportional hazards models that adjust additively for demographic, clinical, and psychoactive drugs, we examined associations of the 9 opioid treatment groups with time to drug overdose. We assessed the validity of the proportional hazards assumption using Schoenfeld residuals.[14]

To compare our highest-risk patients to similar groups in other studies, we conducted a post hoc analysis of characteristics of high-risk subjects who had at least 1 interval with high daily MED (≥100 mg) or a daily MED of 50 to 99 mg combined with high total MED (>1,830 mg). In a multivariate logistic regression model with high risk (Y/N) as the dependent variable, we included all covariates except opioid measures. All statistical tests were conducted at a 2-sided significance level of .05 and all analyses were conducted using Stata/SE (version 13; StataCorp LP, College Station, TX). The study was approved by the University of Texas Health Science Center at San Antonio's institutional review board.

Results

Among 206,869 subjects receiving opioid analgesics for noncancer pain, the mean age was 44.1 years (SD = 12), 56.8% were women, and most resided in the South and Northeast United States (Table 1). The most common pain-related conditions were varied musculoskeletal conditions (49.5%) and back pain (38.9%), whereas the most common mental health conditions were anxiety and/or posttraumatic stress disorder (14.9%). Following the first opioid prescription, subjects were observed for an average of 19.1 months (SD = 10.6, range = 6–42). Over 3.5 years, 1,385 (.67%) of subjects were identified as having a drug overdose.

The daily opioid MED and total MED categories were strongly associated ($P < .001$) but their linear relationship was weak (Pearson's correlation = .405, 95% confidence interval [CI] = .403–.408; Spearman's correlation = .368, 95% CI = .365–.371). The most common daily dose was 20 to 49 mg, occurring in approximately one-third of all 6-month intervals (Table 2). The highest daily dose (≥100 mg) occurred for 6.6% of all intervals. However, among the 6-month intervals when at least 1 opioid prescription was filled (N = 413,767), 10.5% had ≥100 mg daily dose and 25% had >1,830 mg total dose.

Kaplan-Meier plots of the probability of drug overdose over time reveal that before adjusting for other covariates, overdose rates differed significantly by total and daily MED categories (all $P < .001$) (Fig 2). In a model combining both measures, the unadjusted hazard ratios (HRs) for overdose in a 6-month interval were nearly 8-fold greater for ≥100 mg daily dose and 5-fold greater for a 50 to 99 mg daily dose when total dose was high (>1,830 mg), relative to no opioid therapy (Table 3, Model 1). However, when the total dose was lower (1–1,830 mg), the HRs were increased by only approximately 4-fold for ≥100 mg daily dose and by 2-fold for a 50 to 99 mg daily dose versus no opioid therapy. With the exception of the 1 to 19 mg daily dose, risk of drug overdose for daily dose

Table 2. Total MED Versus Daily MED Across All 6-Month Intervals

	Daily MED (mg), N (Column %)					
Total MED (mg)	0	1–19	20–49	50–99	≥100	Total*
0	244,513	–	–	–	–	244,513 (37.1)
1–1,830	–	41,936 (92.2)	189,655 (83.5)	70,356 (72.1)	8,779 (20.1)	310,726 (47.2)
>1,830	–	3,550 (7.8)	37,429 (16.5)	27,194 (27.9)	34,868 (79.9)	103,041 (15.7)
Total†	244,513 (37.1)	45,486 (6.9)	227,084 (34.5)	97,550 (14.8)	43,647 (6.6)	658,280 (100)

*Row margins (% of total MED category).
†Column margins (% of daily MED category).

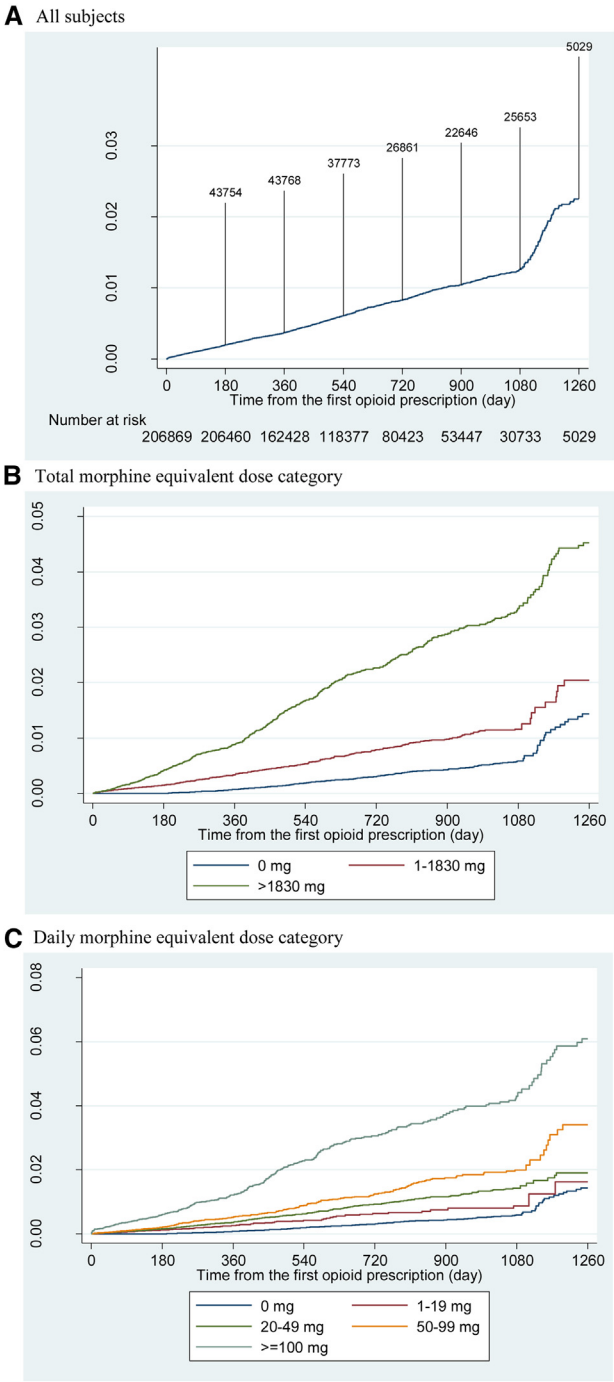

Figure 2. Kaplan-Meier estimation of probability of drug overdose over time. Kaplan-Meier curve in **(A)** shows 1 hash mark at each censoring time and the number censored above hash mark. $P < .001$ for testing the equality of Kaplan-Meier curves across the 3 total MED categories **(B)** and the 5 daily MED categories **(C)**.

categories differed significantly by total dose category (all $P < .05$).

After adjustment for demographics (Table 3, Model 2), differences in the risk of drug overdose within daily dose groups based on the total dose increased. However, additional adjustment for clinical covariates (Table 3, Model 3) moderated these associations significantly, especially for ≥100 mg daily dose, such that the HRs for overdose were roughly the same for lower and high total dose categories. On the other hand, a 50 to 99 mg daily dose continued to have a significant difference in risk of overdose based on the total opioid dose ($P < .001$).

In a fully adjusted model that accounts for receipt of other risky psychoactive drugs in addition to covariates in previous models (Table 3, Model 4), the HR for high (≥100 mg) daily dose combined with high total dose (>1,830 mg) was 2.56 (95% CI = 21.12–3.09), and the HR for high daily dose combined with lower total dose was 3.1 (95% CI = 2.14–4.49), but this difference was not significant from a model-based pair-wise comparison ($P = .32$). The HR for a 50 to 99 mg daily dose combined with a high total dose (HR = 2.12, 95% CI = 1.7–2.63) did not differ significantly from high (≥100 mg) daily dose categories. On the other hand, the HR (1.43, 95% CI = 1.15–1.79) for the 50 to 99 mg daily dose combined with a lower total dose (≤1,830 mg) was significantly lower ($P = .002$) than the HR for the 50 to 99 mg daily dose combined with a high total dose. At lower daily doses (20–49 mg), the risk of drug overdose did not differ significantly by total opioid dose ($P = .27$), and the lowest daily dose category (1–19 mg) did not differ significantly from no opioid therapy ($P = .86$ for lower total dose; $P = .57$ for high total dose).

Overall, the strongest associations with drug overdose were observed for ≥100 mg daily dose regardless of total dose or 50 to 99 mg daily dose combined with a high total dose (>1,830 mg). The subjects who had at least one 6-month interval with higher risk opioid therapy were more likely ($P < .001$) to be younger, men, diagnosed with low back pain or chronic pain, and diagnosed with depression. In addition, these subjects were significantly more likely to have filled prescriptions for benzodiazepines, antidepressants, and/or zolpidem.

Discussion

A high daily MED of prescribed opioid analgesics has been demonstrated to increase the risk of death from drug overdose in diverse populations.[2,8,12,22] The daily dose has become a standard metric for clinical guidelines of chronic pain care[1,21] but it does not take into account the total dose of opioids received by a patient. A patient with a daily opioid dose of 60 mg (eg, hydrocodone 20 mg 3 times a day) may fill a prescription for only 7 days or for 180 days (total dose 420 vs 10,800 mg within a 6-month interval). In this analysis of a national HMO cohort of more than 200,000 beneficiaries with noncancer pain treated with Schedule II or III opioids over a 3.5-year time frame, we confirmed the significant association of daily dose with the risk of drug overdose. However, we also found that the total opioid dose received within a 6-month interval adds significant risk discrimination to that provided by the daily dose. After adjusting for demographics, clinical comorbidities, and treatment with other risky psychoactive drugs, the HR for overdose for a 50 to 99 mg daily dose was increased by more than 2-fold (HR = 2.12) when combined with a high total dose (>1,830 mg), but when combined with a lower total dose (1–1,830 mg),

Table 3. Association of Total MED and Daily MED on Risk of Overdose

			Daily MED (mg)				
			0	1–19	20–49	50–99	≥100
Model	Adjustment	Total MED (mg)	Hazard Ratio (95% CI)				
1	None	0	1	–	–	–	–
		1–1,830	–	1.47 (1.11, 1.96)	1.88 (1.58, 2.23)	1.90 (1.52, 2.37)	3.91 (2.7, 5.67)
		>1,830	–	1.38 (.57, 3.33)	3.09 (2.48, 3.84)	5.43 (4.44, 6.66)	7.84 (6.62, 9.28)
2	Model 1 + demographics	0	1	–	–	–	–
		1–1,830	–	1.57 (1.18, 2.09)	1.90 (1.6, 2.26)	1.89 (1.51, 2.36)	3.86 (2.66, 5.6)
		>1,830	–	1.58 (.65, 3.83)	3.51 (2.82, 4.38)	6.17 (5.03, 7.57)	8.57 (7.23, 10.16)
3	Model 2 + clinical conditions	0	1	–	–	–	–
		1–1,830	–	1.17 (.88, 1.55)	1.48 (1.25, 1.76)	1.53 (1.22, 1.91)	3.26 (2.25, 4.73)
		>1,830	–	.98 (.40, 2.38)	1.93 (1.54, 2.42)	2.73 (2.2, 3.39)	3.35 (2.78, 4.02)
4	Model 3 + other drugs	0	1	–	–	–	–
		1–1,830	–	1.03 (.77, 1.37)	1.35 (1.14, 1.61)	1.43 (1.15, 1.79)	3.1 (2.14, 4.49)
		>1,830	–	.77 (.32, 1.88)	1.53 (1.21, 1.93)	2.12 (1.7, 2.63)	2.56 (2.12, 3.09)

the HR was only 1.43 versus no opioid therapy. Of 6-month intervals analyzed for this cohort, 15% had a 50 to 99 mg daily dose and would have had potentially valuable overdose risk information provided by the total opioid dose. Indeed, a 50 to 99 mg daily dose combined with a high total dose (>1,830 mg) was associated with a similar risk of drug overdose as a high daily dose (≥100 mg).

The risk of overdose for a ≥100 mg daily dose differs markedly from that for a 50 to 99 mg daily dose in other studies that did not consider total dose. In a Washington State HMO cohort, Dunn and colleagues reported that the HR for opioid overdose for ≥100 mg daily dose was 8.9 but was only 3.7 for a 50 to 99 mg daily dose versus <10 mg daily dose. Similarly, in a Veterans Affairs cohort from 2003 to 2008, the adjusted HR of unintentional overdose death was greatest for ≥100 mg daily dose (HR = 7.2) and lower for a 50 to 99 mg (HR = 4.6) versus <20 mg daily dose.[2]

Our study extends the work of Edlund and colleagues, who proposed multiple measures to evaluate the intensity of opioid therapy including daily dose, total dose, and days prescribed.[9] In their analysis of a national commercially insured population and Arkansas Medicaid enrollees with chronic noncancer pain, the total dose of opioids prescribed and total days' supply over 1 year rose significantly in the first half of the last decade.[9] Among the commercially insured population in 2005 in Edlund's study, the 70th percentile for daily dose was 55 mg and for the total dose over 1 year was 900 mg. The daily dose was similar in our cohort but the total dose was higher. Among all 6-month intervals when an opioid prescription was filled by our cohort, the daily dose was ≥50 mg for 34% and ≥100 mg for 10.5%, whereas the total dose was >1,830 mg for more than 25% of the intervals. By comparison, Kobus and colleagues reported that 8.6% of an HMO cohort from the Northwest received ≥100 mg daily dose over a span of at least 90 days from 2003 and 2005.[19] In that study, long-term users of high opioid doses were more likely to be men, have higher comorbidity, be diagnosed with mental health or substance use, and have co-prescriptions of sedative-hypnotics. Edlund also found that mental health or substance use and more chronic noncancer pain diagnoses were associated with significantly greater likelihood of being prescribed high-dose opioids.[9] In our cohort, we observed similar characteristics for subjects who were at increased risk of drug overdose.

A recent systematic review of opioid prescribing guidelines reported that the cutpoint of the daily dose to define the greatest risk ranged from 90 to 200 mg.[21] Our study suggests that the risk of drug overdose is also increased for daily doses from 50 to 89 mg when the total dose is high (>1,830 mg). In terms of policy implications, our study suggests that prescribers, pharmacies, and state prescription-monitoring programs should also monitor the total dose filled by a patient over 6 months or a similarly lengthy interval. Just as prescribers should avoid high daily doses ≥100 mg, the dose may need to be tapered when the patient is taking lower doses over a long term. Based on the results of our study, prescribers should, for example, avoid more than 31 days of 60 mg per day (ie, a total dose of 1,860 mg). One of the strengths of our study is adjusting for the duration of other prescribed psychoactive drugs, particularly benzodiazepines, that are strongly associated with an increased risk of overdose.[17] The risk of overdose may be increased for even lower daily and total opioid doses when patients are co-prescribed benzodiazepines.

This study has several limitations. First, drug overdose events were identified by coded diagnoses from clinical encounters and do not include events that led to outpatient death. Second, we used a broad range of diagnoses for drug overdose because coded diagnoses may not distinguish if opioids were directly contributing to the drug overdose. However, patients who take high doses of opioids may also be more likely to take excessive doses of other drugs such as nonsteriodals. In our national HMO cohort, we observed more drug overdose events (421 per 100,000 person-years) than did Dunn and colleagues in their analysis of only opioid overdose events

in a Northwest HMO population (148 per 100,000 person-years).[8] However, in a case control study using New Mexico's prescription-monitoring program data, Paulozzi and colleagues reported that increasing daily opioid dose was linearly associated with greater risk of unintentional drug overdose (not only due to opioids) and cited studies with similar findings.[22] With growing abuse of heroin by persons who have been or are taking opioids,[6] higher dose opioids may also be associated with drug overdose related to this illicit drug. Although noise from drug overdose due to heroin or other drugs may have attenuated our results, the associations we observed are consistent with those from other studies of opioid overdose.

Third, our analysis considers drug overdose events in either an inpatient or outpatient setting, including the emergency department. Although these differ in severity, other groups have found that emergency department visits for opioid overdose are associated with 3-fold greater odds of future hospitalization for opioid overdose.[16] Furthermore, an analysis of the 2007 Nationwide Emergency Department Sample reported nearly 700,000 drug-related poisoning events and highlighted their underrecognized prevalence.[24] Fourth, days' supply data were used to compute the mean daily MED as in other studies.[3,9] The days' supply may be estimated by the pharmacist and may not reflect actual days when the patient is taking the medication. Some studies have estimated the mean daily dose using the total MED dispensed divided by the total days within a particular time frame (eg, 90 days or 120 days).[8,13] However, this method can seriously underestimate the daily dose for those patients who receive opioid analgesic therapy for only a short period of time.

Fifth, our study could not distinguish ongoing opioid users from new users, but studies of persons who overdose find that the risk of overdose continues for persons who have been taking these drugs for years.[7] Sixth, although we found that a high total dose of opioid prescriptions filled over a 6-month interval increases the risk of overdose, we are unable to evaluate the reason for this increased risk. One possible explanation for this increased risk could be that a person with a high total dose has a greater supply of opioids to overdose on. Finally, although our study cohort is national, it only involves a commercially insured population.

In conclusion, total dose of prescribed opioids over a 6-month interval may offer a potentially important factor to consider when developing approaches to reduce the risk of drug overdose among opioid users. Among persons filling prescriptions for opioids, our data suggest that risk mitigation is required if the daily dose is 50 to 99 mg in conjunction with a high total dose (>1,830 mg) or ≥100 mg over a 6-month period. With increasingly widespread prescription-monitoring programs, it may be feasible to calculate both daily and total dose to help clinicians and other providers to address the risk of drug overdose.

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References

1. Agency Medical Director's Group. Web-Based Opioid Dose Calculator. Available at: http://agencymeddirectors.wa.gov/mobile.html. Accessed April 7, 2014

2. Bohnert AS, Valenstein M, Bair MJ, Ganoczy D, McCarthy JF, Ilgen MA, Blow FC: Association between opioid prescribing patterns and opioid overdose-related deaths. JAMA 305:1315-1321, 2011

3. Braden JB, Russo J, Fan MY, Edlund MJ, Martin BC, Devries A, Sullivan MD: Emergency department visits among recipients of chronic opioid therapy. Arch Intern Med 170: 1425-1432, 2010

4. Calcaterra S, Glanz J, Binswanger IA: National trends in pharmaceutical opioid related overdose deaths compared to other substance related overdose deaths: 1999-2009. Drug Alcohol Depend 131:263-270, 2013

5. Centers for Disease Control and Prevention: National trends in pharmaceutical opioid related overdose deaths compared to other substance related overdose deaths: 1999-2009. Available at: http://www.cdc.gov/media/releases/2013/p0220_drug_overdose_deaths.html. Accessed April 10, 2014

6. Cicero TJ, Kuehn BM: Driven by prescription drug abuse, heroin use increases among suburban and rural whites. JAMA 312:118-119, 2014

7. Darke S: Opioid overdose and the power of old myths: What we thought we knew, what we do know and why it matters. Drug Alcohol Rev 33:109-140, 2014

8. Dunn KM, Saunders KW, Rutter CM, Banta-Green CJ, Merrill JO, Sullivan MD, Weisner CM, Silverberg MJ, Campbell CI, Psaty BM, Von Korff M: Opioid prescriptions for chronic pain and overdose: A cohort study. Ann Intern Med 152:85-92, 2010

9. Edlund MJ, Martin BC, Fan MY, Braden JB, Devries A, Sullivan MD: An analysis of heavy utilizers of opioids for chronic noncancer pain in the TROUP study. J Pain Symptom Manage 40:279-289, 2010

10. Foley KM: The treatment of cancer pain. N Engl J Med 313:84-95, 1985

11. Fredheim OM, Borchgrevink PC, Mahic M, Skurtveit S: A pharmacoepidemiological cohort study of subjects starting strong opioids for nonmalignant pain: A study from the Norwegian Prescription Database. Pain 154: 2487-2493, 2013

12. Gomes T, Juurlink DN, Dhalla IA, Mailis-Gagnon A, Paterson JM, Mamdani MM: Trends in opioid use and dosing among socio-economically disadvantaged patients. Open Med 5:e13-e22. PMID 22046214

13. Gomes T, Mamdani MM, Dhalla IA, Paterson JM, Juurlink DN: Opioid dose and drug-related mortality in patients with nonmalignant pain. Arch Intern Med 171: 686-691, 2011

14. Grambsch PM, Therneau TM: Proportional hazards tests and diagnostics based on weighted residuals. Biometrika 81: 515-526, 1994

15. Hallenbeck JL: Palliative Care Perspectives. New York, Oxford University Press, 2003, pp 36-74

16. Hasegawa K, Brown DF, Tsugawa Y, Camargo CA Jr: Epidemiology of emergency department visits for opioid overdose: A population-based study. Mayo Clin Proc 89: 462-471, 2014

17. Jann M, Kennedy WK, Lopez G: Benzodiazepines: A major component in unintentional prescription drug overdoses with opioid analgesics. Pharm Pract 27:5-16, 2014

18. Jones CM, Mack KA, Paulozzi LJ: Pharmaceutical overdose deaths, United States, 2010. JAMA 309: 657-659, 2013

19. Kobus AM, Smith DH, Morasco BJ, Johnson ES, Yang X, Petrik AF, Deyo RA: Correlates of higher-dose opioid medication use for low back pain in primary care. J Pain 13: 1131-1138, 2012

20. McDonald DC, Carlson K, Izrael D: Geographic variation in opioid prescribing in the U.S. J Pain 13:988-996, 2012

21. Nuckols TK, Anderson L, Popescu I, Diamant AL, Doyle B, Di Capua P, Chou R: Opioid prescribing: A systematic review and critical appraisal of guidelines for chronic pain. Ann Intern Med 160:38-47, 2014

22. Paulozzi LJ, Kilbourne EM, Shah NG, Nolte KB, Desai HA, Landen MG, Harvey W, Loring LD: A history of being prescribed controlled substances and risk of drug overdose death. Pain Med 13:87-95, 2012

23. Vissers KC, Besse K, Hans G, Devulder J, Morlion B: Opioid rotation in the management of chronic pain: Where is the evidence? Pain Pract 10:85-93, 2010

24. Xiang Y, Zhao W, Xiang H, Smith GA: ED visits for drug-related poisoning in the United States, 2007. Am J Emerg Med 30:293-301, 2012

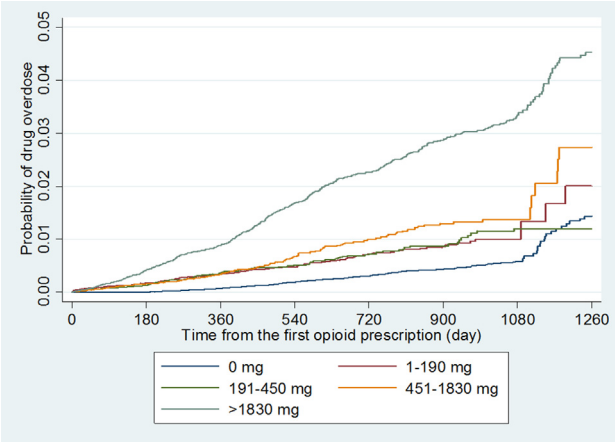
Appendix A

International Classification of Diseases, Ninth Revision, Clinical Modification (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 B

Kaplan-Meier Estimation by 5 Total MED Categories (0 vs. quartiles)



The differences among the 3 lower quartiles of total opioid MED (ie, 1–190, 191–450, and 451–1,830 mg) were not significant.