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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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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