

Bohnert AS, Valenstein M, Bair MJ, et al. Association between opioid prescribing patterns and opioid overdose-related deaths. JAMA 2011;305:1315–21.

PMID: 21467284

Design: Case-cohort study

Purpose of study: to estimate the risks of opioid-related deaths associated with opioid prescribing patterns in a large veterans database

Population/sample size/setting:

- 154,684 veterans who received opioid therapy for pain from the VA in fiscal years 2004 and 2005 and for whom mortality data was available through fiscal year 2008
- Individuals with indications of palliative care or hospice care consultations in their VA medical records were excluded
- Data from the VA National Patient Care Database were used to identify all VA encounters
- Outpatient prescription medication data came from the VA Pharmacy Benefits Management Services database
- Mortality data came from the National Death Index

Ascertainment of exposure:

- Prescribed opioids dispensed by VA pharmacies were codeine, morphine, hydrocodone, oxycodone, oxymorphone, and hydromorphone
 - o All opioid prescriptions were transformed into morphine equivalents in milligrams using established methods
 - o Semisynthetic opioids such as buprenorphine were excluded, as was methadone
- The authors used an “as-prescribed” approach, which assumes that patients take all prescribed opioids at the maximum dose and on the schedule recommended by their clinicians
- Patients who had prescription refills while they still had medication on hand from their previous fills were assumed to have taken all of the medication from that prior fill before beginning to take the medication in the refill
- The total maximum daily dose of opioid was calculated by adding the daily doses of all prescription fills that covered that particular day, and was assumed to be the total number of morphine equivalents in a particular prescription, divided by the number of days on the prescription
- Morphine daily equivalent doses were divided into five categories: 0 mg, 1-20 mg, 20-50 mg, 50-100 mg, and greater than 100 mg

- In addition, a separate classification of prescription was undertaken, which did not look at drug doses but at whether the prescriptions were (1) only regularly scheduled opioids, (2) only as needed opioids, or (3) both a regularly scheduled opioid plus an as-needed opioid

Ascertainment of outcome:

- Death due to opioid overdose was taken from the National Death Index files using a cause-of-death code from ICD-10 X32, X44, Y12, or Y14, in combination with a T code of 40.2
 - o These represent overdose deaths from opioids considered to be unintentional or uncertain
 - o Intentional overdose deaths (suicide) are coded in ICD-10 as X60 through X69, and were excluded from the analysis

Exposure/outcome associations:

- The authors used proportional hazards (Cox) regression for their analyses, which models the time to an event beginning at a defined date
 - o Thus, if, in the first year after filling a prescription for a high-dose opioid, 10 patients per 10,000 die of an overdose, compared to only 5 patients for a lower dose opioid in the first year after filling a prescription, the hazard ratio (HR) is 2.0 for a high dose relative to a lower dose
 - o The Cox regression models were adjusted for demographic (age, sex, ethnicity) and comorbid conditions
- In the fiscal years 2004 to 2008, 1136 individuals died of an opioid overdose, of whom 752 were treated with opioids for pain during FY 2004 to 2008
 - o For 326 (43%) of these decedents, the maximum prescribed opioid dose was 0 mg
- The denominator for opioid overdose deaths was assumed to be 1,834,250 individuals treated with opioid for pain, yielding a rate of fatal overdose of 0.04%
- Overdose deaths were significantly more likely to be white than black, and were also more likely to have substance use disorders and other psychiatric diagnoses
 - o In the adjusted models for chronic pain, the hazard ratio for blacks was 37% of the risk for whites (95% Confidence Interval 24% to 59%)
 - o In the same models, the HR for substance abuse disorders was 2.53 (95% CI 1.99-3.22); for other psychiatric diagnoses, the HR was 1.87 (95% CI 1.48-2.38)
 - o However, for COPD, cardiovascular disease, and sleep apnea, the risk was actually reduced (HR 0.63 with 95% CI 0.50 to 0.80)
- In the adjusted models, the HR among chronic pain patients was elevated at higher prescribed opioid doses, compared to doses of 1 to 20 mg/day

- For doses over 100 mg/day, the HR was 7.18 (95% CI 4.85 -10.65)
- For doses 50-100 mg/day, the HR was 4.63 (95% CI 3.18-6.74)
- For doses 20-50 mg/day, the HR was 1.88 (95% CI 1.33-2.67)
- However, the pattern of prescription was not statistically significant
 - The HR for regularly scheduled opioid prescriptions, as needed prescriptions, and for regularly scheduled plus as needed prescriptions, there were no statistically significant differences in the hazard ratios

Authors' conclusions:

- In a large national database which traced the mortality data for a large cohort of veterans who received prescriptions for opioids, there was a relationship between the prescribed dose and the risk of death, which was elevated by a factor of about 7.18 for daily doses over 100 mg morphine equivalents compared to doses of 1-20 mg
- Patients may obtain opioids outside the VA medical system, as evidenced by a large percentage of the recorded overdose deaths being in patients who had no opioid prescriptions in the VA pharmacy database
- Whether patients had regularly scheduled opioid dosing, or whether it was as needed in addition to regularly scheduled, did not show a relationship with mortality rates
- However, the absolute risks of death due to overdose among opioid-treated veterans were small, on the order of 0.04% for the entire cohort

Comments:

- The study is set up and executed as a well-designed case-cohort analysis from a large database for which efficient sampling of non-cases (veterans who did not have a fatal overdose) is desirable
- The authors also undertook analyses of opioid-related overdose in populations other than chronic noncancer pain, such as acute pain and cancer pain
- A principal vulnerability imposed by the use of a pharmacy benefits database to ascertain exposure is the necessity to rely upon an "as prescribed" classification as a surrogate for an "as taken" classification of opioid exposure
- However, this may be considered as analogous to an "intention to treat" analysis of a randomized trial, and could be relevant to a real world setting in which "as prescribed" and "as taken" are rarely synonymous
- The fact that more than 40% of the overdose deaths had zero prescribed opioids raises questions about the kinds of misclassification of exposure which could influence the interpretation of the study results
 - If a large number of veterans who have low prescribed doses are actually being prescribed opioids from physicians outside the VA system, then the "as

- taken” differences between higher and lower levels of “as prescribed” opioid doses could be narrower than they appear
- If the misclassification of dose exposure operates in this fashion, then the hazard ratios in the results section are not likely to be greatly inflated
 - The lower risk of death in black compared to white veterans is interesting but is not explained by the authors
 - The risks at different dose levels are greater than those estimated by Gomes et al 2011, where doses greater than 200 mg per day were associated with a threefold risk of death, and in this study doses greater than 100 mg were associated with a sevenfold risk of death
 - Both studies use an “as prescribed” estimate of opioid exposure, but “as taken” doses have the true biologic effect
 - Both studies are likely to mismeasure true opioid exposure, but the mismeasurements are probably different
 - There could be differences between Ontario and the US in patterns of opioid diversion, but there are no obvious explanations for the differences in reported risks
 - The VA study was done in the United States, and the estimates of opioid risks from the VA may be more applicable to a US population
 - The authors have published a more recent analysis of VA prescription data (Bohnert 2016), in which they undertook to refine the association between prescribed dose and overdose death in chronic pain patients
 - The design was a nested case-control matched study rather than a case-cohort study, but the data sources were similar and the “as prescribed” approach was also used
 - The authors reported that the median prescribed dose for cases (of opioid-related death) was higher than for controls (opioid-treated patients who did not die)
 - For cases, the median dose in morphine equivalents was 60 mg with an interquartile range from 30 to 120 mg; for controls, the median dose was 25 mg with an interquartile range from 15 to 45 mg
 - The authors also attempted to identify a threshold dose at which there is a distinct increase in risk of death, but the dose distribution did not identify such a clear cutpoint
 - The analysis may have suffered from the fact that the authors attempted to match controls to cases on 13 different variables; even though they had 399 cases to work with, they were only able to match 221 controls
 - This study might have had greater success if it had used propensity scores rather than trying to match on 13 distinct variables

- However, they did report one finding which could contribute to the discussion of safe dosing of opioids: almost half of overdose cases were prescribed more than 60 mg per day and nearly 60% of cases were prescribed more than 50 mg per day; lowering dosages to 50 mg per day would affect less than 25% of control cases, whose doses were mostly under 50 mg
- Also important is the finding that there was not a threshold below which risk is eliminated, and there are risks of opioid overdose even at lower doses
- The authors also note that a recent review of opioid prescribing guidelines (Nuckols 2014) recommend that clinicians avoid doses greater than 90 to 200 mg of morphine equivalent per day, and suggest that lower doses would affect relatively few patients not at risk of overdose while benefitting many who are at risk of overdose

Assessment: Adequate observational study supporting some evidence that compared to an opioid dose under 20 mg morphine equivalent per day, a dose of 20-50 mg nearly doubles the risk of death, a dose of 50 to 100 mg may increase the risk more than fourfold, and a dose greater than 100 mg per day may increase the risk as much as sevenfold. However, the absolute risk of fatal overdose of in chronic pain patients is fairly low, and may be as low as 0.04%

References:

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