Gomes T, Mamdani MM, et al. Opioid dose and drug-related mortality in patients with nonmalignant pain. Arch Intern Med 2011;171:686–91.

Design: Nested case-control study with incidence density sampling

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Purpose of study: to characterize the relationship between opioid dose and opioid-induced mortality

Population/sample size/setting:

- 607,156 people aged 15 to 64 with at least one opioid prescription for nonmalignant paid for by the Ontario public drug plan between August 1997 and December 2006
    - Eligibility criteria for the public drug plan include unemployment, disability, high prescription drug costs relative to household income, residence in a long term care facility, and receipt of home health care services
    - At least 6 months of continuous eligibility for public drug coverage was also required for inclusion in the study database
    - Cancer cases were identified and removed from the study population by using the Ontario Cancer Registry and national hospital discharge databases

Identification of cases:

- Cases were defined as people who died of an opioid-related cause by the Office of the Chief Coroner in Ontario
    - Ontario law requires that all deaths that are sudden, unexplained, or unnatural be reported to the coroner's office
    - The coroner's office has a policy requiring toxicologic testing if drug-related paraphernalia is found at the scene of death, or if an anatomic cause of death is not found at autopsy
        - When an anatomic cause of death is found, toxicology is frequently done to determine if there were additional contributory causes of death
    - The case definition was met if the coroner determined that a combination of drugs, including at least one opioid, resulted in death, or if toxicology revealed opioid levels high enough to cause death

Assessment of exposure:

- The Ontario drug benefit database contains computerized records of prescriptions dispensed to eligible residents of the province
- The study population was identified by selecting beneficiaries aged 15 to 64 who were dispensed at least one prescription for an opioid over the study period, including codeine, morphine, oxycodone, hydromorphone, meperidine, or transdermal fentanyl

    - Parenteral and intranasal opioid prescriptions were excluded
    - Methadone prescriptions were excluded because they are principally used for addiction rather than for chronic pain in Canada
- The date of death of the case was used as the “index date” on which opioid dosage was determined
    - Prescription records were examined and the average daily opioid dose was assumed to be equal to the sum of all opioid drugs which were in effect on the index date
    - That is, if the patient had a prescription for morphine and a prescription for oxycodone, then the number of morphine equivalents was calculated for each prescription, and the sum was entered in terms of total morphine equivalents as the opioid dosage on the index date
    - The daily dose for each drug was assumed to be the number of pills dispensed, divided by the number of days for which the prescription was written
- For all subjects in the study, the authors developed a “disease risk score” which generated predicted probabilities of opioid-related deaths
    - The index used demographics (age, gender, income, residence), medical disorders (heart, lung, diabetes, Parkinson’s, dementia, glaucoma, gout, injury, seizure, stroke, arthritis, drug toxicity), psychiatric disorders, and other variables: suicide attempt in the past three years, number of visits to a physician, care by a psychiatrist, days in a hospital

Selection of controls:

- Any time a case was identified during the course of the study, the authors selected up to four controls with current opioid prescriptions from the drug benefit study database
    - These controls were matched to the cases on the index date for the case
    - The controls were matched to the cases on disease risk score, age, gender, index year, and Charlson Comorbidity Index
    - Because controls were selected as the cases were accrued, a person who was selected as a control early in the study remained eligible to be a case later in the study, if he or she died of an opioid related cause at that later date

Comparison of exposure between cases and controls:

- The focus of the study was the average daily opioid dose for cases versus controls
- The comparison was done with a logistic regression model suitable for matched case-control studies (conditional logistic regression), which was adjusted for variables which could be confounders for the comparison
    - These confounders were previous drug use (antidepressants, benzodiazepines, other psychotropic drugs or CNS depressant drugs, methadone), number of

drugs used in the past six months, duration of opioid treatment, number of pharmacies dispensing opioids, number of doctors prescribing opioids, and the presence of any long-acting opioid dispensed within the exposure window (past six months)

- Over the 113 month study period, 1463 opioid-related deaths were identified
    - Manner of death was ruled accidental in 59% of deaths, suicide in 16.8%, and undetermined in 24.2% of deaths, all of which were eligible for inclusion as cases
    - However, a large number of cases were excluded because of a cancer diagnosis at the time of death, and additional cases were excluded because they did not have drug coverage in the prior 180 days
    - Additional exclusions were done when an eligible control could not be identified from the study database when the case died
    - After exclusions of cases who did not have current opioid prescriptions in the database at the time of death, there were 498 remaining cases for which controls were selected for comparison
    - Of these 498 cases, the coroner found more than one opioid type in 38.8%, benzodiazepines in 60.4%, and ethanol in 18.5%
- After adjusting for the measured confounders in the conditional logistic regression model, the authors found a significant relationship between average daily opioid dose between cases and controls
    - An average daily opioid dose of less than 20 mg/day was taken as the reference category against which the higher dose levels were compared
    - An average daily opioid dose of 200 mg/d or more had an odds ratio of 2.88 (95% CI 1.79 to 4.63)
    - An average daily opioid dose of 100 to 199 mg/day had an odds ratio of 2.04 (95% CI 1.28 to 3.24)
    - An average daily opioid dose of 50-99 mg/day had an odds ratio of 1.92 (95% CI 1.30 to 2.85)
    - An average daily opioid dose of 20-49 mg/day had an odds ratio of 1.32 (95% CI 0.94 to 1.84)
- A sensitivity analysis which was done under slightly different methods agreed with the primary analysis in terms of finding elevated odds ratios at higher average daily opioid doses

Authors' conclusions:

- In this case-control study, average prescribed daily opioid dose was significantly associated with opioid-related mortality, and the risk was highest in patients receiving 200 mg or more of morphine equivalent per day

- Average daily doses between 50 and 199 mg per day of morphine equivalent may also be associated with an increased risk of death, but larger studies are needed to confirm this association
- The absolute risk of opioid-related mortality cannot be estimated for any of the dosage levels in this study
- The population in this study was restricted to a socioeconomically disadvantaged group of Ontario residents under 65 who meet requirements for drug coverage under the Canadian health care system
- Opioid dosages were estimated from publicly funded prescriptions and cannot identify unused prescription drugs, those acquired illicitly, and those paid for out of pocket
- The indications for opioid therapy could not be determined from the available data, but this is not likely to affect the associations between dose and mortality risk
- Cases had more prescriptions for benzodiazepines, antidepressants, and other CNS depressants than controls, but models were adjusted for these confounders and for other comorbidities

Comments:

- The case-control design nested in a defined cohort is advantageous for estimating odds ratios for dose-related opioid mortality in a population receiving prescriptions for opioids, and this study makes generally good use of this design
- The comorbidity adjustment used a disease risk index which the authors developed from a large number of ICD-9 and ICD-10 codes, but the computation of the score derived from these codes is not apparent
    - The corresponding author did furnish a table on request, which gives the ICD codes and a few other variables, but the summation of these codes into a score is not specified
    - The comorbidity score appears to have been modeled on a risk score study referenced by the authors (Park-Wyllie et al 2009) which examined the risk of hospitalization for bradycardia in dementia patients being treated with cholinesterase inhibitors
    - However, Park-Wyllie also does not specify the calculation of the disease risk index, and refers the reader to a paper by Arbogast et al 2008, which reported on the development of a cardiovascular risk score which summarizes numerous risk factors into a single score, which is much simpler than adjusting several risk factors separately in a complex multiple regression model
- There are some issues of interpretation in the discussion section, where the authors discuss the implications of lacking information on opioids obtained outside the

Ontario drug benefit program; they state that the errors in dose calculations would be similar for cases and controls, biasing the risk estimates toward the null value
    - This assumes that the misclassification of out-of-system opioid drug purchases is random in nature, equally likely to affect cases and controls
    - However, it is quite likely that out-of-system access to opioids is associated with factors which could be related to drug-seeking behavior, which could easily be non-randomly distributed between cases and controls
    - Out-of-system access could also be greater at lower prescribed levels than at higher prescribed levels
        - The direction of bias would depend upon which dosing levels were misclassified, and would occur if the "as prescribed" dose levels were underestimating the "as taken" dose levels
        - If the "as taken" dosing were higher than the "as prescribed" doses in the 20 mg range, then the "as taken" differences between the lower and higher reference range would be narrower than it appears, and the risk estimates would be somewhat low (a smaller increase in dose actually does triple the risk of overdose death), but for a reason other than the random misclassification hypothesis proposed by the authors
- Nevertheless, Figure 3 of the study shows a clear dose-response relationship between average daily dose and the odds of opioid related mortality
- In spite of some of the unclear points in the study, it is a well-executed study of a large cohort with a large number of mortality events, and the confidence intervals for the odds ratios are not extremely wide, as often happens in observational studies with fewer events to work with

Assessment: high-quality nested case-control study supporting good evidence that prescription opioids in excess of 200 mg of morphine equivalent average daily doses are associated with a near tripling of the risk of opioid-related death, compared to average daily doses of 20 mg morphine equivalent. Average daily doses of 100-200 mg and doses of 50-99 mg per day may be associated with a doubling of mortality risk, but these risk estimates need to be replicated with larger studies

References:

Arbogast PG, Ray WA (2009) Use of disease risk scores in pharmacoepidemiologic studies. Stat Methods Med Res 18: 67–80.

Park-Wyllie LY, Mamdani MM, Li P, Gill SS, Laupacis A, Juurlink DN. Cholinesterase inhibitors and hospitalization for bradycardia: a population-based study. PLoS Med. 2009;6(9):e1000157