

Ray WA, Chung CP, Murray KT, Hall K, Stein CM. Association of prescription of long-acting opioids and mortality in patients with chronic noncancer pain. JAMA 2016;315(22):2415-2423.

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Purpose of study: In a population of patients with chronic noncancer pain, to compare all-cause mortality among patients treated with opioids versus mortality among patients treated with alternatives to opioids

Design: retrospective matched cohort study

Population/sample size/setting:

- 22,912 patients (60% women, mean age 48) treated with opioids and 22,912 matched patients treated with alternatives to opioids in the Tennessee Medicaid benefits program
- The patients were treated between 1999 and 2012, and was limited to patients not receiving cancer, palliative, or end of life care
- The qualifying conditions were chronic pain (back, other musculoskeletal, abdominal, headache, other neurologic pain) in the past 90 days
- Patients over 75 were excluded; nursing home residents were excluded, and patients taking with recorded evidence of drug abuse were excluded

Definition of exposure:

- The opioid group had filled a prescription for a long-acting opioid such as sustained release morphine, controlled release oxycodone, transdermal fentanyl, and methadone
- The control drugs were anticonvulsants (gabapentin, pregabalin, and carbamazepine) and cyclic antidepressants (amitriptyline, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine, amoxapine, maprotiline, or clomipramine)
- Entry into the cohort happened when a patient filled a new prescription for one of the study drugs with no prior fill for a drug in that class within the previous year, and had not had a prescription in the previous year for any other study drug
 - o However, patients were also allowed into the study if they had filled a study drug prescription in the past 30 days, permitting the inclusion of patients who started the drug after being hospitalized)
 - o Exclusions were made when the starting daily dose was not recommended for chronic pain (such as cyclic antidepressants >150 mg of amitriptyline equivalents, or >180 mg morphine equivalents, or >1800 mg gabapentin equivalents)
- Exit from the cohort happened when a patient either died, completed one year without filling a prescription for a study drug, or filled a prescription for a drug in a different

class (regardless of dose), but a patient could re-enter the cohort if they again met the entry criteria for the study

Definition of outcome:

- The end point was all deaths occurring during the study period, from 1999 to 2012
- Deaths were divided into either in-hospital or out-of-hospital
- Deaths were also subdivided into unintentional overdose and all other deaths

Comparisons between exposed and unexposed groups:

- Because patients who receive a prescription for an opioid are likely to have different risk factors for death from any cause, the authors undertook to match the opioid and non-opioid groups on prognostic factors
- A total of 122 matching factors were considered
 - o Some were basic demographic variables such as age, sex, race, and Medicaid-qualifying disability
 - o Others were a wide variety of pain locations (back, abdominal, etc) and timing conditions (current, persistent, past 90 days)
 - o Many of the other prognostic variables related to past and current drug treatments (benzodiazepines at various dosage levels, antipsychotics, SSRI/SNRI, etc), psychiatric diagnoses, cardiovascular conditions, cardiovascular drugs (statins, ACE inhibitors, diuretics, beta blockers, etc), many common medical conditions (heart, lung, diabetes), use of wheelchairs or walkers, recent injuries, and ER or hospital visits for any drug overdose
- Rather than attempt to match patients on all 122 variables, the authors used propensity score matching
 - o Propensity scores are derived by considering how strongly a given set of 122 variables for one individual predict that individual's probability of filling a prescription for a long-acting opioid, and is a number between 0 and 1
 - o For example, a patient who is 50 years old, white, male, has persistent back pain, has used a short-acting opioid in the past year, has no history of major depression, does not smoke, and takes a statin for any reason, may have a probability of getting an opioid prescription of 25%, which is his propensity score
 - o If that patient actually gets an opioid prescription, then he will be matched with another patient who also has a 25% propensity score, but got a prescription for a non-opioid instead; it is not necessary that the two patients match on all 122 variables which went into making up the propensity score
- Some additional variables were considered when comparing opioid and non-opioid groups; most importantly, duration of treatment defined as the cumulative number of days for which a prescription was filled, and dosage of the study drug

- For purposes of analysis, high/low dose levels were defined for opioids at 60 mg/d morphine equivalents, for anticonvulsants at 600 mg/d gabapentin equivalents, and for antidepressants at 40 mg/d amitriptyline equivalents

Results of the comparison:

- The most common diagnoses were back pain (75%), other musculoskeletal pain (63%), and abdominal pain (18%)
- More than 96% of patients had filled a prescription for a short-acting opioid in the past year, and 68% had a current prescription for a short acting opioid when they were entered into the study cohort
 - Other medications were commonly used: NSAIDs (70%), skeletal muscle relaxants (63%), benzodiazepines (52%), and either SSRI or SNRI (45%)
- Among the 22,912 long-acting opioid patients, 55% had morphine SR, 24% had oxycodone CR, 14% had transdermal fentanyl, and 6% had methadone
- Among the non-opioid patients, 47% had gabapentin, 6% pregabalin, 30% amitriptyline, 6% doxepin, and the remainder took other drugs
- There were 185 deaths during 11,070 person-years of followup time in the opioid group, which equals 167.1 deaths per 100,000 person years
 - This was greater than the 87 deaths in 8066 person-years in the non-opioid group, which equals 107.9 deaths per 100,000 person-years
 - This represented an adjusted hazard ratio of 1.64 for death from opioid versus non-opioid
 - This also represents a risk difference of 68.5 excess deaths per 10,000 patients
- The elevated risks were observed only in the out-of-hospital deaths; in-hospital death rates were not affected by treatment
 - Unintentional overdose was 3.37 times as common with opioids compared to non-opioids
 - Cardiovascular deaths were 1.65 times as common with opioids
 - The increased cardiovascular mortality in the opioid group was observed only within the first 180 days of starting treatment, when the hazard ratio was 4.16; after the 180 day window had passed, the cardiovascular deaths occurred equally with opioid and non- opioid treated groups
- For the predefined low vs. high dose groups as defined above, the opioid group had excess mortality
 - For the low dose comparisons, the hazard ratio was 1.54; for the high dose comparisons, the HR was 1.94
 - If a patient in the opioid group had been taking a short-acting opioid when entering the study, the HR was also elevated, and their mortality was increased by a factor of 1.6

Authors' conclusions:

- Long-acting opioids increased all-cause mortality in a cohort of Medicaid beneficiaries with chronic noncancer pain, who experienced an adjusted risk of death which was 1.64 times that of comparable patients treated with non- opioids, corresponding to an excess of 69 deaths per 10,000 patients treated with opioid
- The excess deaths occurred outside hospital settings
- Unintentional overdose mortality was increased, as expected, but the majority of the excess deaths were from other causes, principally cardiovascular
 - o Of the 69 excess deaths per 10,000 patients, 47 were not overdose deaths, and 29 were cardiovascular
- The increase in cardiovascular deaths could be related to known properties of opioids, which can cause or exacerbate sleep-disordered breathing, including both central and obstructive sleep apnea, increasing the risk of nocturnal arrhythmias, myocardial ischemia, and sudden death
- The cohort had excluded patients with high expected mortality, such as those over 75, nursing home residents, and those with cancer and with evidence of receiving palliative or end-of-life care
- These risks should be considered when evaluating harms and benefits of treatment

Comments:

- The application of propensity score matching (PSM) with stratification, as was done in this study, offers many advantages which can strengthen an observational study and can make a cohort study more like a randomized trial (Austin 2011)
- Randomization achieves prognostic balance between treatment groups by making treatment allocation completely independent of prognostic factors; conceptually, this means that for any participant allocated to the experimental treatment, there is a very similar participant in the control group
- PSM seeks out “hidden randomization” which is embedded in a large cohort, such that for any chronic pain beneficiary in Tennessee Medicaid who had an opioid prescription, there was a very similar beneficiary with a non-opioid prescription
- PSM is as susceptible as any other nonrandomized allocation method to unmeasured confounders, which are difficult to estimate in this setting
 - o For example, intangible personality factors could be associated with expressing a preference for opioid treatment, which could lead to getting a prescription for an opioid, and these factors could be risk factors for mortality, which would thereby explain some of the mortality data independent of the pharmacology of the long-acting opioid
- Most of the mortality information came from death certificates; the authors also looked at selected medical records in order to perform a sensitivity analysis on a portion of the data, and the results were not materially altered

- In Table 6 of the data supplement, short-acting opioids at various doses were currently being taken by 68.2% of the opioid group and by 67% of the control groups, and a dose >60 morphine equivalents was recorded in 13.1% of the opioid group and by 14.1% of the control group
- Overdose deaths were classified as “unintentional,” and no mention is made of intentional overdoses; death certificates may not capture suicides with opioids and in this sense the database is incomplete
- However, the majority of excess mortality among the opioid group was from non-overdose causes, and this is an important finding

Assessment: High quality cohort study which supports good evidence that in generally healthy patients with chronic musculoskeletal pain, treatment with long-acting opioids, compared to treatments with anticonvulsants or antidepressants, is associated with an increased risk of death of approximately 69 percent, most of which arises from non-overdose causes, principally cardiovascular in nature. The excess cardiovascular mortality principally occurs in the first 180 days from starting opioid treatment.

Reference: Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. *Multivariate Behavioral Research* 2011;46:399-424.