

Edlund MJ, Martin BC , et al. The role of opioid prescription in incident opioid abuse and dependence among individuals with chronic noncancer pain: the role of opioid prescription. Clin J Pain 2014;30:557-564

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Purpose of study: to estimate the risk of incident opioid use disorder (OUD) among patients with recently diagnosed chronic noncancer pain (CNCP)

Design of study: Retrospective cohort study using claims data from a large health care database

Population/sample size/setting:

- 568,640 individuals in the HealthCore Integrated Research Database, containing medical and pharmacy administrative claims from 5 commercial health plans representing the West, Midwest, and Southeast regions of the United States, collected between 23000 and 2005
- The criteria for entry into the study cohort were age over 18 with a new episode of CNCP, defined by these conditions:
 - o Two or more claims containing primary or secondary diagnoses of the same type of CNCP (back pain, neck pain, headache, arthritis, HIV) that occurred at least one month but less than one year apart
 - The date of the first diagnosis was defined as the index date for the case
 - o No CNCP of the same type in the six months before the first qualifying CNCP diagnosis
 - o Continuous insurance eligibility for at least 12 months before the index date and for at least 18 months after that date
 - o No prescription opioid use in the six months prior to the index date
 - o No prior diagnosis of OAD
 - o No cancer diagnosis at any time during the 12 months before or the 18 months after the index date
 - o Not residing in nursing homes or hospice

Ascertainment of exposure:

- The main exposure of interest was prescription opioid use derived from pharmacy claims in the database
- Opioid exposure was defined in two dimensions: number of days for which opioids were prescribed and average daily opioid dose for the 12 months after the index date
 - o Days' supply was defined in three categories: none, acute (1 to 90 days), and chronic (91 days or longer)

- Average daily opioid dose was defined in terms of morphine equivalents and grouped as none, low dose (1 to 36 mg), medium dose (36 to 120 mg), and high (120 mg or more)
- These two criteria were used to define seven levels: (1) no opioid use; (2) low dose, acute; (3) low dose, chronic; (4) medium dose, acute; (5) medium dose, chronic; (6) high dose, acute; and (7) high dose, chronic

Ascertainment of outcome:

- The diagnosis of OUD was derived from ICD-9-CM codes 304.00 (Opioid type dependence, unspecified) and 305.50 (Opioid abuse, unspecified) in the claims database, entered into the record at any time in the 18 months following the index date

Assessment of association between exposure and outcome:

- The main association of interest was the risk of OAD in relation to the seven levels of opioid use
- The association was calculated in a logistic regression model which considered several important confounders
 - Sociodemographic factors
 - Mental health and substance use disorders (adjustment disorders, anxiety disorders, mood disorders, personality disorders, eating disorders, and somatoform disorders)
 - The authors summed the number of mental health diagnoses to create a three-level indicator variable: no diagnosis, one diagnosis, and two or more diagnoses
 - Previous substance use or dependence disorders (classified as alcohol use or nonopioid drug use disorders)
 - Physical health and pain diagnoses
 - Some pain conditions were selected as tracer pain diagnoses: joint pain, back pain, neck pain, headache, or HIV
 - Additional pain diagnoses were also used to estimate the total pain burden: extremity pain, abdominal pain, chest pain, kidney stones/gallstones, pelvic pain, rheumatoid arthritis, fractures, neuropathic pain, fibromyalgia, and temporomandibular joint pain
 - The Charlson comorbidity index, which is used to estimate the one-year risk of mortality when certain major organ disorders have been diagnosed (heart or lung disease, dementia, liver disease, diabetes, renal failure, tumors, HIV)
- The authors then estimated odds ratios for the diagnosis of OAD when different levels of opioid use were present, adjusted for the above confounders

Results of the analysis:

- There were 568,640 individuals in the health claims database who had a new episode of CNCP and had no previous exposure to opioids and no prior diagnosis of an OAD
- The majority (65.3%) of these individuals had no opioid exposure as determined from pharmacy databases, and the remainder of the individuals fit into one of the opioid use levels
 - o Low dose, acute: 15.9%
 - o Low dose, chronic: 1.2%
 - o Medium dose, acute: 14.7%
 - o Medium dose, chronic: 0.6%
 - o High dose, acute: 2.2%
 - o High dose, chronic: 0.1% (n=378)
- There were 497 individuals who had a new diagnosis of an OAD during the 18 months after the index date, with different frequencies of OAD in the different dose categories
 - o No prescribed opioids: 0.004% (n=150)
 - o Low dose, acute: 0.12% (n=111)
 - o Low dose, chronic: 0.72% (n=50)
 - o Medium dose, acute: 0.12% (n=101)
 - o Medium dose, chronic: 1.28% (n=47)
 - o High dose, acute: 0.12% (n=15)
 - o High dose, chronic: 6.1% (n=23)
 - o Thus, for all three categories of acute opioid use, the proportion of patients who developed an OAD was 0.12%, confirmed by making calculations from Table 2
- Men had an elevated odds ratio for OAD compared to women (OR=2.27, 95% confidence interval 1.85-2.78)
- Age was strongly associated with OAD; the youngest group (age 18-30) had an OR of 10.51 (95% CI 5.47-20.2) compared with the group over 65
- The diagnosis of a mental health disorder was associated with OAD; compared to no diagnosis, the OR for one mental health diagnosis was 3.85, and for two or more diagnoses, the OR was 8.37
- Previous substance abuse was strongly associated with OAD: for nonopioid use, the OR was 60.95, and for alcohol use, the OR was 23.35
- Level of opioid use was associated with OAD in logistic regression models which were adjusted for age, sex, and mental health disorders
 - o For the three levels of acute use (low, medium, high) the adjusted OR was approximately 3.0
 - o For the three levels of chronic use, the adjusted OR were greater: 14.9 for low dose, 28.7 for medium dose, and 122.45 for high dose

Authors' conclusions:

- In the setting of opioid prescription for recent onset chronic noncancer pain, there is a risk of the development of an opioid use disorder which is a function of two factors: dose and duration of the prescription
- When opioids are prescribed for fewer than 90 days, there is approximately a tripling of the risk of opioid use disorder compared to when opioids are not prescribed, and this risk does not depend on whether the dose was low, medium, or high
- If opioids are prescribed for more than 90 days, there is a dose-dependent risk of opioid use disorder, which is multiplied by a factor of approximately 15 at low dose, 29 at a medium dose, and 122 at a high dose
- The absolute risk of opioid use disorder when a high dose is prescribed for more than 90 days is approximately 6.1% in the first 18 months after treatment is begun
- The 6.1% risk may be an underestimate of the true risk, since the data were derived from administrative databases with a limited followup period, and the condition may be present but not diagnosed
- There are numerous limitations and caveats with interpreting the data, which are observational in nature and not derived from a randomized trial
 - o The data had no information on pain severity or functional impairment
 - o The criteria for an opioid use disorder in the DSM-IV are likely not to be optimal for prescription drug disorders
 - o Detection bias is likely to be present if patients on higher doses of opioids are monitored more carefully than those on lower doses
 - o Although the administrative database would have detected an opioid use disorder which had begun in the 6 month period prior to the onset of a chronic pain condition, it would not have detected a previous problem
 - o Although the sample was very large, covering several states and settings, it may not have been representative of the entire population with new onset chronic pain, such as those who are not enrolled in an insurance plan
 - o The cutoff point for high dose opioid of 120 mg morphine equivalents is arbitrary, even though it is based on Washington State guidelines

Comments:

- The discussion section is well-written and points out several of the limitations of estimating risk of adverse events from large databases, but not all of the limitations point in the same direction
- That is, the estimate that 6.1% of patients prescribed high dose opioids for longer than 90 days would be too high if detection bias had motivated physicians to follow these patients more closely and monitor them more vigilantly for signs of opioid abuse
- However, some factors could make the 6.1% risk estimate too low
 - o One is the weakness in the DSM-IV criteria which the authors point out

- Another is the 18 month time frame of the study, which is likely to miss cases where an opioid use problem becomes obvious only much later
- Another is the fact that the data derive from the period 2000 to 2005, when it was widely taught that opioids used to treat pain do not lead to addiction, leading to a low index of suspicion and a less proactive system for detecting the emergence of opioid misuse, dependence, and addiction
 - For example, since public awareness of opioid prescription abuse has grown, a patient who repeatedly asks for a higher dose of an opioid is likely to be diagnosed with an opioid use disorder
 - Between 2000 and 2005, when many CME programs taught that opioid treatment of pain did not lead to addiction, a request for a higher opioid dose in that same patient was likely to be attributed to inadequate analgesia from the existing dose, and the dose was likely to be increased
- The finding that there is a large dose-response relationship in patients who had prescriptions lasting longer than 90 days, which measures relative risks of OAD, is likely to be unaffected by many of the limitations discussed above, which affect estimates of absolute risk of OAD
 - The fact that the effect sizes in terms of OR are quite large means that these observational data satisfy two criteria by which such data can qualify as evidence: large effect size and clear dose-response relationship
- In Table 3, the unadjusted odds ratios are similar to the adjusted odds ratios for opioid use and duration, and the same is true of age and sex
 - However, for previously existing substance abuse/dependence diagnoses, the adjusted odds ratios are much lower than the unadjusted OR, perhaps because they were confounded by mental health diagnoses which were present in the adjusted but not in the unadjusted odds ratio; the reason is not obvious

Assessment: a retrospective cohort which supports good evidence that in the setting of new onset chronic noncancer pain, there is a clinically important relationship between opioid prescription and subsequent opioid use disorder. Compared to no opioid use, short-term opioid use approximately triples the risk of opioid use disorder in the next 18 months. Use of opioids for over 90 days is associated with very pronounced increased risks of the subsequent development of an opioid use disorder, which may be as much as one hundredfold when doses greater than 120 mg of morphine equivalent are taken for more than 90 days. The absolute risk of these disorders is very uncertain, but is likely to be greater than 6.1% for long duration treatment with a high opioid dose.