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Brief Academy

Critical appraisal of "Prescription of long-acting opioids and mortality in patients with chronic nonmalignant pain"☆

Lectura crítica del estudio "Prescripción de opioides de acción prolongada y mortalidad en pacientes con dolor crónico no oncológico"

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Introduction

These remarks represent a critical appraisal of the article by Ray et al.[1] The approach is based on the reading questions for cohort studies developed by the CASPe (*Critical Appraisal Skills Programme Spanish*) group discussed in the text[2] and an analysis of the authors' methodological strategies and analytical techniques.

One of the cornerstones in the management of patients with chronic pain, whether of cancer etiology or not, are opioids. There is a clear increase in the use of opioids in patients with cancer pain and it is estimated that approximately 20% of people receive opioids in the United States.[3] This rise is concerning due to the potential side effects that these agents may cause,[4] not just associated with overdosing,[5] but also as a result of cardiovascular, endocrine, gastrointestinal, and metabolic adverse effects.[6] Based on these concerns, the need to validate the association between the prescription of opioids and morbidity/mortality was identified.

Objective of the study

The objective was to compare any cause mortality, mortality in patients with chronic, moderate, or severe nonmalignant pain who were prescribed potent opioids, versus other co-adjuvant alternative medications (control group).

Design of the study

Retrospective cohort observational trial based on the *Tennessee Medicaid* data between 1999 and 2012 – this is a pharmacovigilance database in the United States. This registry includes information about drug prescriptions in the population and death certificates information. During the study period all patients with chronic nonmalignant pain diagnosed 90 days before were selected; these patients would have been prescribed potent opioids (sustained release morphine, controlled release oxycodone, transdermal fentanyl

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or methadone) or neuromodulators (anticonvulsants such as gabapentine, pregabaline, carbamazepine or tricyclic antidepressants). Patients with a diagnosis of cancer or life-threatening pathologies were excluded; patients in palliative care or advanced disease stages, people older than 75, or living in nursing homes, patients with a history of substance abuse, patients that had been hospitalized in the last 30 days or who were receiving or had received opioids in the past year (whether for chronic pain or any other medical indication), as well as patients receiving unusually high doses of the drugs mentioned.

The starting point for the cohort (exposure) in which the patient collected the prescribed medications. Any patients who for one year failed to collect their medication, asked for a different medication, or whenever the starting date of the medications coincided with the end of the trial, were classified as lost to the cohort (censored). During the cohort follow-up, the total number of days for which the medication was dispensed in each prescription was measured.

The primary outcome of the trial was death during follow-up. Mortality was classified as in-hospital or extra-hospital and non-intentional overdose, and other causes.

The statistical analysis compared the death-adjusted risk during follow-up between the opioid and control groups. The relative risk was estimated measuring the *Hazard Ratio* (HR) through a proportional risk regression model. Additionally, the adjusted risk of death difference between groups was estimated and the subgroups analysis for mortality during the first 180 days of therapy as well as death from cardiovascular causes was made.

Results

The initial selection considered 23,308 patients with strong opioid prescription and 131,883 patients who received co-adjuvant neuromodulators (control group). After screening, 22,912 patients with opioids were included and matched to an equal number of patients from the control group, using a propensity score that considered 122 co-variables.

The mean age was 47.9 years old (1SD = 10.7 years). There was a higher prevalence of females (60%) and the most frequent diagnosis was low back pain (75%). 96% of patients had received low strength opioids during the last year and 68% were still taken them.

185 patients from the opioid group died during follow-up (167.1 per every 10,000 persons-year) and 87 in the control group (107.9 per every 10,000 persons-year). The adjusted HR for any cause of death was 1.64 (95% CI 1.26–2.12) and the absolute risk difference was 68.5 (95% CI 28.2–120.7) excess deaths per 10,000 persons-year. 79% of the deaths in the opioid group were extra hospital (HR 1.90; 95% CI, 1.40–2.58). This difference was not significant for in-hospital mortality.

This increase in extra hospital mortality was maintained for non-related non-intentional overdose deaths (HR 1.72 95% CI 1.24–2.39) and was consistent with deaths from cardiovascular causes (HR 1.65 95%CI 1.10–2.46). Likewise, the increase was significant during the first 30 days of therapy and up to 180 days and was present for high and low opioid doses.

All the sensitivity analyses performed showed similar results in the initial analysis. Following the adjustment for probable poor classification of the "cardiovascular death" outcome (comparing medical records with death certificates) the mortality HR declined to 1.58 (IC 95% 1.05–2.36). In one extreme the poor classification could have been 1.36 with no statistical significance.

Reviewers' comments

The analysis for internal validity of an observational study requires evaluating and identifying the presence (or absence) of random error and systematic errors (or biases). Initially, the large number of patients studied reduces the probability of random error.

It is impossible to approach a study if the report is incomplete or fails to provide enough information. The evaluation of this manuscript with STROBE statement, meets twenty of the twenty-two completeness criteria. No funding sources are mentioned and it lacks a more detailed description about the type of study.[7] The absence of these two domains does not make a considerable impact on completeness and is an acceptable report.

Bias risks

The retrospective cohort trials use data already existing in large information systems, as in this case. They follow the clinical course of the disease and therefore start with exposure (prescription of medications) until the occurrence of an outcome (in this case, mortality). Based on its design, the researcher does not measure directly the exposure or outcomes and depends on the quality of information.[8]

Potential selection biases

The characteristics of any particular patient directly impact the decision of the clinical practitioner to prescribe or not a long-acting opioid; for example, pain intensity. This "indication" to prescribe is one of the key sources of selection bias in observational studies and is called *indication bias*. It means that for some reason a patient was prescribed the medication the medication and this decision is systematically different for another patient for whom the medication has not been prescribed. For this reason, the groups compared (in this case patients treated with co-adjuvant therapies) are not balanced and affects the estimate of the association between exposure and outcome. This *confounding by indication* is probably one of the main challenges for the internal validity of observational studies.

A strategy to reduce the impact of this "indication" or the residual confusion that may be generated, is the randomization used in clinical trials aimed at balancing the groups into probable outcome-related known and unknown variables. However, in many alike situations, it is unfeasible or unethical to do it and other strategies must be used for adjustment purposes.

Possible information biases

In this design the information biases are the result of the way in which exposure and outcomes were classified. Considering that the primary outcome in the study was death, it is quite unlikely that it is improperly classified (hard outcome). However, the cause of death may depend on the quality of the death certificates or medical records. The authors did a sensitivity analysis aimed at evaluating whether a poor classification affected the risk estimate. With regards to the exposure, the quality of the classification depends on the database, about which little details are given. Additionally, the dispensing of medicines was considered but not the treatment compliance directly.

Confusion control

Even with adequate selection and ensuring the quality of the information obtained, observational trials are required to control the presence of factors or variables that may be related to exposure and with the outcome occurrence that affects the risk estimate. In epidemiology this phenomenon is known as confusion and there are several methods to approach it (i.e., restriction, stratification, pairing, multivariate analysis, inter alia).

Since the specific indication whereby a patient was assigned to a specific treatment (indication bias) may imbalance the comparison groups, and at the same time this may create confusion in estimating the effect of the exposure to the outcome (indication confusion), this study uses a special technique called *Propensity score*.

The propensity score is a statistical technique that estimates the conditional probability of a particular individual to receive treatment (or exposure), given its characteristics (covariables) expressed in a vector.[9,10] Thus, by estimating the individual probability of having been assigned to an exposure the scores may be matched and balanced between the comparison groups.[11–13] This strategy may complement the regression analysis but is mainly used to minimize the indication confusion.[14] The group matching resulting from the process is aimed at simulating the randomization in a clinical trial within the context of an observational trial.

Additionally, the Cox proportional risk model was used; this is a multivariate analysis technique suitable for "time to event occurrence" type of outcomes.[15]

Interpretation of results

Considering that observational studies are not exempt from risk, there is an evident effort to control risks. Following a critical analysis of the quality of the methodology, it must be emphasized that the results are clinically relevant. The prescription of long-acting opioids increases the risk of death from any cause (not just overdosing) and probably from cardiovascular causes. This result shows that adverse cardiovascular, endocrine, gastrointestinal, and metabolic effects from these types of drugs are beyond our current understanding.

The rise in mortality was important from the beginning of treatment and until day 180, emphasizing the need for adequate control and short follow-up at the beginning of treatment.

Adverse events from using potent long-acting opioids have recently been a relevant topic and their risk-benefit ratio has been evaluated. This concern and the recent evidence have influenced the recommendations for the current clinical practice guidelines to use these agents in non-cancer pain. The recent guidelines from the *Center for Disease Control and Prevention (CDC)* recommends that whenever the pain intensity and other non-cancer chronic pain characteristics permit, non-opioid therapy shall be preferred.[16] This is also the case with regards to lumbar pain due to the high prevalence in the population.[17,18]

Colombia is aware of this discussion and even more so of the increase in opioid prescription. Approximately 1.06% of the population has used opioids at some point in their lives and there is a high prevalence of non-cancer chronic pain in the population.[19,20]

The exclusion criteria applied herein may curtail the external validity of its results; however, the probability of finding patients similar to those in the trial in the daily pain clinic practice is high, and hence emphasizes the value of the results.

In conclusion, this fact forces the practitioner to judiciously evaluate the risk-benefit ratio of this therapy in non-cancer pain and involve the patient in the decision to start and/or continue treatment after a short trial period, evaluating whether the pre-established objectives have been attained.

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Conflicts of interest

The authors claim not having any conflicts of interest.

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