SPPH 502: Epidemiology Methods I

Final Paper

Is prescription opioid use for chronic pain associated with higher mortality rates?

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Introduction

Over the past 30 years, opioids including oxycodone, fentanyl, codeine, morphine and hydromorphone have become a first-line medication for the treatment of severe pain. Pain treatment is a clinical challenge for many healthcare providers as it is difficult to determine the proper balance between under- and overuse of opioid analgesics. Over-treated pain can lead to hyperalgesia, opioid addiction or even death, while undertreated pain can result in depression, anxiety, hypertension, immune suppression, and accelerated disease progression.[1,2]

In the last two decades, significant increases in opioid prescribing rates and average prescription volumes have been documented in both the United States[3] and Canada[4]. These trends are concerning because high-dose opioid therapy is associated with considerable morbidity and mortality, including drug toxicity, overdose death, falls, fractures, and motor vehicle injury.[4-7] Even with these risks, long-term opioid treatment for non-cancer pain has become common practice in North America, although little evidence supports the practice.[8,9]

With previous literature suggesting the association between opioid therapy and mortality, this paper aims to determine if this association is true and if opioids can be safely used at any dose for the treatment of chronic pain. To explore this, we will conduct a literature review to address the following question: to what extent is opioid use in chronic pain treatment associated with increased mortality? This research question will be limited to the adult population as opioids are generally prescribed to this population for chronic pain.[8,9] Additionally, studies included will be restricted to Canada and the United States as this paper aims to inform policymakers of these countries, if opioid therapy is associated with increased mortality. The aim of this literature search is to provide insight to this research question and ultimately whether

improved strategies and programs surrounding opioid therapy for the treatment of chronic pain are needed.

Methods

Literature Search Strategy

A search of five databases (Medline, Embase, PubMed, PsychINFO, and AMED (Allied and Complementary Medicine)) was undertaken. The search strategy combined concepts related to prescription opioids, complications from prescription opioids, and opioid-related mortality. In PubMed, this was performed using the MeSH terms *Analgesics, Opioid AND Chronic Pain OR Drug Overdose OR Mortality*. A similar approach was performed in Medline, Embase, PsychINFO, and AMED, however these keywords were inputted in the advanced keyword search rather than as MeSH terms. A variety of combinations of keywords were trialed, it was found that the keywords selected provided identification of the majority of studies that explore prescription opioid use and related mortality in a chronic pain setting. Additionally, inclusion criteria for the literature search included English language, adult population, and publication between January 2000 and December 2015. These restrictions were applied as a focus on current literature is needed to inform policymakers on the research topic and so that a population that used opioids for chronic pain was included. Duplicate articles were removed from the collected abstracts and deleted. Abstracts were then screened such that only those that contained the words *Opioid* and *Mortality* were included in the final collection (n=121).

Selection Criteria for Three Studies

From the study abstracts obtained, three were selected for review. The studies were initially included if they had specified opioid-related mortality as an outcome. Among these remaining studies, we excluded those whose population was not reflective of the adult population that receives opioids for non-cancer pain, which includes studies that included populations over the age of 65, receiving palliative care, or diagnosed with cancer. Since the focus of this review was to describe the association between opioid use and opioid-related mortality, studies where opioid use and/or dosing was specified and/or quantified were preferred. Additionally, if the same geographic location was given for multiple studies they were also preferred, as it has been suggested that opioid use varies significantly by geographic region.[10] Through this preference, strong evidence can be obtained to either support or refute the relationship between exposure and outcome. To determine the aspects of opioid use that can lead to death, a case-control was preferred to reduce the impact that confounding of variables could have on opioid-related mortality. Additionally, a cohort study was ideal to include because it would provide insight to the effects of opioid use on mortality over a long-term period. Finally, a population based cross-sectional study was preferred so that opioid-related mortality rates in the general population could be characterized.

Description and Assessment of Selected Studies

Studies that were obtained in full text were individually assessed on several aspects including outcome, population included, sample size, exposure definition, geographical location, conflict of interests, and study design. Factors that were considered for assessing outcome included if opioid-related mortality could generally be restricted to prescription opioids. This meant that individuals who may have had a heroin (a recreational drug) related mortality, or mortality

where opioid levels were insufficient to cause death alone were excluded from the study outcome. The focus population of this review is adults who use opioids for chronic pain. Therefore, any studies that included palliative care or cancer populations were excluded. From these remaining studies, sample size was considered as large samples were preferred to improve the generalizability of this review and reliability of study results. Exposure definition was opioid use and dose from all opioids received. Therefore, studies that included dosing in morphine equivalents were preferred. Studies were reviewed for factors that could distort results mainly study designs that used methodology which could misclassify exposure or outcome from the use of outdated databases, case definitions or dosing calculations. Finally, studies were reviewed for industry sponsorship so that no conflict of interest would be present.

Results

Synthesis of the Literature Search

From the search of each database a total of 121 abstracts were reviewed: approximately 15% were case-control studies, 10% were case reports, 36% were cohort studies, 14% were literature reviews and 25% were letter to the editor/commentaries. Overall, findings from the abstracts indicated an association between opioid use in chronic pain and associated mortality where there were no limitations on the type of opioid or maximum dose. Where restrictions on prescribing dose and types of opioids were present, lower opioid-related mortality rates were reported after implementation. The remaining abstracts showed mixed results depending on type of opioid prescribed and dosing, these were generally cohort studies with small populations (n>30).

Selected Studies

The three selected studies for assessment included an exploratory cohort study, cross-sectional study, and nested case-control study. All three studies included exposure to opioids and the outcome of opioid related mortality. Additionally, two quantified exposures to opioids by dose in mg of morphine equivalents daily (MED) to determine if dosing of opioid rather than opioid use was associated with opioid-related mortality. A summary of the studies included and their findings can be found in Table 1.

Table 1: Summary of the Three Included Studies

	Study 1: Gomes T et al. (2011)	**Study 2:** Gomes T et al. (2014)[10]	**Study 3:** Gomes T et al. (2011)[8]
Study Design	Population Exploratory Cohort Study	Cross-Sectional Study	Population-Based Nested Case-Control
Primary Objective	Examine the relationship between opioid dose and mortality.	To measure annual rates of opioid-related mortality between 1991 and 2010.	To measure the association between daily opioid dose on opioid-related mortality and risk of opioid-related mortality.
Population	Cohort: Beneficiaries of Ontario's public drug plan aged 15-64 years in 2004. * Reference: Ontario population aged 15-64 years who did not receive an opioid prescription in 2004	Individuals who had an opioid related deaths in Ontario.	Cases and Controls: Beneficiaries of Ontario's public drug plan aged 15-64 years between 1997 and 2006*.
Outcome	Mortality rates by opioid dose	Rates of opioid-related mortality	Opioid related death, Risk of opioid-related death by dose
Exposure	Opioid prescription dispensed in 2004	Opioid related deaths between 1991 and 2010	Cases: Opioid-related death between 1997 and 2006. Controls: Opioid prescription

			dispensed that overlapped with death date of the case
Comparator	Ontario population aged 15-64 years who did not receive an opioid prescription in 2004	Death from all causes in Ontario	Individuals with the opioid prescription in equivalent MED matched for confounding factors
Main Result	Of the 154 411 individuals included in the cohort, within 2 years of their first prescription 3722 died from any cause of which 302 (8.1%) of these deaths were classified as opioid-related. Compared to the reference population, death from all causes was 5 times higher in opioid users. Compared to moderate dose users, opioid-mortality rates were 5 times higher for high dose users and 6 times higher for very high dose users.	Rates of opioid-related death increased substantially, rising 242% from 12.2 deaths per million in 1991) to 41.6 deaths per million in 2010 During the 20-year study period, the proportion of all deaths related to opioids rose threefold from 0.2 to 0.6%. The proportion of opioid related deaths in individuals aged 25–34 increased from 3.3% in 1991 to 12.1% in 2010. Additionally, during this time period, among people aged 35–44 years a 3-fold increase, from 2.3 to 7.3% in opioid-related deaths.	Adjusting for other factors that could affect mortality, there was a significant relationship found between opioid-related mortality and daily dose. Using patients receiving less than 20 MED daily as a reference population, those with daily doses greater than 200 MED had much higher odds of opioid-related mortality (2.88). Additionally, those with doses greater than 50 MED had significantly higher odds compared to the reference group (1.92 for 50-99 MED; 2.04 for 100-199 MED)
***Beneficiaries were excluded if they had any prior diagnosis of cancer or if in the preceding 180 days of their first opioid prescription each year if they had received palliative care**			

Individual Study Assessments

Study 1: Gomes T et al. (2011)

The main strength of this study was that exposure to opioids was quantified by daily dose using an equivalence scale that standardized different types of opioids (i.e. oxycodone, fentanyl,

hydromorphone) into a common measure of mg MED. This method is valuable as daily dose in individuals receiving more than one type of opioid can have their daily dose calculated as sum of all opioid medications in mg MED rather than each medication separately (i.e. a daily dose 25 mg of oxycodone and 25 mg of morphine). Through this, the study is able to compare opioid dosing groups to each other rather than individual opioid medications allowing for the generalization between opioid dosing and related mortality.

One limitation that could affect the study outcome is drop-out from the study cohort due to ineligibility for Ontario Public Drug Program. Eligibility for the program for individuals in this cohort would be if they are unemployed, disabled or have high prescription drug costs relative to net income. The most likely reason for drop-out would be due to employment. Generally, individuals who are employed have lower mortality rates, therefore drop-out due to employment to bias results away from the null hypothesis which is that opioid use is associated with increased mortality.[14] Additionally, classifying opioid dose category based on the MED in the first 90 days of therapy, leads to the possibility of misclassification bias. During the cohort time period, MED could change to be either higher or lower than the initial group assignment. Therefore, if death occurred to an individual who had their dose changed during the study period it would still be classified according to their initial study group. However, it could be that this change in dose leads to individuals actually belonging to another group at time of death. This is nondifferential misclassification which would mean that we would be less likely to determine if an association between opioid dose and mortality exists. These limitations may have attenuated or distorted the study results.

Study 2: Gomes T et al. (2014)

A strength of this study is that it incorporates a large study population by using the Office of the Chief Coroner to obtain all opioid-related deaths in Ontario. Since unexpected and unnatural deaths are reported, this excludes the majority deaths in palliative care and cancer populations where higher mortality rates are likely not related to opioid use. Additionally, individuals were not classified as an opioid-related death if heroin or opioids in combination with other medications was indicated on the postmortem toxicological report or if opioid concentration were not sufficiently high to cause death. These exclusion criteria allow for some implication that the majority of these deaths are driven by prescription opioids though it is difficult to determine what were the opioids prescribed for in these individuals.

One limitation of this study is that opioid-related deaths are often determined through postmortem toxicological blood analysis. Since this study period is between 1992 and 2010, increased rates of opioid-related mortality could be due to improved developments in toxicological analysis rather than increasing incidence. Another limitation is that only unexpected and unnatural deaths in Ontario are investigated by a coroner, therefore an underreporting of opioid-related deaths could be occurring. Additionally, with this limitation, if awareness of the potential for opioid-related mortality has increased over the study period, higher numbers of opioid-related deaths could be reported resulting from this increased awareness rather than increasing incidence.

Another limitation in using proportionate mortality in comparing opioid-related deaths to death from all causes is that the risk associated with opioid use and death is unknown. It is stated that

the proportion of opioid-related deaths between 1992 and 2010 increased from 3.3% percent to 12.1% in the 25-34 age group. These statistics, when calculated in rates per thousand deaths for this population, show an increase from 32.7 to 120.9 opioid-related deaths. With only describing proportionate mortality, increases in opioid-related deaths could be due to decreases in death from other accidental causes, limiting determination from this statistic alone if opioid-related deaths are increasing or decreasing.

Study 3: Gomes T et al. (2011)

A strength of this study is that it uses nested case-control design which prevents selection bias by taking both cases and controls drawn from the same population. Additionally, using matching of multiple cases to controls based on characteristics such as age, gender, disease risk allows for similarity with respect to certain characteristics that could affect mortality other than opioid dose. Additionally, a sensitivity analysis was performed to determine if opioid-dosing (exposure) was defined differently if it would impact the study's conclusions on opioid-dose and mortality.

One limitation of this study was that in the primary analysis the measurement of opioid dose could be underestimated as only prescriptions overlapping the outcome date were used to calculate dose in MED. This would mean that prescriptions that ended just before the index date would not be included leading to an underestimate of actual calculated average daily dose. This would bias the results towards the null hypothesis and underestimate the association between opioid dose and mortality.

Another limitation that may have weakened this study's results is misclassification bias if an opioid-related death was classified as a non-opioid-related death due to if the information on the coroner report was incomplete or in error. Additionally, cases and controls differed on several characteristics including use of other medications including benzodiazepines and antidepressants which may associated with opioid-related mortality. These occurred primarily in the case group which would lead to bias away from the null if these medications were associated with increased likelihood of opioid-related mortality. Lastly, only opioid dosing was estimated from reimbursed claims, therefore unused opioids, opioids obtained illicitly, or paid out of pocket would not be included in the daily dose calculations. These limitations would lead to an underestimate of opioid dosing, leading the results to be biased towards the null hypothesis.

Discussion

Compare/Contrast of Selected Studies

Exposure Assessment

Studies 1 and 3 had very similar exposure assessment measures. Study 1 involved the dispensing of at least 1 prescription for an opioid over the study period, while study 3 involved an overlapping prescription on death date. Using databases that monitor health-care billing codes, coroner reports, and prescription reimbursement claims, Studies 1 and 3 provided very accurate information for determining study eligibility, opioid dose, and opioid-related mortality. This provided reduced limitations commonly associated with these study designs, including missing data and subject recall bias. Study 2 exposure was assessed as opioid concentrations sufficiently high to cause death through postmortem toxicological analysis. This allows a high

likelihood that exposure was a prescription opioid, though it is a limitation as one cannot be certain of this or its prescription indication.

Outcome

Studies 1, 2, and 3 defined opioid-related mortality using the records from chief coroner of Ontario. One limitation of these records is that opioid concentrations defined as significantly high to cause death may have changed over the study period. Additionally, increased awareness of prescription opioid-related mortality and improved toxicological methods to examine it may have led to increased classification of deaths as opioid-related. This could affect reported rates in study 2 which lasted over a period of 20 years.

Factors that may Attenuate/Distort Results

All three studies contain some level of information bias because the means for obtaining information about the subjects in the study cannot measure exposure to opioids or opioid-related mortality entirely. In study 1, individuals could be opioid users but be placed in the unexposed group due to over–the-counter use or cash payments. Since these individuals would be placed in the controls, this would lead to our results being biased towards the null hypothesis (i.e. there is no relationship between opioid-use and increased mortality). Additionally, in studies 1 and 3 those who were classified as exposed could have their dose underestimated as medications paid for in cash were not recorded leading to a bias towards the null. In all of the studies, there could be a misclassification bias as death could be from causes other than opioids such as disease though be classified as an opioid-related death. This would lead to the increased likelihood of accepting the alternate hypothesis that prescription opioid-use is related to increased mortality. Though there are factors that may attenuate results, the

studies included attempts to reduce their impact through employing stringent exposure and outcome criteria such that any bias will be towards the null leading to reduced possibility of false positive study results.

"Best Evidence" and Supporting Evidence

Among the three studies assessed in this paper, the nested case-control study (Gomes T, et al.) provided the best evidence between opioid exposure and opioid-related mortality in adults. Confounding variables that could influence mortality rates including disease risk, gender, age, year of death were controlled for in the study design which matched cases with up to 4 controls. This ensured that both groups of cases and controls were similar, reducing selection bias, improving internal validity of the study and the ensuring legitimacy of the study results. The findings of the study demonstrate the extent to which opioid dosing in chronic pain treatment is related to opioid-related death suggesting that with daily doses greater than 50 MED there were increased odds of death. This suggests potentially that doses below 50 MED could be suitable for treatment of chronic pain. Other studies support these findings suggesting that doses above 50 mg MED have led to between 3 to 8 fold increases in the odds of opioid-related mortality compared to below 50 mg MED.[5,15] A limitation of one of these studies[16] is the number opioid-related mortalities is small, which could lead to inaccurate characterization of odds of outcome. Study 3 reduces this potential for this by using a larger sample size (n=1463). Additionally, in these papers calculation of daily doses is different as different MED for certain opioids have been used. Previous challenges surrounding comparability of results due to differences in quantification of opioid dosing has been reduced with standardization across United States[16] and Canada[17]. Now where further research should be focused on is improving

classification systems for opioid-related mortality so that research in this area can be carried out reliably.

Public Health and Policy Implications

The implication of this literature review suggest that in Ontario opioid mortality rates are increasing and that opioid dosing above 50 MED leads to significantly higher odds of opioid-related mortality. These studies exclude those with cancer and who are receiving palliative care suggesting that the included study population are generally those who use opioids for pain management.

Policy implications include restrictions on opioid dosing as the findings suggest that above 50 MED the risk of opioid-related mortality outweighs any potential benefit. Additionally, another policy that could be implemented could be first failure on all other options for chronic pain treatment before opioids are given to ensure that opioid treatment for chronic pain is used as a last resort rather than a first option.

Conclusion

This paper concludes that there is likely an association between opioid use for the treatment of chronic pain and opioid-related mortality. Additionally, it is concluded that higher opioid doses are associated with increased odds of opioid-related mortality. Using studies conducted in the same geographic region may limit these finding specifically to Ontario. However, it is clear with opioid prescribing rates for chronic pain increasing in Ontario[3], it is vital to improve strategies and programs for pain management before the epidemic begins.

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