CHC report: Assessing the comparative safety of opioid medications for non-cancer pain (pathfinder project)

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Abstract

COMPARATIVE RISK OF RESPIRATORY DEPRESSION IN PATIENTS TREATED WITH OPIOIDS FOR NON-MALIGNANT PAIN (Initial results last presented at the International Conference of Pharmacoepidemiology, Prague 2018)

Background: Opioid use for non-cancer pain has increased considerably and has been associated with fatal overdoses, the majority being unintentional. The most serious opioid-related adverse event is respiratory depression (RD).

Objectives: To (i) assess the comparative risk of RD in opioid users for non-malignant pain (ii) use routinely-collected electronic patient records (EPR) in secondary care for research.

Methods: Opioid users from Salford hospital EPR were identified (2014-17). Patients with prior malignancy were excluded using ICD-10 codes. Electronic National Early Warning Scores were used to define an RD event as any one of the following: respiratory rate (RR) ≤8/min, RR ≤10/min and O2 saturations<94%, RR≤10/min and altered consciousness, or dispensed naloxone use. Administered medication was categorised as opioid monotherapy or combination of opioids. Primary analysis attributed RD to opioids during a risk window of 'on drug+1 day', unless the patient switched to another opioid. Patients contributed follow up time for a particular drug from dispensed drug start date until day after discontinuation, 1st RD event, death or end of hospital admission. Crude rates/1000 person years (pyrs) and Cox proportional hazards models were used to examine comparative risk of administered opioids and RD, adjusted using propensity scores derived using inverse probability of treatment weights. Daily dose converted to MME, was entered as an interaction term.

Results: 33,341 opioid users were included: 18,325 female (55%); mean age (SD) 53(20) years. There were 515 RD events on treatment. The highest crude rates (95% CI) were on fentanyl [222 (106, 465)], oxycodone [221 (182, 270)] and combination opioids [260 (224, 300)]. Compared to codeine the highest risk was observed in combination opioid [HR 3.1 (95% CI 2.4, 4.0)] and fentanyl groups [HR 3.5 (95% CI 1.6, 7.7)]. In the adjusted model using MME, compared to codeine, patients on combination opioids had an adjusted HR of 1.01 (95% CI: 1.0, 1.02). Patients experienced RD on opioid doses as low as codeine 30mg PRN; fentanyl patch 50mcg/hr every 72 hrs; oxycodone 1.25mg QDS; tramadol 50mg PRN.

Conclusion: Fentanyl, oxycodone and combination opioids have the highest risk of RD, however following adjustment the risk no longer remained significant. The study's strengths include physiological parameters to define RD and dispensed medications to define exposure. Access to this rich, novel data source for pharmacoepidemiological research will deliver an improved understanding of how opioids can affect patient safety.

Introduction

Opioid use for non-malignant pain has increased significantly in recent years in the UK [1], other European countries [2] and the U.S. [3]. Efforts to improve pain management have led to quadrupled rates of opioid prescribing [4], perhaps influenced by safety concerns with other analgesics including NSAIDS [5]. Use of potent opioids (such as morphine, hydromorphone, oxycodone, and fentanyl) specifically has also increased [6]. It has become increasingly apparent that opioids are associated with considerable risks and uncertain benefits, which has recently led the Centres for Disease Control and Prevention in the U.S. to release a guideline for prescribing opioids for chronic pain [7] to enable safer prescribing of these drugs.

Opioids are known to be associated with serious risks such as increased risk of myocardial infarction [9,10] and fractures [11]. They can cause a range of adverse events including constipation, sedation, respiratory depression, falls and increased mortality. However the pharmacological properties and potency differ between opioids, likely leading to different adverse event profiles [12]. Risk estimates have been limited from randomised controlled trials due to low patient numbers and strict eligibility criteria. Previous community studies of the comparative safety of opioids in older adults have suggested differences in all-cause mortality between opioids [12]. Observational studies to examine opioid safety are challenged by confounding by indication, whereby different opioids are given to populations of patients with different inherent risks of the outcomes of interest. Whilst previous efforts have been made to adjust for confounding by indication using strategies such as propensity score matching [12], variables included in such models are limited by those that are measured in the database. Therefore residual confounding may bias results, as factors such as frailty may be poorly captured in large claims databases.

Opioids are widely used during hospital admissions for a number of indications. Information captured within inpatient admissions and in the electronic patient record may allow better control for confounding by indication, giving a clearer picture of causal associations. For example, risk of falls is captured within inpatient nursing assessments and could be used to match patients taking different opiates. Additional advantages include accurate drug administration data (rather than prescribing) and accurate dosage information using e-prescribing. However inpatient records are infrequently used in pharmacoepidemiology due to lack of well-structured electronic patient records (EPR) or adequate coded information about relevant covariates and drug exposure.

Aims

To (i) use routinely-collected EPR in secondary care for drug safety research (ii) assess the comparative risk of a range of safety outcomes in opioid users for non-malignant pain

Methods

Study design

A retrospective observational cohort study was performed

Eligibility criteria

- All patients aged ≥ 18 years who have an inpatient admission at Salford Royal since January 2009-May 2017 (restricted from Sept 2014- May 2017 for the respiratory depression analyses due to availability of electronic early warning scores used to define the outcome).
- To restrict opioid prescription to non-malignant usage, patients with a diagnosis of cancer were excluded

Establishing the study and preparation of data:

- We obtained Health Research Authority approvals for receiving pseudonymised data from Salford Royal Foundation Trust (SRFT) (IRAS ID 190543; June 2016), established a workflow for obtaining inpatient data for research purposes and processes for deidentification of datasets.
- The first analysis of the comparative safety of opioids has been completed, using administered prescribing information and electronically collected vital signs to define the outcome of respiratory depression**.**
- **Data preparation from unstructured data:**
    - For this project we required identification of new users of opioids in an inpatient setting. Previous opioid users were identified using the Medicines Reconciliation document, which is a free text document completed by the pharmacist when a patient is admitted to hospital. A list of opioid names was generated, which were used to perform free text searches and text mining of the medicines reconciliation document.
- **Data preparation for creating drug exposure:**

SRFT captures prescribed and administered opioid exposure data for clinical care, through its electronic prescribing system. This part of the project has taken a number of iterations, as there were a number of challenges from using semi-structured data to obtain robust drug exposure information that could be utilised for a drug safety analysis. Data preparation code was developed as part of the opioid safety study in order to convert raw data in opioid treated patients supplied by the NHS into research-ready datasets for analysis (prepared in STATA version 13.1).

Aggregating the time-stamped drug administration data into daily dose of opioids presents a number of challenges. The following listed below were some challenges that were overcome following testing different versions of the datasets for analysis by the researchers and regularly liaising with the SRFT staff about outstanding queries.

- **Prodcodes:** There is no unique identifier in the data for a drug product. To facilitate data processing, a prodcode is created from the substance, route and form of the drug administered
- **Visit structure:** Patients may have multiple hospital visits on a single day or readmission within a short time period. Additionally, there are rare cases where the discharge date is missing or there is more than one discharge time for single given admission date.
- **Drugs administered outside the visit window:** Drugs may be administered to the patient outside the official admission/discharge date-time window. Therefore it was necessary to decide how to proceed in cases where drugs are given before admission or after discharge.
- **A number of drug administration events are excluded from the analysis**
    - **Missing time-stamps:** Events in the raw data have no dispensing time-stamp and therefore cannot be included in the analysis. These are filtered out of the

dataset early in data processing. SRFT confirmed that these are either cancelled prescriptions or events that were never marked as given (either not given or not-documented).

  - **Discharge drugs:** A large number of drug-administration events in the raw data are prescriptions intended for outpatient use e.g. discharge orders. These are identified and excluded.
  - **Pending/overdue administration events:** Time-stamped drug administration events are assigned a task status. This can be performed, not performed, overdue, pending, missing. Only performed events are retained.

- **Data entry error:** The dose administered to the patient is recorded in a variable –given dose. This is affected by data entry error (miss-typing of dose) and unit error (miss-specification of units). These values must be detected and corrected/dealt with. Extreme values are identified and actioned.
- **Start date-times only:** prescriptions are assigned a unique identifier and have a prescription start date-time and estimated end date-time. Some drug administration events are nested within prescriptions and only have a start date. For oral drugs this does not present a problem. However, for infusions and patches where the dose delivered depends on the duration of exposure, administration end times must be estimated.
- **Missing dose:** the dose administered to the patient may be missing. The degree of missing data varies by "prodcode" and is close to 100% in some cases e.g. PCA infusions. In these instances, the missing dose must be estimated, applying a variety of assumptions.

Data Analysis

- Patients with prior malignancy were excluded using ICD-10 codes.
- **Outcome definition (Respiratory depression):** Electronic National Early Warning Scores were used to define an RD event as any one of the following: respiratory rate (RR) ≤8/min, RR ≤10/min and O2 saturations<94%, RR≤10/min and altered consciousness, or dispensed naloxone use.
- Administered medication was categorised as opioid monotherapy or combination of opioids. Primary analysis attributed RD to opioids during a risk window of 'on drug+1 day', unless the patient switched to another opioid.
- Patients contributed follow up time for a particular drug from dispensed drug start date until day after discontinuation, 1st RD event, death or end of hospital admission.
- Crude rates/1000 person years and Cox proportional hazards models were used to examine comparative risk of administered opioids and respiratory depression, adjusted using propensity scores derived using inverse probability of treatment weights. Daily dose converted to MME, was entered as an interaction term.

Results/ Initial Outputs

- **Best practice guidance:** Since this was one of the first studies to use routinely collected data from SRFT for a drug safety project, best practice guidelines have been developed on how best to utilise EPR data from SRFT for research
- **Data preparation code** was developed to utilise raw drug exposure data in opioid treated patients into research-ready datasets for analysis

- **Analysis of first outcome:** The first analysis of the comparative safety of opioids has been completed, using administered prescribing information and electronically collected vital signs to define the outcome of respiratory depression**.** 33,341 opioid users were included: 18,325 female (55%); mean age (SD) 53(20) years. There were 515 RD events on treatment. The highest crude rates (95% CI) were on fentanyl [222 (106, 465)], oxycodone [221 (182, 270)] and combination opioids [260 (224, 300)]. Compared to codeine the highest risk was observed in combination opioid [HR 3.1 (95% CI 2.4, 4.0)] and fentanyl groups [HR 3.5 (95% CI 1.6, 7.7)]. In the adjusted model using MME, compared to codeine, patients on combination opioids had an adjusted HR of 1.01 (95% CI: 1.0, 1.02). Patients experienced RD on opioid doses as low as codeine 30mg PRN; fentanyl patch 50mcg/hr every 72 hrs; oxycodone 1.25mg QDS; tramadol 50mg PRN.

Impact of preliminary work

Dissemination:

Conference presentations:

- American College of Rheumatology Annual Conference 2017
- Association of Physicians Annual Conference 2018
- British Society for Rheumatology Annual Conference 2018
- International Conference of Pharmacoepidemiology, Prague 2018

Prizes

- Manchester Medical Society Section of Medicine Annual Prize for best research oral presentation 2017
- Royal Society of Medicine Eric Bywater Prize 2017
- Daniel Turnberg Cup 2018 (Awarded by the University of Manchester across all medical and surgical specialties to a clinical academic trainee)

Contribution in part towards larger programmes of work:

Fellowships/ grant funding

- ICES/ Farr fellowship (July-Oct 2018): £15,000/ $30,000 to spend 3 months at the Institute of Clinical Evaluative Science to extend the opioid project to a Canadian dataset and build collaborations for the future(More details here: http://farrinstitute.org/news/congratulations-to-ices-farr-institute-research-fellowship-recipients)
- Presidential fellowship (Dec 2018, to commence Sept 2019): This is a personal fellowship with the goal of preparing early career clinical academics for clinical intermediate fellowships from UK funding bodies such as MRC and Wellcome. The proposed fellowship will allow generation of future publications from this work, extend the project further as outlined below and will complement a larger new programme of work on opioid safety.

National impact

- **Invitation to be part of the MHRA Expert Committee Working group** to examine the benefit: risk of opioids and the risk of dependence and addiction. It is anticipated that the expert working group will provide advice on the safety of opioids, taking into consideration

the ongoing Public Health England review for dependence on, and withdrawal reactions associated with prescribed medicines, inclusive of the opioids.

Publications in preparation

Project	Publication title (and description as required)	Target journal	Lead/ Senior Authors	Actual/Intended date of submission	Status
Opioids safety	1) Comparative risk of respiratory depression in patients treated with opioids for non-malignant pain 2) Comparison of secondary care opioid utilisation for non-cancer pain in 2 tertiary centres in England and Canada	Annals of Internal Medicine (for both)	Meghna Jani/ Will Dixon	April-19	In Preparation

Conclusion/Discussion

For this pathfinder project we were able to develop a process to utilise routinely collected data from secondary care for drug safety research. Strengths of the analysis include using physiological parameters to define respiratory depression and dispensed medications (rather than prescribed) to define exposure. Access to this rich, novel data source for pharmacoepidemiological research will deliver an improved understanding of how opioids can affect patient safety.

Future Plans/ sustainability

- **Future outcomes:** We next plan to use this learning to subsequently study a range of other inpatient safety outcomes in relation to opioids such as falls and fractures.
- **Linkage to primary care:** The data obtained for this study will be linked to primary care via the Salford Integrated Record to assess the longitudinal prescribing trends of opioids when they are discharged from hospital (and vice versa)
- **Impact/ Implementation**: The results of this and future work will be submitted to high impact general medical journals, given the implications across specialties. It will also better characterise the strata of patients at increased risk of such events, and allow development of targeted interventions, actionable analytics and clinical decision tools to better personalise care.
- **Collaborations**: We are also replicating parts of the project in a Canadian dataset obtained via the ICES as part of a new collaboration. Following the ICES/Farr fellowship, a dataset linking data from a large Canadian secondary care tertiary organisation across 3 sites (The Ottawa Hospital) to ICES data (~60,000 patients) was established and prepared. The linkage allows access to unique data sources such as the Narcotics Monitoring System (with all dispensed opioid prescriptions in the Ontario community since 2014) and coroner level information on drug related deaths. These data will be used to develop risk prediction models in new opioid users for (i) respiratory depression (ii) delirium (iii) chronic opioid use

following 1 year post discharge using both traditional and machine learning approaches, with validation performed in this existing Salford cohort.

- **Future funding where this work will form part of the research programme:** (i) Oliver Bird Fund for research into musculoskeletal conditions http://www.nuffieldfoundation.org/OBF (Lead: Will Dixon; stage 1 submitted, ~ £1.4 M) (ii) Clinician Scientist application to MRC/ Wellcome/ NIHR Autumn 2019.

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