The effect of opioid analgesics, benzodiazepines, gabapentinoids, and opioid agonist treatment on mortality risk among opioid-dependent people

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The Difference is Research

Background

- Benzodiazepines and gabapentinoid dispensings have increased in recent years
- Increased mortality risk has been identified when using these medicines, particularly when used with opioids
- Research examining use of these medicines among people with opioid dependence and according to opioid agonist treatment (OAT) status has been limited

Aims

1. Examine the effect of opioid analgesic (OPD), benzodiazepine (BZD) and gabapentinoid (GBP) use on cause-specific mortality,
2. Examine whether medicine exposure effects vary according to OAT status, and
3. Examine whether the effect of BZD and GBP vary according to the amount of OPD used

Concurrent use of opioids with benzodiazepines and/or gabapentinoids was associated with a substantial increase in accidental opioid overdose risk

Methods

Setting

- The POPPY II study [1] study based in New South Wales, Australia, includes a population-based cohort of adult residents who initiated a new opioid analgesic dispensing episode between July 2003 and Dec 2018
- Medicine dispensing records from the Pharmaceutical Benefits Scheme [2] were linked with data on OAT, mortality, health service use and cancer notifications

Cohort definition

1. Initiated a new opioid analgesic dispensing episode during follow-up,
2. Had a prior documented history of opioid dependence, indicated by a diagnosis in health service datasets or receipt of OAT, and
3. Had no prior history of cancer or palliative care

Outcomes

1. Accidental overdose involving opioids
2. Non-drug-induced accidents
3. Non-drug-induced suicides

Exposure to medicines

- A method based on individual dispensing patterns [3] was used to define time-varying exposure periods for opioid analgesics (OPD, incl. dose measured by oral morphine equivalent milligrams per day [4]), benzodiazepines (BZD), and gabapentinoids (GBP)
- OPD exposure excludes dispensings of methadone and buprenorphine for opioid dependence
- Antidepressant exposure and antipsychotic exposure were defined and adjusted for in all models

Other covariates

- Time in opioid agonist treatment (OAT)
- Demographics: age, sex, year of cohort entry, remoteness, and socio-economic disadvantage captured at the start of an individual's observation
- Comorbidities: time-varying past-year indicators of self-harm, HIV/AIDS, Hep C, cardiovascular disease, respiratory disease, renal disease, IRID, alcohol use disorder, drug use disorder, depression/anxiety, and psychosis

Statistical analysis

- Cox proportional hazard models accounting for competing risks and adjusting for all covariates; cause-specific hazard estimates (and 95% CIs) are reported

Results

Study population (n=38,035)

- 70% dispensed BZDs; GBP exposure less common (20%)
- 3,434 overall deaths (9% of cohort)
  - 28% accidental overdose inv. opioids
  - 6% non-drug-induced suicides
  - 4% non-drug induced accidents

Individual medicine exposure (Fig 1)

- OPD exposure associated with a 17% increased hazard of accidental overdose
- >2-fold increase in accidental overdose risk when either BZD or GBP exposed
- Risks associated with medicine effects were reduced during time in OAT
- Only BZD exposure was found to be associated with non-drug-induced accidents and non-drug-induced suicides

Concurrent opioid and other medicine exposure (Fig 2)

- Compared to OPD exposure only, concurrent exposure to other psychotropics were associated with an increased risk of accidental overdose, and to a lesser extent all-cause mortality

Concurrent medicine exposure by level of opioid dose (Fig 3)

- The association between increased accidental overdose risk and GBP and BZD exposure was evident at all levels of OPD dose

FIG 1. EXPOSURE TO INDIVIDUAL MEDICINES

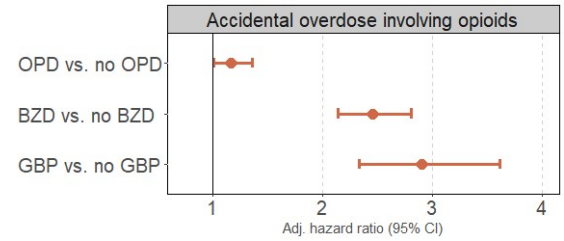


FIG 2. CONCURRENT OPIOID AND OTHER MEDICINE EXPOSURE

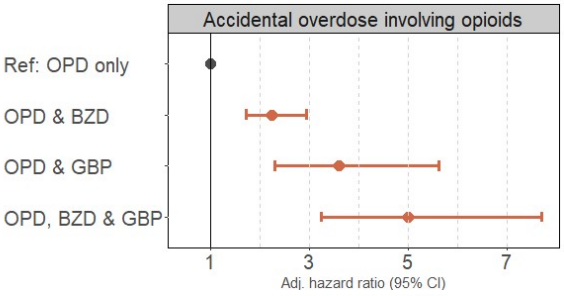
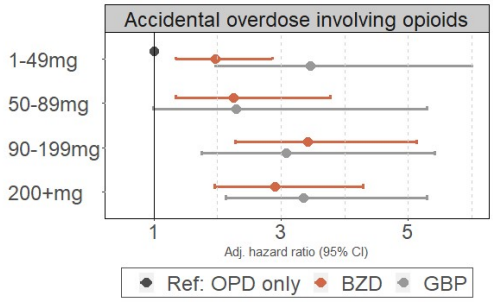


FIG 3. CONCURRENT MEDICINE EXPOSURE BY OPIOID DOSE



Conclusion

- When co-prescription is necessary, prevention strategies become even more important for minimizing the sequelae of interaction effects e.g., provision of take-home naloxone
- Examining if and how medicine exposure effects vary according to OAT status could help to identify subgroups of the population in greatest need

Limitations

- Potential confounding by indication
- Unable to capture non-subsidized medicines, actual medicine use or non-prescribed drugs

References

[1] Nielsen, S et al. (2016) *Pharm Drug Safety*; 25(6)
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[4] Bharat, C et al. (under review)

Acknowledgements

We wish to acknowledge the POPPY II Investigator team for their input into the design of the larger study from which data were accessed, and Tom Murphy for preparing the datasets for analysis. We would also like to acknowledge the NSW Ministry of Health, the Centre for Health Record Linkage and the Australian Institute of Health and Welfare for providing the data.