64.2–71.7] vs. 33.1% [32.8–33.5]), anxiety (60.2% [56.2–64.0] vs. 22.6% [22.3–22.9]), substance use disorders (70.5% [66.7–74.0] vs. 13.9% [13.7–14.2]), previous suicide attempts (21.2% [18.1–24.6] vs. 2.4% [2.3–2.6]), and non-fatal poisonings with pharmaceuticals (35.5% [31.7–39.4] vs. 2.7% [2.62.9]). The individuals who had died of an overdose were less frequently born outside Norway (5.9% [4.3–8.2] vs. 18.8% [18.5–19.1]) and had less frequently attained a university-level education (11.7% [9.4–14.6] vs. 20.7% [20.4–21.0]) compared to matched controls.

Conclusions: Among persons with chronic pain, overdose deaths were connected to substantial psychiatric morbidity and frequent prescription drug use prior to death. High proportions of non-intentional overdoses and of pharmaceutical opioids as the cause can be considered alarming for prescribers and other healthcare professionals.

138 | Use of antipsychotics and the risk of acute respiratory failure

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Background: In addition to the known adverse effects of antipsychotics, findings from case reports and two population-based Taiwan studies, conducted by the same investigators, have indicated a potential new safety signal of severe adverse respiratory distress and failure associated with antipsychotic medications. Further population-based research is warranted to evaluate the association between antipsychotics and acute respiratory failure, and to provide evidence that is generalizable to the United States.

Objectives: To evaluate the association between the use of antipsychotics and risk of respiratory depression among commercially insured adults in the United States.

Methods: We performed a retrospective new-user cohort study of adults ≥18 years prescribed an antipsychotic or an active comparator, anticonvulsant medication, during an eight-year period spanning 2007 to 2015, using a 1% random sample of enrollees within the IQVIA PharMetrics® Plus for Academics Database. Propensity score-adjusted Cox models were used to estimate hazard ratio (HR) and 95% confidence interval (CI) for the outcome of acute respiratory failure comparing antipsychotics users to anticonvulsants users. Bias analysis was conducted to assess the sensitivity of the observed relationship between antipsychotics and respiratory depression to an unmeasured confounder.

Results: A total of 8232 antipsychotic initiators and 4400 anticonvulsant initiators contributed 113 722 person-years of follow-up (median duration 923 days/person). During follow-up, there were 1041 respiratory depression events. In the unadjusted analysis, antipsychotic exposure was associated with increased hazard of respiratory depression compared with anticonvulsant exposure (HR: 1.18; 95% CI: 1.03, 1.34). After inverse probability of treatment weighting adjustment, the hazard increased (HR: 1.21, 95% CI: 1.07, 1.36). Propensity score matching and stratification resulted in similar accentuation of the HR estimates, 1.27 (95% CI: 1.09, 1.47) and 1.21 (1.14, 1.65), respectively. These findings were robust to bias analysis, as the results did not suggest an unmeasured confounder would explain away the observed association.

Conclusions: In commercially insured adult patients, antipsychotics were associated with an increased hazard of acute respiratory failure. This finding warrants enhanced clinical guidelines to ensure patient safety.

139 | Evaluating the long-term effect of allopurinol use in gout using marginal structural models: A primary care electronic health records study

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Background: Allopurinol is intended to be taken for life in the treatment of gout. In UK primary care, treatment is suboptimal with up to 30% of indicated patients being treated within five years of diagnosis and once prescribed allopurinol, treatment adherence is poor. Studies evaluating effect of allopurinol have ignored the time-varying propensity for treatment, which may be due to changing patient health and risk of poor outcome over time.

Objectives: To estimate the effect of allopurinol on a range of outcomes in people with gout accounting for time-varying confounding by indication.

Methods: Cohort study of primary care medical records from the UK Clinical Practice Research Datalink (CPRD) included adults aged ≥18 years consulting for gout between 1997 and 2002, and not prescribed urate-lowering drugs 2 years prior. Allopurinol prescription ≥3 months and covariates (demographics, comorbidities, other medication usage, and number of years previously prescribed allopurinol) were measured yearly from the date of first gout consultation. Marginal structural models estimated the effect of allopurinol on time to reaching target serum urate (SU) level ≤360μmol/L, mortality, hospitalization due to gout, hip or knee joint replacement, and various comorbidities. Confounding was accounted for using inverse probability of treatment weights. Weights were derived in each year of follow up by estimating the propensity of initiating and continuing allopurinol given covariates via logistic regression models. Subsequently, weighted Cox regression models estimated the effect of allopurinol on outcome.

Results: A 16 876 adults (mean age 62 years, 77% male) consulted for gout and were followed up for a median 10.7 years. A 46% were prescribed allopurinol, of which 40% discontinued treatment and within this group, 44% resumed treatment. Allopurinol users were more likely to reach target SU level (hazard ratio 5.00 (95% CI 4.00, 6.23)) and had increased risk of hospitalization due to gout (2.22 (1.91, 2.58)), coronary heart disease (1.11 (1.01, 1.23)) and renal disease (1.27 (1.13, 1.43)) compared to non-users. There was no increased risk of mortality (0.93 (0.83, 1.06)), joint replacement (0.93 (0.76, 1.13)), cerebrovascular disease (1.01 (0.82, 1.25)) and peripheral vascular disease (1.13 (0.87, 1.46)) for allopurinol users compared to non-users.

Conclusions: This is the first primary care population-based study to model changes in allopurinol use and patient health over time in the evaluation of the effect of allopurinol in gout. Although allopurinol use was associated with reduced SU levels below target, it increased the risk of gout hospitalization and some comorbidities, which may be due to inadequate allopurinol dosing or poor adherence to allopurinol.

140 | Association between fluoroquinolones and uveitis, retinal detachment, and aortic aneurysm or dissection: An application of self-controlled study designs with active comparators

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Background: Non-interventional studies have led to concerns over the safety of fluoroquinolone antibiotics. Whether observed adverse events are causally related, or due to confounding by indication is unclear.

Objectives: To estimate the association and investigate the plausibility of a causal effect of fluoroquinolones on uveitis, retinal detachment, and aortic aneurysm or dissection.

Methods: We applied self-controlled study designs to control for time-invariant confounding and used cephalosporins as an active comparator to try to control for time-varying confounding. We conducted separate self-controlled case series (SCCS) for acute uveitis and retinal detachment and a case-time-control (CTC) study for hospitalization with aortic aneurysm or dissection. We included patients with a first outcome recorded in UK Clinical Practice Research Datalink Aurum primary care data or in linked hospital records (Hospital Episode Statistics Admitted Patient Care) between the 1 April 1997 and 31 June 2019. To account for prescribing trends in the CTC study we matched each case to three controls on calendar date, primary care practice, and birth year. We included first outcome only in each study. Risk windows were 60 days following each prescription in the SCCS and 1–60 days and 91–150 days preceding outcome in the CTC study. We fitted conditional Poisson models adjusting for age and calendar year for the SCCS and a conditional logistic model for the CTC study. We used the interaction term approach of Hallas et al. 2021 to estimate ratios relative to active comparator.

Results: We identified 68 612, 23 701, and 84 886 eligible individuals respectively with uveitis, retinal detachment, and aortic aneurysm or dissection. The adjusted rate ratio for fluoroquinolone exposure and uveitis was 1.08 (95% CI 0.97–1.21) and for retinal detachment was 1.04 (0.84–1.29). We found an increased odds of aortic aneurysm or dissection (adjusted odds ratio [aOR] 1.44, 1.28–1.62) with fluoroquinolone exposure. Relative to cephalosporin there was no evidence for an association with uveitis (aRR 1.00, 0.87–1.15), retinal detachment (aRR 1.06, 0.80–1.41) or aortic aneurysm or dissection (aOR 0.99, 0.85–1.15).

Conclusions: We found no evidence of an association between fluoroquinolones and retinal detachment or uveitis and the harmful association we observed with aortic aneurysm or dissection appears to be driven by time varying confounding. Given that fluoroquinolones are prescribed for acute infections, disentangling the effects of the drug from the infection is vital. To account for both time-invariant and time-varying confounding active comparator self-controlled studies appear to be useful for this class of medication.

141 | Death, cardiac event, and acute liver injury associated with bedaquiline or delamanid in patients with multidrug resistant tuberculosis: A nationwide cohort study

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Background: Bedaquiline and delamanid are newly approved drugs for the treatment of multidrug resistant tuberculosis (MDT-TB), yet there is limited evidence on their safety beyond the trial setting. Bedaquiline carries a black box warning of increased risk of death compared to the placebo arm, and there is a need to establish the magnitudes of additive QT prolonging effect and hepatotoxicity of bedaquiline and delamanid.

Objectives: To assess risk of mortality and serious adverse events for bedaquiline- or delamanid-containing regimen compared with the standard regimen.

Methods: We used the South Korea National Health Insurance System database to identify individuals aged 18 years or older diagnosed with pulmonary MDR-TB (ICD-10: A15-A16 and U84.3) and received at least 4 second-line anti-TB drugs (i.e., minimum number of drugs required for MDR-TB treatment) between 2016 and 2019. Bedaquiline and delamanid groups included those who initiated treatment with bedaquiline- or delamanid-containing regimen, respectively, and standard regimen group with fluoroquinolone and/or aminoglycoside-containing regimen. Follow-up began on the day after treatment initiation. Primary outcome was all-cause mortality at 12-month of follow-up, and secondary outcomes were long QT-related cardiac event and acute liver injury assessed until discontinuation of the index drugs or end of study period