100 False dichotomies and health intervention research designs: Randomized trials are not always the answer

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Some researchers argue that only results of randomized trials (RCTs) are valid. They argue that evidence from "quasi-experimental" research designs that depend on use of administrative data is always spurious and cannot be used to make valid inference about the effects of health policies and natural experiments in the real world. Many acknowledge biases caused by poor study designs—such as secular trends (history bias), natural progression of illness (maturation bias) and non-comparable study and control groups (selection bias). In this address I argue that several valid designs using administrative data can produce strong findings, particularly the interrupted time series design (ITS). Many policy studies neither permit nor require an RCT for valid cause-and-effect inference. We show that some quasi-experimental designs, especially ITS, can produce valid estimates of effects (or non-effects) of policies as diverse as public health insurance coverage, speed limits, and hospital safety programs.

In the second part of the address, I will describe Fretheim's re-analysis of RCTs conducted while he was a fellow in our group that compared the results of single-arm and controlled ITS with those of cluster RCTs (the latter using single pre-and post-observations). Overall, the ITS findings were concordant with those of the RCTs. However, several RCTs failed to detect large, clearly observable effects that were evident in the controlled ITS analyses at follow-up. These findings suggest that group-randomized RCTs of health policies and interventions collecting repeated observations before and after an intervention might benefit from controlled ITS analysis instead of simple difference-in-difference analysis in order to make baseline comparability and changes in outcomes at follow-up more clearly observable.

101 Comparative effectiveness and safety of low and high strength novel oral anticoagulants: a propensity-score study with sequential cohort design

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Aim: To compare the effectiveness and safety of low and high strength novel oral anticoagulants (NOACs, apixaban, dabigatran and rivaroxaban) with warfarin.
Methods: The Australian Government Department of Veterans' Affairs (DVA) administrative claims database was used to conduct a comparative effectiveness study. Five sequential cohorts from August 2013-March 2015 were created to limit channelling bias, with cohorts 2-5 combined. For each cohort, subjects who initiated a NOAC or warfarin were included if aged at least 18 years, not in residential aged care and had full DVA entitlements for at least 12 months prior. To help remove bias due to confounding by indication inverse probability of treatment weighting was used, with weights based on propensity scores. Subjects were followed over one-year for outcomes of stroke (ischaemic, unspecified) haemorrhagic stroke, myocardial infarction (MI) and death. NOACS were classified as low or high dose and were compared to warfarin.
Results: Both low and high strength NOACs were as effective as warfarin in preventing stroke, with a greater reduction seen in high strength (low: HR 0.97, 95% CI 0.66-1.42; high: HR 0.72(0.40-1.29)). Neither low nor high strength had an effect on MI risk (low: HR 1.45(0.99-2.14); high: HR 0.74(0.41-1.31)) while high strength was associated with reduced mortality risk (low: HR 0.84(0.68-1.02) high: HR 0.44, (0.32-0.61)). A reduced risk of bleeding was seen for high-strength (HR 0.57(0.43-0.77)), while there was an equivalent risk for low-strength (HR 0.84(0.66-1.06)). For haemorrhagic stroke there was an equivalent risk for both low and high (Low: HR 0.57(0.24-1.36); High: HR 1.14(0.51-2.55)).
Conclusion: We demonstrated that NOACs are comparable to warfarin in terms of benefit and safety. Low and high strength formulations were equivalent to warfarin in preventing ischaemic, unspecified or haemorrhagic stroke and MI. High-strength formulations were associated with a significantly reduced risk of death and bleeds.

102 Signal evaluation of adverse drug reaction caused by non-vitamin K dependent oral anticoagulants (NOACs) in Korean adverse drug reporting system (KAERS) database

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Objective: NOACs (new oral anticoagulants/Non-vitamin K dependent oral anticoagulants) are recently developed drugs for replacing warfarin which is used for the prevention of stroke in patients with atrial fibrillation. The objective was to detect and evaluate the signal of the NOACs-induced adverse drug reactions.
Methods: We detected signals of NOACs (included dabigatran, rivaroxaban, and apixaban) through data mining by using the Korean Adverse Event Reporting System(KAERS) database between 2010 and 2015. The KAERS database was composed of diagnosis coded WHO adverse reaction terminology(WHO-ART), drug chemistry, and results of severity and causality assessment by reporters. We calculated 9 indices including proportional reporting ratio(PRR), reporting odds ratio(ROR), and information component(IC) within all reports, reports evaluated as serious events, and reports suggested that more than possible association between drug and event, separately. For prioritization, we defined the signal as all of the 9 indices are statistically significant. To evaluate the signal, we used ROR adjusted for age and gender.
Results: In total 2,749,929 reported adverse events, dabigatran, rivaroxaban, apixaban, and warfarin were reported 936, 2,101, 536, and 5,426 events, respectively. Signals of dabigatran, rivaroxaban, and apixaban within all reports were 41, 84, and 37, respectively. After prioritization, 3, 16, and 1 signals were detected in dabigatran, rivaroxaban, and apixaban, respectively, and all the signals were associated with diagnoses or laboratory results of bleeding. For evaluating the signals, we selected 69 diagnostic codes of WHO-ART associated with bleeding. In bleeding risk of dabigatran, rivaroxaban, apixaban, and warfarin, adjusted RORs were 8.9(95% confidence interval(CI): 7.2-11.1), 12.7(10.9-14.9), 6.5(4.8-8.8), and 14.7(13.6-15.8), respectively.
Conclusion: In our study result, rivaroxaban had relatively higher reporting rate on bleeding risk compared with dabigatran and apixaban. More pharmacoepidemiologic studies will be needed to evaluate comparative risk of bleeding among NOACs.

103 The representativeness of direct oral anticoagulant clinical trials to hospitalized patients with atrial fibrillation

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Aim: Trials of the direct oral anticoagulants (DOACs) provide the basis for prescribing for the prevention of stroke and systemic embolism in atrial fibrillation (AF). The objective of this study was to assess the representativeness of the three pivotal DOAC randomised controlled trials of dabigatran, rivaroxaban and apixaban for unselected hospitalized patients with AF.
Methods: A cross-sectional study was undertaken using diagnosis data and electronic medical record discharge prescribing data. All patients discharged with AF between 2012 and 2015 from a large public hospital network in Melbourne, Australia, were identified. Inclusion and exclusion criteria from the DOAC trials were applied. The proportions of hospitalized patients with AF who would have been eligible for the dabigatran (RE-LY), rivaroxaban (ROCKET-AF) and apixaban (ARISTOTLE) trials were estimated, as was pooled eligibility for all three trials. Characteristics of eligible and ineligible patients were compared.
Results: 4734 patients with AF were included in this study (mean age 78.3 ± 11.5 years; 53% were female). Application of the inclusion and exclusion criteria resulted in 60.5%, 52.6% and 35.8% of patients being eligible for the apixaban, dabigatran and rivaroxaban trials, respectively. Pooled eligibility across all three trials demonstrated that 33.4% of patients would have been eligible for all three trials but 36.7% were ineligible for all three trials. Ineligible patients were older and experienced more comorbidities.
Conclusion: The apixaban and dabigatran trials may be most representative of hospitalized patients with AF. The DOAC trial results can readily be extrapolated to, and guide prescribing for, at least two thirds of patients discharged from a large metropolitan health service in Australia.

104 Aspirin reduces the risk of out-of-hospital cardiac arrest with ventricular tachycardia/ventricular fibrillation in patients with coronary artery disease

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Objective: Sudden cardiac arrest due to ventricular tachycardia/ventricular fibrillation (VT/VF) often occurs as a complication of myocardial infarction. This study aimed to assess the association between the use of antiplatelet drugs and out-of-hospital cardiac arrest with confirmed VT/VF (OHCA) in persons in the general population with coronary artery disease (CAD).
Methods: This case-control study was conducted in OHCA cases from the AmsteRdam REsuscitation STudies (ARREST) registry and age-, sex- and OHCA date-matched non-OHCA controls from the Dutch PHARMO Record Linkage System. Cases and controls were selected if they were dispensed one or more antiplatelet drugs in the year before the OHCA date, as a proxy for CAD. The exposure was the use of antiplatelet drug(s) as an overall group and as individual regimens at OHCA date (current use). Conditional logistic regression was used to analyze the association between exposure and outcome, adjusted for potential confounders.
Results: A total of 755 OHCA cases and 3296 matched controls were included. There were 30.6% aspirin monotherapy users and 42.6% carbasalate calcium monotherapy users in the cases; while there were 42.2% aspirin monotherapy users and 32.1% carbasalate calcium monotherapy users in the controls. Current use of antiplatelet drugs was not associated with the risk of OHCA (OR 1.00, 95%CI 0.75-1.32). Current use of aspirin monotherapy was significantly associated with a lower risk of OHCA (OR 0.72, 0.53-0.98), while current use of carbasalate calcium monotherapy was associated with a higher risk (OR 1.35, 1.01-1.82).
Conclusion: Current use of aspirin was associated with a decreased risk of OHCA in patients with CAD, whereas current use of carbasalate calcium was associated with an increased risk.

105 Hospital admissions due to dysglycaemia and antidiabetic medications prescriptions in England and Wales: an observational study

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Objective: to examine the trends of hospital admissions due to dysglycaemia and the rates of antidiabetic medications prescriptions.
Methods: We conducted an ecological study in England and Wales, the United Kingdom. The rates of hospital admissions for hypoglycaemia and hyperglycaemia and antidiabetic medications prescriptions were estimated. Hospital admission data was extracted from the Health Episode Statistics (HES) database in England and Patient Episode Database for Wales (PEDW) for the duration between April 1999 and March 2015. Antidiabetic medications prescriptions data was extracted from Prescription Cost Analysis (PCA) database for the duration between April 2004 and March 2015. Hospital admissions for hypoglycaemia and hyperglycaemia were identified using the 4-digits diagnostic codes from the 10th version of the International Classification of Diseases (ICD) system and antidiabetic medications prescriptions data using the British National Formulary (BNF) drug codes for antidiabetic medications. Mid-year population data was collected from the Office for National Statistics (ONS).
Results: Hypoglycaemia admission rates between 1999 and 2015 increased by 169.6 % (from 17.23 [95% CI, 16.88 – 17.59] to 46.47 [95% CI, 45.91 – 47.02] per 100,000 persons) and for hyperglycaemia the increase rate was 144.9% (from 22.83 [95% CI, 22.42 – 23.24] to 55.92 [95% CI, 55.31 – 56.52] per 100,000 persons), trend test, p<0.01]. Prescriptions rate for all antidiabetic medications between 2004 and 2015 increased by 107.0% (from 37,294.20 [95% CI, 37,281.19 – 37,307.21] to 77,205.66 [95% CI, 77,194.85 – 77,216.47] prescriptions per 100,000 persons), trend test, p<0.01].
Conclusions: this study suggests that there is a concurrent increase in the rates of admissions due to dysglycaemia and the rates of antidiabetic medications prescriptions in England and Wales. Further analytical studies are required to identify the risk factors and the causes of the increased hospital admissions due to hypoglycaemia and hyperglycaemia.

106 Cardiovascular safety of glucose lowering drugs in patients with type 2 diabetes mellitus and cardiovascular disease: a network meta-analysis

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Objective: The cardiovascular safety of glucose lowering drugs (GLDs) has aroused great concern. This study will assess the extent to which GLDs increase the risk of hospitalization for heart failure (HHF), cardiovascular (CV) death, and all-cause mortality in patients with type 2 diabetes mellitus (T2DM) and established cardiovascular disease (CVD).

Methods: PubMed and Scopus were searched systematically up to September 2016 for randomized controlled trials (RCTs) involving patients with T2DM and CVD comparing GLDs. The primary outcomes included HHF, CV death, and all cause death. We did random-effects network meta-analysis to obtain the odds ratio (OR) with 95% confidence interval (CI).

Results: A total of 12 RCTs comprising 69,394 patients with were eligible for network meta-analysis.

For HHF, SGLT-2i had a significant lower risk compared to placebo (OR 0.65, 0.48 to 0.88), DPP-4i (OR 0.57, 0.41 to 0.80) and TZD (OR 0.46, 0.30 to 0.70). TZD had a significant higher risk of HHF compared to placebo (OR 1.42, CI 1.07 to 1.89) and GLP1-RA (OR 1.52, 1.09 to 2.11), and SU (OR 2.43, CI 1.20 to 5.0).

For CV death, SGLT-2i was associated with a significant lower risk compared to placebo (OR 0.61, 0.48 to 0.78), DPP-4i (OR 0.61, 0.46 to 0.81), GLP1-RA (OR 0.70, 0.52 to 0.94), and TZD (OR 0.64, 0.45 to 0.90).

For all-cause mortality, SGLT-2i was associated with a lower risk compared to placebo (OR 0.89, 0.78 to 1.01), DPP-4i (OR 0.67, 0.53 to 0.85), GLP1-RA (OR 0.77, 0.61 to 0.98), and TZD (OR 0.72, 0.53 to 0.97).

Conclusions: Our study suggests that SGLT2i is associated with a lower risk of HHF , CV death, and all-cause death compared to placebo, TZD, DPP4i, and GLP1-RA. GLP1-RA has a lower risk of HHF compared to TZD and placebo. However, furthermore studies are required to confirm our findings.

107 Beyond symptom control in ADHD – The contribution of pharmacoepidemiology in addressing benefit and risk

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Attention-deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterised by hyperactivity, impulsivity, and cognitive dysfunction. It affects 5% of children and often has a major negative impact on daily life. Pharmacological treatments such as stimulants are effective in the treatment of ADHD symptoms. In the past 2 decades, ADHD prescribing trends have risen rapidly worldwide. Various case reports and data from spontaneous reporting systems have raised serious safety concerns on the use of these medications in children and adults. Furthermore, data from clinical trials mainly focus on short-term symptom control which is useful in licensing applications but less helpful in the overall evaluation of benefit and risk of these medications clinical use. This session will explore the contribution of pharmacoepidemiology in addressing the benefit and risk of pharmacological treatment of ADHD.

108 Doubt of association between the proton pump inhibitors and the risk of dementia: signal detection using prescription sequence symmetry analysis

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Aim/Objective: Previous studies about association between the use of proton pump inhibitors (PPI) and dementia may be the results of lag-time bias, and the absence of active comparator. To detect the possible association between PPI use and dementia as compared with active comparator, histamine-2 receptor antagonist (H2RA).
Methods: We conducted prescription sequence symmetry analysis (PSSA), which is based on analyzing the sequences of exposure and outcome of interest, using South Korea nationwide 2% sampled database between 2002 and 2013. Exposure was defined as new users of PPI and outcome was defined as new diagnosis of dementia (ICD-10: F00-03, F051, G30, G311, G319, G3182). We included exposure and outcome pairs within 3 years and excluded pairs whose duration was less than 6 months to minimize protopathic bias against dementia. The time-tend adjusted sequence ratio (aSR) with 95% confidence interval (CI) were estimated to detect possible association. We conducted repeated analyses with the use of active comparator as H2RA, with the variation of 1-, and 2-year duration of pairs, and varying the definition of outcome as the user of anti-dementia medication (ATC: N06D).
Results: PPI associated 3-year risk of dementia was similar with that of H2RA (PPI=8,213 pairs, aSR=1.26, 95% CI=1.20-1.31; H2RA=5,409 pairs, aSR=2.13, 95% CI=2.00-2.26). The repeated analyses with the 1- and 2-year duration of dementia were consisted with main results (1-year: PPI=2,064 pairs, aSR=1.19, 95% CI=1.09-1.29; H2RA=1,118 pairs, aSR=1.70, 95% CI=1.50-1.92/ 2-year: PPI=5,468 pairs, aSR=1.25, 95% CI=1.19-1.32; H2RA=3,380 pairs, aSR=1.97, 95% CI=1.83-2.12). The finding restricted with the use of anti-dementia medication were also consisted with main results (PPI=3,123 pairs, aSR=1.39, 95% CI 1.29-1.49; H2RA=2,149 pairs, aSR=2.29, 95% CI=2.07-2.54).
Conclusion: Current result imply previously reported risk of PPI associated with dementia may be overestimated. The further study should be warranted to identify the risk of dementia with the PPI use.

109 Risk of dementia in proton pump inhibitors users as compared with histamine-2 receptor antagonist: Propensity-score matched cohort study in Korea

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Aim/Objective: To investigate the risk of proton pump inhibitors (PPIs) to dementia compared with histamine-2 receptor antagonist (H2RA).
Methods: We conducted retrospective propensity score matched cohort study using the Korean nationwide health insurance sampled database. Study subjects were defined as new-users of PPI or H2RA (index date) between 1 January 2003 and 31 December 2013 without prior 1-year prescription. We followed up to first diagnosis of dementia (ICD-10 codes, F00-03, F051, G30, G311, G319, G3182) based on index drug, intention-to-treat approach. Lag-time of 1-year was introduced to reduce the protopathic bias. To control confounding, propensity-score matching cohort in a 1:2 ratio were constructed. Matched Cox regression models were used to compare the risk of dementia between the PPI and H2RA groups within propensity-score matched cohort. We also conducted subgroup analyses according to age group and dementia type.
Results: After propensity score matching in a 1:2 ratio, 89,586 patients were on PPI, 167,349 patients on H2RA. We found no significant risk of dementia associated with PPI as compared with H2RA (hazard ratio 0.64, 95% CI 0.40-1.04). Age-group and type of dementia-stratified analyses were also consisted with main results of no association between PPI and the risk of dementia.
Conclusions: Our finding showed PPI use was not significantly associated with dementia as compared with H2RA.

110 Calcium channel blocker use reduces incident dementia risk in elderly hypertensive patients: A meta-analysis of prospective studies

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Objective: Calcium channel blockers (CCB) are an established class of drug for the management of hypertension. Observational studies have found CCB to be associated with a reduction in the risk of dementia. Hence, this meta-analysis is aimed to assess the reduction in risk of incident dementia among elderly CCB user.
Methods: To further the existing evidence, we searched PubMed, Embase, and Cochrane Central from 1st Jan, 2015 to 12th June, 2017. Articles were screened on the basis of title and abstract. The primary outcome of this study was to estimate the reduction in risk of dementia associated with CCB use. Newcastle-Ottawa Scale was used to assess the quality of the study. Heterogeneity was assessed using Cochrane Q and I2 statistic. The pooled relative risk (RR) was calculated using generic inverse variance method and hazard ratio was considered comparable to RR. Subgroup analysis was performed based on CCB class. Statistical analysis was performed using Review Manager Version 5.3.
Results: This meta-analysis included five studies constituting a pooled sample of 45,343 patients (53.5% female) with a median age and median follow-up duration of 68.5 years and 8.4 years respectively. All included studies were of high quality. A significant protective effect of CCB use in reducing dementia risk (RR 0.68 [95% CI 0.56 to 0.83] p= <0.0001) was found. The CCB use was associated with a 32% reduction of dementia risk, while the protective effect of CCB was consistent in both, the adjusted and unadjusted analysis. Subgroup analysis showed that, the dihydropyridine class reduced the dementia risk by 42% [RR 0.58 (95% CI 0.41 – 0.83) p = 0.003], and non-dihydropyridine reduced the risk by 31% [RR 0.69 (95% CI 0.44 – 1.09) p = 0.12].
Conclusion: The CCB use was found to significantly reduce the risk of dementia in elderly hypertensive patients.

111 Incidence and risk factors of mortality among schizophrenia and antipsychotic-treated patients in Taiwan

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Aim/Objective: To evaluate the risk of all-cause mortality and identify patient demographic and clinical characteristics associated with these outcomes among antipsychotic-treated patients in Taiwan.
Methods: A retrospective cohort study design was used to characterize the risk of all-cause mortality among patients exposed to antipsychotics, focusing on schizophrenia patients. The study population covering a period of 2001–2015 was identified using the linkage of the Taiwan National Health Insurance (NHI) claims and National Register of Death databases.
Results: After study inclusion and exclusion criteria were applied, a total of 522,492 antipsychotic-treated patients were analyzed, of which 162,931 (31.2%) had a diagnosis of schizophrenia and 359,561 (68.8%) had diagnoses other than schizophrenia. Compared to patients with other mental health conditions, patients with schizophrenia were younger (mean age 39.4 versus 65.2 years), predominantly male (52.8% versus 43.3%), and generally healthier (mean Charlson comorbidity score 0.23 versus 1.07). Patients without schizophrenia had the following mental health conditions: 22,285 (6.2%) bipolar disorder (BD); 100,193 (27.9%) major depressive disorder (MDD); 188,989 (52.6%) dementia; and 48,094 (13.4%) comorbid BD, MDD, or dementia. The baseline profiles of patients with schizophrenia, BD, and MDD tended to be similar, whereas patients with dementia were older and had higher comorbidity scores. The incidence of all-cause mortality for antipsychotic-treated patients with schizophrenia was similar to patients with other mental health conditions, with the exception of dementia which had higher incidence estimates.
Conclusion: This study provides background incidence rates of mortality among antipsychotic-treated patients with various mental health conditions in the Asia Pacific Region. Mortality risk estimates varied according to mental health diagnosis and were associated with baseline characteristics, notably age and non-psychiatric comorbidities.

112 A Group Based Trajectory Analysis of Longitudinal Psychotropic Agents Use and Associated Adverse Outcomes in the Elderly

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Aim/Objectives: Existing studies regarding long-term use of multiple psychotropic agents (or psychotropic polypharmacy) and associated adverse effect in the elderly are very limited. This study thus aims to identify distinct trajectories of longitudinal psychotropic agents use and to examine the association between risk of all-cause mortality and unplanned hospitalization, according to distinct trajectories.
Methods: Adults who aged 65 years or older and newly initiated their oral psychotropic agents in 2004 were identified from Taiwan's National Health Insurance Research Database. Group-based trajectory modeling with a zero-inflated Poisson distribution and third order polynomials was used to identify distinct group of longitudinal psychotropic agents use (monthly consumption by defined daily dose) during a 5-year follow-up period for our study subjects. Cox proportional hazard model was used to examine the association between distinct trajectories of longitudinal psychotropic agents use and clinical adverse outcomes (unplanned hospitalization and all-cause mortality) over 3 years after 5-year follow-up of psychotropic agents use.
Results: Of the 54192 eligible older people, we identified 5 trajectories of longitudinal psychotropic agents use over a 5-year follow-up: sustained intense users (7.13 %), continued users (12.14 %), decreasing users (13.45 %), increasing users (15.67 %), and infrequent users (51.61 %). The positive associations between clinical adverse outcomes (unplanned hospitalization and all-cause mortality) and different trajectories were statistically significant, after adjusting age, sex and baseline comorbidities. Compared to infrequent users, sustained intense users had the highest risk of unplanned hospitalization and all-cause mortality (3-year unplanned hospitalization: HR=1.35 (95 % CI: 1.25-1.45); 3-year all-cause mortality HR=1.28 (95 % CI: 1.16-1.39)).
Conclusion: We identified 5 distinct trajectories of longitudinal psychotropic agents use in the elderly in Taiwan. Sustained intense users were associated with the highest risks of death and unplanned hospitalization.

113 Evaluating the impact of two Pharmaceutical Benefits Scheme (PBS) restriction changes on quetiapine use: An interrupted time series analysis

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Aim: We evaluated the impact of two PBS-restriction changes on quetiapine dispensing. Policy change 1 (July 2007) removed the need for prior approval for prescribing and policy change 2 (January 2014) did not permit repeats for 25mg quetiapine.
Methods: We used PBS dispensing claims for people with complete dispensing histories from 1st July 2005 to 31st December 2015. For both policy changes we measured monthly dispensings for 25mg quetiapine, >25 mg quetiapine, and all other antipsychotics. For policy change 2 we also measured monthly rates of 25mg discontinuation and switching from 25mg to other quetiapine formulations, other antipsychotics and benzodiazepines. We performed interrupted time series analysis using ARIMA methodology to evaluate each policy change. We also compared the pattern of use following initiation of 25mg quetiapine before and after each policy change.
Results: Following removal of prior approval, the rate of dispensing of 25mg quetiapine and >25 mg quetiapine increased by 11/month (95% CI: 2-21) and 14/month (95% CI: 8-20) respectively with no change in the rate of other antipsychotic dispensings. Following removal of repeats for 25mg quetiapine dispensing decreased by 1072 (95% CI 773-1371) over 22 months and discontinuation of this formulation increased (290/1000 users 95% CI 180-410) only half of these people continued to use other forms of quetiapine. There was also a small increase in switching, mostly to 100mg quetiapine (6/1000 users, 95% CI 1-10). Around 80% of 25mg quetiapine use was potentially inappropriate (i.e. no evidence of dose escalation) and this did not change following either policy.
Conclusion: More targeted policies are needed to ensure access to 25mg for dose-escalation but discourage off-label prescription of low dose quetiapine.

114 The discrepancy between Mantel-Haenszel and conditional logistic estimators in a case-crossover study: An exploratory study followed by a simulation study

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Objectives: In a recent case-cross over study, we found a remarkable discrepancy of the estimators for hazard ratio between Mantel-Haenszel method (MH) and conditional logistic regression (CL). We examined the underlying mechanism by the simulation study.
Methods: In a multi-center exploratory study on the possible association between the obscure gastrointestinal bleeding (OGIB) and any drug, we collected the information on up to 8 drugs used during the 24 weeks preceding OGIB. We divided 24 weeks into 24 periods and the data were analyzed using 20 control periods between W24 and W5 (Wx is the x'th week counted backward). In the simulation, we assumed that the exposure status does not change at least for 24 weeks in each subject and the true OR=4.
Results: In the OGIB study, 57 OGIB cases used aspirin (mainly for prevention of ischemic vascular diseases) at least once during the 24-week observation period. Of those, 37 used aspirin continuously and in all but one of the 20 remaining subjects, the switch of the exposure status occurred only once. In the OGIB study, OR was 2.6 (95% confidence interval: 1.1 to 6.2) in MH and 11.5 (3.1 to 42.9) in CL. In the simulation, OR was 4.4 (1.4 to 4.1) in MH and 11.3 (2.3 to 10.4) in CL with 5,000 iterations.
Discussion: In 2001, Vines and Farrington reported that under the within-subject dependence of exposures in successive time periods, the estimators may differ between MH (which is better) and CL. Our simulation study suggested that a remarkable discrepancy between MH and CL in our OGIB study was due to the similar within-subject dependence. The MH estimator was better but the simulation study suggested that some bias of the MH estimator (4.4 when the true value=4.0) could occur.

115 Data linkage and patients' perspective: Insights from a national survey in the United States

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Introduction: The ability to efficiently link multiple databases maximizes the value of existing data for pharmacoepidemiologic research. However, the patient perspective on the risks and benefits of linking existing data has not been well-characterized.
Methods: Between December 2015 and February 2016, we conducted a national survey to ascertain patient views on health data linkage. Respondents were recruited from PatientsLikeMe, an online patient community representing over 2,500 health conditions. The survey was developed using subject matter expertise and patient feedback from a concept elicitation phase (N=57 patients). The final survey consisted of 37 items.
Results: Of 3516 respondents with complete survey results, 73.8% were women, 86.4% were Caucasian, 14.5% were 65 or older, and 44.9% had completed college or post-graduate education. Survey respondents indicated that the most important benefits of sharing data were "helping my doctor make better decisions about my health" (94%) and "helping make new therapies available faster" (94%). Major data sharing risks identified included health data being "stolen by hackers" (87%) or "re-identified and disclosed to employers" (73%). The majority indicated that they were comfortable with researchers not involved in their care accessing their de-identified data for research purposes (63%). Of 693 patients who were not comfortable with this type of data sharing, most reported that their comfort levels would increase if they were able to learn how their data was protected (84%). In general, responders felt more comfortable when unique identifiers such as social security number (90%), insurance ID (82%), and name (77%) were removed from the data for linkage and research use.
Conclusions: The majority of patients in a US-based online community are comfortable with researchers accessing their de-identified data for linkage and research purposes. Developing methods to link databases without unique identifiers may improve patient comfort levels with linking data for research purposes.

116 Investigating use of administrative data sets for safety signal verification in the setting of therapeutic goods regulation in Australia

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Keywords: signal verification, data linkage.
Aim: The Therapeutic Goods Administration's current methods for verifying safety signals are largely reliant on analysis of spontaneous reports of adverse drug reactions (ADRs), data provided by medicine sponsors, data available in the medical literature and information shared by international agencies. Whilst sophisticated, these current methods have limitations, including under-reporting, incomplete data and publication bias. This project aims to explore the use of administrative health data to enhance current methods of signal verification.
Methods: The 45 and Up Study is an on-going longitudinal study of NSW residents aged 45 years and over. Participants have consented to their survey data being linked to data sets such as the Medicare Benefits Scheme (MBS), Pharmaceutical Benefits Scheme (PBS) and Admitted Patients Data Collection. The NSW Centre for Health Record Linkage (CHeReL) performed data linkage. MBS and PBS data were provided by the Department of Human Services. This project involves analyses to test associations between two known drugs – ADR associations as test cases, using 45 and Up Study data. The evidence from the analysis will be synthesised into an assessment of the feasibility and value of using administrative data for signal verifications in Australia. Attributes of the data sources that will be assessed include quality, representativeness, timeliness, simplicity, acceptability and flexibility.
Results: This presentation will outline the project methodology, results of descriptive analyses of drug utilisation, challenges encountered so far and if available, results from one of the test cases (novel anticoagulants and intracranial haemorrhage). Early insights into the potential use of administrative data sets for safety signal verification will be discussed.
Conclusion: The verification of medicine safety signals requires analysis of information from a variety of sources. Determination of the potential contribution of linked administrative data is an important outcome for drug regulation in Australia.

117 Development of a risk proportionality framework for the selection of risk minimisation interventions in Asia: Results of a pre-Delphi panel

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Objective: Existing risk minimisation interventions (RMIs), frequently used in the European Union and the United States, may not be applicable to Asian countries. This study aims at developing explicit criteria for the evaluation of risk proportionality applicable to RMIs in Asia.
Methods: Project consists of two phases: A Consultation Phase (pre-Delphi) and A Modified Delphi Study. Consultation phase involved a purposeful sample of 8 experts from regions of the world with the highest experience in therapeutic risk management (EU, US, Australia, Canada, Singapore, Taiwan, Japan). In-depth individual interviews were conducted in order to identify key factors (criteria) and circumstances used in the assessment of risk proportionality and their impact on RMIs (low, medium, high stringency interventions).
Results: The majority of respondents identified the following factors as always justifying a stringent RMI: the teratogenic potential, the risk of serious and sudden harm (e.g., sudden death), permanent disability, continued progression of damage to a vital organ despite treatment discontinuation. For a given harm, the proportionality of the risk for the RMI varied depending upon the severity and prognosis of the indication, as well as the target population (e.g., higher acceptance for oncology indications but lower acceptance in vulnerable populations). Level of RMI is also influenced by preventability of the adverse event. Medication errors and frequency of occurrence were mentioned by a minority of respondents. The main country specific factor influencing the selection of the RMI is the local treatment practice (prescription and follow-up by specialists versus general practitioners) as well as access to specialists or procedures for monitoring (e.g., ECG or biomarkers).
Conclusion: Themes and determinants of risk proportionality were identified and will be used as a framework for the construct of the Delphi questionnaire to be administered to an Asian panel of regulators.

118 But what is the cost? Application of pharmacoepidemiological methods assist payers in quantifying uncertainties in cost of medicines

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Objective: Payers need manageable budgets and equitable, sustainable subsidy schemes while the cost of medicines increase and their population ages. Estimating the total expenditure requires judgement and statistical extrapolation from current use but these are often poor predictors of actual use. In 2002 the Australian government commissioned the Drug Utilisation Subcommittee (DUSC) of the Australian government's expert HTA committee, the Pharmaceutical Benefits Advisory Committee (PBAC), to develop a formal process to evaluate estimates of patient utilisation and total cost for subsidised medicines, also known as budget impact assessment.
Method: A literature review of forecast methodology and factors influencing utilisation guided DUSC to propose a structured evaluation methodology. This was piloted and implemented in consultation with key stakeholders during 2002-2003 and formally adopted in 2004. The reliability of the method was examined using a set of 38 medicine indication pairs listed in 2006-2007. The predicted use and actual use were compared. An acceptable variation in the predicted/actual ratio was 0.75 – 1.33.
Results: Statistical forecasting relied on pharmacoepidemiological and epidemiological data sources and qualitative study methods. The DUSC evaluation framework that was developed included applicability and reliability of data sources, reasonableness of assumptions, and the need to identify uncertainties that are likely to have a critical impact on estimates.
The factors associated with variability of estimates were tested using data from 38 PBS medicine indication pairs. This study established that 51% overestimated and 23% underestimated actual cost. Key factors in variance from predictions corresponded to factors in evaluation framework and included quality of information of eligible patients from epidemiological studies, submissions where medicines where for a previously untreated patient group, the first submission to PBAC for the medicine, extrapolations based on market share.
Conclusion: The DUSC methodology provided a robust framework giving greater confidence in budget impact for government.

119 The predictive validity for mortality of a prescription-based comorbidity index: an updated Rx-Risk index

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Objective: Rx-Risk is a pharmacy based measure of comorbidity. Due to continual advances in pharmaceutical disease management Rx-Risk requires periodical updating and re-validation. The aim of this study was to validate an updated version of the Rx-Risk index by determining its utility in predicting one-year mortality in an outpatient population.
Methods: Individuals with one or more health care encounters in the Australian Government Department of Veterans' Affairs administrative claims database were included in the study (N=135,406). There were 43 comorbidity conditions mapped to ATC codes and the Rx-Risk score was the count of the number of conditions for which the patient had at least one prescription dispensed. Prescription claims from January to December 2014 were used to calculate the Rx-Risk score. The Rx-Risk was measured in the following forms: unweighted Rx-Risk score, weighted Rx-Risk score, and individual comorbidity categories indicating the presence or absence of 43 conditions. Logistic regression analyses were used to determine the relationship between the Rx-Risk measures on mortality during the year January to December 2015; adjusted for age and gender. Akaike information criterion (AIC) model fit and the c-statistic were used to compare the models.
Results: The updated Rx-Risk was predictive of one-year mortality; unweighted scores (c-statistic=0.751, 95%CI=0.747-0.754), weighted scores (0.786, 95%CI=0.782-0.789) or individual comorbidities (0.791, 95%CI=0.788-0.795). The Rx-Risk measures improved prediction of one-year mortality over the base model including age and sex alone (0.738, 95%CI=0.734-0.742).
Conclusions: The updated Rx-Risk index is a valid measure of comorbidity and was predictive of one-year mortality in an outpatient population; irrespective of whether it was modelled as a score or modelled as individual covariates. Simulation studies will be required to determine the most appropriate application of the Rx-Risk comorbidity score as a tool for confounding adjustment.

120 Drug-induced anaphylaxis in the hospital setting in Beijing, China: A retrospective analysis of the Beijing Pharmacovigilance Database

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Objective: Anaphylaxis is a severe life-threatening systemic allergic reaction that occurs rapidly after exposure to an offending agent. Few studies on the causes of drug-induced anaphylaxis (DIA) in the hospital setting are available. We aimed to use the Beijing Pharmacovigilance Database (BPD) to identify the causes of DIA in Beijing, China.

Methods: DIA cases collected by the BPD from January 2004 to December 2014 were adjudicated and analyzed for demographics, causative drugs and route of administration, and clinical signs and outcomes. Drugs implicated were classified into various pharmacotherapeutic groups and subgroups according to the Martindale - The Complete Drug Reference (37th edition) and World Health Organization (WHO) Model Formulary.

Results: A total of 1,189 DIA cases were analyzed. The mean age was 47.6 years, 1,098 patients (92.3%) were adults, and 91 (7.7%) were children. A total of 627 patients (52.7%) were females. A total of 249 different drugs were involved. DIAs were mainly caused by antibiotics (39.3%), traditional Chinese medicines (TCM) (11.9%), radiocontrast agents (11.9%), and antineoplastic agents (10.3%). Cephalosporins accounted for majority (34.5%) of antibiotic-induced anaphylaxis, followed by quinolones (29.6%), beta-lactam/beta-lactamase inhibitors (15.4%) and penicillins (7.9%). Among 36 different TCM injections identified, Ciwujia (15.6%) was the leading cause followed by Qingkailing (11.9%), Houttuynia cordata (8.9%), and Shuxuening (8.1%). Of these radiocontrast-induced anaphylaxis cases, the majority (80.1%) were caused by iodine-based contrast agents. Blood products and biological agents (3.1%), and plasma substitutes (2.1%) were also important contributors to DIAs.

Conclusion: A variety of drug classes were implicated in DIAs. Patients should be closely monitored for signs and symptoms of anaphylaxis when medications are administered especially with antibiotics, TCM, radiocontrast agents and antineoplastic agents.

121 Factors associated with intravenous and repeated use of epinephrine for drug-induced anaphylaxis: A retrospective analysis of the Beijing Pharmacovigilance Database

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Aim/Objective: Studies assessing epinephrine use in drug-induced anaphylaxis (DIA) in the hospital setting are limited. We aimed to evaluate factors associated with intravenous (IV) and repeated use of epinephrine during DIA management utilizing the Beijing Pharmacovigilance Database.

Methods: DIA cases from January 2004 to December 2014 were adjudicated and analyzed. Baseline characteristics, anaphylactic symptoms, treatment, and epinephrine administration route and dosing were evaluated. Bivariate logistic regression and multivariate logistic regression analysis were performed to derive odds ratio (OR) and 95% confidence interval (CI) of different variables.

Results: The cohort included 1,189 patients, 708 patients (59.5%) received epinephrine. Among 529 patients reported administration route, 53.9% were given by an IV route. Among 594 patients reported epinephrine dosing, 82.5% received only a single-dose compared to 17.5% who received repeated doses. The IV route were more likely to be given to patients with baseline hypertension (OR 4.48, 95% CI 1.15 to 13.31, P=0.007) or experiencing respiratory arrest (OR 2.25, 95% CI 1.21 to 5.38, P=0.014). Patients who received only a single-dose of epinephrine were less likely to experience angioedema (OR 0.47, 95% CI 0.23 to 0.95, P=0.035), cyanosis (OR 0.48, 95% CI 0.27 to 0.85, P=0.011), respiratory arrest (OR 0.27, 95% CI 0.09 to 0.76, P=0.014), hypotension (OR 0.15, 95% CI 0.05 to 0.44, P=0.001) and cardiac arrest (OR 0.26, 95% CI 0.08 to 0.88, P=0.031) symptoms, however they were more likely to experience central nervous system symptoms overall (OR 2.53, 95% CI 1.50 to 4.26, P=0.001). These patients were also less likely to receive bronchodilators therapy (OR 0.19, 95% CI 0.06 to 0.63, P=0.007).

Conclusion: Patient factors associated with the use of epinephrine IV route were baseline hypertension or experiencing respiratory arrest during DIA. Factors identified with the repeated doses of epinephrine were angioedema, cyanosis, respiratory arrest, hypotension, and cardiac arrest symptoms.

122 The Association between Parkinsonism and drugs possibly related with Parkinsonism in Korea: A population-based case-control study

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Objective: To assess the association between parkinsonism and drugs possibly related with parkinsonism such as propulsives, antipsychotics, and flunarizine.

Methods: We performed a matched case-control study design using the National Health Insurance Service—National Sample Cohort database between January 1, 2007 and December 31, 2013. We defined cases as patients who experienced parkinsonism and matched controls individually with cases by sex, age, income, type of insurance, and comorbidity. In this study, drugs possibly related with parkinsonism were defined as propulsives including metoclopramide and levosulpiride, antipsychotics including haloperidol and risperidone, and flunarizine, an anti-vertigo agent. Exposures to drugs during the 1 year before the first date of parkinsonism were stratified according to the recency of exposure and the level of cumulative doses. A conditional logistic regression was performed to assess odds ratios (ORs).

Results: We identified 5,496 cases and 5,496 controls. The ORs (95% confidence interval) of current use of propulsives, antipsychotics, and flunarizine compared to never use of these drugs were 2.714 (2.394-3.075), 4.265 (2.421-7.513), and 5.691 (3.150-10.281), respectively. The ORs were greater in those more recently exposed and those exposed to higher cumulative doses. The ORs tend to be higher in those more recently exposed (propulsives: never use, 1.000 [reference]; very-late use, 1.144 [1.005-1.303]; late use, 1.274 [1.147-1.416]; early use, 1.975 [1.704-2.288]; current use, 2.714 [2.394-3.075]) and those exposed to higher cumulative doses (propulsives: never use, 1.000 [reference]; low, 1.259 [1.117-1.420]; modest, 1.302 [1.156-1.466]; moderate, 1.813 [1.605-2.049]; high, 2.511 [2.206-2.858]).

Conclusion: The current use of propulsives, antipsychotics, and flunarizine had significant association with increased risk of parkinsonism depending on the recency and cumulative dose of exposure. Health-care practitioners and patients should be aware of the risk of parkinsonism when using these kinds of drugs.

123 Adverse effects of β-Blockers in older nursing home residents after Acute Myocardial Infarction

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Aim/Objective: Prior studies suggest that β-blockers are associated with functional decline in nursing home (NH) residents, but the mechanism is unclear. We examined the association of β-blockers after acute myocardial infarction (AMI) with hypotension and breathlessness among NH residents ≥65 years.
Methods: This retrospective, new-user cohort study of U.S. long-stay NH residents with AMI from 2007 to 2010 used data from the Minimum Data Set (MDS) and Medicare Parts A and D. Individuals with β-blocker use ≥4 months before AMI were excluded. The main outcomes were symptomatic hypotension--including hypotension, orthostasis, syncope, or dizziness--and breathlessness in the first 90 days after AMI. Hypotension and orthostasis were ascertained using ICD-9 codes in Part A hospital claims. Other outcomes were ascertained via the MDS. Multinomial logistic regression models were used to determine odds ratios (OR) with 95% CIs of each outcome for post-AMI β-blocker new users versus nonusers after propensity score matching while accounting for the competing risk of death.
Results: The study cohort (mean age, 84 years; 70.9% female; 81.7% white) included 5,496 β-blocker initiators matched to 5,496 nonusers. In our matched sample, the incidence of each outcome in β-blocker users versus non-users was: hypotension, 7.2% versus 6.3%; orthostasis, 5.2% versus 4.8%; syncope, 0.2% versus 0.2%; dizziness, 0.8% versus 0.7%; and breathlessness, 29.0% versus 27.8%. β-blocker users were more likely than nonusers to be hospitalized for hypotension (OR=1.20, 95%CI 1.03-1.39) or experience breathlessness (OR=1.10, 95%CI 1.01-1.20). Estimates for other outcomes, though not statistically significant, were consistent with a potential elevated risk of orthostasis (OR=1.14, 95%CI 0.96-1.35), syncope, (OR=1.24, 95%CI 0.55-2.77), and dizziness (OR=1.28, 95%CI 0.82-1.99) among β-blocker users.
Conclusion: New use of β-blockers after AMI is associated with hypotension and breathlessness in frail older NH residents. These adverse effects may mediate the association between β-blockers and functional decline documented in prior studies.

124 Active surveillance systems for vaccine safety: a systematic review of the surveillance models

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Objectives: To globally identify Active Surveillance System for Vaccine Safety (ASSVS) and learn about the surveillance models.
Methods: PubMed, SCOPUS and the Cochrane Library were searched for English articles describing ASSVS published until 31 March 2017 and government websites were explored for unpublished documents. Systems matched with our definition of ASSVS were identified from the literature and information about their structures, data features and operating mechanisms were extracted in formative tables. Framework synthesis was performed to sketch different models of ASSVS and the advantages and limitations of the surveillance models were compared.
Results: 11 ASSVS were identified from 96 literature, including 4 systems in USA (VSD, PRISM, VAMPSS, RTIMS), 2 in Canada (IMPACT, VISION), 2 in Australia (PAEDS, AusVaxSafety), 2 in Asia (Vietnam VSD, Singapore system for childhood vaccines) and 1 in Europe (VAESCO). All the systems are funded by governments while the participant institutions involve government agencies, colleges, professional associations, healthcare providers and enterprises. Surveillance data sources include immunization registries, electronic medical records, claim data, administration data, case reports, questionnaires and observational study data. We sketched 4 models of ASSVS: Data Linkage, Investigator Network, Automatic Survey Platform and Study Arms Integration. Among the models, data collection is conducted by computer programs or manual work and data updating frequencies vary from weekly to annually. Multi-source data are standardized using common data model, data dictionary or unified reporting form and original data are de-identified by transformation or randomization. Distributed database and centralized database are two types of data storage, based on which different analysis methods are applied to detect safety signals.
Conclusion: Data Linkage, Investigator Network, Automatic Survey Platform and Study Arms Integration are 4 surveillance models of existing ASSVS across the world, and each model has its own advantages and limitations based on different contexts.

125 What do consumers want to know about their medicines? Consumer queries compared to medicines use?

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Aim: Consumer help seek to address concerns and information gaps about their medicines. We aimed to examine the characteristics of callers to an Australian medicines call centre and compare their medicines interest with population use.
Methods: We compared patterns of consumer medicines interest (individual medicines and classes using Anatomical Therapeutic Classification (ATC) of medicines, level 2) derived from consumer calls to NPS Medicines Line (1 January 2006 to 30 June 2010) with medicine utilisation data sourced from the Australian Statistics on Medicines (first available from January 2006).
Results: The callers were mainly female, median age 48 years, help-seeking for themselves (71.7%), a child (13.3%) or their partner (5.5%). A third of calls related to safety (34.7%), 24.1% to efficacy and 14.9% to interactions. There were 85,416 calls over a 4.5year period, with 124,177 counts of individual medicines involved in questions. These distilled to 976 unique 'medicines of interest'. However, approximately half of these individual medicine counts (61,810) were represented in questions by just fifty unique medicines. Nervous system medicines (antiepileptics, psycholeptics, analgesics) and antibacterials consistently ranked highest for medicines interest in relation to their use. In contrast, agents acting on the renin-angiotensin system, 'statins' and drugs for acid related disorders ranked low for interest despite widespread use.
Conclusion: To maximise benefit, clinicians should target their education to the relatively small number of medicines of real concern to their patients.

126 Prenatal antidepressant exposure and the risk of attention-deficit hyperactivity disorder in children: A systematic review and meta-analysis

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Objective: To perform a systematic review of the literature and a meta-analysis of published studies to assess the association between prenatal antidepressant exposure and the risk of ADHD in children.
Methods: PubMed, EMBASE, PsycINFO and Cochrane review databases up to May 2017 were searched for observational studies. Published observational studies were included in the review and subsequently included for the meta-analysis if the data were available. Pooled estimates were obtained on using a random-effect model. We included all the studies that examined the association between prenatal antidepressant exposure and the risk of ADHD in children. Two authors independently screened titles and abstracts, read full-text articles, and extracted data. The quality of the studies was also assessed by Newcastle-Ottawa scale. Pooled risk ratio (RR) of maternal antidepressant use during pregnancy and ADHD in children. The corresponding pooled risk ratios in each individual trimester, maternal antidepressant use before pregnancy, maternal psychiatric disorders were also evaluated.
Results: Six studies included in the meta-analysis represented a total of 2,742,096 children. The pooled estimates comparing gestational users to non-users showed adjusted RR of 1.44 (95%CI 1.22-1.70). The corresponding risk ratios in first and second trimester were similar but different in the third trimester. Similar to the results for prenatal exposure, increased risk were found comparing previous antidepressant users and non-users: adjusted RR=1.65 (95%CI 1.32-2.06). Relationship between maternal psychiatric conditions and ADHD in children yielded a pooled adjusted RR of 2.07 (95%CI 1.73-2.48). Three studies conducted sibling-matched analyses. The pooled RR of exposed sibling is 0.94 (95%CI 0.75-1.16).
Conclusions: The findings suggest that the association between prenatal use of antidepressants and risk of ADHD in offspring can be partially explained by confounding by indication of antidepressants. If there is a causal association, the size of the effect is probably smaller than that reported previously.

127 Metabolic side effects of antipsychotics in children, adolescents and young adults – an international multi-database pharmacoepidemiologic study

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Aim/objective: To evaluate metabolic side effects of antipsychotic use in children, adolescents and young adults.
Methods: We conducted a multi-database pharmacoepidemiologic study, leveraging data from seven countries (Taiwan, Denmark, Korea, Hong Kong, Thailand, Australia, and Japan). We conducted sequence symmetry analyses (SSA), which is based on analyzing the sequences of medication prescriptions. If the initiation of the outcome drugs is more often after the index drug, it indicated an adverse effect of the index drug. We included new users of oral antipsychotics aged 2-30 years in the analyses, using the antipsychotic as the index drug and medications for hyperglycemia, dyslipidemia and hypertension as a combination of outcome indicator for metabolic side effects.
Results: Antipsychotic use was associated with metabolic side effects in children, adolescents and young adults from the data of Taiwan (3674 index-outcome drug pairs; adjusted sequence ratio, aSR 1.1; 95% CIs 1.03-1.18), Denmark (591 pairs, aSR 1.24; 95%CIs 1.05-1.46) and Hong Kong (7 pairs; aSR 6.4; 95%CIs 0.77-53.1) but not in Korea (125 pairs, aSR 1.05, 95%CIs 0.74-1.50) or Australia (57 pairs, aSR 1.18, 95%CI 0.70-1.99). Specifically, we found antipsychotic use to be associated with dyslipidemia (aSR 1.30, 95%CIs 1.11-1.53 in Taiwan; aSR 1.51, 95%CIs 1.03-2.21 in Denmark) and hypertension (aSR 1.09, 95%CIs 1.01-1.17 in Taiwan; aSR 1.51; 95%CIs 1.03-2.21 in Denmark). The findings from analyses of individual antipsychotics indicated that olanzapine, quetiapine and risperidone were associated with dyslipidemia; quetiapine was associated with hypertension and olanzapine was associated with hyperglycemia. Analyses from Thailand and Japan are ongoing.
Conclusion: International multi-database studies provide opportunities to promote research on drug safety. The findings indicated antipsychotic use was associated with metabolic side effects in children, adolescents and young adults, which warrants clinical attentions to prevent unintended outcomes of patients.

128 An ecological study of the extent and factors associated with the use of fentanyl across Australia

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Objective: To examine fentanyl utilisation in the Australian community and determine the geographic and socio-demographic factors associated with higher rates of fentanyl utilisation.
Methods: National sales data (supplied by IMS Health) were used to estimate fentanyl utilisation (in pack sales and milligrams) in Australia during 2013, mapped to Australian Bureau of Statistics (ABS) Statistical Local Areas (SLAs) and Remoteness Areas. Socio-demographic characteristics and total population estimates of SLAs were obtained from the ABS. SLA-level data on sex, age distribution, income, occupations involving physical labour and number of pharmacies, were included in linear regression analyses to examine their association with fentanyl use.
Results: An estimated 12.3 kg (or 859,518 packs) of fentanyl was sold across Australia in 2013, equating to an average of 0.55 mg/person over the year. Transdermal patches accounted for the majority (99%; 850,923 packs) of fentanyl sales. South Australia had the highest rate of utilisation per person. Rates of fentanyl utilisation were higher among more remote areas in three jurisdictions. Overall, higher utilisation rates were observed in SLAs that were less populated (ß 0.12; $p<0.001$) and those with a higher proportion of older people (ß 0.12; $p<0.001$), low-income households (ß 0.12; $p<0.001$) and people working in jobs requiring physical labour (ß 0.08; $p<0.05$).
Conclusions: Transdermal fentanyl patches account for the majority of fentanyl utilisation in the Australian community. There is marked variation in fentanyl utilisation across geographic areas, with higher use apparent in areas with a higher proportion of older people and indicators of greater socio-economic disadvantage.

129 Predictors of persistent use of prescription opioid analgesics among people without cancer

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Aim: Long-term opioid use is a clinical concern due to the risk of opioid dependence and other adverse effects. This study aimed to determine the predictors of persistent use of prescription opioid analgesics among people without cancer.
Methods: A population-based cohort study of Australians initiating prescription opioids from July 2013-December 2016 was conducted using the 10% sample of the Pharmaceutical Benefits Scheme. A 12-month look-back period was used to: define opioid initiation, exclude people with cancer, and determine comorbidities. Persistence was measured as the number of months (1,2,3,≥4) during which opioids were dispensed over a 12-month follow-up period. Ordinal logistic regression was used to estimate adjusted odds ratios (OR) and 95% confidence intervals (CIs) for predictors of opioid persistence, including age, sex, comorbidities, total baseline oral morphine equivalents (OMEs) and previous medication use.
Results: The cohort comprised 553,261 people (median age 47, 52.7% female). Over the 12-month follow-up, 73.7% were dispensed opioids for 1 month where an opioid was dispensed, 15.2% had 2 months, 4.8% had 3 months, and 6.3% had ≥4 months. The predictors of persistence include being dispensed transdermal opioids (OR=3.28, 95%CI 3.14-3.41), dispensed total OME≥750mg (OR=2.53, 95%CI 2.41-2.65), having depression (OR=1.51, 95%CI 1.49-1.53), psychotic illness (OR=1.46, 95%CI 1.41-1.51) and alcohol dependence (OR=1.25, 95%CI 1.11-1.42). Compared to people aged 18-44 years, those ≥75 years were 1.81 times more likely (95%CI 1.78-1.86) to have an additional month of opioid use. Previous use of benzodiazepines (OR=1.52, 95%CI 1.50-1.55), paracetamol (OR=1.81, 95%CI 1.78-1.84), pregabalin (OR=1.77, 95%CI 1.71-1.82) and stimulants (OR=1.15, 95%CI 1.04-1.27) predicted opioid persistence.
Conclusion: Mental health comorbidities, older age, and opioid initiation with a transdermal formulation and higher OMEs strongly predicted persistent opioid use among people without cancer. Knowledge of these characteristics will enable prescribers to target monitoring and early intervention efforts in order to prevent opioid-related problems developing.

130 Change in utilisation of long-acting oxycodone after introduction of oxycodone/naloxone in Australia: A population-based study

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Objective: Recent changes to the oxycodone market in Australia include introduction of the oxycodone/naloxone combination (December 2011) and withdrawal of 5 mg controlled release (CR) oxycodone (April 2014). We aim to quantify the impact of these changes on dispensing of oxycodone CR, oxycodone/naloxone, and both long-acting formulations combined.
Methods: Using national dispensing data, an interrupted time series analysis was conducted to measure changes in quarterly dispensing and initiation of: oxycodone CR, oxycodone/naloxone, and any long-acting oxycodone. The characteristics of people initiating long-acting oxycodone before and after the market changes were compared.
Results: After introduction of oxycodone/naloxone, the number of new long-acting oxycodone treatment episodes per quarter increased from 48 (95% CI 43 to 52) to 102 (95% CI 95 to 109), driven by an increase in oxycodone/naloxone (212 per quarter; 95% CI 196 to 238) while initiation on oxycodone CR declined (-120 per quarter, 95% CI -131 to -109). The greatest change was in the 5mg strength, where the number of new treatment episodes per quarter increased from 21 (95% CI 19 to 23) to 56 (95% CI 48 to 64). The withdrawal of 5 mg oxycodone CR had little impact on initiation of long-acting oxycodone. Between 2009 and 2015, initiation on long-acting oxycodone increased by 111% (95% CI 105% to 115%). The greatest increases occurred for the 5mg strength (261%, 95% CI 244% to 280%), people ≥85 years (166%, 95% CI 145% to 188%) and people initiating on long-acting oxycodone with no other opioids dispensed before or after initiation (155%, 95% CI 139% to 171%).
Conclusion: Oxycodone/naloxone has nearly supplanted oxycodone CR, and is associated with a doubling of the initiation rate of long-acting oxycodone. Oxycodone is increasingly being used at low doses and as a one-off dispensing which suggests use for non-chronic or less severe pain.

131 Quantifying the extent that PBS/RBS claims data under-estimate opioid analgesic utilisation in Australia

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Objective: Although pharmaceutical claims are an essential data source for pharmacoepidemiological studies, these data may potentially under-estimate opioid utilisation. Therefore, this study aimed to quantify the extent to which pharmaceutical claims from Australia's national medicines subsidy programs (the Pharmaceutical Benefits Scheme (PBS) and Repatriation Schedule of Pharmaceutical Benefits (RPBS)), under-estimate prescription-only and total national opioid utilisation across time and for different opioids. A secondary aim was to examine the impact of the 2012 policy change to record all PBS/RPBS dispensed medicines, irrespective of government subsidy, on the degree of under-estimation.
Methods: Aggregated data on Australian opioid utilisation were obtained for the 2010-2014 calendar years, including all single ingredient and combination opioid analgesic preparations available on prescription or over-the-counter (OTC). Total opioid utilisation (oral morphine equivalent kilograms) was quantified using sales data from IMS Health and compared to pharmaceutical claims data from the PBS/RPBS.
Results: PBS/RPBS claims data did not account for 12.4% of prescription-only opioid utilisation in 2014 and 19.1% in 2010 and 18.4%-25.4% of total opioid use when accounting for OTC preparations. Between 2010-2014, 5.6%-5.3% of buprenorphine, 8.1%-6.3% fentanyl, 17.7%-10.7% oxycodone, 18.4%-11.0% tramadol, 38.4%-21.0% hydromorphone and 28.6%-21.0% of prescription-only codeine utilisation were not accounted for in PBS/RPBS claims.
Conclusions: Despite increased capture of less expensive (under co-payment) opioid items since 2012, PBS/RPBS claims still under-estimate opioid use in Australia, with varying degrees across opioids. The estimates generated in this study allow us to better understand the degree of under-estimation and account for these in research using Australia's national pharmaceutical claims data.

132 Exposure to teratogenic medicines before, during and after pregnancy in New South Wales (NSW), Australia

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Aims: Teratogenic medicines are categorised as D or X (D/X) by therapeutic regulatory agencies. Given the potential hazards of D/X category medicine exposure to a developing fetus during pregnancy, monitoring their use around pregnancy is imperative. We aimed to estimate the utilisation of D/X category medicines in Australian women from 24 months before conception until 3 months after delivery.
Methods: We used linked population-based datasets including Pharmaceutical Benefits Scheme dispensing data and the NSW Perinatal Data Collection. Our cohort comprised women with complete ascertainment of dispensings in our time periods of interest and had pregnancies resulting in a birth between 2005 and 2012. Our pre-pregnancy, during-pregnancy and post-partum periods were each of 91 days duration and were based on delivery dates and gestational age. We determined the prevalence of exposure as percent of pregnancies with at least one dispensing of a D/X medicine in the respective time periods.
Results: Of 191,588 pregnancies, 31,952 (17%) were exposed to a D/X category medicine between 24 months before conception and 3 months after delivery. There was a notable decrease in the exposure prevalence from pre-pregnancy periods (mean prevalence 3.4%) to the first trimester (1.4%), which further decreased thereafter (0.7% in the second trimester, and 0.6% in the third trimester). Post-partum there was an increase to pre-pregnancy prevalence (3.2%). We observed a similar pattern in the prevalence of exposure to category D/X antibiotics, psychotropics, antihypertensives, and statins, which comprised >80% of all D/X dispensings.
Conclusions: While it is encouraging that there is a decline in prescribed teratogenic medicines during pregnancy, the elevated prevalence in the first trimester relative to late pregnancy suggests there still may be some inadvertent during-pregnancy exposure. Greater physician review of pharmacological treatment among women of childbearing age may thus be warranted.

133 Risk of adverse perinatal outcomes associated with early pregnancy use of renin-angiotensin system blockers for the management of chronic hypertension.

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Background: There is some evidence of increased risk of congenital malformations associated with early pregnancy exposure to renin-angiotensin system (RAS) blockers which include angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB). However, the evidence about the safety of RAS blockers on perinatal outcomes remains limited. This study examines the effects of RAS blockers on preterm deliveries and birth weight when used in the first trimester for chronic hypertension.
Methods: Perinatal data for all deliveries in New South Wales, Australia, between 2005 and 2012, were linked to hospital discharge and pharmaceutical dispensing records. The analyses were restricted to women for whom complete pharmaceutical dispensing history was available and those who had chronic hypertension.The risk of preterm delivery (<37 weeks of gestation), low birth weight (LBW, birthweight < 2500 grams) and small for gestational age (SGA, birth weight <10th percentile) among pregnancies exposed to ACEIs (N= 71) and ARBs (N=75) in early pregnancy, were compared to 486 methyldopa exposed pregnancies using backward elimination logistic regression, adjusting for maternal age, socioeconomic status, remoteness of residence, parity, smoking and comorbidities like gestational diabetes.
Results: Adjusted odds ratios and 95% confidence intervals for ACEI-exposed neonates relative to methyldopa-exposed neonates were 0.6 (0.3-1.3), 0.8 (0.4-1.5) and 1.1 (0.5 – 2.1) respectively for preterm delivery, low birth weight (LBW) and small for gestational age (SGA). Likewise, for ARB compared to methyldopa, estimates were: 0.7 (0.4-1.4), 1.3 (0.7-2.4) and 1.1 (0.5-2.3) respectively for the same outcomes.
Conclusions: For pregnant women with chronic hypertension, RAS blocker use during the first trimester was not associated with increased risk of preterm delivery and low birth weight. Previous reports about the substantial increase in the risk of these outcomes associated with ACEI use were likely due to non-equivalent comparison group which included women without hypertension.

134 Safety of varenicline versus prescription nicotine patches during pregnancy: Findings from Smoking MUMS (Maternal Use of Medications and Safety) Study

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Aim: Current evidence regarding the safety of varenicline and nicotine replacement therapy (NRT) during pregnancy is insufficient, which limits the ability of physicians and patients to make informed decisions regarding appropriate smoking cessation medicines during pregnancy. This study compared several birth outcomes between the use of varenicline and prescription NRT patches during the first and second trimesters of pregnancy.
Methods: Perinatal data for all deliveries in two Australian States (New South Wales and Western Australia) were linked to pharmaceutical dispensing and hospital separation records. Women who used varenicline and NRT in the first and second trimesters (based on the date and quantity of the medicine dispensed) and smoked during pregnancy were included. Women who had the first dispensing in the third trimester were excluded. Birth outcomes, restricted to singleton pregnancies conceived Jan 2009-Apr 2012, included preterm birth (gestation<37 weeks), small for gestational age (SGA), newborn admission to special care units (SCU), neonatal resuscitation, premature rupture of membranes (PROM), and 5-minute Apgar score <7. Logistic regression models assessed the outcomes among varenicline users versus NRT users, adjusting for maternal sociodemographic, obstetric characteristics, diabetes, hypertension, quantity smoked, and duration of medicine use during pregnancy.
Results: Compared to 293 NRT users, varenicline users (n=892) had similar likelihood of having a preterm delivery (adjusted odds ratio [OR]: 0.77: 95%CI: 0.46-1.29) and PROM (1.11: 0.51-2.38). Babies born to varenicline users had similar likelihood of being SGA (OR 0.93: 0.60-1.44), requiring resuscitation (0.91: 0.54-1.55), having a SCU admission (0.85: 0.55-1.31), and 5-minute Apgar<7 (1.14: 0.36-3.58) relative to infants born to NRT users.
Conclusion: There were no significant differences in several birth outcomes between the use of varenicline and NRT. Further evidence about rare and long-term safety outcomes are needed. The choice of medicine for smoking cessation should be guided by its indications, contraindications and patient preference.

135 Patterns of care for long-term surviving trastuzumab-treated patients with HER2-positive metastatic breast cancer (HER2+MBC): an Australian whole-of-population cohort study

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Objectives: Subsidy decisions for new cancer medicines are based on registration trials and resource estimates over a 5-year time horizon. Median survival estimates from clinical trials of first-line trastuzumab for HER2+ MBC range from 2 to 3.5 years. We describe the characteristics, time-on-trastuzumab, overall survival (OS), and other cancer treatments for an Australian cohort surviving ≥5 years from the initiation of trastuzumab for MBC.
Methods: We identified long-term survivors using national dispensing records. We estimated time-on-trastuzumab from first dispensing date until the last dispensing, plus 30 days; defining a break of ≥90 days between dispensings as a separate treatment course. We estimated OS as time from first trastuzumab dispensing until death and used Kaplan-Meier methods to estimate time-on-trastuzumab and OS. We used dispensing dates to determine the frequency and timing of additional cancer treatments given during or after trastuzumab.
Results: We identified 1,015 patients surviving ≥5 years from first dispensing of trastuzumab: 28% of all trastuzumab-treated patients between 2003-2011. Median age at initiation was 55 years (IQR: 46–64); 64% were dispensed hormonal therapies. Median time-on-trastuzumab was 5.0 years (2.2–7.9); 435 patients (43%) had at least one break in trastuzumab therapy. Median OS was 11.6 years (7.0–not reached); median duration of all chemotherapy was 14.4 months (6.3–41.3). Taxanes and hormonal therapies were frequently dispensed during Year 1 of therapy; capecitabine, lapatinib, and vinorelbine in Years 4 and 5; and trastuzumab and hormonal therapies beyond 5 years.
Conclusions: At the time cancer medicines are registered for use we understand little about the patterns of treatment and outcomes in real-world practice. This study provides data about the treatment and outcomes in long-term survivors with HER2+MBC that can inform policy makers about resource use in long-term cancer survivors.

136 Incidence of comorbidities in women treated with tamoxifen or an aromatase inhibitor: an Australian population based cohort study

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Objective: Cancer patients are at high risk of developing new chronic diseases but there are limited studies on the pattern of comorbid diseases associated with the use of different types of endocrine therapy. This study aims to assess the pattern of comorbidities among Australian women treated with tamoxifen or an aromatase inhibitor.
Methods: Retrospective cohort study using Pharmaceutical Benefits Scheme data (10% sample) between January 2003 and December 2014. Breast cancer cohort who initiated tamoxifen or aromatase inhibitor between 2004 and 2011 with no switching between types of endocrine therapy was identified. The breast cancer cohort for each individual comorbidity evaluated as an outcome was age- and sex-matched with a specific control group (at 1:10 ratio) without any dispensing record of anti-neoplastic agents throughout the study period. Dispensing claims data were used to identify comorbidities and classified with Rx-Risk-V model. Cox regression models were used to analyse the time to the development of each of eight individual comorbidities.
Results: Women treated with tamoxifen had a significant higher risk of developing cardiovascular conditions, depression, pain/pain-inflammation and diabetes but a lower risk of hyperlipidaemia compared to the non-cancer control groups. Women in the aromatase inhibitor subgroup had a significant higher risk of developing cardiovascular conditions, depression, pain/pain-inflammation, gastric acid disorders and osteoporosis compared to the non-cancer control groups. When comparing aromatase inhibitor to tamoxifen, the risks of developing hyperlipidaemia and osteoporosis were lower among women who have been treated with tamoxifen.
Conclusion: Women with hormone-dependent breast cancer treated with an endocrine therapy had a higher incidence of selected comorbid conditions than women without cancer. Difference in comorbidities between tamoxifen and aromatase inhibitor reflects the side effect profile of the two drugs. Understanding the incidence of comorbidities is important for the planning and implementation of better models of care for breast cancer survivors.

137 Statins use and the risk of prostate cancer: A nationwide population-based cohort study

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Aims/Objective: First, to analyze the statins use and the risk of prostate cancer in Taiwan. Second, to access whether different characteristics of statins will affect the risk of prostate cancer differently.
Methods: This is a retrospective cohort studies using National Health Insurance Research Database from January 1, 2000 to December 31, 2013. Patients aged over 55 and were newly diagnosed with acute coronary syndrome between January 1, 2001 to December 31, 2008 without any cancers diagnosis prior to or 180 days after index date were included. Propensity score was used to match statin users and non-users. Time-dependent cox regression model was used to calculate the risk of prostate cancer between drug exposure group and non-exposure group.
Results: After 1:1 propensity score matching, a total of 26,628 men were included. Statins use was associated with significant lower risk of both total and advanced prostate cancer (HR: 0.719, 95% CI: 0.570-0.908; HR: 0.718, 95% CI: 0.530-0.908 respectively). Compared with statins non-users, the HR (95% CI) were 1.328 (0.931-1.654) for the group with cumulative dose <84 cDDD, 1.203 (0.903-1.604) for the group 312>cDDD≧84, 0.712 (0.513-0.989) for the group 818>cDDD≧312, and 0.426 (0.298-0.609) for the group cDDD≧818. Simvastatin, fluvastatin, atorvastatin, and rosuvastatin users showed significant 26.6%, 30.2%, 30.9%, and 37.8% reduction in total prostate cancer risk respectively. Lipophilic statins were not different from hydrophilic statins in total and advanced prostate cancer risk (HR: 1.014, 95% CI: 0.638-1.61; HR: 0.806, 95% CI: 0.445-1.459). However, high intensity statins showed a significant reduction in total and advanced prostate cancer risk compared to non-users (HR: 0.548 ,95% CI:0.367-0.820; HR: 0.487, 95% CI: 0.284-0.836).
Conclusions: In Taiwan ACS population, dose-dependent reduction in risk of prostate cancer were observed in statins users, especially patients used simvastatin, fluvastatin, atorvastatin, rosuvastatin or high intensity statins.

138 Pharmacoepidemiology in Nordic countries, a fairy tale?

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The Nordic countries have a tradition for publicly funded health care with universal coverage, irrespective of income or working status. Owing to a mutual identifier in all health databases, it is possible to link data sources across primary and secondary health care. The political and structural conditions underlying this development will be described.
Using Denmark as an example, the research opportunities will be described in detail. Among other data sources, Denmark has offered nationwide coverage of all cancers since 1943, all hospitalizations since 1977 and all prescriptions since 1995, with an organizational structure that has facilitated linkage. This has led to a plethora of high-quality pharmaco¬epidemiological methods development and applied research. The limitations will be described, among others the lack of good diagnostic data from primary care and lack of good structures for conducting cross-national Nordic studies. Some promising new developments will be described as well.