3rd Pharmacoepidemiology Research Network Symposium

Wednesday 22 November 2017, 10:00am – 4:30pm
Valentine Common Room
St Margaret's College
University of Otago
Dunedin

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ABSTRACTS

‘Real-world’ health care Big Data: from chaos to causality

Eelko Hak

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Annual costs of pharmaceuticals are high, estimated at 4 billion euro for the Netherlands alone. Randomised controlled trials (RCTs) are presently the ‘gold standard’ for the causal evaluation of drug benefits, because randomised allocation of patients to either drug or placebo minimises both measured and unmeasured confounding (interference by spurious factors that may inappropriately influence the results) between comparison groups. In other words, randomisation in the study of drug therapy assures that patients who receive the therapy are similar in their clinical prognosis to control patients.

However, there are many instances in which evidence from RCTs will either not become available or is not a useful to guide healthcare-policy decisions, as RCTs are commonly expensive, logistically challenging, and limited by the choice of study patients and patient outcomes. For this reason, much evidence for the effectiveness of drug therapies is derived from non-randomised, observational studies using widely available ‘Big Data’ from health care databases or individual patient data-analyses. Such causal studies are, however, controversial, as their validity is uncertain because they lack the rigor of randomisation in RCTs, and because confounding is often insufficiently taken into account.

In this keynote lecture, clinical pharmacoepidemiologist Eelko Hak will illustrate the issue of confounding with some ‘real-world’ examples and will show various promising design methodologies for controlling and quantifying confounding bias in observational studies of drug effectiveness, thus making these studies more scientifically valid and reliable. The examples will be from high-quality ‘Big Data’ sources such as the University of Groningen’s prescription database IADB.nl covering 1.2 million people in the Netherlands and the UK Clinical Practice Research Datalink (CPRD) covering 7 million people from the United Kingdom, as well as from a global Individual Patient Data-analysis.

Patterns of use of long-acting bronchodilators in New Zealanders with chronic obstructive pulmonary disease: are they consistent with international treatment guidelines?

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Background
Previous studies have shown that the prescription of inhaled therapy for chronic obstructive pulmonary disease (COPD) is inconsistent with treatment guidelines, but none of these studies have examined longitudinal patterns of use of inhaled long-acting beta$_2$-agonist (LABA) and long-acting muscarinic antagonist (LAMA) therapy across an entire country.

Aim
We aimed to describe treatment patterns in new users of long-acting bronchodilators across New Zealand.

Methods
Using national health and pharmaceutical dispensing data, we identified patients aged $\geq$ 45 years who started LABA and/or LAMA therapy for COPD between 1 February 2006 and 31 December 2013. Dispensings of LABAs, LAMAs, and inhaled corticosteroids (ICSs) were then aggregated and combined into episodes of use of therapeutic regimens. We described the duration of the first regimen, the sequences in which unique regimens were used, and the patterns of use and non-use during follow-up using Kaplan-Meier curves, sunburst plots, and sequence index plots, respectively.

Results
The study cohort comprised 83,435 patients and 290,400 person-years of follow-up. The most commonly initiated regimen was a LABA with an ICS, and the median duration of the first regimen was 46 days. Patients used multiple regimens over time, and periods of non-use were common.

ICS use was inconsistent with international guidelines: patients with infrequent and frequent exacerbations were over- and under-treated, respectively, and many patients' treatments included periods of ICS mono-therapy.

Conclusions

In this nation-wide follow-up study of patients initiating inhaled LABA and/or LAMA therapy for COPD, treatment was often inconsistent with guidelines, and there were complex patterns of therapy, including periods of non-use. Further work is required to address the reasons for the long-standing discrepancy between guideline recommendations and prescribing practices.

Are doses of lamotrigine or levetiracetam adjusted during pregnancy?

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Background
Sub-therapeutic levels of lamotrigine and levetiracetam are more likely to occur during pregnancy due to the effect of pregnancy on their pharmacokinetics. This can lead to suboptimal control of epilepsy and guidelines recommend proactive dose adjustment in the second and third trimesters alongside therapeutic drug monitoring (TDM).

Methods
This is a retrospective cohort study using three of New Zealand's administrative databases between 2010 and 2015. Women who gave birth were identified by the National Minimum Dataset and were linked by encrypted national health index (NHI) to the Pharmaceutical Collection to determine whether they were dispensed lamotrigine or levetiracetam in the preceding 12 months. Average doses per trimester were calculated to investigate the rate of dose escalation during the second half of pregnancy. The Laboratory Claims Database was used to determine whether TDM was used to manage dose adjustment.

Results
In 460 individual pregnancies, the dose was increased in the second and third trimester 276 times (60.0%). Only 57 women (12.4%) had any therapeutic monitoring (TDM). The dose was not always decreased post-partum, 157 women (56.9% of those who had escalated doses during pregnancy) had their dose reduced following birth. Between 2012 and 2015 only 29 women in the cohort had a hospital discharge with an ICD 10 code for epilepsy. If these were all seizure events then the data shows that women who had a seizure were more likely to have their dose increased than those who did not (Pearson Chi-square p=0.021). There was no difference in recorded seizures for women who had any TDM during pregnancy (p= 0.278).

Conclusions
While women were more likely to have their dose increased than not during their pregnancy, there was still a significant proportion (40.0%) whose dose was not increased. Dose changes were not guided by TDM and doses were not always reduced post-partum. Women who had hospital recorded epilepsy were more likely to have their dose increased during pregnancy but TDM did not significantly affect the likelihood of a seizure. We believe that standardized guidelines and education around the monitoring and titration of antiepileptic drug doses during pregnancy are required.

Codeine and tramadol use in a paediatric population in New Zealand

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Background
There are concerns regarding codeine in the <2 years age group, particularly in the context of post-tonsillectomy analgesia. Tramadol, although approved for children in New Zealand, is not approved <2 years of age. From 2014, practice guidelines in New Zealand discouraged the use of codeine and tramadol in children. The WHO analgesic ladder for children advocates a two-step approach: simple analgesia (paracetamol or ibuprofen) as the first step with the second step for moderate or severe pain being morphine.

Aim
To examine the dispensing of codeine, tramadol and morphine for children in New Zealand in order to identify trends in usage.

Methods
All New Zealand community dispensing data for codeine phosphate, tramadol and morphine were extracted from national administrative databases (National Pharmaceutical Collection and National Minimum Dataset) for the period 1 January 2010 to 31 December 2015. The data were summarized for each calendar year by age group: <2 years, 2 to <6 years, 6 to <12 years and 12 to <17 years.

Results
In the <2 year age group there was little use of either codeine or tramadol, but usage of both increased to 2014, with an abrupt drop in usage of codeine in 2015. In the 2 to <6 year age group there was greater use of codeine, also increasing to 2014 with an abrupt drop in usage in 2015; tramadol usage increased in both 2014 and 2015. In the older age group there was greater usage of both codeine and tramadol with progressively increasing use of tramadol. Morphine use in all the age groups appeared stable.

Conclusion
These data suggest that prescribers have adopted recommendations with regard to codeine but there may be substitution of codeine with tramadol.

Co-prescribing of contraindicated and use-with-caution drugs in a national cohort of new users of simvastatin: how well are prescribing guidelines being followed?

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Background
Statins are a class of drugs widely prescribed for lowering lipid levels, and thus contributing to prevention of cardiovascular morbidity and mortality. While statins have been demonstrated to be relatively safe, some adverse effects are known to occur. Simvastatin and atorvastatin (to a lesser extent) are metabolised by the isoenzyme cytochrome P450 3A4 (CYP3A4). Co-prescription of a drug which inhibits CYP3A4 may increase plasma concentrations of the statin, and hence increase the risk of adverse events. Potent inhibitors of CYP3A4 include macrolide antibiotics, azole antifungals, and protease inhibitors.

Methods
Data from the Ministry of Health's National Collections were used to identify all people aged $\geq$ 18 years who were first dispensed simvastatin between January 2006 and December 2013, and to identify dispensing of any medicines listed as contraindicated or use-with-caution. Cumulative incidence of co-prescribing of contraindicated and use-with-caution drugs while on simvastatin was estimated using Kaplan-Meier methods, and Cox regression was used to determine factors associated with dispensing of contraindicated medicines.

Results
In the cohort of 349,371 simvastatin users, the cumulative incidence of contraindicated drug dispensing after 2 years of simvastatin use was 11% (11.2%, 95% CI: 11.1 to 11.3). For use-with-caution drugs the cumulative incidence was 16% (95% CI: 15.8 to 16.0). Contraindicated drugs were more commonly co-prescribed to women, those aged 18–39 years, and those with greater co-morbidity. There was also variation by ethnicity.

Conclusions
Prescribing of contraindicated drugs to patients on simvastatin does occur in New Zealand despite the available information. It may be possible to reduce the risk of adverse drug reactions by use of an alternative drug, where available, or an alternative statin.

Simvastatin dose and acute kidney injury without concurrent muscle injury: is there a relationship?

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Background
Recent studies have reported an excess risk of acute kidney injury (AKI) in users of high versus low dose (or potency) statin regimens, although the relationship was not consistently found in all patient groups. AKI occurs with rhabdomyolysis but none of the studies explored the possibility that the well-established relationship between statin dose and serious muscle injury (severe myopathy, rhabdomyolysis) might have accounted for their findings.

Aim
To examine the relationship between simvastatin dose and AKI without concurrent serious muscle injury in two cohorts of new users of simvastatin: (i) people with no history of renal disease, and (ii) people with non-dialysis dependent chronic kidney disease.

Methods
The study was based on data from the Ministry of Health's National Collections. We used pharmaceutical dispensing and hospital discharge data to identify 334,710 people aged ≥ 18 years without a history of renal disease (cohort 1) and 5,437 with non-dialysis dependent chronic kidney disease (cohort 2) who initiated simvastatin therapy between 1 January 2006 and 31 December 2013. Cohort members were classified as cases if (i) they were admitted to hospital during follow-up with a principal diagnosis of AKI and in the same admission there were no additional diagnoses coded to the muscle-related ICD-10-AM rubrics under which rhabdomyolysis may be classified, or (ii) the underlying cause of death was AKI without mention of rhabdomyolysis or myopathy. For each case we used risk set sampling to randomly select up to 10 controls, matched on date of birth, sex, and cohort entry date. Case-control analyses nested within each cohort were undertaken using conditional logistic regression.

Results
In the analysis nested in cohort 1, the adjusted odds ratios and 95% confidence intervals (95% CI) for current use of 40mg and 80mg simvastatin daily, relative to current use of 20mg, were 0.9 (95% CI 0.7–1.2) and 1.3 (95% CI 0.7–2.3), respectively. The adjusted odds ratio for 40mg in cohort 2 was 1.1 (95% CI 0.7–1.9); the numbers taking 80mg were very small and the 95% was consequently very wide.

Conclusion

These findings suggest that a relationship between statin dose and AKI may not exist independent of muscle injury.

Medsafe: a life-cycle approach to medicines safety in New Zealand

Geraldine Hill

Medsafe, Ministry of Health

Medsafe, the New Zealand Medicines and Medical Devices Regulatory Authority, takes a life-cycle approach to medicines safety in New Zealand. Beginning with pre-market assessment, Medsafe ensures medicines that are approved for distribution in New Zealand meet international standards for quality, safety and efficacy. In the post-approval phase, Medsafe continues to monitor the safety profile of medicines to ensure that the benefit-risk balance remains positive.

This presentation will focus on post-marketing benefit-risk evaluation, including how Medsafe identifies and responds to emerging post-marketing safety issues (with current examples), and where you can find information on pharmacovigilance activities currently being undertaken by Medsafe.

PHARMAC and research: what we've got, and what we need

Scott Metcalfe

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PHARMAC decides which medicines, medical devices etc. are subsidised in the community and public hospitals – from District Health Boards' funds – to get best health outcomes from the money the Government spends on pharmaceuticals, affordably. PHARMAC is thus an evidence-based organisation and has a statutory mandate to engage in research. Beyond our own business-as-usual analysis, we collaborate, support, and fund a range of Health Services Research activities. PHARMAC engages in clinical trials, clinical epidemiology, pharmacoepidemiology, literature reviews, 'business-as-usual' budget impact analyses and systematic cost effectiveness analyses, evaluations of patient medicines adherence, population health programme evaluations, other health services research, and project evaluations.

The talk will cover some research PHARMAC has been involved with previously, especially pharmacoepidemiology. Also the joint PHARMAC/HRC research fund and priorities for that in this year's funding round (improving pharmaceutical adherence; improving optimal use of pharmaceuticals; measuring the impact of PHARMAC's decisions on health outcomes; assessing and improving the value for money from new and currently funded pharmaceuticals). There are PHARMAC's new strategic goals and what that means for future research priorities; with emphasis on PHARMAC's new Bold Goal 1 – the elimination of inequities in access to medicines by 2025; and updates to Māori medicines gap analysis to support that.

Using a non-randomised step-wedge design to control for unmeasured confounding in pharmacoepidemiology studies with chronic exposures and outcomes

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Background
Pharmaceutic datasets often contain scarce information on participant characteristics, putting traditional cohort or case-control analysis at risk of unmeasured confounding. Case-only designs, including case-crossover and self-controlled case-series, can eliminate confounding caused by time-invariant characteristics and population-level time-varying characteristics may be controlled through use of time-matched controls including future cases. However, these approaches still require that outcomes are time-limited.

Aims
To develop methods to control for confounding in studies with chronic exposures and outcomes. These methods will be used to investigate associations between starting a statin or anti-hypertensive agent with subsequent prescription of metformin.

Methods
National prescribing data for the years 2005 to 2011 on patients aged 40 to 60 years was obtained from the New Zealand Pharmaceutical Collection for statins, anti-hypertensives, insulin and hypoglycaemic agents. Data were combined and individuals aggregated into cohorts according to exposure drug and year of first exposure. Individuals with prescriptions in 2005 were excluded. Annual crude incidence rates of starting metformin were calculated before and after commencement of exposure medication. General estimating equations (GEE) and cox proportional hazard regression with time-dependent covariates were used to estimate changes in incidence rates over time.

Results
Descriptive presentation of the incidence of first metformin prescription over time highlighted differences in risk prior to exposure, and the possible presence of effects that were immediate (same year as exposure) or long-lived (years proceeding exposure). GEE provided a useful model to estimate baseline incidence rates (statins = 20.2 per 1000 person-years [95% CI = 19.6, 20.9], anti-hypertensives = 14.8 per 1000 person-years [95% CI = 14.3, 15.4]), and post-exposure effects. In the same year as starting statins or anti-hypertensives individuals experience an almost six-fold increase in risk of starting metformin, however this dropped to only 1.6 fold above baseline by the second year of exposure.

Conclusions

The use of a non-randomised ‘step-wedge’ design incorporating observations pre- and post-exposure can partially control for unmeasured confounders in studies with chronic exposures and outcomes. However, results are still susceptible to individual-level time-varying confounders, and care must be taken in developing and interpreting statistical models due to possible presence of co-prescribing and referral biases.

What causes the geographical variation of Parkinson's in New Zealand?

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Background
Parkinson's is a progressive neurodegenerative disorder affecting around 10 000 people in New Zealand and this is predicted to double within the next 25 years. It is currently unknown how the prevalence and incidence of Parkinson's varies geographically in New Zealand. Research in other countries has suggested a history of rural living may increase the risk of developing Parkinson's disease.

Aims
To estimate geographical variation of Parkinson's within NZ using drug-tracing methodologies and explore factors that may contribute to this variation.

Methods
Information on Parkinson's-related medications was extracted from the national pharmaceutical database of community-dispensed medications for the period 1 January 2005 to 31 December 2014. Diagnoses for a large subset of individuals were determined through national and local datasets. A Bayesian model, taking into account uncertainty in diagnoses and sources of biases, was used to estimate the number of people with Parkinson's. The New Zealand Index of Multiple Deprivation was used to measure regional deprivation.

Results
There was large variation in age-sex standardised prevalence of Parkinson's by District Health Board region. Prevalence was higher in the South Island (253 per 100 000 people, 95% uncertainty interval [242,265]) than the North Island (165 [158,172] per 100 000 people). This difference persisted when calculating prevalence only for individuals of European ethnicity. Higher regional prevalence was correlated with a lower rank of regional deprivation.

Conclusions
There is large variation in the geographical prevalence of Parkinson's disease. One potential contributor to this is rural versus urban living. Another potential contributor is social deprivation, with greater levels of deprivation potentially leading to lower access to health services resulting in not being diagnosed or exposure to factors such as smoking

that potentially decrease the risk of Parkinson's. We are planning to use the Integrated Data Infrastructure to explore these factors and better understand the geographical variation of Parkinson's in New Zealand.

Creation of a New Zealand pregnancy cohort for medicine utilisation and safety studies

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Background
Administrative health databases are increasingly being used to undertake retrospective cohort studies investigating medicine utilisation and medicine safety during pregnancy. These studies typically link prescribing or dispensing records with health information in other databases, and can be undertaken more quickly and at a lower cost than prospective studies.

Aim
The aim of this study was to create a pregnancy cohort from national health collections in New Zealand, including early pregnancy losses as well as pregnancies resulting in live births and stillbirths.

Methods
Pregnancies in New Zealand from 2005-2015 were identified in four national collections. Pregnancies resulting in a liveborn or stillborn infant were sourced from the National Maternity Collection (MAT). Early pregnancy losses as well as deliveries were identified in the National Minimum Dataset (NMDS) using ICD-10 diagnosis and procedure codes. Pregnancies were identified in the Mortality Collection (MORT) through records of stillbirths and maternal deaths. Records of antenatal blood tests were used to identify pregnancies in the Laboratory Claims Collection (LAB).

Women having more than one pregnancy during the study time period had all their recorded pregnancies included. To be eligible for inclusion in the cohort, each pregnancy required a last menstrual period date and a pregnancy-end date (recorded or estimated), and the woman's encrypted NHI. Infant records in MAT and MORT that could be linked with a cohort member formed the baby cohort.

Results
The final cohort consists of 946,185 pregnancies to 494,433 women, with 633,255 infant records linked to cohort members. One third of the pregnancies identified were not recorded in MAT. There were 625,221 pregnancies that resulted in ≥1 live birth and 2061 pregnancies that resulted in ≥1 stillbirth; including 70 pregnancies in which both stillborn and live-born infants were delivered. Outcomes of pregnancy also included

88,624 terminations, 50,511 miscarriages and 5075 other early pregnancy losses. The pregnancy outcome was not able to be determined for 174,763 pregnancies, the vast majority of which (166,202) were identified only through an antenatal lab test. Of these LAB-only records, 94.5% had only undergone the first blood test, suggesting these records are likely to represent additional early pregnancy losses managed without an inpatient hospital admission.

Conclusion

Sourcing pregnancies from four National Collections has produced a pregnancy cohort that includes early pregnancy losses as well as deliveries, and well represents the pattern of pregnancy outcome in New Zealand over the past decade. Results of medicine utilisation studies undertaken with this cohort will be reflective of the pregnant population.

Improving metformin adherence and persistence in people with type 2 diabetes

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Background

Type 2 diabetes mellitus (T2DM) imposes a substantial burden on New Zealanders, particularly Māori and Pacific Peoples. Metformin is the first-line medication for the treatment of T2DM, but overseas research has found that many patients have suboptimal metformin adherence and persistence. Overseas research has also found that adherence and persistence are dynamic processes, with variation in the levels of adherence and persistence over time common. We seek to assess the dynamics of adherence and persistence in new metformin users in the New Zealand context and identify potential factors which may influence these adherence and persistence patterns. Such knowledge is important, as suboptimal metformin adherence and persistence are associated with increased risk of diabetes complications.

Aims and objectives

The study aims are to:

1. Provide a national picture of:
    a. Metformin adherence and persistence among people with T2DM;
    b. The role person- and healthcare-related factors play in adherence and persistence; and
    c. The health impacts of suboptimal metformin adherence and persistence.
2. Undertake a qualitative study to provide an insight into the factors, from the point of view of people with type 2 diabetes, which help and hinder optimal metformin adherence and persistence.

The study's objectives are to:

1. Describe patterns of adherence, discontinuation, and reinitiation over the follow-up period in new users of metformin, overall and by person- and healthcare-related factors;
2. Explore associations between person- and healthcare-related factors and the first metformin discontinuation and reinitiation events;
3. Identify acute factors associated with reinitiation of metformin;

4. Quantify the relationship between metformin adherence and discontinuation, and subsequent diabetes-related hospitalisation and all-cause mortality; and
5. Identify enablers of, and barriers to, metformin adherence and persistence.

Methods

A national cohort of people with T2DM who initiated metformin treatment between 1 January 2006 and 30 September 2014 was identified from the Virtual Diabetes Register. Data from Ministry of Health data collections (NHI, Pharms, NMDS, GMS, PHO, LAB, Mortality, NZCR) were obtained for this cohort, and a follow-up history of medication use and health events from metformin initiation until dispensing of another antidiabetic, death, or end of follow-up (31 December 2015) was created.

These data are currently being analysed to describe patterns of metformin adherence (measured by the medication possession ratio), discontinuation and reinitiation across the follow-up period as well as assessing the factors associated with these. The associations between adherence, persistence, and subsequent hospitalisation and mortality are also being examined.

Once completed, the findings from this quantitative component of the study will be used to inform the subsequent qualitative investigation of barriers to, and enablers of, metformin adherence and persistence.

What difference do prescription charges make? A proposed RCT

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Although prescription charges in New Zealand are low compared with many other countries, many people report that they cannot afford the medicines they need, and there are strong socio-economic and ethnic differences in this. In the latest New Zealand Health Survey 6.3% of the population, including 15% of Māori adults and 19% of Pacific adults, reported not picking up at least one medicine in the last 12 months because of cost. Analysis of SOFIE data suggested that being unable to afford prescriptions was associated with a decline in health. There is however a lack of experimental data on the impact of charges for prescriptions.

We plan to conduct a randomised controlled trial of prescription charges to investigate whether removing charges would improve people's health. We will recruit a group of people who are likely to be at high risk of negative consequences if they cannot afford their prescriptions. They will have diabetes and/or ongoing mental health problems requiring medications, and live in deprived neighbourhoods. The intervention group will be exempted from prescription charges for twelve months. The primary outcome will be hospital bed-days. Secondary outcomes will be: all-cause hospitalisations, prescription medicines dispensed (number and type), hospitalisations for diabetes/mental health problems, deaths, and emergency department visits. We will also do a qualitative study of a small number of participants, to record and explore their experiences, and the impact of the intervention on their daily lives and expenditure. We hope the study will generate useful evidence to inform policy in New Zealand and internationally.