8th Pharmacoepidemiology Research Network Symposium

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ABSTRACTS

Exposure to systemic antimicrobials during pregnancy and risk of miscarriage: a population-based register study

Thomas Boissiere-O'Neill[1], Marleen MHJ van Gelder[2, 3], Hilde M Engjom[4], Hedvig ME Nordeng[2, 3]

[1] *Children's Health and Environment Program, Child Health Research Centre, University of Queensland, Australia*

[2] *PharmacoEpidemiology and Drug Safety Research Group, Department of Pharmacy, Faculty of Mathematics and Natural Sciences, UiORealArt convergence environment, University of Oslo, Oslo, Norway*

[3] *Department of Child Health and Development, Norwegian Institute of Public Health, Oslo, Norway*

[4] *Department of Health Promotion and Department of Health Registry Research and Development, Norwegian Institute of Public Health, Bergen, Norway*

Background

Antimicrobials are the most prescribed drugs during pregnancy, accounting for 80% of all prescriptions. Previous studies suggested an association between certain antimicrobials in pregnancy, such as macrolides, tetracyclines, metronidazole, quinolones, and fluconazole, and an increased risk of miscarriage. However, these studies are conflicting and limited by biases such as immortal-time bias, reverse causation, competing risks, and confounding by indication.

Aim

To estimate the risk of miscarriage following antimicrobial exposure, addressing biases that hampered previous studies.

Methods

Using a population-based cohort study design, four nationwide registries were linked: the Medical Birth Registry of Norway (MBRN), the Norwegian Prescription Registry (NorPD), the Norwegian Patient Registry (NPR), and the Primary Care Registry (KUHR). Miscarriage and gestational age at miscarriage were captured using diagnosis codes from NPR, KUHR, and MBRN, using a pregnancy algorithm previously developed.

Information on sociodemographic factors, obstetric history, chronic comorbidities, and common maternal infections were gathered. Time-varying antimicrobial exposures with a 14-day lag period were considered to avoid protopathic bias, and elective terminations were right-censored to account for competing risks. Daily overlap weights were used to minimise characteristics differences between treatment groups throughout follow-up. Crude and weighted time-stratified Cox regression models were employed, and probabilistic bias analysis was conducted to address confounding by indication, using four scenarios varying in infection prevalence and association strength.

Results

The study included 704,088 pregnancies from 2009 to 2018, with 92,672 (13.2%) exposed to antimicrobials in pregnancy and 611,416 (86.8%) unexposed pregnancies. Most common antimicrobials appeared safe during pregnancy. However, metronidazole (HR 1.48 [95% CI 1.34 – 1.63]), cephalexin
(HR 1.20 [95% CI 1.01 – 1.43]), fluconazole (HR 1.16 [95% CI [1.05 – 1.29]), and doxycycline (HR 1.24 [95% CI 1.14 – 1.35]) in pregnancy were associated with miscarriage. Fluconazole was the only antimicrobial with a consistent association in the bias analyses.

Conclusion

Our findings suggest that the most common antimicrobials during pregnancy are not associated with miscarriage risk. However, caution is warranted when prescribing less common antimicrobials, such as fluconazole. Further research is needed to determine the impact of infection type and severity. Pregnant women presenting with an infection should be treated as per clinical guidelines.

Competing interests

None reported.

Funding

The University of Oslo covered costs related to Norwegian registry data. Thomas Boissiere-O'Neill was funded through the International Alliance for PharmacoGenetic Epidemiology Excellence (iAPOGEE) visiting grant scheme (Norwegian Research Council, grant no. 322176).

The association between nitrate in drinking water during pregnancy and adverse pregnancy outcomes: potential effect modification by nitrosatable drug intake

Tim Chambers [1], Hana Royal [2]

[1] *Ngāi Tahu Research Centre, University of Canterbury - Te Whare Wānanga o Waitaha, Aotearoa New Zealand*

[2] *Department of Public Health, University of Otago - Ōtākou Whakaihu Waka, Wellington - Pōneke, Aotearoa New Zealand*

Background

Epidemiological research has observed associations between nitrate in drinking water intake during pregnancy and a range of adverse pregnancy outcomes including preterm birth, low birthweight, and congenital abnormalities. In humans, nitrate metabolites can combine with nitrosatable compounds (amines and amides) to form N-nitroso compounds (NOC) that are teratogenic. Nitrosatable drugs are one source of amines and amides which could moderate the association between nitrate in drinking water and adverse pregnancy outcomes.

Aims

The current study aims to:

1. Investigate the association between nitrate in drinking water during pregnancy and adverse pregnancy outcomes; and
2. Understand the potential impact of nitrosatable drug use on this association.

Methods

The study design is a retrospective cohort identified through the National Maternity Collection (MAT) from 2008 – 2021 (~700,000 births using the Integrated Data Infrastructure [IDI]). All outcome data will be sourced from the IDI including preterm birth, low birthweight, and potentially congenital anomalies. The exposure assessment contains five main steps:

1. Identification of the mother's meshblock of residence for each pregnancy
2. Identification of the water supply for each meshblock
3. Nitrate level estimation for each water supply, for each year (2008 – 2021)
4. Linking of the above data to obtain a nitrate level estimate for each pregnancy; and

5. Identifying nitrosatable drug use during pregnancy using the Pharmaceutical Collection.

Results

The first results are expected in early 2025.

Competing interests

None reported.

Funding

This work is funded by a Health Research Council of New Zealand project grant (grant no. 22/0559), the Ministry for the Environment, and a Health Research Council of New Zealand Māori Health Clinical Research Training Fellowship (grant no. 24/113).

Use of antinausea medications during the first trimester of pregnancy in Aotearoa New Zealand, 2005 – 2020

Sarah Donald[1, 2], Katrina Sharples[2, 3], Dave Barson[1, 2], Karyn Maclennan[1, 2], Leanne Te Karu[4], Diana Phone[5], Hedwig van Asten[6], Mike Stitely[7], Lianne Parkin[1, 2, 8]

[1] *Department of Preventive and Social Medicine - Te Tari Hauora Tūmatanui, University of Otago - Ōtākou Whakaihu Waka, Aotearoa New Zealand*

[2] *Pharmacoepidemiology Research Network, University of Otago - Ōtākou Whakaihu Waka, Aotearoa New Zealand*

[3] *Department of Mathematics and Statistics - Te Tari Pākarau me te Tatauraka, University of Otago - Ōtākou Whakaihu Waka, Aotearoa New Zealand*

[4] *Department of General Practice and Primary Health Care, University of Auckland – Waipapa Taumata Rau, Aotearoa New Zealand*

[5] *Health New Zealand - Te Whatu Ora (Waitematā), Aotearoa New Zealand*

[6] *Department of Women's and Children's Health - Te Tari Hauora Wāhine me te Tamariki, University of Otago - Ōtākou Whakaihu Waka, Aotearoa New Zealand*

[7] *Health New Zealand - Te Whatu Ora (Southern), Aotearoa New Zealand*

[8] *The New Zealand Pharmacovigilance Centre, University of Otago - Ōtākou Whakaihu Waka, Aotearoa New Zealand*

Background

In recent decades the use of antinausea medications during pregnancy has risen in a number of high-income countries. The preferred agents for treating nausea and vomiting in pregnancy vary by country, and the use of ondansetron has become very common in the United States. Some evidence suggests that exposure to ondansetron in early pregnancy increases the risk of congenital anomalies. Although increasing use of antinausea medications during pregnancy has been documented in Aotearoa New Zealand, no detailed descriptions of the specific medications used have been reported.

Aims

To describe the patterns of antinausea medication dispensing during the first trimester of pregnancy in Aotearoa New Zealand, 2005 – 2020

Methods

A retrospective cohort study was undertaken by linking community dispensings of antinausea medications recorded in the Pharmaceutical Collection with pregnancies in the New Zealand Pregnancy Cohort (NZPC). Exposed pregnancies were considered those with at least one dispensing in Trimester 1. Proportions exposed to any antinausea drug, and to specific medications, were calculated for each year of the study period. Maternal characteristics were compared (i) between exposed and unexposed pregnancies, and (ii) between three mutually-exclusive treatment groups among those exposed. The sequence in which antinausea medications were dispensed was also examined.

Results

The proportion of pregnancies exposed in Trimester 1 increased from 4.1% in 2005 to 21.1% in 2020. Metoclopramide was the most commonly dispensed antinausea medication in all years; however, there was a substantial increase in ondansetron use over the study period (from 0.1% to 9.8% of pregnancies). Dispensing of an antinauseant was less likely during pregnancies of individuals who were older, of Māori ethnicity, smokers, and living rurally. Among exposed pregnancies, ondansetron was more likely to be dispensed than metoclopramide to those who were over 40 years of age, of European/Other ethnicity, less deprived, and who had been admitted to hospital for hyperemesis gravidarum. Metoclopramide monotherapy as a first-line treatment decreased from 70.0% of exposed pregnancies in the period 2005 – 2010 to 46.5% in 2016 – 2020, whereas ondansetron monotherapy as first-line treatment increased from 1.9% to 26.5%.

Conclusions

Use of ondansetron increased substantially over time despite uncertainties around its safety in pregnancy. Further exploration of both the context of ondansetron prescribing in Aotearoa New Zealand and its potential adverse impacts is warranted.

Competing interests

None reported.

Funding

This study is part of a larger project funded by the Health Research Council of New Zealand (grant no. 21-279).

Validation of small for gestational age coded diagnoses in Aotearoa New Zealand's administrative health datasets

Mei-Ling Blank[1], Sarah Donald[1, 2], Lianne Parkin[1, 2, 3]

[1] *Department of Preventive and Social Medicine - Te Tari Hauora Tūmatanui, University of Otago - Ōtākou Whakaihu Waka, Aotearoa New Zealand*

[2] *Pharmacoepidemiology Research Network, University of Otago - Ōtākou Whakaihu Waka, Aotearoa New Zealand*

[3] *The New Zealand Pharmacovigilance Centre, University of Otago - Ōtākou Whakaihu Waka, Aotearoa New Zealand*

Background

Inaccurate coding of small for gestational age (SGA) infants in routinely collected health data impacts research based on those data.

Objectives

To estimate the sensitivity and specificity of coded SGA diagnoses in Aotearoa New Zealand's hospitalisation and mortality administrative data, and to determine whether sensitivity and specificity varied by infant, pregnancy, and maternal characteristics.

Methods

We estimated birthweight centiles for live and stillborn infants delivered in Aotearoa New Zealand (2005 – 2020) using the Fenton Population Reference and GROW Customised Bulk Centile (New Zealand version) calculators. Relevant variables (including gestational age, birthweight, infant sex, and others) were sourced from routinely collected national health data. We compared coded SGA diagnoses (ICD-10-AM P051) in hospitalisation and mortality data with SGA status derived from the two calculators. We used a generalised linear model to estimate relative sensitivities and specificities by comparing coded diagnoses with each of the birthweight calculators, adjusting for infant, pregnancy, and maternal characteristics.

Results

This analysis included 887,871 infants, with 15,850 (1.8%) having a coded SGA diagnosis. By contrast, the Fenton and GROW calculators classified 80,541 (9.1%) and 138,866 (15.6%) babies as SGA, respectively. Compared with the Fenton calculator, the sensitivity of coded SGA diagnoses was 13.1% (specificity 99.3%); compared with the GROW calculator, sensitivity was 9.8% (specificity 99.7%).

For both calculators, higher adjusted relative sensitivities (aRS) for coded SGA diagnoses were observed for severe SGA (<3% birthweight centile), older maternal age, and increasing year of last menstrual period. Lower aRS were seen for stillborn infants, males, and not nulliparous pregnancies.

Conclusion

In Aotearoa New Zealand, population-level research involving SGA status should use birthweight centiles from an appropriate calculator instead of coded diagnoses.

Competing interests

None reported.

Funding

None reported.

Colchicine poisoning in Aotearoa New Zealand – using data to gather insights and inform actions

Nevin Zhong[1], Tegan Coventry[1], Susan Kenyon[1], Maria Storey[1]

[1] *Clinical Risk Management Branch, Medsafe, Ministry of Health - Manatū Hauora, Aotearoa New Zealand*

Introduction and aim

Colchicine is a medicine used for the treatment of acute gout. It is also prescribed for the prevention of gout flares when starting urate-lowering therapy (unapproved use). Recent deaths secondary to colchicine ingestion have prompted a review of risk mitigating strategies.

We discuss how data from various sources can be used to investigate colchicine poisonings and inform actions to minimise risk.

Methods

We used data from the Pharmaceutical Collection and the National Poisons Centre (NPC), and reports from the Centre for Adverse Reactions Monitoring (CARM) to characterise colchicine usage and poisonings to inform strategies to mitigate harm.

Results

In 2023, 28% of dispensed colchicine prescriptions were for Pacific Peoples, 24% were for Māori, 9% were for people in the Asian ethnic group, and 39% were for people in the European and Other group. The greatest number of dispensed prescriptions was in the 50 – 60 year age band for Māori and Pacific Peoples and the 70 – 80 year age band for other ethnic groups. Most dispensed prescriptions were for people living in Counties Manukau (25%), Waitematā (13%), and Auckland (12%).

Between 2016 and 2024, 113 unique incidents were reported to the NPC in relation to colchicine exposure. Therapeutic error and self-harm were the most common unintentional and intentional reasons for exposure, respectively. Forty-one percent of the incidents concerned Māori and Pacific Peoples. A third of exposures were in children aged 0 – 5 years and 40% were in adults aged 20 – 59 years.

Recent CARM reports showed a significant number of poisonings were in adolescents who had access to large quantities of colchicine in their home.

The following actions were taken:

- Publishing a Prescriber Update (www.medsafe.govt.nz/profs/PUArticles/June2021/Colchicine-painful-insights-recent-poisoning-data-New-Zealand.html) article reminding healthcare professionals about the risk of colchicine.
- Updating a patient leaflet on gout medicines (www.medsafe.govt.nz/Consumers/educational-material/Medicines-for-Gout-Jun-2021.pdf), with emphasis on storage and disposal of medicines. This was translated to Te Reo and Samoan.
- Advocating the use of blister packs and child resistant closures to minimise intentional and unintentional exposures.
- Advocating to limit the dispensing frequency to monthly to reduce the number of tablets stored at home.

Conclusions

Reducing harm from colchicine in the community requires a cross-sector approach. We continue to monitor to see if these actions have been successful or if more needs to be done.

Competing interests

None reported.

Funding

None reported.

The long-term effects of opioid use before total joint replacement surgery: a dose-response trial emulation with New Zealand linked administrative data

Ross Wilson[1], Yana Pryymachenko[1], J. Haxby Abbott[1], Peter Choong[2], Michelle Dowsey[2]

[1] *Centre for Musculoskeletal Outcomes Research, Department of Surgical Sciences - Te Tari Hāparapara, University of Otago - Ōtākou Whakaihu Waka, Aotearoa New Zealand*
[2] *Department of Surgery, St. Vincent's Hospital, University of Melbourne, Australia*

Background
Opioid analgesics are commonly used to manage pain associated with osteoarthritis, particularly by patients awaiting joint replacement surgery, despite multiple international guideline recommendations discouraging such use. Patients using opioids preoperatively have worse surgical outcomes—reduced pain relief and greater risk of surgical complications or early revision—than patients without preoperative opioid use. There is also some evidence of sustained detrimental effects of preoperative opioid use up to as much as 5 years post-surgery.

There are limited alternatives to opioids for the management of preoperative pain, with some alternatives contraindicated for some patients, making it challenging for many patients to eliminate preoperative opioid prescribing. It is therefore important to understand the dose-response relationship between preoperative opioid use and postoperative outcomes: are efforts to minimise the *amount* of preoperative opioid use warranted, even short of complete opioid avoidance?

Methods
We are conducting a trial emulation study using linked administrative data via the Integrated Data Infrastructure (IDI). The target trial is a dose-response trial of opioid use prior to hip or knee joint replacement surgery for people with osteoarthritis.

The 'participants' in the emulated trial are all patients who had a joint replacement surgery for osteoarthritis in the New Zealand public healthcare system between July 2011 and June 2017. We assigned patients to emulated treatment groups based on their opioid prescribing over the 3 months before surgery: no opioid prescribing (control group), and four equal quartiles of the observed distribution of the total morphine-equivalent opioid dose (cutoffs at 187mg, 352mg, and 780mg). The random allocation of trial participants to treatment strategies was emulated using inverse probability of treatment weighting,

achieving very good (weighted) covariate balance across a large set of baseline confounders.

Outcomes were measured over 6-year follow-up from the date of surgery, and included public healthcare utilisation and costs, employment and income, and adverse events including mortality, opioid overdose, and revision surgery.

Results

Our preliminary results show that most of the adverse effects of preoperative opioid prescribing were consistent across all treatment groups compared to the no opioid control group, with little evidence of a meaningful dose-response relationship. Exceptions were increased postoperative opioid use, where a strong dose-response relationship was found (although the effects were still significant even in the lowest opioid treatment group), and reduced income and employment, which was only found for the higher opioid treatment group.

Conclusion

If confirmed in our final analyses, these results suggest that reducing, but not eliminating, preoperative opioid prescribing is unlikely to significantly improve postoperative outcomes. Efforts should continue to be made to develop appropriate alternatives to opioid analgesics for people awaiting joint replacement surgery.

Competing interests

None reported.

Funding

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A systematic review of global long-term cost-effectiveness of newer antidiabetic drugs: trends in type 2 diabetes mellitus research

Dan Li[1,2], Carlo Marra[1,3], Alesha Smith[1]

[1] *School of Pharmacy - He Rau Kawakawa, University of Otago - Ōtākou Whakaihu Waka, Aotearoa New Zealand*

[2] *Department of Clinical Pharmacy, Inner Mongolia Medical University, Hohhot, Inner Mongolia Autonomous Region, China*

[3] *Faculty of Health Sciences, Curtin University, Perth, Australia*

Background

By 2030, 1 in 9 adults globally will have type 2 diabetes, posing a significant socio-economic burden. The 2024 American Diabetes Association (ADA) guidelines highlight the crucial role of Newer Antidiabetic Drugs (NADs) in reducing cardiovascular and kidney disease risks. However, there is an urgent need for an updated synthesis of evidence regarding long-term cost-effectiveness analyses of these medicines. The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) 2022 is a gold standard checklist for ensuring health economic evaluations are identifiable, interpretable, and useful for decision-making.

Aim

This systematic review is intended to help payers and clinicians make informed decisions about incorporating NADs into routine clinical practice. It does this by gathering and synthesizing high-quality interventional studies and utilizing the CHEERS-2022 checklist to assess study quality.

Methods

The PubMed, Embase, Cochrane, EBSCOhost, Scopus and Web of Science databases were searched from 1 January 2008 to 30 May 2024. Eligible studies were:

1. Cost-effectiveness analyses of the comparisons of interest between (i) NADs and other classes of NADs, such as: glucagon-like peptide-1 receptor agonists (GLP-1RA) compared to dipeptidyl peptidase-4 inhibitors (DPP-4i), or dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 (GIP/GLP-1) receptor agonists compared to sodium-glucose cotransporter-2 inhibitors (SGLT2i) and (ii) NADs and standard treatment (SoC);

2. Full-text publications in English.

Three reviewers independently screened studies for relevance and eligibility, extracted data from full texts and appendices, and assessed quality using the CHEERS 2022 guidelines.

Results

The search yielded 1465 records, and 136 studies were eligible for inclusion. The Centre for Outcomes Research Diabetes Model was the most frequently employed model for determining long-term health impact. Additionally, 89% of the included studies adopted the payer's perspective, while approximately 85% utilized time horizons exceeding 40 years.

Most NADs are cost-effective compared to standard treatments. Studies show that semaglutide is cost-effective compared to other drugs (GLP-1RA, DPP4i, SGLT2i) except when compared with empagliflozin. The latest GLP-1RA/GIP (tirzepatide) is considered cost-effective compared to subcutaneous semaglutide at a Willingness To Pay (WTP) threshold of 100,000 USD/QALY.

Conclusion

NADs are often more cost-effective than traditional therapies such as SoC or insulin. This evidence can help funders and policymakers gain a broader perspective when making decisions about new diabetes treatments, which is especially important in a growing healthcare environment.

Competing interests
None reported.

Funding
This study was funded by the University of Otago - Ōtākou Whakaihu Waka.

How does risk communication by pharmacists impact how people with asthma perceive and respond to risk?

Eliza J. McEwin[1], Barbara J. Mintzes[1], Bandana Saini[2]

[1] *Charles Perkins Centre and School of Pharmacy, Faculty of Medicine and Health, University of Sydney, Australia*

[2] *Woolcock Institute of Medical Research and School of Pharmacy, Faculty of Medicine and Health, University of Sydney, Australia*

Background

Pharmacists have a unique role communicating about medicines and their potential risks. About 1 in 9 Australians has asthma. Inhaled medicines are the cornerstone of asthma management, but people may experience side effects. Our previous work provided some insights into how people with asthma prefer risk to be communicated to them, and how they perceive and respond to risks associated with their asthma and their medicines.

Aim

We wished to assess the extent of research on pharmacists' risk communication with people who have asthma and how this impacts their perception of and response to risk.

Methods

For this scoping review the participants were pharmacists, the concept was risk communication with people who have asthma, and the context was any health / patient care setting (e.g. hospital, community pharmacy, aged care facility etc). Six electronic databases were searched (CINAHL, EMBASE, MEDLINE, PsycINFO, SCOPUS and Web of Science) for articles published to 1 March 2024.

Results

Six articles met the inclusion criteria with pharmacists and people with asthma > 18 years. Five studies occurred in community pharmacies and one study in a university medical centre asthma clinic. Data analysis, using the situated rationality and extended parallel process models for risk perception and response, respectively, showed that despite pharmacists' risk communication, there was scope for working towards positive change for how people with asthma perceive and respond to risks associated with their asthma and their medicines.

Conclusions

We found that pharmacists vary in many aspects of their risk communication with people who have asthma. Several factors contribute to this which impact how they perceive and respond to risk. Further research could focus on understanding more of why people with asthma perceive and respond to risks and its impact on their asthma management. In particular, it would be useful to understand more about the variation in pharmacists' risk communication.

Competing interests

None reported.

Funding

None reported.

Drug use evaluations for Australia's Pharmaceutical Benefits Scheme to assess quality use of medicines: a document analysis study

Judith Mackson[1], Barbara Mintzes[2], Sallie-Anne Pearson[3]

[1] *PhD candidate, University of Sydney, Australia*

[2] *School of Pharmacy and Charles Perkins Centre, Faculty of Medicine and Health, University of Sydney, Australia*

[3] *Medicines Intelligence Research Program, School of Population Health, University of New South Wales, Australia*

Background

Subsidised access to cost-effective medicines through the Pharmaceutical Benefits Scheme (PBS) is a fundamental component of Australia's health system and National Medicines Policy. Drug use evaluations conducted by the funding agency are an ongoing component to ensure the program's viability and quality use of medicines (QUM) for individuals and populations.

Objectives

To determine how the findings of drug use evaluations for PBS-listed medicines are used to identify, assess, and address inappropriate use and promote better quality of medicines use.

Methods

We conducted a document analysis retrieving all publicly available drug use evaluations and comprehensive post-market review documents published between 2012 and 2022. We developed a standardised tool to extract information on review type, medicines reviewed, and patterns of use, and characterised policy recommendations to the funding agency.

Results

We identified 111 standard and 8 comprehensive whole-of-medicine class or disease management reviews. Among the standard reviews, 51 examined single medicines or combination products and 60 examined multiple medicines or medicine classes. The most frequent single medicine reviews were for eculizumab and testosterone, and the most frequent classes were antipsychotics, immunosuppressants, diabetes medicines, protein kinase inhibitors, monoclonal antibodies, and antibody drug conjugates. Comprehensive reviews examined medicines in smoking cessation, pulmonary arterial hypertension,

chronic obstructive pulmonary disease, dementia, childhood asthma, type 2 diabetes, biologics in psoriasis, and ezetimibe.

Pharmaceutical Benefits Advisory Committee (PBAC) decisions were available for 103 standard reviews, 29 of which were linked to QUM concerns, including inappropriate over/under use, safety concerns, and cost-ineffective use outside restrictions. The most frequent PBAC recommendations were: no intervention required (55%), further analysis needed (17%), review/change listing (8%), educate prescribers (5%), and consult on findings (6%). A case study of multiple reviews of pregabalin use illustrates how these evaluations were used to monitor uptake after listing and identify and reduce inappropriate use.

Conclusions

Drug use evaluation is embedded within the complex decision making, governance, and implementation of reimbursement decisions to ensure that program goals are met and the scheme is sustainable. This is a rare 'upstream' approach to addressing QUM concerns in use of publicly-funded medicines.

Competing interests

JM was formerly a member of the Australian Government Drug Utilisation Sub-Committee (DUSC). SP is a member of the DUSC. The views expressed here do not reflect the views of this committee.

Funding

None reported.

Systematic reviews of observational studies of harms of medicines: a case study of application of two risk of bias tools within a controversial research area

Barbara Mintzes[1], Alice Fabbri[2], Nick Chartres[1], Jeff Wang[3, 4], Lisa Bero[5]

[1] *School of Pharmacy and Charles Perkins Centre, Faculty of Medicine and Health, University of Sydney, Australia*

[2] *Department for Health, University of Bath, United Kingdom*

[3] *School of Pharmacy, Faculty of Medicine and Health, University of Sydney, Australia*

[4] *National Centre for Immunisation Research and Surveillance, Australia*

[5] *Centre for Bioethics and Humanities, University of Colorado Anschutz Medical Campus, United States*

Background

Systematic reviews of research evidence have become increasingly prominent within an evidence-based medicine framework for clinical care. To comprehensively assess treatment outcomes, systematic reviews often include pharmacoepidemiologic research as well as RCTs. Risk of bias assessment, using standardised tools, is a key component of evidence syntheses. Two tools are often used for cohort and case-control studies: ROBINS (Cochrane tool) and the Newcastle-Ottawa Scale (NOS).

Aims

Although RCTs have found that menopausal hormone treatments (MHT) increased the risk of dementia, a recent systematic review [1] concluded that MHT prevents dementia, based on meta-analyses of cohort and case-control studies. This review did not assess risk of bias. A case study approach is used to assess the application of ROBINS and NOS to recent studies included in this review to determine whether risk of bias accounts for divergent outcomes.

Methods

The *Nerratini et al.* review includes 6 RCTs and 45 observational studies; 11 studies (in 10 reports) were published since 2017, the date of the last relevant Cochrane review. We used NOS and ROBINS to assess these 11 studies, using duplicate independent coding. Each was classified as having low, moderate, or high risk of bias based on *a priori*

[1] Nerratini et al. *Front Aging Neurosci* 2023 ; DOI 10.3389/fnagi.2023.1260427

thresholds. Coders also qualitatively assessed key study weaknesses and strengths. Chi-square analysis compares findings versus assessed risk of bias per study.

Results

The 11 studies include 6 nested case-control studies (5 finding increased dementia risks; 1 no difference), 5 cohort studies (3 dementia prevention; 2 no difference), and no RCTs. Key differences between studies include whether exposure was assessed via administrative data or self-report, comprehensiveness of adjustment for confounders, exclusion of reverse causality, and completeness of follow-up. Coding and analysis is still underway, but preliminary results indicate serious limits to both tools, with weighting of domains leading to overall study ratings that are not empirically supported, especially with NOS.

Conclusions

Risk of bias assessment is a key component of systematic review methods. Our results suggest a need for better risk of bias tools that reflect best practices in pharmacoepidemiology.

Competing interests

None reported.

Funding

None reported.

Is it really 10 years?

Lianne Parkin[1, 2, 3]

[1] *Department of Preventive and Social Medicine - Te Tari Hauora Tūmatanui, University of Otago - Ōtākou Whakaihu Waka, Aotearoa New Zealand*

[2] *Pharmacoepidemiology Research Network, University of Otago - Ōtākou Whakaihu Waka, Aotearoa New Zealand*

[3] *The New Zealand Pharmacovigilance Centre, University of Otago - Ōtākou Whakaihu Waka, Aotearoa New Zealand*

This session will provide a very brief overview of some of the activities of the Pharmacoepidemiology Research Network since it was established in 2014.

Competing interests
None reported.

Funding
None reported.