The big data revolution: What does it mean for Australian pharmacoepidemiology research?

Sallie Pearson
Today

- What is value-add of pharmacoepidemiology research?
- How does Australia contribute to the global activity?
- Current opportunities
  - CRE in Medicines and Ageing
  - Early projects
- Reflections
Background

• Pharmacoepidemiology
  – Drug use and impact in large populations

• Growing trend - observational studies in ‘routine care’
  – Greater access to linked population-based health data
    o Routine collections (cancer notifications)
    o Administrative/payment data (dispensing claims)

Well-recognised limitations of clinical trials
Why do we need observational (post-market) studies?

• Medicines tested in clinical trials
  – Gold standard for efficacy BUT
    o Under-represent key patient groups
    o Short duration (even for drugs taken for a lifetime)
    o Limited safety focus

  › General public prescribed medicines before comprehensive risk/benefit assessment

• Observational studies using routine data collections
  the only opportunity to study outcomes in large numbers of typical patients
Observational (post-market) studies

*Using linked routinely collected data*

**Strengths**

- Large numbers of typical patients
- Reflects standard care
- Can focus on vulnerable populations
- Relatively quick and modest cost
- Can identify rare adverse events
- Long-term patient follow-up
- Continuous assessment
## Observational (post-market) studies

*Using linked routinely collected data*

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large numbers of typical patients</td>
<td>Susceptible to confounding (underlying patient differences influencing treatment)</td>
</tr>
<tr>
<td>Reflects standard care</td>
<td>Associations not causality</td>
</tr>
<tr>
<td>Can focus on vulnerable populations</td>
<td>Methodologically difficult</td>
</tr>
<tr>
<td>Relatively quick and modest cost</td>
<td>Reliance on data generated for purposes other than research</td>
</tr>
<tr>
<td>Can identify rare adverse events</td>
<td>Limited validation of proxies</td>
</tr>
<tr>
<td>Long-term patient follow-up</td>
<td></td>
</tr>
<tr>
<td>Continuous assessment</td>
<td></td>
</tr>
</tbody>
</table>
Tips for new PBS punters!

The Australian Pharmaceutical Benefits Scheme data collection: a practical guide for researchers

Leigh Mellish¹, Emily A. Karanges¹, Melisa J. Litchfield¹, Andrea L. Schaffer¹, Bianca Blanch¹, Benjamin J. Daniels¹, Alicia Segrave² and Sallie-Anne Pearson¹,³*

Abstract
Background: The Pharmaceutical Benefits Scheme (PBS) is Australia’s national drug subsidy program. This paper provides a practical guide to researchers using PBS data to examine prescribed medicine use.

Findings: Excerpts of the PBS data collection are available in a variety of formats. We describe the core components of four publicly available extracts (the Australian Statistics on Medicines, PBS statistics online, section 85 extract, under co-payment extract). We also detail common analytical challenges and key issues regarding the interpretation of utilisation using the PBS collection and its various extracts.

Conclusions: Research using routinely collected data is increasing internationally. PBS data are a valuable resource for Australian pharmacoepidemiological and pharmaceutical policy research. A detailed knowledge of the PBS, the nuances of data capture, and the extracts available for research purposes are necessary to ensure robust methodology, interpretation, and translation of study findings into policy and practice.

Keywords: Pharmacoepidemiology, Drug prescriptions, Drug utilisation, Databases, Australia
Australian landscape

› Universal health care arrangements and public subsidy of prescribed medicines
  › *By product: lots of routinely collected data*

› PBS is a billion dollar enterprise
  › FY 2014-2015: $9 billion+ (>200 million scripts)
  › ‘*PBS buys health outcomes NOT drugs*’

› What is our return on investment?
Assessing our return on investment

Legislation has crippled research: One exception
Impact for pharmacoepi research

Exposure – Commonwealth

Outcome – States & Territories
## Opportunities

<table>
<thead>
<tr>
<th>Collection</th>
<th>Scope</th>
</tr>
</thead>
<tbody>
<tr>
<td>DUSC</td>
<td>Aggregated</td>
</tr>
<tr>
<td></td>
<td>• PBS + under co-payment + private scripts</td>
</tr>
<tr>
<td>IMS</td>
<td>Aggregated</td>
</tr>
<tr>
<td></td>
<td>• Prescription + OTC</td>
</tr>
<tr>
<td>10% PBS sample</td>
<td>Standardised unit record dataset</td>
</tr>
<tr>
<td></td>
<td>• PBS-listed medicines + FOD</td>
</tr>
<tr>
<td>PBS</td>
<td>Ad-hoc unit record datasets</td>
</tr>
<tr>
<td></td>
<td>• PBS-listed medicines + FOD + under co-payment (2012)</td>
</tr>
<tr>
<td>PBS+</td>
<td>Unit record</td>
</tr>
<tr>
<td></td>
<td>• MBS</td>
</tr>
<tr>
<td></td>
<td>• Hospitalisations</td>
</tr>
<tr>
<td></td>
<td>• Emergency department visits</td>
</tr>
<tr>
<td></td>
<td>• Cancer notifications</td>
</tr>
<tr>
<td></td>
<td>• Residential aged care admissions</td>
</tr>
<tr>
<td></td>
<td>• Cause of death</td>
</tr>
</tbody>
</table>
## More realities

<table>
<thead>
<tr>
<th>Collection</th>
<th>Scope</th>
<th>Pain Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>DUSC</td>
<td>Aggregated</td>
<td>+++</td>
</tr>
<tr>
<td></td>
<td>- PBS + under co-payment + private scripts</td>
<td>------------</td>
</tr>
<tr>
<td>IMS</td>
<td>Aggregated</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>- Prescription + OTC</td>
<td>------------</td>
</tr>
<tr>
<td>10% PBS sample</td>
<td>Standardised unit record dataset</td>
<td>++</td>
</tr>
<tr>
<td></td>
<td>- PBS-listed medicines + FOD</td>
<td>------------</td>
</tr>
<tr>
<td>PBS</td>
<td>Ad-hoc unit record datasets</td>
<td>+++</td>
</tr>
<tr>
<td></td>
<td>- PBS-listed medicines + FOD + under co-payment (2012)</td>
<td>------------</td>
</tr>
<tr>
<td>PBS+</td>
<td>Unit record</td>
<td>++++++++++</td>
</tr>
<tr>
<td></td>
<td>- MBS</td>
<td>++++++++++</td>
</tr>
<tr>
<td></td>
<td>- Hospitalisations</td>
<td>++++++++++</td>
</tr>
<tr>
<td></td>
<td>- Emergency department visits</td>
<td>++++++++++</td>
</tr>
<tr>
<td></td>
<td>- Cancer notifications</td>
<td>++++++++++</td>
</tr>
<tr>
<td></td>
<td>- Residential aged care admissions</td>
<td>++++++++++</td>
</tr>
<tr>
<td></td>
<td>- Cause of death</td>
<td>++++++++++</td>
</tr>
</tbody>
</table>
Medicines safety study?

<table>
<thead>
<tr>
<th>Approvals</th>
<th>Whole-of-Population Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jurisdictions</td>
<td>9</td>
</tr>
<tr>
<td>Agencies</td>
<td>15+</td>
</tr>
<tr>
<td>Data collections</td>
<td>30+</td>
</tr>
<tr>
<td>Statutes</td>
<td>30+</td>
</tr>
<tr>
<td>Data custodians</td>
<td>25+</td>
</tr>
<tr>
<td>HRECs</td>
<td>10+</td>
</tr>
</tbody>
</table>

Adapted from Judy Allen, UWA
What do we know?

- Routine monitoring
- PBS data as a pharmacoepidemiology resource
  - Systematic review (1987-2013)
  - Published research: R/PBS claims
  - Methods
    - Medline, Pre-Medline, Embase, key authors, back references
    - Reviewed 3000+ abstracts
    - Eligible studies: extracted research and medicines focus, analytical approach (claims versus individual-level)
25 years of effort........
Study focus

<table>
<thead>
<tr>
<th>No. publications</th>
<th>Claims-level</th>
<th>Individual-level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug utilisation</td>
<td>80</td>
<td>0</td>
</tr>
<tr>
<td>Clinician practices</td>
<td>40</td>
<td>0</td>
</tr>
<tr>
<td>Patient practices</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>Intervention impacts</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>Drug use &amp; outcomes</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>Methods</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Drug use and outcomes studies

- 8 ecological approach (claims level analysis)
- 25 linked individual level analysis
  - All published post-2007
  - 21 safety focus
    - 4 drug use in pregnancy
    - 5 NSAIDs
    - 5 antipsychotics
  - More than half in DVA clients
  - Study quality?
  - Impact on clinical or policy practice?
Stark realities

DVA treatment population projections

<table>
<thead>
<tr>
<th>Year</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012</td>
<td>233,800</td>
</tr>
<tr>
<td>2013</td>
<td>222,500</td>
</tr>
<tr>
<td>2014</td>
<td>211,000</td>
</tr>
<tr>
<td>2015</td>
<td>199,800</td>
</tr>
<tr>
<td>2016</td>
<td>189,100</td>
</tr>
<tr>
<td>2017</td>
<td>179,000</td>
</tr>
<tr>
<td>2018</td>
<td>169,700</td>
</tr>
<tr>
<td>2019</td>
<td>161,100</td>
</tr>
<tr>
<td>2020</td>
<td>153,300</td>
</tr>
<tr>
<td>2021</td>
<td>146,300</td>
</tr>
<tr>
<td>2022</td>
<td>140,100</td>
</tr>
</tbody>
</table>
Nordic experience (2005-2010)

Punching below our weight!!!

- Despite global leadership in pharmaceutical policy
- No comprehensive population-based, post-market evaluation framework
  - Limited, fragmented research to date
  - Linking medicines use to outcomes particularly problematic
- Not all bad news
1000 flowers blooming

• Opportunism to careful planning
• More timely, comprehensive data access
  – National Collaborative Research Infrastructure Strategy
  – Post-market surveillance budget initiatives (DoHA, NPS)
  – Integrating Authorities (cross-jurisdictional linkages)
  – Large cohort studies – 45 and Up, ALSWH
  – SURE (improved data security and privacy protection)
CRE in Medicines and Ageing

• Building
  – Evidence base and strengthening translation
  – Data infrastructure and strong data governance
  – Collaborations
  – Talent

• Research themes
  – Judicious use of medicines
  – Medicines safety
  – Real-world costs and cost-effectiveness

› More than the sum of the parts………..
The crux of the matter......

Australian Broadcasting Corporation (ABC) *Catalyst* program

- Aired in October 2013
- Claimed the link between cholesterol and heart disease a myth; benefits of statins overstated, harms downplayed
- ~1 million viewers
- Concerns raised about health effects of program
ABC TV show Catalyst could cause 3000 heart attacks

Professor urges ABC to pull Catalyst episode on cholesterol drugs, says it could result in deaths

ABC's Catalyst program on cholesterol will kill people: Dr Norman Swan

Who do you trust, your GP or the TV?

Keep taking cholesterol medication

The National Heart Foundation of Australia is urging people not to change their medication or ignore their cholesterol levels following ABC media reports questioning the benefits of statins in the treatment of heart disease.
Objectives

- Quantify the impact of Catalyst on statin dispensing and discontinuation;
- Determine whether the impact varied by background risk of cardiovascular events
Data

• Standardised dataset of a 10% random sample of PBS beneficiaries and their dispensing history
  • 1 July 2009 to 30 June 2014

• Restricted to population with complete capture of dispensing: concessional beneficiaries for entire period

• Included all PBS-listed statins: atorvastatin, fluvastatin, pravastatin, rosuvastatin, simvastatin, and combination products

• Proton pump inhibitors: comparison group
Methods

- Outcomes
  - Weekly dispensing
  - Weekly discontinuation: no dispensing for a period of 3 times (30 days + 5-day grace period)

- Interrupted time series analysis

- Used autoregressive integrated moving average (ARIMA) approach to account for seasonality, long-term trends and autocorrelation

- Stratified analysis by risk categories
  - Defined using dispensing of other medicines to treat cardiovascular disease and diabetes
Results

• 191,833 people dispensed statins during the study period
  • Mean age = 72 years (standard deviation 12 years)
  • 55% female

• Prior to Catalyst there was a weekly average of:
  • 27,536 statin dispensings
  • 576 people who discontinued

• Risk categories
  • 13%: no other cardiac or diabetes medicines
  • 25%: 1-2 other cardiac medicines/no diabetes medicines
  • 36%: ≥3 other cardiac medicines/no diabetes medicines
  • 27% dispensed diabetes medicines
Results – Overall dispensing, accounting for seasonal fluctuations

- Statins
- PPIs

Catalyst program aired
## Results – Overall dispensing

<table>
<thead>
<tr>
<th>Population</th>
<th>Weekly % change (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>-2.6 (-3.8 to -1.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No cardiac or diabetes medicines</td>
<td>-6.0 (-8.3 to -3.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1-2 cardiac medicines</td>
<td>-2.8 (-4.5 to -1.1)</td>
<td>0.002</td>
</tr>
<tr>
<td>3+ cardiac medicines</td>
<td>-2.4 (-3.3 to -1.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes medicines</td>
<td>-1.9 (-3.5 to -0.4)</td>
<td>0.01</td>
</tr>
</tbody>
</table>
Results

- Extrapolated to the Australian population, in the 36 weeks after the program aired there were an estimated:
  - 14,000 fewer statins dispensings per week
  - 61,000 people discontinued, did not initiate, or reduced their statin use
Summary

• Immediate and sustained decrease in statin dispensing

• Statin dispensing has not returned to expected levels as of June 2014

• Statin dispensing decreased even in individuals at high risk of cardiovascular events

• With an estimated >60,000 fewer statin users than expected, potential for additional heart attacks or strokes

• ABC withdrew the program following an independent review, which found that it had breached impartiality standards
‘Demonstrates the substantial impact of the media on health behaviour, and emphasises the need for balanced and informed reporting’
Andrea Schaffer from the University of Sydney's Faculty of Pharmacy

Posted 15 Jun 2015, 12:01am
The POPPY Research Programme

- Better understand population-level opioid use (including potential misuse), costs, harms
- Leverage from multiple data national data sources
- Improved tools for post-market surveillance
First steps

- Ecological analysis using publically available data over 20 years period
  - 15 fold increase in PBS-subsidised opioids
  - Costs to government $8.5 to $271 million
  - Increase in opioid related hospitalisation
  - Increase in death due to accidental poisoning
Total community use of prescribed opioids

*Excludes pethidine and tapentadol

Karanges et al, Twenty-five years of prescription opioid use in Australia: A whole-of-population analysis using pharmaceutical claims, *British Journal of Clinical Pharmacology* (Accepted for publication)
What about ‘misuse’?

- Defining the problem using person-level dispensing data
- 52 studies
- Four proxies (alone or in combination): # prescribers, # dispensing pharmacies, early refills, volume dispensed
- 89 unique measures
- Heterogeneity
- Thresholds/dichotomising
- Validation?
Reflections

• Pharmcoepidemiology an emerging field internationally
• Rules of the road are not well established
  – ‘Adolescence’
  – Limited experience so accident-prone
  – Cautious optimism
• Need to share successes and failures – it’s a team sport!!!
• Need to realise return on investment in pharmacoepidemiology
• Capacity building is the key
Questions?