Drug Safety in P(a)ediatrics
Shifting from Catching Up to Moving Forward
Michael Rieder MD Ph.D
CIHR-GSK Chair in Paediatric Clinical Pharmacology
Conflict of Interest Disclosures

Dr. Michael Rieder

- I have had in the past 3 years, a financial interest, arrangement or affiliation with the following organizations that could be perceived as a direct or indirect conflict of interest in the content of this presentation.
  - CIHR-GSK Chair in Paediatric Clinical Pharmacology
  - President, Canadian Society of Pharmacology and Therapeutics
  - Member, Human Drug Advisory Panel, Health Canada
  - Member, Drug Therapy Committee, Canadian Paediatric Society
  - Editorial Board, *Paediatrics and Child Health, British Journal of Clinical Pharmacology*
Objectives

- **Expert**
  - to describe the burden of adverse drug reactions in children
  - to identify risk factors for adverse drug reactions and how they apply to specific groups of children

- **Scholar**
  - to identify new directions in the evaluation and diagnosis of adverse drug reactions
  - to identify new trends in therapeutics and their potential impact on adverse drug reactions
“Pediatrics does not deal with miniature men and women, with reduced doses and the same class of diseases in smaller bodies, but ... it has its own independent range and horizon and gives as much to general medicine as it receives from it.

- Abraham Jacobi, 1889
The Ideal Medication

- Effectively treats or prevents disease
- Has no adverse events
The reality

• Drugs are never safe and effective in all patients
• Variability in patient response can have serious consequences
Context

• Drug use in children
• Myths
  – Drugs are not commonly used in the care of children
  – When they are used, antibiotics are essentially the only drugs used
Some Inconvenient Truths

• Perception - Rare
• Fact - Common
  – In an average year, the average Canadian child is prescribed 3.9 prescriptions; the average US child 3.6 prescriptions in a year
    • Paed Child Health 2003; 8 Suppl A
• Perception - Only antibiotics
• Fact - Many drugs/drug classes
  – Among a cohort of 1,000,000 Canadian children in a year, more than 1,200 different drugs were prescribed
    • Paed Child Health 2003; 8 Suppl A

---

<table>
<thead>
<tr>
<th>Both sexes</th>
<th>Under 18 years</th>
<th>18–44 years</th>
<th>45–64 years</th>
<th>65 years and over</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>20.5</td>
<td>31.3</td>
<td>54.8</td>
<td>73.6</td>
</tr>
<tr>
<td></td>
<td>23.8</td>
<td>35.9</td>
<td>64.1</td>
<td>84.7</td>
</tr>
<tr>
<td></td>
<td>24.7</td>
<td>37.4</td>
<td>65.2</td>
<td>89.4</td>
</tr>
<tr>
<td></td>
<td>23.5</td>
<td>38.1</td>
<td>67.2</td>
<td>89.8</td>
</tr>
<tr>
<td></td>
<td>2.4</td>
<td>5.7</td>
<td>20.0</td>
<td>35.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8.4</td>
<td>30.8</td>
<td>51.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10.6</td>
<td>62.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

Western
**TABLE 1**
Distribution of claimants and prescriptions and number of prescriptions per claimant for selected therapeutic areas

<table>
<thead>
<tr>
<th>Therapeutic class</th>
<th>Distribution of claimants</th>
<th>Distribution of prescriptions</th>
<th>Prescriptions per claimant</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of Claimants</td>
<td>Share of total claimants</td>
<td>Number of prescriptions</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>780,684</td>
<td>76%</td>
<td>1,740,446</td>
</tr>
<tr>
<td>Respiratory drugs</td>
<td>182,271</td>
<td>18%</td>
<td>522,216</td>
</tr>
<tr>
<td>Analgesics and anti-inflammatory drugs</td>
<td>84,024</td>
<td>8%</td>
<td>116,005</td>
</tr>
<tr>
<td>Acne drugs</td>
<td>72,504</td>
<td>7%</td>
<td>223,700</td>
</tr>
<tr>
<td>Contraceptives</td>
<td>40,512</td>
<td>4%</td>
<td>194,796</td>
</tr>
<tr>
<td>Stimulants</td>
<td>33,882</td>
<td>3%</td>
<td>161,184</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>16,731</td>
<td>2%</td>
<td>64,929</td>
</tr>
<tr>
<td>Antipsychotic agents</td>
<td>3,873</td>
<td>0.4%</td>
<td>20,023</td>
</tr>
<tr>
<td>Anti-convulsant agents</td>
<td>6,409</td>
<td>0.6%</td>
<td>46,261</td>
</tr>
<tr>
<td>Gastrointestinal agents</td>
<td>16,267</td>
<td>2%</td>
<td>40,299</td>
</tr>
<tr>
<td>Antidiabetic drugs</td>
<td>3,583</td>
<td>0.3%</td>
<td>41,682</td>
</tr>
<tr>
<td>All drugs (total)</td>
<td>1,031,731</td>
<td>100%</td>
<td>4,028,502</td>
</tr>
</tbody>
</table>

*The sum of claimants by therapeutic class exceeds the total 1.03 million claimants because some claimants were dispensed drugs from more than one therapeutic class.*
Double Edged Sword

- A blade with two sharp edges
- A term used to describe a situation in which good or bad effects
- Roots from Arabic (sayf ǧū ḥadayn, “double-edged sword”) and Biblical origins as to the Word of God (Hebrews 4:12)” Sharper than any double-edged sword, it penetrates even to dividing soul and spirit, joints and marrow”
- Applies to the beneficial and adverse effects of medication (NEJM)
Pre-Market

Global Product Development ... safety, quality, efficacy, therapeutic effectiveness, cost-effectiveness ... Access by providers and patients and parties through the health care system

Post-Market

Surveillance, inspection, investigation for safety and regulatory compliance

- Pre-Clinical Studies
- Clinical Trials
- Regulatory Product Submission
- Submission Review
- Market Authorization by Health Canada (NOC, NOC-c, NON)
- Labelling (including the product monograph)
- Summary Basis of Decision
- Marketing Decision by Drug Companies
- Price Review (PMPRB)
- Common Drug Review (CADTH)
- Public and private drug plans/policies
- Listing & reimbursement decisions
- Patient Access/Real World Use
- Patient-Provider Interactions
- Prescribing practices (including off-label use)
- Therapeutic & cost-effectiveness studies (clinical trials, research, etc.)
- Information for clinicians and patients
- Collection and communication of ADRs and other post-market information
- NPDUIS COMPUS
- Withdrawal of products from Marketplace by regulator or company
Life-Cycle of Product and Knowledge

- Drug Discovery
- Pre-clinical Studies
- Clinical Trials
- Drug Submissions
- License
- Submission Review
- Extraordinary Needs
- Clinical Trial Review
- Health Canada Regulatory Role
- Pharmacovigilance
- Early Post-Market Period
- Increasing Knowledge
- Re-evaluation of Benefit-risk
- Evolution of Products and Knowledge
- Removal of Product
- Monitoring and Intervention
1. Clinical trials provide evidence of efficacy and safety at usual doses in populations.

2. Physicians treat individual patients who can vary widely in their response to drug therapy.

- Efficacious & Safe
- No Response
- Efficacious & Safe
- Adverse Drug Reaction
An ADR is an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dose regimen, or withdrawal of the product

Adverse Drug Reactions

- 4th leading cause of death in the USA\(^1\)
- Health care costs: $137-177 billion annually (USA)\(^2-3\)
- Cause 7% of all hospital admissions\(^4\)
- Cause serious reactions in over 2,000,000 hospitalized patients (6.7%) each year in the USA\(^1\)
- Cause fatal reactions in over 100,000 hospitalized patients each year in the USA\(^1\)
- 95% of all ADRs are unreported

Yet nowhere is this reported

Why?

Nosology
• 6 year old child presents with nephroblastoma; following surgery undergoes chemotherapy including ifosfomide
• During chemotherapy it is noted that there is evidence of renal injury including aminoaciduria
• Over the next 10 years following therapy there is no evidence of tumour recurrence
• During these 10 years there is progressive decline in renal function to the point where dialysis is needed
• While waiting renal transplant the patient expires of complications of end-stage renal failure
• Cause of Death?
Nephroblastoma

• This seems somewhat paradoxical as the tumour had been, by all accounts, successfully eradicated
• It would be reasonable to assume that the treated team of oncologists did not desire or plan for this outcome
• This nosological anomaly is one of the reasons that ADRs are under-estimated in their impact on child health
Cultural Issues
Risk Factors for ADRs

• History of a previous ADR
• Large drug doses
• Polypharmacy
• Impairment of the organs of excretion (hepatic or renal dysfunction)
• Extremes of age
• Female sex
• Specific genetic polymorphisms
• General Anaesthesia
  • *Pediatr Clin North Am* 2012
Are ADR Rates in Children Difference than those in Adults?

• Has been relatively little data with respect to ADRs in children compared to adults
• What data is present suggests that overall rates may be similar
• In some circumstances, controversy as to whether risks may be lower or in fact may be higher; despite the impression, when actual data is reviewed risks are never lower and often higher
• In some groups of children and for some conditions, the risk of an adverse drug event is nearly 100%
  – *BMC Med* 2013 Nov 7;11:237
Drug Safety

• For many years pharmacovigilence was conducted using passive surveillance involving data capture by regulatory agencies
• This approach resulted in serious adverse events being recognized by regulatory authorities many years after they had been recognized in the peer reviewed literature
• This approach also is associated with serious under-reporting of adverse drug events
Tragedies Over Time
Pemoline Induced Hepatic Injury

- Pemoline is a CNS stimulant used in the therapy of ADHD
- Entered the US market in 1975
- Withdrawn 30 years later
- However, an active search of the literature clearly demonstrated increased risk for hepatic injury – as early as 1978
Fig. 1. Cumulative chart of children developing acute liver failure after receiving pemoline (cases from the US FDA and the medical literature for the period 1975–98).
Progress Over Time

- There has been slow but steady progress on improving drug dosing and drug safety in children, largely in the area of dosing and largely driven by academic investigators and enhancing our understanding of developmental pharmacology
  - Once-daily gentamicin in NICU
  - Identification of unique risks in children
    - Valproic acid hepatotoxicity
    - Cefaclor serum sickness like reactions
      - *Drug News & Perspectives* 2010, 23(7)
At-Risk Populations

- Neonates, especially premature neonates
- Children with cancer
- Children with complex chronic disease
- Children in the PICU
- Toddlers

— *Eur J Clin Pharmacol* 2012;68(5):801-10
ADRs Classification & Epidemiology

According to the Nomenclature Review Committee of the World Allergy Organization:

- **Type A (Augmented)**: 80-90%
- **Type B (Bizarre)**: 10-20%

**Idiosyncrasy**

**Type C**

**Type D**

**Gell and Coombs**

- Type I
- Type II
- Type III
- Type IV

**Hypersensitivity reactions (DHRs)**

- Phases I and/or phase II metabolism abnormalities
- Abnormalities in target organ

**Causes**

- Pharmacokinetics
- Pharmacodynamic
- Genetic

**DHRs**

- Drug Allergic Reactions
- Non-immune DHRs

**If definite immunological mechanism, either IgE or T-cell, is demonstrated**

**If clinically resemble an allergy, but immun. Process is not proven**

**Incidence unknown**: 1:1000 – 1:10,000

**Non-immune**
Special Cases in Children

• Drug Substitution
• 10 fold errors
  – Unique problem in Paediatrics
  – More common among certain staff
  – May be addressed by EMRs

• Drug Errors
  – Probably more common in children than adults
  – Again, may be more common among certain staff
  – May be addressed by EMRs but there is no data that EMRs actually make drug therapy safer for children
Special Issues

• Much of the ADR literature in children has focused on adverse events related to ontogeny.
• It is well appreciated that premature infants are at a substantially increased risk for adverse events compared to older children and adults.
• What is less appreciated is that some activation-induced events occur at substantially higher rates in toddlers and pre-school children.

Off-Label Use

• Many studies on off-label/unlicensed use of drugs in children
• Almost all of them are incidence or utilization studies
• Off-label drug use is actually quite common, even among adults
• However, off-label drug use in adults is often guided by evidence
Table 5  ADR risk factors assessed by multivariate analysis

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Female</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Female</td>
<td>1</td>
<td>0.152</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>0.896 (0.770, 1.042)</td>
<td></td>
</tr>
<tr>
<td>Age on admission (years)</td>
<td>1.036 (1.021, 1.052)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Received a GA</td>
<td>No</td>
<td>1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>5.295 (4.417, 6.349)</td>
<td></td>
</tr>
<tr>
<td>Oncology</td>
<td>No</td>
<td>1</td>
<td>0.655</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>0.926 (0.661, 1.298)</td>
<td></td>
</tr>
<tr>
<td>Number of authorised medicines</td>
<td>1.217 (1.171, 1.263)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Number of off-label and/or unlicensed medicines</td>
<td>1.267 (1.201, 1.336)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Number of uncategorised medicines</td>
<td>1.138 (0.969, 1.338)</td>
<td>0.116</td>
<td></td>
</tr>
</tbody>
</table>
Paediatric Investigation Plans

Data on efficacy, safety and quality (formulation, dosage form), Timelines (ref ICH guideline E11)

In practice, discussion on potential paediatric use and unmet needs to decide on the development and formulation for each age group, from birth to 18 years.

Formulations

Toxicology, Pharmacology, Juvenile Animals studies

Safety, Proof concept

Dose finding PK

Efficacy

Safety issues...

FDA Guidance for Pediatric Studies
Pediatric Study Decision Tree - Integration of PK-PD

Reasonable to assume (pediatrics vs. adults)
• Similar disease progression?
• Similar response to intervention?

NO

YES TO BOTH

Is there a PD measurement that can be used to predict efficacy?

NO

YES

Conduct PK studies
• Conduct safety/efficacy trials

Conduct PK studies to achieve levels similar to adults
• Conduct safety trials

Conduct PK studies to get C-R for PD measurement
• Conduct PK studies to achieve target concentrations based on C-R

Pediatric Pharmacology Research Network (PPRU)
ADR Case Detection

Biologically plausible mechanism

Temporal Response

Dose-response Relationship

Clinically detectable effect

• ADR Probability
  - possible, probable, definite (using WHO scale)
  - Naranjo scale
A coding variant in RARG confers susceptibility to anthracycline-induced cardiotoxicity in childhood cancer


Affiliations | Contributions | Corresponding author

Nature Genetics 47, 1079–1084 (2015) | doi:10.1038/ng.3374
Received 25 December 2014 | Accepted 10 July 2015 | Published online 03 August 2015

Cardiotoxicity highest in first year but continues to increase over time in high risk groups

$P_{\text{trend}} = 6.7 \times 10^{-25}$

High Risk (17%)
Intermediate Risk (37%)
Low Risk (46%)

J Clin Oncol 2012 May 1;30(13):1422-8
Pathophysiology of DHRs – The Reactive metabolite Hypothesis

Drug Bioactivation

A = Activation
D = Detoxification

Antigen processing and presentation

The p-I Hypothesis

T-cell Activation

The reactive metabolite Hypothesis

Necroptosis

The danger Hypothesis

The hapten Hypothesis

Modified from: Elzagallaei et al., J Popul Ther Clin Pharmaco, 2011
### TABLE 6
Rate of use of the new drugs in the therapeutic area for both paediatric and adult claimants

<table>
<thead>
<tr>
<th>Drug</th>
<th>Rate per 1000 active claimants</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Paediatric Claimants</td>
<td>Adult Claimants</td>
<td></td>
</tr>
<tr>
<td>Celecoxib</td>
<td>27</td>
<td>210</td>
<td></td>
</tr>
<tr>
<td>Citalopram</td>
<td>59</td>
<td>93</td>
<td></td>
</tr>
<tr>
<td>Rofecoxib</td>
<td>17</td>
<td>207</td>
<td></td>
</tr>
<tr>
<td>Bupropion</td>
<td>85</td>
<td>162</td>
<td></td>
</tr>
<tr>
<td>Montelukast sodium</td>
<td>49</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>Formoterol fumarate</td>
<td>4</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>1</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Tazarotene</td>
<td>6</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Zarfirlukast</td>
<td>2</td>
<td>14</td>
<td></td>
</tr>
</tbody>
</table>
Big Data in Life Sciences*

- Sequencing and gene expression data
- Drug data (pathways, structure etc.)
- Clinical Trial & Hospital Electronic Record data
- In vitro diagnostics & X-ray results
- Patient self-reported and social media data
- Telemedicine data

- Drug repurposing
- New biomarkers
- New drug targets
- Personalized healthcare
- Adverse event detection
  Etc.

*This and the following nine slides contributed by Edward Currie, AVP Life Sciences, Infosys

Prescription (Rx) data
Social media analytics

Identify otherwise unreported drug side-effects/interactions

Drug safety

BIG DATA ANALYSED  INSIGHT DELIVERED  STRATEGY ENABLED
The Future

<table>
<thead>
<tr>
<th>Small Molecule Drug</th>
<th>Large Molecule Drug</th>
<th>Large Biologic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>hGH</td>
<td>IgG Antibody</td>
</tr>
<tr>
<td>21 atoms</td>
<td>~ 3000 atoms</td>
<td>~ 25,000 atoms</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Size</th>
<th>Complexity</th>
<th>Complexity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>Bike</td>
<td>~ 20 lbs</td>
</tr>
<tr>
<td>~ 3000 atoms</td>
<td>Car</td>
<td>~ 3000 lbs</td>
</tr>
<tr>
<td></td>
<td>Business Jet</td>
<td>~ 30,000 lbs (without fuel)</td>
</tr>
</tbody>
</table>
Acknowledgments
mrieder@uwo.ca

- Dr. t’Jong. ASCPT Leadership and Staff
- Drs. Ralph Kauffman, Stuart MacLeod, Stephen Spielberg
- CIHR-GSK Chair in Paediatric Clinical Pharmacology
- CIHR/DSEN/NIH/PSI Foundation/CHRI
- London
  - Dave Knoppert, Drs. Koren, Tirona, Kim, Matsui, Bend, Dresser, Hackam, Railton, Gryn
  - Anda Marcu, Thu Chau, Lauren Hanly, Lauren Kelly, Evan Russel, Justin Chan, Abdelbaset Elzagallaai, Kemi Adeyanju, Blanca del Pozza, Becky Malkin, Paula Huegin, Mike Greff, Fatma Ethwal, Venita Harris
- USA
  - Drs. Mike Reed, Greg Kearns, John van den Anker, Steven Leeder, Sander Vinks
- UK
  - Drs. Purmohammed, Nesbitt, Smyth, Nunn, Choonara and Simmons
- Vancouver (CPNDS Network)
  - Drs. Bruce Carleton/Michael Hayden