Watch the time: complex modelling of time-varying drug exposure

Will Dixon, on behalf of Michal Abrahamowicz

Support: Canadian Institutes for Health Research (CIHR) grant MOP 81275
Objectives

• Challenges in assessing the impact of past and current drug doses

• Introduce a new statistical method to assess the effects of time-varying treatments

• Illustrate the ability of the proposed new methods to yield new insights
2009-2010
Fall 2013

Timetable [.pdf]

+ EPIB 507 Biostatistics for Health Professionals
+ EPIB 525 Health Care Systems in Comparative Perspective
+ EPIB 527 Economics for Health Services Research and Policy - Not offered in 2013/2014
+ EPIB 528 Economic Evaluation of Health Programmes - Not offered in 2013/2014
+ EPIB 591 Regression Analysis for Health Professionals
+ EPIB 601 Fundamentals of Epidemiology
+ EPIB 602 Foundations of Population Health
+ EPIB 604 Epidemiologic Analysis
+ EPIB 607 Inferential Statistics
+ EPIB 609 Seminar on Advanced Methods in Epidemiology - Not offered in 2013/2014
+ EPIB 613 Introduction to Statistical Software - Not offered in 2013/2014
+ EPIB 623 Research Design in Health Sciences
+ EPIB 624 Public Health Ethics and Policy
+ EPIB 628 Measurement in Epidemiology
+ EPIB 630 Public Health Project
+ EPIB 641 Principles in Study Design
+ EPIB 648 Methods in Social Epidemiology

+ EPIB 676 Advanced Modeling of Survival and Other Multivariable Data
+ EPIB 677 Knowledge Synthesis - NEW COURSE
+ EPIB 682 Introduction to Bayesian Analysis in Health Sciences - NEW COURSE
Michal Abrahamowicz
Benzodiazepines and falls

Doses of flurazepam in elderly subjects in Quebec
Importance of Accounting for TIMING in Statistical Analyses of Adverse Effects of Medications

1. Drug use and dose varies both across the users and over time
2. Risks (as well as benefits) associated with a specific drug depend on the dose, duration & timing of treatment
3. Understanding how past dosage history affects the current risk may help ‘Rationalize’ the PRESCRIBING PRACTICE to Achieve ‘Optimal TRADE-OFF between Therapeutic BENEFITS Vs RISKS of Adverse Reactions’

[ *** DRUGS are Prescribed BECAUSE They HELP -> Simply Banning them because of Adverse Reactions is (usually) NOT a (rational) Option !!

➢ In Contrast: IF we can design relatively “safe” Patterns-of-Use then the RISKS can be Considerably Reduced while still offering Therapeutic Benefits]
Conceptual and Analytical Challenges in Modeling Effects of Time-Varying Exposures

- **Challenge:**
  to Assess ‘current’ Relative Risk at time $T$ as a Function of the History of Past Drug Doses $[X(0); X(1); ....X(t).... for 0<t\leq T ]$

- **2-Step Solution:**
  1. Define Time-Dependent covariate $M(T)$ representing Current Value of an ‘Etiologically Correct Exposure Metric’ that Aggregates the information on Past Doses/Exposures:
     $M(T) = f [X(1), X(2),..., X(T-1), X(T)]$
  2. Use standard regression methods to Estimate Relative Risks associated with $M(T)$
Many challenges, including **dynamic pattern of use**
Oral GC

Time from presentation (years)

GC therapy (prednisolone equivalent mg)

Disease severity (DAS28)

Intra-muscular GC

Intra-articular GC

Oral GC

80

80

80

80

80

80
Intra-muscular GC

Intra-articular GC

Current dose = 10mg
Recent dose = 10mg
Cumulative (average) dose = 8.75mg

Time from presentation (years)

Disease severity (DAS28)

Infection
Conventional model assumptions

• Current dose
  – Treatment taken today important, but yesterday of no importance

• Recent dose (e.g. 30 days)
  – Treatment taken 29 days ago important, but 31 days ago of no importance

• Peak dose
  – Highest dose is the only dose of interest, irrespective of when it was taken

• Average/ cumulative dose
  – Doses taken 3 years ago as important as doses yesterday
Need to Assess CUMULATIVE Effects

• Our work was motivated by the beliefs that:
  (1) the Effects of Past Exposure to Medications often Cumulate over Time
  (2) Yet, in real-life studies it is Not clear:
  what is the Relative Importance of Exposures that occurred at different times in the past?
  (e.g. 2 days versus 2 months ago)
Based on above considerations, we propose:

recency-Weighted Cumulative Exposure (WCE) model, where the Cumulative Effect of Exposure History is modeled as a Weighted Sum (**) of all Past Doses,

(**) with Weights representing the Relative Importance of Doses (Exposures) as a function of the Time Elapsed since the Exposure
where:

\[ WCE(u) = \sum_{t \leq u} w(u - t) \times X(t) \quad (1) \]

\[ WCE(u) = Weighted\ Cumulative\ Effect\ of\ the\ Past\ Doses\ on\ Risk\ at\ time\ u \]

\[ X(t) = Dose\ at\ time\ t\ (t \leq u) \]

\[ u-t = Time\ elapsed\ since\ Dose\ X(t)\ was\ received \]

\[ w(u-t) = Weight\ (Relative\ Importance)\ assigned\ to\ Dose\ X(t)\ as\ a\ function\ of\ Time\ Elapsed\ (u-t) \]

Example of two Sigmoidal Weight Functions

From Abrahamowicz et al. (2006, Journal of Clinical Epidemiology, Figure 1)
Hypothetical example of calculating cumulative weighted exposure WCE

<table>
<thead>
<tr>
<th>$t$</th>
<th>$X(t)$</th>
<th>$u-t$</th>
<th>$w(u-t)$</th>
<th>$w(u-t) \times X(t)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>23</td>
<td>0.5</td>
<td>7</td>
<td>0.50</td>
<td>0.25</td>
</tr>
<tr>
<td>24</td>
<td>0.5</td>
<td>6</td>
<td>0.60</td>
<td>0.30</td>
</tr>
<tr>
<td>25</td>
<td>0.5</td>
<td>5</td>
<td>0.70</td>
<td>0.35</td>
</tr>
<tr>
<td>26</td>
<td>0.5</td>
<td>4</td>
<td>0.80</td>
<td>0.40</td>
</tr>
<tr>
<td>27</td>
<td>0.5</td>
<td>3</td>
<td>0.88</td>
<td>0.44</td>
</tr>
<tr>
<td>28</td>
<td>0.5</td>
<td>2</td>
<td>0.94</td>
<td>0.47</td>
</tr>
<tr>
<td>29</td>
<td>1.5</td>
<td>1</td>
<td>0.99</td>
<td>1.48</td>
</tr>
<tr>
<td><strong>30</strong></td>
<td>1.5</td>
<td>0</td>
<td>1.00</td>
<td><strong>1.50</strong></td>
</tr>
</tbody>
</table>

$\sum = 5.19$

$w(7 \text{ days}) = 0.5$

Weighted cumulative dose
Variation over Time of Dose $X(t)$

From Abrahamowicz et al. (2006, Journal of Clinical Epidemiology, Figure 2)
Flexible Modeling of the Weight Function

• In most real-life studies, there is Insufficient prior knowledge to determine:

• (i) Exact Shape, &

  (ii) the Exact Values of the Weight Function

• Therefore, we proposed to Estimate the Weight Function Directly from the Data, using a very Flexible method (Cubic Regression B-Splines)
  — avoids \textit{a priori} assumptions about the shape of the weight function

[Sylvestre & Abrahamowicz, Statistics-in-Medicine 2009]
Regression splines

- Smooth piecewise polynomials

Quadratic piecewise spline
The $m+p+1$ splines $B_j(x)$ of the B-spline basis

- Here the splines in the basis are cubic splines ($p=3$) and 3 interior knots were used ($m=3$)
- $f(x) = 0.6 \cdot B_1(x) + 0.6 \cdot B_2(x) + 0.6 \cdot B_3(x) + 0.9 \cdot B_4(x) + 0.4 \cdot B_5(x) + 0.2 \cdot B_6(x) + 0.2 \cdot B_7(x)$
Flexibility of cubic splines

Cubic splines, $m=3$ (0.2, 0.4, 0.7), 7 df
16 random sets of coefficients $\alpha_j$ (-1.0 ≤ $\alpha_j$ ≤ 1.0)

Slide courtesy of Michal Abrahamowicz
Estimation of the WCE model

- To estimate the Cumulative Effects of Time-Varying treatments, we include the WCE(u) as a Time-Dependent Covariate in the Cox’s proportional hazards model
- the Program in R language is available on request
  [michal.abrahamowicz@mcgill.ca]
Study population

Setting
• Quebec administrative database, 1985-2003

Inclusion
• Patients aged $\geq 65$ (drug dispensing records)
• RA code & DMARD use
Case-control design

**Serious infection cases**
- First occurrence of a primary hospital discharge diagnosis of infection (index date)

**Controls**
- Risk set identified for each case of infection
- For each case, up to five controls selected
  - matched on age, sex and duration in study
Analysis

• Several multivariable models, each representing GC exposure differently
  – 10 conventional models using multivariable conditional logistic regression
  – Novel weighted cumulative dose model

• Goodness of fit compared using Akaike Information Criteria (AIC)
Conventional models

1. Current use on the index date

Any use in

2. Previous 30 days
3. Previous 90 days
4. Any time in the past (indicator of ever exposed)

5. Current daily dose at index date
Conventional models

Average past dose over
6. Previous 30 days
7. Previous 90 days
8. Entire time since the subject’s entry into the cohort

Peak dose over
9. Previous 30 days
10. Previous 90 days
## Relationship between serious infection risk and oral GC exposure for the ten conventional models

<table>
<thead>
<tr>
<th>Model</th>
<th>OR (95% CI) **</th>
<th>OR for 5mg PEQ increase (95% CI)</th>
<th>AIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Current use</td>
<td>1.85 (1.65, 2.08)</td>
<td>---</td>
<td>5830.2</td>
</tr>
<tr>
<td>(2) Any use last 30 days</td>
<td>2.05 (1.83, 2.31)</td>
<td>---</td>
<td>5787.9</td>
</tr>
<tr>
<td>(3) Any use last 90 days</td>
<td>2.22 (1.97, 2.49)</td>
<td>---</td>
<td>5754.1</td>
</tr>
<tr>
<td>(4) Ever use</td>
<td>1.66 (1.47, 1.88)</td>
<td>---</td>
<td>5865.2</td>
</tr>
<tr>
<td>(5) Current dose</td>
<td>1.05 (1.04, 1.06)</td>
<td>1.3 (1.23, 1.36)</td>
<td>5824.9</td>
</tr>
<tr>
<td>(6) Average dose in last 30 days</td>
<td>1.08 (1.06, 1.09)</td>
<td>1.45 (1.37, 1.55)</td>
<td>5790.0</td>
</tr>
<tr>
<td>(7) Average dose in last 90 days</td>
<td>1.10 (1.09, 1.12)</td>
<td>1.63 (1.51, 1.75)</td>
<td>5753.2</td>
</tr>
<tr>
<td>(8) Average dose since study entry</td>
<td>1.09 (1.07, 1.10)</td>
<td>1.51 (1.40, 1.64)</td>
<td>5818.2</td>
</tr>
<tr>
<td>(9) Peak dose in last 30 days</td>
<td>1.04 (1.04, 1.05)</td>
<td>1.24 (1.19, 1.29)</td>
<td>5806.1</td>
</tr>
<tr>
<td>(10) Peak dose in last 90 days</td>
<td>1.04 (1.03, 1.04)</td>
<td>1.20 (1.16, 1.24)</td>
<td>5805.1</td>
</tr>
</tbody>
</table>

OR: odds ratio, adjusted for all *a priori* confounders  
AIC: Akaike information criterion  
WCD: weighted cumulative dose  
PEQ: prednisolone equivalent  
** For dose-specific models (5-10), OR represents risk per 1mg PEQ increase
Flexible weighted cumulative dose

- Far superior fit vs conventional models
  - AIC 25-150 units higher
  - AIC >10 considered very important
Table 2. Relationship between serious infection risk and oral GC exposure for the ten conventional models and the best fitting cumulative weighted dose model

<table>
<thead>
<tr>
<th>Model</th>
<th>OR (95% CI)</th>
<th>OR for 5mg PEQ increase (95% CI)</th>
<th>AIC</th>
<th>AIC – AIC of the WCD model</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Current use</td>
<td>1.85 (1.65, 2.08)</td>
<td>---</td>
<td>5830.2</td>
<td>105.4</td>
</tr>
<tr>
<td>(2) Any use last 30 days</td>
<td>2.05 (1.83, 2.31)</td>
<td>---</td>
<td>5787.9</td>
<td>63.0</td>
</tr>
<tr>
<td>(3) Any use last 90 days</td>
<td>2.22 (1.97, 2.49)</td>
<td>---</td>
<td>5754.1</td>
<td>29.3</td>
</tr>
<tr>
<td>(4) Ever use</td>
<td>1.66 (1.47, 1.88)</td>
<td>---</td>
<td>5865.2</td>
<td>140.4</td>
</tr>
<tr>
<td>(5) Current dose</td>
<td>1.05 (1.04, 1.06)</td>
<td>1.3 (1.23, 1.36)</td>
<td>5824.9</td>
<td>100.1</td>
</tr>
<tr>
<td>(6) Average dose in last 30 days</td>
<td>1.08 (1.06, 1.09)</td>
<td>1.45 (1.37, 1.55)</td>
<td>5790.0</td>
<td>65.2</td>
</tr>
<tr>
<td>(7) Average dose in last 90 days</td>
<td>1.10 (1.09, 1.12)</td>
<td>1.63 (1.51, 1.75)</td>
<td>5753.2</td>
<td>28.4</td>
</tr>
<tr>
<td>(8) Average dose since study entry</td>
<td>1.09 (1.07, 1.10)</td>
<td>1.51 (1.40, 1.64)</td>
<td>5818.2</td>
<td>93.3</td>
</tr>
<tr>
<td>(9) Peak dose in last 30 days</td>
<td>1.04 (1.04, 1.05)</td>
<td>1.24 (1.19, 1.29)</td>
<td>5806.1</td>
<td>81.3</td>
</tr>
<tr>
<td>(10) Peak dose in last 90 days</td>
<td>1.04 (1.03, 1.04)</td>
<td>1.20 (1.16, 1.24)</td>
<td>5805.1</td>
<td>80.2</td>
</tr>
<tr>
<td>(11) Final WCE (3-year with 1 knot)</td>
<td>***</td>
<td>***</td>
<td>5724.8</td>
<td>0 (minimum AIC)</td>
</tr>
</tbody>
</table>

OR: odds ratio, adjusted for all *a priori* confounders
AIC: Akaike information criterion
WCD: weighted cumulative dose
PEQ: prednisolone equivalent
** For dose-specific models (5-10), OR represents risk per 1mg PEQ increase
Flexible weighted cumulative dose

• Current and recent GC doses highest impact on risk
• Doses taken up to 2.5 years ago also associated with increased infection risk
Flexible weighted cumulative dose

Recent doses have highest impact

Relative risks with different exposure patterns

<table>
<thead>
<tr>
<th>Pattern of use</th>
<th>Reference</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current user, 5mg, for last 28 days</td>
<td>Non-user</td>
<td>1.11 (1.07, 1.26)</td>
</tr>
<tr>
<td>Current user, 5mg, for last 3 months</td>
<td>Non-user</td>
<td>1.33 (1.21, 1.46)</td>
</tr>
<tr>
<td>Current user, 5mg, for last 6 months</td>
<td>Non-user</td>
<td>1.53 (1.38, 1.75)</td>
</tr>
<tr>
<td>Current user, 5mg, for last 3 years</td>
<td>Non-user</td>
<td>2.05 (1.77, 2.32)</td>
</tr>
<tr>
<td>Current user, 30mg, for last 28 days</td>
<td>Non-user</td>
<td>1.92 (1.50, 4.05)</td>
</tr>
<tr>
<td>Past user, 5mg, for 6 months</td>
<td>Non-user</td>
<td>1.06 (0.99, 1.27)</td>
</tr>
<tr>
<td>Stopped 6 months ago</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Clinical Usefulness

• Consider an RA patient, scheduled for an elective surgery in 3 months, on (moderate) 10mg GC daily dose for the last 2 years

• GC therapy will increase the risk of serious infection (at the time of surgery) by 55% relative to STOPPING the GC therapy for the next 3 months
  – (Not considering flare and surgical outcome)
Discussion

• Risk of infection with GC varies with dose and recency
  – Current and recent doses have greatest effect
  – Cumulative effects affect risk even 2-3 years later
  – Accounting for long-term exposure improves risk prediction
  – WCD allowed estimate of risks after stopping
CONCLUSIONS

- Pharmaco-Epidemiologists should consider alternative (A Priori Clinically/Biologically Plausible) models linking time-varying drug exposure with the risk of adverse events and rely on statistical goodness-of-fit criteria to identify the model(s) most consistent with the data.


- Ultimately, the WCE model results can help unravel the (possibly complex) mechanisms linking drug exposure to adverse events and suggest how treatment regimens may be optimized to improve the Benefits/Risks ratio.
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References


