New Methods for assessing Cumulative Effects of Time-Varying Exposures: with applications in Pharmaco-epidemiology and Cardiovascular epidemiology

Does it still matter?

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OBJECTIVES

• Outline Challenges in Assessing the Joint Impact of Past and Current Exposures or Risk Factors on Health Outcomes

• Introduce New Statistical Methods to deal with these challenges

• Illustrate the ability of the proposed New Methods to yield New Insights in Longitudinal Pharmaco-Epi & Cardiovascular Epi Studies
1. Challenges in Assessing the effects of Time-Varying Risk Factors, Exposures & Treatments

2. Flexible “Weighted Cumulative Exposure (WCE)” Model

3. Applications: Adverse Effects of Medications

4. Joint modeling of Cumulative & Non-linear effects of Continuous time-varying risk/prognostic factors:
   re-assessing the impact of SBP on Cardiovascular risk

5. Conclusions and Future Challenges
2 Examples of Time-varying exposures/ risk factors
## Longitudinal (within-subject) Variation in the use of Benzodiazepines (> 40,000 elderly in Québec, Canada)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (SD)</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>observation time (days)</td>
<td>1,625.1 (407.0)</td>
<td>1,826</td>
<td>10 - 1,826</td>
</tr>
<tr>
<td>duration of hospitalization periods (days)</td>
<td>53.6 (58.8)</td>
<td>34</td>
<td>8 - 1,306</td>
</tr>
<tr>
<td>observation time excluding hospitalization (days)</td>
<td>1,595.2 (420.8)</td>
<td>1,809</td>
<td>1 - 1,826</td>
</tr>
<tr>
<td>observation time after first benzodiazepine prescription excluding periods of hospitalization (days)</td>
<td>896.5 (570.2)</td>
<td>904</td>
<td>1 - 1,826</td>
</tr>
<tr>
<td>Total Duration of benzodiazepine use (days)</td>
<td>228.6 (327.3)</td>
<td>83</td>
<td>1 - 1,826</td>
</tr>
<tr>
<td>Number of Periods of Un-interrupted Benzodiazepine Use</td>
<td>3.2 (3.3)</td>
<td>2</td>
<td>1 - 32</td>
</tr>
<tr>
<td>Average Duration of uninterrupted periods of benzodiazepine use (days)</td>
<td>75.5 (137.2)</td>
<td>31</td>
<td>1 - 1,826</td>
</tr>
<tr>
<td>Average Duration of Interruption between periods of benzodiazepine use (days)§</td>
<td>187.1 (239.9)</td>
<td>95.6</td>
<td>15 - 1,773</td>
</tr>
</tbody>
</table>
Importance of Accounting for TIMING in Statistical Analyses of Effects of Medications

- In Clinical Practice, Drug use and Doses Vary both (i) Between the users & (ii) Within-user Over time
- Risks (as well as benefits) associated with a specific drug likely depend on the dose duration & timing of treatment


- for any given drug: Relationships between Past Dosage/Use and Risk of an Adverse Event (AE) likely varies between different types of Adverse Events identified e.g. in the WHO classification


(A) Immediate (known mechanism); (B) Idiosyncratic ; (C) Cumulative (chronic use); (D) Long-Delayed e.g. Teratogenic or Carcinogenic; (E) Drug Interactions
Conceptual and Analytical Challenges in Modeling Effects of Time-Varying Exposures

- **Challenge:**
  to Assess ‘current’ Relative Risk (RR) at time \( T \) as a Function of the History of Past Drug Doses \([X(t) \text{ for } 0<t\leq T]\):
  \[ \text{RR} \left[ T | X(1), X(2), \ldots, X(T-1), X(T) \right] ? \]

- **2-Step Solution:**
  1. Define Time-Dependent covariate \( M(T) \) representing Current Value of an ‘Etiologically Correct Exposure Metric’:
     \[ M(T) = f [X(1), X(2), \ldots, X(T-1), X(T)] \]
  2. Use standard regression methods to Estimate RR associated with \( M(T) \)
How the History of Drug Use is modeled in current Pharmaco-Epidemiologic research?

- Most current published Observational Population-based studies of Drug Safety or Effectiveness rely on very simple *Ad Hoc, Arbitrarily defined* ‘Conventional’’ Exposure Models, e.g.:
  - Current Use
  - Current Dose
  - Any Use in an Arbitrary Time Interval in the Past (e.g. last month or last 3 months…)
  - Total Duration of Past Use
  - (Cumulative) Sum of All Past Doses:
Example of Arbitrary Definitions of M(T) in Different Phramaco-epi studies of the SAME association

- Alternative models used in studies of Glucocorticoids use Vs. risk of Infections:
  - ‘Current use’
  - ‘Recent use’
  - ‘Ever use’
  - ‘Total past dose’

Why Pharmaco-Epidemiologic studies need to use ‘etiollogically correct’ exposure metrics?

- Yet, Different Exposure Models are mutually Incompatible and only One of these models may be ‘etiollogically correct’ for the association of interest

- NEXT 2 SLIDES illustrate
  Discrepancies between Changes over time in Risk implied by selected “Conventional models” for the SAME VECTOR of PAST DOSES (‘EXPOSURE PATTERN’)
Exposure Pattern (Variations of Daily Doses on Y axis) over 365 days (X axis) used to illustrate Implications of Different Models for Assessing “Current Hazard”
Comparison of HR[T|M(T)] for the SAME Exposure Pattern across 6 Alternative “Conventional” Models
Need to Assess CUMULATIVE Effects

- Our work was motivated by the beliefs that:
  1. the Effects of Past (Continuous or Intermittent) Use of Medications often Cumulate over Time
  2. Yet, in real-life studies it is Not clear: what is the Relative Importance of Exposures that occurred in Different Periods in the Past, (e.g. 2 days versus 2 months ago) ?
     [Grim et al, *Clinical Pharmacokinetics* 2003, 42: 139-151]
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.
recency-Weighted Cumulative Exposure (WCE)

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

where:

\( u \) = current time (when Risk is being assessed)

\( WCE(u) \) = 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 (\( u-t \))
Hypothetical example of calculating cumulative weighted exposure $WCE \ (u=30)$

<table>
<thead>
<tr>
<th>$t$</th>
<th>$X(t)$</th>
<th>$u-t$</th>
<th>$w(u-t)$</th>
<th>$w(u-t)X(t)$</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><strong>1.5</strong></td>
<td><strong>0</strong></td>
<td><strong>1.00</strong></td>
<td><strong>1.50</strong></td>
</tr>
</tbody>
</table>

$\sum=5.19$
Example of a Weight Function

From Abrahamowicz et al. (2006, Journal of Clinical Epidemiology, Figure 1)
Variation over Time of Dose $X(t)$ [Upper graph] & the resulting $M(u) = WCE(u)$ calculated using $w(u-t)$ on slide 13 [Lower graph]

From Abrahamowicz et al. (2006, Journal of Clinical Epidemiology, Figure 2)
Comparison of HR[T|M(T)] for the SAME Exposure Pattern across 6 Alternative “Conventional” Models

- Hazard: Current use
- Hazard: Cum. duration of use
- Hazard: Current dose
- Hazard: Cumulative dose (past 30 days)
- Hazard: Non-linear effect of current dose
- Hazard: Cumulative dose (past 30 days)
Weight functions implied by “Conventional” models: 1/ Current Dose; 2/ Total (Cumulative UN-weighted) Past Dose; 3-4/ Total Dose (Past 3 OR 7 days)
Need for Flexible Modeling of the Weight Function

• In previous publications [Vacek (1997), Abrahamowicz et al. (2006)], the Weight function $w(u-t)$ was Defined A Priori

• Yet, in most real-life prognostic studies, there is little A priori knowledge about the (i) Exact Shape, and (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 of Cubic Regression B-Splines

[Sylvestre & Abrahamowicz, Statistics-in-Medicine 2009]
Flexible spline-based WCE Model
[Sylvestre & Abrahamowicz (SIM 2009)]

- We have proposed a **Flexible WCE model**, with the **Weight function estimated by Cubic Splines**:

\[
 w(u - t) = \sum_{j=1}^{m} \theta_j B_j(u - t) 
\]  

(2)

where \( B_j, j=1,\ldots,m \), represent the \( m \) functions in the Cubic Spline basis, and \( \theta_j \) represent the estimable coefficients of the linear combination of the basis splines.
Examples of Cubic Regression B-Splines (with 3 Interior Knots)

The $m$ functions $B_j$ of the cubic spline basis

Regression spline

$\theta = (0.6, 0.6, 0.6, 0.9, 0.4, 0.2, 0.2)$

$\theta = (0.5, 0.1, 0.2, 0.4, 0.2, 0.5, 0.5)$

$\downarrow$ Interior knots
To estimate the Cumulative Effects of Time-Varying treatments, we include the

$WCE(u)$ as a Time-Dependent Covariate in the ‘standard’ Cox’s proportional hazards model

- the Program in R language is available on the free-access CRAN site:
  
  http://cran.rproject.org/web/packages/WCE
Spline Basis is defined over a **Limited Support Interval** $[0; a]$ where:

\[ a = \text{user-specified) maximum length of the ‘etiologically relevant exposure time window’} \]

[Past Doses $X(t)$ at $t<u-a$ are *a priori* considered irrelevant for the risk at time $u$ and, thus, are assigned the weight=0]

**Sensitivity Analyses** are often recommended to compare fit of models with **Alternative Time Windows** (e.g. 1 vs 2 vs 3 yrs)
Validation in Simulations:
100 estimated weight functions True model = Current Dose, 500 events & moderate effect [HR(1SD)=2.0]
Validation in Simulations:

True model = (Cumulative) Sum of Past doses,
500 events & moderate effect [HR(1SD)=2.0]
(1) Assess the Ability of Statistical Criteria to Identify the “Etiologically Correct” among several alternative models for M(u)
(2) Illustrate the Implications of Using an “IN-Correct” model:
   Reduced Ability to detect Adverse Effects
(3) Evaluate the usefulness of our WCE model
Simulations Design

• **Design:** Cohort study of Adverse Effect of a Drug
  • Cohort of N=600 new drug users
  • $t_0 =$ time of 1$^{\text{st}}$ prescription
  • Follow-up duration up to 1 year
  • (i) 200 OR (ii) 500 “Adverse EVENTS” per sample
  • 12 simulated scenarios
    [12 different ‘True’ $M(u)$ models]
Simulations Design

• **Time-Varying Patterns of Drug Use/Dose** $X(t)$:
  (Same Pattern used for All Simulated Scenarios)
  - subjects Repeatedly Stop and Re-start Drug Use
  - both Inter- & Intra-subject Variation in the
    (i) Length of consecutive Periods of Use/Non-use & (ii) in the “Current” Dose $X(t)$
  - Dose Constant within Each period of Use (but varied from one period to another)
“True” M(T) for the SAME Exposure Pattern for 12 Data-Generating “True” Models in Simulations
Analysis of Simulated Data: 10 Estimation Models

• Each simulated sample analyzed with 10 Alternative Time-Dependent Cox's models:
  - Models 1-9 = 9 ‘parametric’ Cox’s models used to Generate Data in different scenarios
  - Model 10 = Cubic spline (constrained) WCE model **

(** AIC/BIC selection: $a=180$ vs. $a=365$; 1 vs. 2 vs. 3 knots)

[Abrahamowicz et al, Stat in Medicine 2011]
for Each simulated sample, the Fit of the 10 Alternative ‘Estimation models’ were compared using 2 Criteria:

- AIC = Deviance + 2 * df  [Akaike 1974]
- BIC = Deviance + df * Ln{# Events} [Schwartz 1978]

df = Model’s degrees-of-freedom ***

[*** the ‘optimal’ Flexible (cubic spline-based) WCE models were “penalized” for the number of estimable spline coefficients: 2-4 depending on the number of knots (1-3)]
POWER LOSS due to relying on the “incorrect model”: (200 events, TRUE model = ‘Total CUMUL. DOSE’)
POWER LOSS due to relying on the “incorrect model”: (200 events, TRUE model = ‘CURRENT USE’)
% of Samples with “TRUE” model Identified by AIC
200 Events & MODERATE Effect [HR(1SD)=2.0]

<table>
<thead>
<tr>
<th>TRUE Model</th>
<th>Best AIC</th>
<th>&lt; 4.0 from Best AIC</th>
<th>Best BIC</th>
<th>&lt; 4.0 from Best BIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current Use</td>
<td>89%</td>
<td>100%</td>
<td>99%</td>
<td>100%</td>
</tr>
<tr>
<td>Current Dose</td>
<td>78%</td>
<td>99%</td>
<td>86%</td>
<td>99%</td>
</tr>
<tr>
<td>Cum. Duration</td>
<td>81%</td>
<td>96%</td>
<td>85%</td>
<td>96%</td>
</tr>
<tr>
<td>Cum. Dose</td>
<td>38%</td>
<td>94%</td>
<td>42%</td>
<td>97%</td>
</tr>
<tr>
<td>Cum. Dose (past 30-days)</td>
<td>78%</td>
<td>95%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Dose Increment + Cum. Dose</td>
<td>24%</td>
<td>92%</td>
<td>35%</td>
<td>98%</td>
</tr>
<tr>
<td>Dose Increment + Current Dose</td>
<td>10%</td>
<td>53%</td>
<td>11%</td>
<td>58%</td>
</tr>
<tr>
<td>Withdrawal</td>
<td>20%</td>
<td>90%</td>
<td>21%</td>
<td>98%</td>
</tr>
<tr>
<td>Non-Linear Current Dose</td>
<td>71%</td>
<td>91%</td>
<td>18%</td>
<td>36%</td>
</tr>
<tr>
<td>WCE (Exp. Decay)</td>
<td>60%</td>
<td>95%</td>
<td>16%</td>
<td>40%</td>
</tr>
<tr>
<td>WCE (Inverted U)</td>
<td>61%</td>
<td>91%</td>
<td>10%</td>
<td>32%</td>
</tr>
<tr>
<td>WCE (Early Peak)</td>
<td>71%</td>
<td>98%</td>
<td>15%</td>
<td>48%</td>
</tr>
</tbody>
</table>
Objective: To explore the relationship between the risk of serious infection and both current and prior oral glucocorticoid (GC) therapy in patients with rheumatoid arthritis (RA) in Quebec, Canada.


Design: Nested case-control with up to five controls matched on age, gender and time in cohort for each of the 1,851 cases of serious infection.

Analyses adjusted for several clinical confounders.

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
Estimated Weight function for the association between prior oral GC exposure and serious infection: **SHORT- & LONG-Term Effects**?
Table 3. Adjusted odds ratios (with 95% bootstrap CI) for the association between various clinical patterns of GC therapy during the past 3 years and risk of current serious infection

<table>
<thead>
<tr>
<th>Pattern of use</th>
<th>Reference</th>
<th>OR *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current user, 5mg, for last 7 days</td>
<td>Non-user</td>
<td>1.03 (1.02, 1.10)</td>
</tr>
<tr>
<td><strong>Current user, 5mg, for last 28 days</strong></td>
<td>Non-user</td>
<td><strong>1.11 (1.07, 1.26)</strong></td>
</tr>
<tr>
<td><strong>Current user, 5mg, for last 3 months</strong></td>
<td>Non-user</td>
<td><strong>1.33 (1.21, 1.46)</strong></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 1 year</td>
<td>Non-user</td>
<td>1.66 (1.47, 1.97)</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>Past user, 5mg, for 6 months, stopped 6 months ago</td>
<td>Non-user</td>
<td>1.09 (0.97, 1.26)</td>
</tr>
<tr>
<td>Current user, 5mg, for last 6 months</td>
<td>Past user, 5mg, for 6 months, stopped 6 months ago</td>
<td>1.41 (1.14, 1.70)</td>
</tr>
<tr>
<td><strong>Current user, 30mg, for last 7 days</strong></td>
<td>Non-user</td>
<td><strong>1.19 (1.10, 1.77)</strong></td>
</tr>
<tr>
<td><strong>Current user, 30mg, for last 28 days</strong></td>
<td>Non-user</td>
<td><strong>1.92 (1.50, 4.05)</strong></td>
</tr>
<tr>
<td><strong>Current user, 30mg, for last 3 months</strong></td>
<td>Non-user</td>
<td><strong>5.51 (3.17, 9.54)</strong></td>
</tr>
<tr>
<td>Current user, 30mg, for last 6 months</td>
<td>Non-user</td>
<td>12.70 (7.03, 29.23)</td>
</tr>
</tbody>
</table>

* Odds ratio represents the relative risk of infection for the pattern of use in column one compared to the reference pattern of use in column two.
Example of Clinical Usefulness of Results

- Consider an RA patient, scheduled for an Elective Surgery in 3 months, on (moderate) 10mg GC daily dose for the last 2 years.
- For this patient, the GC therapy will increase the risk of serious infection (at the time of surgery) by 55% (95% CI: 33% to 103%) relative to STOPPING the GC therapy for the next 3 months.
Attempt at Explanation of “Bi-modal” Effect

- GC act on both Innate & Adaptive Immune Systems
- Short-Term effect of use in last 3-6 months on Innate system was Expected
- Long-Term effect on Adaptive system may be Indirect and may involve T-lymphocyte apoptosis & failure to generate pathogen-specific adaptive immune responses [McMaster & Ray, 2008], and/or prolonged adrenal suppression ***

[*** This requires Further Research]
Prospective study based on Administrative Health Data (Prescription Claims database) from the Canadian province of Quebec

Cohort of N=4,666 elderly New Users of Flurazepam (started use in 1990-1994)

T₀ = Jan. 1, 1990 (Delayed Entry at the time of the 1st Flurazepam prescription)

Event = Fall-related Injury [252 events]

Available Data for Each Prescription: (i) Duration & (ii) Daily Standardized Dose

“time window” = 30 days

[Abrahamowicz et al, Statistics in Medicine 2011]
Table 4. Comparison of AIC and tests of association for alternative models linking Flurazepam use with risk of fall-related injuries

<table>
<thead>
<tr>
<th>Model #</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7-10</th>
<th>11</th>
<th>12</th>
<th>13</th>
</tr>
</thead>
<tbody>
<tr>
<td>True model</td>
<td>Current use</td>
<td>Current dose</td>
<td>NL current dose</td>
<td>Dur. past use</td>
<td>Cumu. past dose</td>
<td>WCE with 3 knots &amp; 30-day window</td>
<td>WCE with 3 knots &amp; 30-day window</td>
<td>Incr. &amp; current dose</td>
<td>Incr. &amp; cumu. past dose</td>
<td>Withdrawal</td>
</tr>
<tr>
<td>AIC</td>
<td>4118.2</td>
<td>4116.9</td>
<td>4118.0</td>
<td>4118.3</td>
<td>4118.2</td>
<td>4102.7</td>
<td>4118.9</td>
<td>4120.1</td>
<td>4106.3</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>0.8225</td>
<td>0.2263</td>
<td>0.3730</td>
<td>0.9452</td>
<td>0.7671</td>
<td><strong>0.0164</strong></td>
<td><strong>0.0001</strong></td>
<td>0.5008</td>
<td>0.8959</td>
<td><strong>0.0009</strong></td>
</tr>
</tbody>
</table>
Weight function for the association between Recent Flurazepam Doses and Fall-related Injuries: **WITHDRAWAL Effect**?

Figure 6. Weight function estimates $\hat{w}(u-t)$ for WCE models with 30-day window for Flurazepam users: bold curve for best-fitting WCE (3 knots), dashed curve for WCE model with 1 knot, and dotted curve for WCE model with 2 knots.
Table 5. Hazard ratios for specific patterns of exposure for the best-fitting WCE model

<table>
<thead>
<tr>
<th>Pattern of exposure</th>
<th>Reference</th>
<th>Hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Dose=0.5</td>
</tr>
<tr>
<td>Current user for 2 weeks</td>
<td>Non-user</td>
<td>1.33</td>
</tr>
<tr>
<td>Current user for 1 week</td>
<td>Non-user</td>
<td>1.34</td>
</tr>
<tr>
<td>Past user for 1 week, who stopped 3 days ago</td>
<td>Non-user</td>
<td>2.86</td>
</tr>
<tr>
<td>Past user for 1 week, who stopped 1 week ago</td>
<td>Non-user</td>
<td>0.99</td>
</tr>
</tbody>
</table>
3\textsuperscript{rd} Application: Didanosine (DDI) use vs Cardiovascular (CVD) Risks in HIV+ subjects

Background:

Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study reported [Sabin et al, *Lancet* 2008]

**Increased Cardiovascular (CVD) Risks** with use of 2 Nucleoside Analog Reverse Transcriptase Inhibitors (NRTIs):

Abacavir (ABC) & Didanosine (DDI)

- However, the **results of subsequent studies of DDI were inconsistent** [Lang et al, *Arch Int Med* 2010; Lundgren et al, *AIDS* 2008; Worm et al, *J Infect Dis* 2010]
Re-assessing the impact of Didanosine (DDI) use on Cardiovascular Risks in HIV+ subjects

- **Our OBJECTIVE:**
  to Re-assess the impact of DDI use on CVD risks in a Large Cohort with Long Follow-up

- **Data Source:** Swiss HIV Cohort

- **Study population:**

- **11,625 HIV+ patients**

**Follow-up:**
> from April 2000 (start of routine CVD risk assessment) to October 2012
> Monthly visits with risk factors assessment
Re-assessing the impact of Didanosine (DDI) use on Cardiovascular Risks in HIV+ subjects

- Time 0 = 1st visit after April 2000
- **Composite CVD Endpoint =** MI, CVD Death or Invasive Cardiac Procedure (as in original D:A:D report [Sabin et al, Lancet 2008])
- Censoring at Non-CVD death or Loss to follow-up
- **Median Follow-up = 6.9 yrs** (IQR: 3.1 – 11.8 yrs)
- 350 CVD events (3% of the 11,625 pts) during f-up

[Xiao, Abrahamowicz, Moodie, Weber, Young; J Am Stat Assoc 2014]
Covariates Adjustment through Marginal Structural Models with IPTW weights

- **Baseline covariates** included in All the Models: age, sex, ethnicity, education, HIV transmission group
- **Time-Dependent covariates**, assessed & updated at Monthly visits, and Controlled for through Marginal Structural Models with Inverse Probability of Treatment (IPTW) weighting:
  - number of previously failed TX regimens, hepatitis (chronic B or C), diabetes, fat loss, nervous system or GI toxicity, clinical stage of HIV, concurrent use of 3 other ARV drugs, calendar year
<table>
<thead>
<tr>
<th></th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 2A</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative use (per year)</td>
<td>1.04 (0.95,1.13)</td>
<td>1.02 (0.92,1.12)</td>
<td>1.01 (0.92, 1.12)</td>
<td>1.04 (0.93, 1.16)</td>
</tr>
<tr>
<td>Recent exposure (within last 6 months)</td>
<td></td>
<td>1.23 (0.68,2.21)</td>
<td></td>
<td>1.02 (0.49, 2.10)</td>
</tr>
<tr>
<td>Current exposure</td>
<td></td>
<td></td>
<td>1.27 (0.48,3.38)</td>
<td></td>
</tr>
<tr>
<td>Past exposure within 1-6 months</td>
<td></td>
<td></td>
<td>1.03 (0.39, 2.69)</td>
<td></td>
</tr>
<tr>
<td>Past exposure more than 6 months ago</td>
<td></td>
<td></td>
<td></td>
<td>0.81 (0.54, 1.21)</td>
</tr>
</tbody>
</table>
DDI vs CVD risks: *Our WCE model fits Much Better than any of the Conventional Models 1-3*

<table>
<thead>
<tr>
<th></th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 2A</th>
<th>Model 3</th>
<th>WCE MSM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model's df</td>
<td>20</td>
<td>21</td>
<td>22</td>
<td>22</td>
<td>21</td>
</tr>
<tr>
<td>Deviance</td>
<td>6328</td>
<td>6327</td>
<td>6326</td>
<td>6325</td>
<td>6317</td>
</tr>
<tr>
<td>AIC</td>
<td>6368</td>
<td>6369</td>
<td>6370</td>
<td>6369</td>
<td>6359</td>
</tr>
<tr>
<td>BIC</td>
<td>6445</td>
<td>6450</td>
<td>6455</td>
<td>6454</td>
<td>6440</td>
</tr>
<tr>
<td>QIC</td>
<td>6390</td>
<td>6394</td>
<td>6396</td>
<td>6395</td>
<td>6383</td>
</tr>
</tbody>
</table>
Estimated Weight Function of the cumulative effect of DDI on the cardiovascular risk with 95% CI
Estimated Total Cumulative Effect (HR) of Being Always treated with DDI (versus never treated) as a function of treatment duration (WCE model)
Summary of DDI results

- All Conventional Models suggested LACK of Any Significant Effect of DDI use on CVD risks
- In contrast, our WCE model:
  (i) predicted CVD outcomes much better than any of the conventional models
  (ii) demonstrated Statistically Significant & Clinically Important Short-Term Risk Increase associated with Recent DDI Exposure
  (iii) showed that CVD risk may be increased by more than 100% after 1 year of Uninterrupted DDI use (adjusted HR = 2.6; 95% CI: 1.3 to 6.4)
  (iv) indicated that this Impact is Limited to first 1,5-2 yrs of DDI use, & long-term DDI users have NO increased risk at > 2 yrs after the initiation start of the DDI therapy
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

- Flexible Weighted Cumulative Exposure (WCE) model [Sylvestre & Abrahamowicz, Statistics in Medicine 2009] may yield New Insights about the underlying ‘biological mechanism’ and Improve Risk Prediction

- 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
Some Limitations of Our Methods

- Our methods require frequent measurements of dose (or “exposure status”) \( X(t) \)
- If the underlying function(s) are simple, the flexible estimates show moderate over-fit bias
- Need to account for Exposure Measurement Errors (e.g. if Drug Dose/Use based on Prescriptions database)
- Need to extend to control for Unmeasured Confounding (e.g. by adapting Instrumental Variables to WCE modeling)
Selected References


- [http://cran.rproject.org/web/packages/WCE](http://cran.rproject.org/web/packages/WCE)
THANK YOU, MERCI!

- Michal.Abrahamowicz@McGill.ca
- http://cran.rproject.org/web/packages/WCE
  (WCE program in R with guidelines, help files & example)
Simulations Results: True $w(u-t)$ (white) vs 100 Constrained Estimates [$a=180$ days]

Figure 2. A random sample of 100 normalized estimated weight functions for the constrained models with the true weight function in thick white: (a) exponential; (b) bi-linear; (c) early peak; (d) inverted U; (e) constant; and (f) hat. Note that, to make the label of the X-axis readable, we show time in days, while in the text, we use 1 year as the unit of time, so that the values on the axes should be divided by 365.

From Sylvestre and Abrahamowicz (2009, Statistics in Medicine, Figure 2)
Correcting for the “too short” initial support interval (in scenario “f")
In many applications, it may be *A Priori* evident that the Weight Function $w(u-t)$ should asymptotically decay to 0 at the either end of the support interval $[0;a]$

- This can be easily achieved by Constraining the WCE model:
  - $\theta_1=0$ & $\theta_2=0$ ensures, respectively, that $w(0)=0$ & $w'(0)=0$ so that Current Value $X(u)$ has No Impact on Current Risk at $u$ (e.g., Current Smoking is Irrelevant for Current Cancer Risk)
  - $\theta_{(k+4)}=0$ & $\theta_{(k+3)}=0$ ensures that $w(a)=0$ & $w'(a)=0$ so that the Value of $X(u-a)$ has No Impact on the Current Risk (e.g., Drug Use $a$ days/weeks ago is Irrelevant for Current Risk of Adverse Events)
Model Selection

- We fit models with $k=1, 2$ or $3$ ‘interior knots’ (Uniformly Distributed within $[0; a]$ support interval)
- (in addition, 4 ‘exterior knots’ are placed at both $u=0$ and $u=a$)
- The resulting Cubic Spline has, respectively, 5, 6 or 7 functional segments, i.e. model (6) [slide 21] requires estimating $k+4 = 5-7$ coefficients $\theta_j$
- In some applications, the users may also want to consider Sensitivity Analyses with respect to $a$
  (= the Upper Limit of the Support Interval $[0; a]$)

* $BIC$ or $AIC$ are used to select the Best-fitting of the Spline Models with Different $k$ and/or $a$
Inference about the Estimated Weight Function $\hat{w}(\cdot)$

- Quasi-parametric LRT tests* of:
  
  i. $H_0 =$ No Association between $X(t)$ and risk: 
     
     $w(u-t)=0$ for $0<t<u$  $(df=k+4)$
  
  ii. $H_0 =$ Equal Weighting of All past values: 
      
      $w(u-t)=V$ for $0<t<u$  $(df=k+3)$

  (* with Simulation-based correction of critical values for a posteriori model selection)

- Bootstrap-based pointwise confidence bands around $\hat{w}(\cdot)$ [with BIC-based model selection repeated in each Bootstrap Re-sample]