New Challenges for Longitudinal Data Analysis

Joint modelling of Longitudinal and Competing risks data

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Acknowledgment
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Outline

- Introduction – anti-epileptic drug (AED) trials
  - Competing risks
  - Questions of interest
  - Joint modelling and Extension to competing risks
  - Results from Simulation study
  - Application – Relative effects of AEDs on treatment failure
Epilepsy drug trials

- Epilepsy – a common neurological condition characterised by seizures
- Newly diagnosed usually prescribed single anti-epileptic drug (AED) treatment
- AED considered successful if the person taking it becomes seizure free with little in the way of side effects
- SANAD (Standard and new antiepileptic drugs) trial recruited ≈ 2500
- Standard AED - Carbamazepine (CBZ)
- New AEDs - Lamotrigine (LTG), Gabapentin, etc
- Primary endpoint of AED trials - Time to treatment failure
  Defined as the time to withdrawal of a randomised drug or addition of another/switch to an alternative AED
Competing risks event time data

- Patients decided to switch to an alternative AED because of inadequate seizure control (ISC) or to withdraw from a treatment because of unacceptable adverse effects (UAE).

When there are several reasons why the event can occur, or some informative censoring occurs, it is known as ‘competing risks’.

- Competing risks - considers reasons for treatment failure: ISC and UAE
Competing risks of treatment failure

- Analysis of “overall” treatment failure – failure for any reason

- Fail to examine differential effects of AEDs on the reason for withdrawal

- Assumes reasons of failure are of equal importance (which may not be the case)
  - Different consequences: loss of driving license due to continued seizures vs common side effects such as nausea, dizziness or rash

- AEDs are considered equivalent as a result of similar overall treatment failure when in fact the drugs have very different effects on withdrawal due to adverse effects and poor seizure control

- Ignoring this aspect of an outcome by analysing events overall can result in misleading conclusions
Questions of interest

- CBZ (standard) Vs LTG (new) includes 605 patients.
- Reasons for treatment failure – competing risks
  - Inadequate seizure control (ISC)
  - Unacceptable adverse effects (UAE)

- 94 (15%) patients withdrew from the randomised AED due to UAE while 120 (20%) withdrew due to ISC.

Is LTG superior to CBZ in terms of seizure control? tolerability?
- LTG is significantly more tolerable than CBZ
- LTG is similar to CBZ in terms of seizure control
Biased in favour of new drug?

- Not blinded

- Different titration rates may have been to the disadvantage of standard drug CBZ

- AED titrated more quickly brings benefits in terms of seizure control but be more likely to cause adverse effects

- Criticism at previous AED trials
What is the effect of drug titration?

Investigate the effect of drug titration on the relative effects of LTG and CBZ on reasons of treatment failure

A large variation across patients in the initial titrated dose was observed

Average dose increased over time but the rate of increase was observed to vary across individuals

After adjusting for drug titration is LTG still superior to CBZ in terms of UAE/ISC?
Model
Does rate of drug titration affect risk of drug withdrawal?
Joint model

In many studies, inference about a longitudinal outcome is of primary interest

- problem of non-ignorable missing data can be addressed through joint modelling of the time to dropout

Joint models can also address questions concerning the association between a longitudinal outcome and clinically defined time to event outcome.

E.g.

- relationship between prothrombin index and survival in cirrhosis patients
- prognostic value of CD4 cell count in relation to the time of AIDS onset
Longitudinal sub-model – Gaussian linear model

\[ Y_t = X_1(t)\beta_1 + W_1(t) + \varepsilon_t \]

where \( W_1 \) is a latent process.

Event times are associated with the longitudinal response through a second latent process \( W_2 \).

Conditional on \( W_2 \), proportional hazards model is assumed for time to event outcome

\[ \lambda(t \mid X_2, W_2) = \lambda_0(t) \exp\{X_2(t)\beta_2 + W_2(t)\} \]

Allow for a single time to event outcome.
Competing risks joint model

- Analyse data arising from competing events and longitudinal processes simultaneously exploiting dependencies between the components.
- Association between longitudinal and competing risks data via latent processes.

\[ Y_t \]
Longitudinal process

\[ W^{(l)} \]
Latent variables

\[ S_1 \]

\[ S_2 \]

\[ S_K \]

Competing Risks
Competing risks joint model

Let $\eta$ be the cause of failure and competing event type indicator is defined by

$$\delta = \{I(T \leq C), \eta\} = \begin{cases} l & \text{if } \eta = l, \ l = 1, ..., K \\ 0 & \text{non-informative censoring} \end{cases}$$

where $T = \min(T_1, ..., T_K)$ and $C$ is non-informative censoring times.

- Allow for competing risks through a cause-specific hazards sub-model with a separate latent association between longitudinal process and each cause of failure.

- Longitudinal sub-model – Gaussian linear model

$$Y_t = X_1(t)\beta_1 + W_1(t) + \varepsilon_t$$

- Sub-model for each competing cause of failure follow a cause-specific proportional hazard; and for cause $l$

$$\lambda^{(l)}(t \mid X_2, W_2) = \lambda_0^{(l)}(t)\exp\{X_2(t)\beta_2^{(l)} + W_2^{(l)}(t)\}$$
In the model fitted here, $W_1$ and $W_2^{(l)}$ are assumed to be proportional:

$$W_2^{(l)}(t) = \gamma^{(l)} W_1(t), \quad l = 1, \ldots, K$$

$\gamma^{(l)}$ indicates the level of association between the $l$th competing event and longitudinal process.

Longitudinal responses and competing risks event time are assumed to be conditionally independent given $W_1$ and $W_2^{(l)}$.
Choice of latent processes

Linear combinations of Gaussian random effects

\[ W_1(t) = U_0 \text{ or } W_1(t) = U_0 + U_1 t \text{ and } W_2^{(l)}(t) = \gamma W_1(t) \]

where \( U_0 \) and \( U_1 \) are random intercept and random slope, follow zero-mean bivariate Gaussian process

or

\[ W_2^{(l)}(t) = \gamma_1 U_0 + \gamma_2 U_1 + \gamma_3 (U_0 + U_1 t) \]

or

\[ W_2^{(l)}(t) = \gamma_1 U_0 + \gamma_2 U_1 + \gamma_3 (U_0 + U_1 t) + U_3 \]

More complex models including a continuous-time stochastic processes
Conditional on latent processes, the competing risks are independent of themselves and of the measurements $Y$

Factorise the likelihood for observed data as the product of the marginal distribution of $Y$ and the conditional distributions of competing events $\eta \in (1, \ldots, K)$ given the observed values of $Y$

$$L(Y, \theta, \eta) = L_Y(Y, \theta) \prod_{l=1}^{K} L^{(l)}_{\eta|Y}$$

where

$\theta$ denote the combined vector of unknown parameters

$L_Y(Y, \theta)$ is the standard likelihood corresponding to the marginal multivariate normal distribution of $Y$

$$L^{(l)}_{\eta|Y} = E_{W_2^{(l)}|Y} \{ L_{\eta|W_2^{(l)}}(\theta, \eta = l \mid W_2^{(l)}) \}$$
Estimation

Estimate the parameters of interest by maximising the likelihood of the observed data

Deploy the EM algorithm

**E-step:** Expectation of the complete data log-likelihood is evaluated. Evaluate expectation of the form

\[ E\{g(W) \mid Y, S_1, \ldots, S_K, \hat{\theta}\} \]

Computationally burdensome and less mathematically transparent.

**M-step:** Parameter estimates are computed via maximisation of the expected log-likelihood

Plausible starting values – estimates from separate analyses of the longitudinal and competing risk components

For more details of the estimation process, see Williamson et al 2008.
### Simulation study

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Positively associated risks</th>
<th>Negatively associated risks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>True value</td>
<td>Estimate (SE)</td>
</tr>
<tr>
<td><strong>Longitudinal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept $\beta_{10}$</td>
<td>0</td>
<td>-0.07 (0.07)</td>
</tr>
<tr>
<td>Continuous covariate $\beta_{11}$</td>
<td>0</td>
<td>-0.01 (0.06)</td>
</tr>
<tr>
<td>Binary covariate $\beta_{12}$</td>
<td>0</td>
<td>0.01 (0.07)</td>
</tr>
<tr>
<td>Time $\beta_{13}$</td>
<td>0</td>
<td>-0.00 (0.02)</td>
</tr>
<tr>
<td><strong>Survival</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Continuous covariate $\beta^{(1)}_{21}$</td>
<td>0</td>
<td>-0.04 (0.17)</td>
</tr>
<tr>
<td>Binary covariate $\beta^{(1)}_{22}$</td>
<td>0</td>
<td>0.02 (0.17)</td>
</tr>
<tr>
<td>$\gamma^{(1)}$</td>
<td>1</td>
<td>1.01 (0.19)</td>
</tr>
<tr>
<td>Continuous covariate $\beta^{(2)}_{21}$</td>
<td>0</td>
<td>-0.02 (0.09)</td>
</tr>
<tr>
<td>Binary covariate $\beta^{(2)}_{22}$</td>
<td>0</td>
<td>0.03 (0.13)</td>
</tr>
<tr>
<td>$\gamma^{(2)}$</td>
<td>1</td>
<td>1.03 (0.11)</td>
</tr>
<tr>
<td><strong>Variances</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\sigma_{U0}$</td>
<td>1</td>
<td>1.00 (0.10)</td>
</tr>
<tr>
<td>$\sigma_{U1}$</td>
<td>0.10</td>
<td>0.10 (0.03)</td>
</tr>
<tr>
<td>$\sigma_Z$</td>
<td>0.10</td>
<td>0.10 (0.04)</td>
</tr>
</tbody>
</table>
Application – SANAD trial

Standard AED - CBZ vs New AED - LTG

Competing reasons for treatment failure

(1) Inadequate seizure control (ISC)
(2) Unacceptable adverse effects (UAE)

After adjusting for drug titration is LTG still superior to CBZ in terms of UAE/ISC?
Longitudinal outcome - Calibrated dose

- Standardise the dose of each drug relative to the midpoint of the maintenance dose range for that particular drug.

- Change-point at $t = 500$ days

- Spline (piecewise) mixed-effect model

- Define a new time scale $d_t = t - 500$, and set an indicator $\zeta_t$ for the change point

$$
\zeta_t = \begin{cases} 
1 & \text{if } t \leq 500 \\
0 & \text{if } t > 500
\end{cases}
$$
Longitudinal sub-model
Piecewise mixed-effect model

Longitudinal sub-model is defined by

\[ Y_t = \beta_0 + \zeta_t d_t \beta_{11} + (1 - \zeta_t) d_t \beta_{12} + X_t \zeta_t \beta_{21} + X_t (1 - \zeta_t) \beta_{22} + W_1(t) + \varepsilon_t \]

where \( X_1 \) is the treatment group.

Latent process \( W_1 \) is defined by

\[
W_{1i}(t) = U_{0i} + \zeta_t d_t U_{1i} + (1 - \zeta_t) d_t U_{2i}
\]

\[
\begin{pmatrix}
U_{0i} \\
U_{1i} \\
U_{2i}
\end{pmatrix} \sim N_3 \begin{pmatrix}
0 \\
0 \\
0
\end{pmatrix}, \begin{pmatrix}
\nu_{00} & \nu_{01} & \nu_{02} \\
\nu_{10} & \nu_{11} & \nu_{12} \\
\nu_{20} & \nu_{21} & \nu_{22}
\end{pmatrix}
\]
## Competing risks joint model estimates (longitudinal sub-model)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Coef (95% CI)</th>
<th>Coef (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>2.2870 (2.129, 2.452)</td>
<td>Before 500 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After 500 days</td>
</tr>
<tr>
<td>Time (Slope)</td>
<td>0.0009 (0.0006, 0.0012)</td>
<td>0.0000 (-0.0003, 0.0001)</td>
</tr>
<tr>
<td>Drug LTG vs CBZ</td>
<td>0.2580 (-0.002, 0.477)</td>
<td>0.3000 (0.023, 0.540)</td>
</tr>
<tr>
<td>Drug x Time interaction</td>
<td>0.0009 (0.0005, 0.0014)</td>
<td>0.0002 (-0.0001, 0.0005)</td>
</tr>
</tbody>
</table>
### Competing risks joint model estimates (cause-specific hazards sub-model)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Competing risks joint analysis</th>
<th>Standard competing risks analysis*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>UAE: LTG vs CBZ</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.519 (0.358, 0.789)</td>
<td>0.545 (0.359, 0.826)*</td>
</tr>
<tr>
<td>$\gamma^{(1)}$ (95% CI)</td>
<td>-0.579 (-0.890, -0.289)</td>
<td></td>
</tr>
<tr>
<td><strong>ISC: LTG vs CBZ</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.004 (0.709, 1.397)</td>
<td>1.020 (0.709, 1.450)*</td>
</tr>
<tr>
<td>$\gamma^{(2)}$ (95% CI)</td>
<td>0.282 (0.167, 0.396)</td>
<td></td>
</tr>
</tbody>
</table>

* Fitting cause-specific model to each competing event alone (as in Marson et al, *Lancet*; 2007)
Conclusion
Is LTG superior to CBZ after adjusting for titration in terms of UAE? ISC?

- If LTG is titrated at the same rate as CBZ, the beneficial effect of LTG on UAE would still be evident.

- LTG and CBZ still appear to provide similar seizure control.
Model diagnostic

The marginal assumption of normality of random effects in the measurement sub-model and proportionality assumption of cause-specific hazards sub-model hold reasonably well.

- Deviations from assumption of Gaussian random effects in longitudinal sub-model has little impact on the model estimates.

- Fitted an accelerated failure time sub-model in a single event time setting where the proportionality assumption was not satisfied.

- Further work is needed to develop/extend diagnostic methods for joint models which include a competing risks survival sub-model.

- Software is developed in R language (joineR library in CRAN); proposed EM algorithm converged in < 4 minutes.
References


Marson AG et al, on behalf of the SANAD Study group. Carbamazepine, gabapentin, lamotrigine, oxcarbazepine or topiramate for partial epilepsy: results from the SANAD trial. Lancet 2007; 369: 1000-1015.

