The analysis of incontinence episodes and other count data in patients with Overactive Bladder (OAB) by Poisson and negative binomial regression

Martina R, Kay R, van Maanen R, Ridder A

Speaker: Richard Kay
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Problem Area

- Number of incontinence episodes recorded in a 3-day diary prior to randomisation into the study and at the end of treatment

- Data from two sets of trials from the clinical development of solifenacin and mirabegron
  - 4 trials compared solifenacin 5mg and 10mg doses to placebo
  - 3 trials compared mirabegron 25mg and 50mg to placebo

- Focus on subgroups of patients who recorded ≥ 1 episode at baseline

- The pre-specified methods of analysis were rank ANCOVA on change from baseline in number of episodes
Problem Area

Observed number of incontinence episodes for mirabegron at end of treatment
Poisson and Negative Binomial Models

- Data are counts – Poisson and related models seem to be more appropriate

- Poisson model

\[ P(Y = y | \lambda) = \frac{\lambda^y}{y!} e^{-\lambda} \quad y = 0, 1, 2, ... \]

\[ \log \lambda_i = \beta_0 + \beta_1 x_{i1} + \beta_2 x_{i2} + \cdots + \beta_p x_{ip} \]

- Poisson model assumptions
  - Number of events in distinct, non-overlapping, intervals of time are independent of each other
  - The likelihood of an event occurring in an interval of time is the same for all intervals of the same width/duration
  - The probability that two or more events happen simultaneously is zero

- In this application the time interval is 3-days
Poisson and Negative Binomial Models

- Model assumptions unlikely to be satisfied – episodes tend to be clustered

- Including covariates and a treatment indicator allow some heterogeneity but model assumes homogeneity for patients with same covariate values and in same treatment group (mean = variance) – data tend to be ‘over-dispersed’ – variance patient-to-patient greater than that allowed by model

- Add random effect

  \[ \log \lambda_i = \beta_0 + \beta_1 x_{i1} + \beta_2 x_{i2} + \cdots + \beta_p x_{ip} + \epsilon_i = \mu_i + \epsilon_i \]

- Assume \( \ln(\epsilon_i) \) is gamma, mean 1 and variance \( \frac{1}{\tau} \), distribution of \( Y \) then negative-binomial
Missing Data

- Not uncommon to have incomplete diary data

- Let $t_i$ denote time period for which data available – for the full 3 days, $t_i = 1$, for only 2 days data, $t_i = 2/3$

- Model can include an offset $t_i$;

$$\log(\lambda_i/t_i) = \beta_0 + \beta_1 x_{i1} + \beta_2 x_{i2} + \cdots + \beta_p x_{ip} + \epsilon_i$$

or equivalently

$$\log \lambda_i = \beta_0 + \beta_1 x_{i1} + \beta_2 x_{i2} + \cdots + \beta_p x_{ip} + \log t_i + \epsilon_i$$
Zero Inflation

- Treatments are effective and many patients will have $Y = 0$ at end of treatment – so-called ‘dry’ patients

- Models sometimes not able to capture this bolus at zero

- Further generalisation - introduce a zero-inflation term

$$P(Y = y) = \rho_0 I_{Y=0} + (1 - \rho_0) f(y)$$

where $f(y)$ is either the Poisson or negative-binomial probability function
Results - ANCOVA

- Covariates were sex, age group and geographical region
- Study also included as a stratification factor
- ANCOVA response was change from baseline in mean number of incontinence episodes/24h
- Missing data handled by calculating mean over available days
- Parametric ANCOVA used for estimates and Cis, p-values obtained through rank ANCOVA as normality of residuals from parametric models not satisfied
# Results - ANCOVA

ANCOVA\(^1\) on Change from Baseline to EOT in Mean Number of Incontinence Episodes/24 Hours for Solifenacin and Mirabegron

<table>
<thead>
<tr>
<th>Drug</th>
<th>Treatment group</th>
<th>n</th>
<th>Baseline mean (SE)</th>
<th>Mean change from baseline to EOT (SE)</th>
<th>Model-based estimate of difference from placebo in mean change (95% CI)</th>
<th>p-value(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solifenacin</td>
<td>Placebo</td>
<td>781</td>
<td>2.9 (0.10)</td>
<td>-1.1 (0.09)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5 mg</td>
<td>314</td>
<td>2.6 (0.14)</td>
<td>-1.5 (0.11)</td>
<td>-0.73 (-1.01, -0.45)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>10 mg</td>
<td>778</td>
<td>2.9 (0.10)</td>
<td>-1.8 (0.09)</td>
<td>-0.72 (-0.91, -0.52)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mirabegron</td>
<td>Placebo</td>
<td>878</td>
<td>2.7 (0.09)</td>
<td>-1.1 (0.07)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>25 mg</td>
<td>254</td>
<td>2.7 (0.16)</td>
<td>-1.4 (0.15)</td>
<td>-0.40 (-0.74, -0.06)</td>
<td>0.005</td>
</tr>
<tr>
<td></td>
<td>50 mg</td>
<td>862</td>
<td>2.7 (0.09)</td>
<td>-1.5 (0.07)</td>
<td>-0.40 (-0.58, -0.21)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

\(^1\) Parametric ANCOVA used for estimates, standard errors (SE) and confidence intervals (CI).

\(^2\) Stratified rank ANCOVA used to obtain p-values
Results – Poisson, ZIP, Negative Binomial and ZINB

Model fit can be assessed through the Akaike Information Criterion (AIC)

AIC = -2(maximised log likelihood-number of model parameters)

<table>
<thead>
<tr>
<th>Model Type</th>
<th>Solifenacin</th>
<th>Mirabegron</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANCOVA</td>
<td>11,938.6</td>
<td>12,719.2</td>
</tr>
<tr>
<td>Poisson</td>
<td>14,393.1</td>
<td>15,710.5</td>
</tr>
<tr>
<td>ZIP</td>
<td>10,873.8</td>
<td>11,666.4</td>
</tr>
<tr>
<td>Negative Binomial</td>
<td>8,213.8</td>
<td>8,959.5</td>
</tr>
<tr>
<td>ZINB</td>
<td>8,209.4</td>
<td>8,921.8</td>
</tr>
</tbody>
</table>
Problem Area

Observed number of incontinence episodes for mirabegron at end of treatment

[Bar chart showing the observed number of incontinence episodes by treatment group (placebo, 25 mg, 50 mg).]
Results – Poisson, ZIP, Negative Binomial and ZINB

**Poisson**

**Zero-Inflated Poisson**

**Negative Binomial**

**Zero-Inflated Negative Binomial**
Results – Poisson, ZIP, Negative Binomial and ZINB

Negative Binomial Model for Number of Incontinence Episodes for Solifenacin and Mirabegron

<table>
<thead>
<tr>
<th>Drug</th>
<th>Treatment</th>
<th>n</th>
<th>Rate Ratio vs. placebo (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solifenacin</td>
<td>Placebo</td>
<td>781</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 mg</td>
<td>314</td>
<td>0.57 (0.46, 0.72)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>10 mg</td>
<td>778</td>
<td>0.59 (0.50, 0.69)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Mirabegron</td>
<td>Placebo</td>
<td>878</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25 mg</td>
<td>254</td>
<td>0.70 (0.55, 0.90)</td>
<td>0.004</td>
<td></td>
</tr>
<tr>
<td>50 mg</td>
<td>862</td>
<td>0.74 (0.64, 0.85)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

Rate ratio = $e^\beta$ where $\beta$ is the coefficient of the treatment indicator ($x = 0/1$) so that

\[
 e^\beta = \frac{\lambda(x = 1)}{\lambda(x = 0)}
\]
Model Choice

- Key clinical element is estimating $P(Y = 0)$

<table>
<thead>
<tr>
<th>Development programme</th>
<th>Treatment</th>
<th>n</th>
<th>Observed data</th>
<th>Negative-Binomial Model</th>
<th>ZINB Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solifenacin</td>
<td>Placebo</td>
<td>781</td>
<td>0.35</td>
<td>0.32</td>
<td>0.35</td>
</tr>
<tr>
<td>5 mg</td>
<td></td>
<td>314</td>
<td>0.49</td>
<td>0.46</td>
<td>0.50</td>
</tr>
<tr>
<td>10 mg</td>
<td></td>
<td>778</td>
<td>0.52</td>
<td>0.51</td>
<td>0.51</td>
</tr>
<tr>
<td>Mirabegron</td>
<td>Placebo</td>
<td>878</td>
<td>0.38</td>
<td>0.35</td>
<td>0.37</td>
</tr>
<tr>
<td>25 mg</td>
<td></td>
<td>254</td>
<td>0.46</td>
<td>0.44</td>
<td>0.45</td>
</tr>
<tr>
<td>50 mg</td>
<td></td>
<td>862</td>
<td>0.44</td>
<td>0.43</td>
<td>0.44</td>
</tr>
</tbody>
</table>

- Adding zero-inflation term helps a little
Model Choice

- Negative-binomial and ZINB seem to fit data well - zero-inflation seems to add a little extra data explanation but not much

- Clear improvements over rank ANCOVA

- Zero-inflated models can be extended to allow the mixing term $\rho_0$ to depend on treatment and covariates

- Treatment effect then appears in both ‘parts’ of the model but then simple ‘measure’ of treatment effect not available

- Statistical significance obtained through testing a composite null hypothesis using the likelihood ratio test
References

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- Keene, ON; Jones, MRK; Lane, PW; Anderson, J ‘Analysis of exacerbation rates in asthma and chronic obstructive pulmonary disease: example from the TRISTAN study.’ Pharmaceutical Statistics 2007; 6: 89-97

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