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

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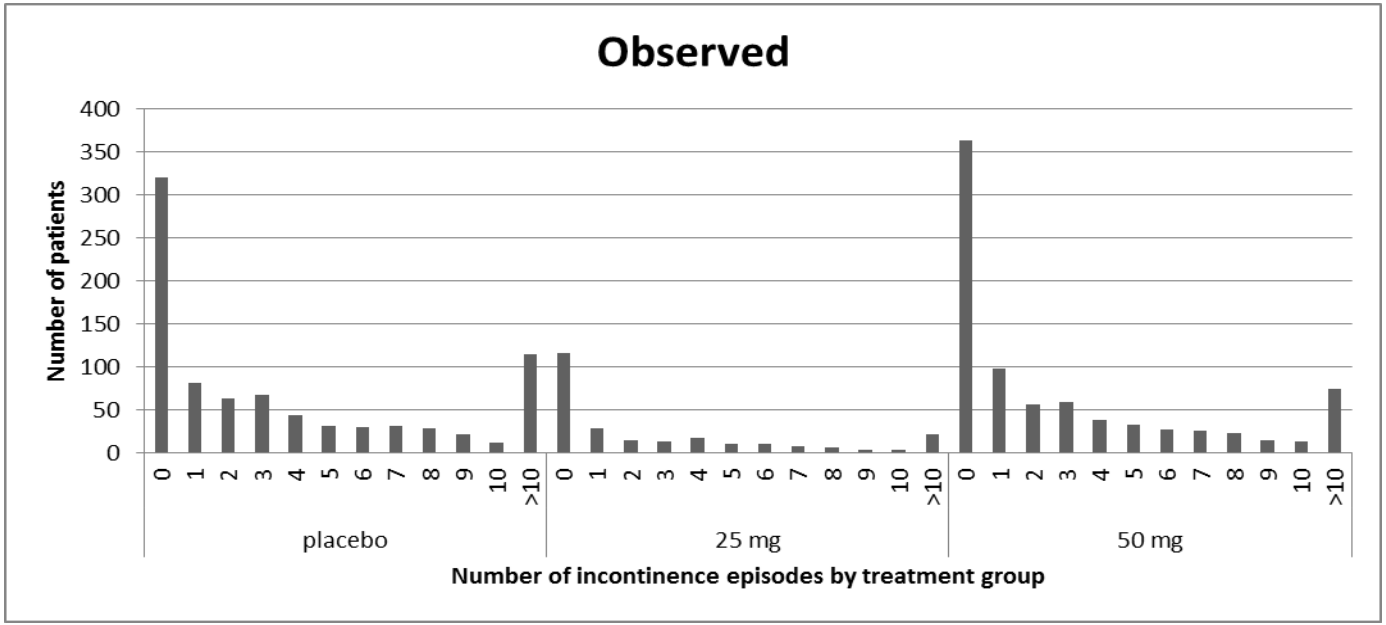
Problem Area

- 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 and10mg 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

$$P(Y = y|\lambda) = \frac{\lambda^y}{y!}e^{-\lambda} \qquad y = 0, 1, 2, \ldots$$

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

- 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

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

[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)

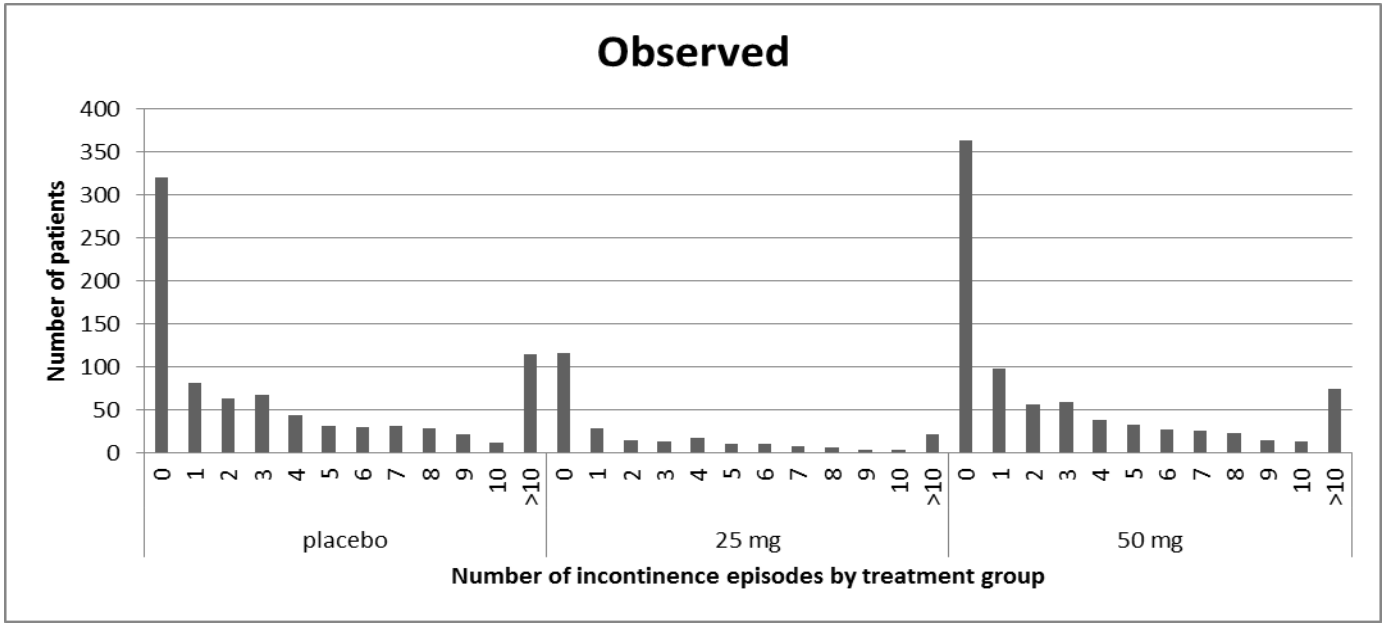
AIC=-2(maximised log likelihood-number of model parameters)

Goodness of Fit (AIC) Statistics for Solifenacin and Mirabegron

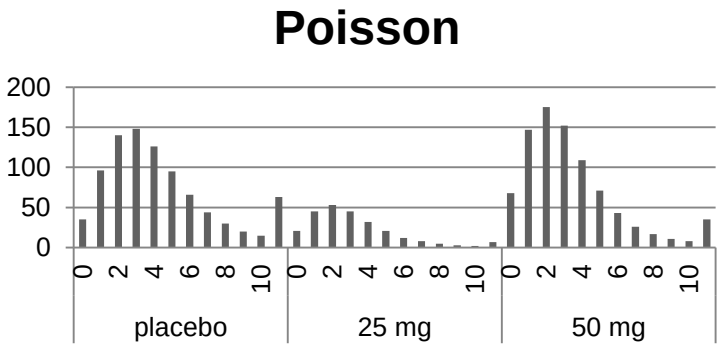
	Solifenacin	Mirabegron
ANCOVA	11,938.6	12,719.2
Poisson	14,393.1	15,710.5
ZIP	10,873.8	11,666.4
Negative Binomial	8,213.8	8,959.5
ZINB	8,209.4	8,921.8

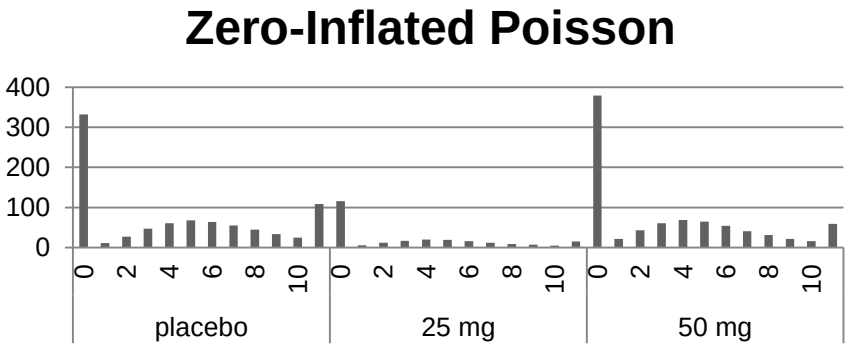
Problem Area

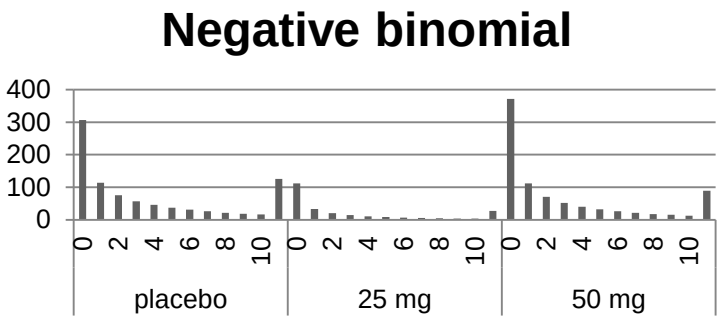
Observed number of incontinence episodes for mirabegron at end of treatment

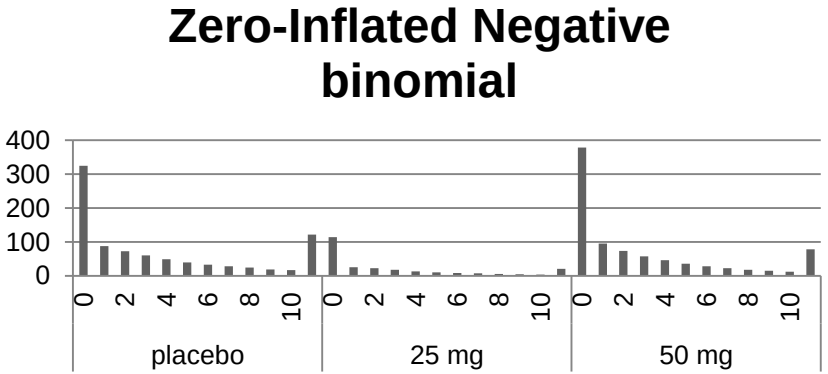


Results – Poisson, ZIP, Negative Binomial and ZINB









Results – Poisson, ZIP, Negative Binomial and ZINB

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

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

Rate ratio $= e^{\beta}$ where β 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 $P(Y = 0)$

Dry Rates and Estimated Probabilities for the Negative-Binomial Models for Solifenacin

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

- 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 ρ_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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