Modeling urge urinary incontinence data assuming non-Poisson dispersion of counts within individual provides a major model fit improvement.

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Introduction:

Daily number of urge urinary incontinence (UUI) episodes is a count endpoint for assessing overactive bladder disease activity and commonly modeled using Poisson (PS) regression.

PS assumes equi-dispersion, meaning that expected mean count is equal to the variance. However, UUI data are generally over-dispersed, i.e. the overall variance is much larger than the mean value. Deviation from equi-dispersion occurs both between patients, as well as within individual patient experience.

Poisson regression does not describe observed UUI data well, because the distribution of counts is skewed and contains a large number of zeroes, which result in poor model fits under the standard PS models, which rely on log-transformation of the data.

Appropriate specification of the distribution of UUI rates between patients via a Poisson-Gamma model [4], and accounting for dispersion characteristics within patients result in substantial improvement in the model fit. Two general strategies to account for within-patient dispersion were examined here: 1) Use of a generalized Poisson (GP) model, and 2) Use of zero-inflated (ZIP) models.

Objective:

To evaluate methods for describing count data that is not equi-dispersed between or within patients.

Methods:

Placebo UUI count data from 500 patients participating in 7 studies were used. Three-day patient diaries were collected at study start, and at various times up to 7 weeks after the start of treatment

Models

Urinary Urge Incontinence counts (uui) were modeled as follows:

$$\widehat{uui_{i,t}} = uui_{BLi} \cdot \left(1 - Eff \cdot \left(1 - e^{-k_{plc} \cdot t}\right)\right)$$

$$uui_{BLi} \sim gamma(\alpha \cdot \beta)$$

$$Eff = \frac{e^{logitEff}}{1 + e^{logitEff}}, \qquad 0 < Eff < 1$$

$$uui_{i,t} \sim P(\widehat{uui_{i,t}})$$

Count Models

Poisson

$$P(Y = n) = \frac{e^{-\lambda} \cdot \lambda^n}{n!}$$

Generalized Poisson

$$GP(Y = n) = \frac{e^{-\lambda - n\delta} \cdot \lambda(\lambda + n\delta)^{n-1}}{n!}$$

Note a Poisson distribution is a generalized Poisson distribution with dispersion factor δ = 0. Mean count and variance are given by:

$$\bar{x} = \frac{\lambda}{1 - \delta} \qquad var(x) = \frac{\lambda}{(1 - \delta)^3}$$

Zero-Inflated Poisson

$$P(Y = n) = p_0 \cdot I_{Y=0} + (1 - p_0) \cdot f(Y = n)$$

where f(y) is either a Poisson or Generalized Poisson

Methods (continued)

Estimation method

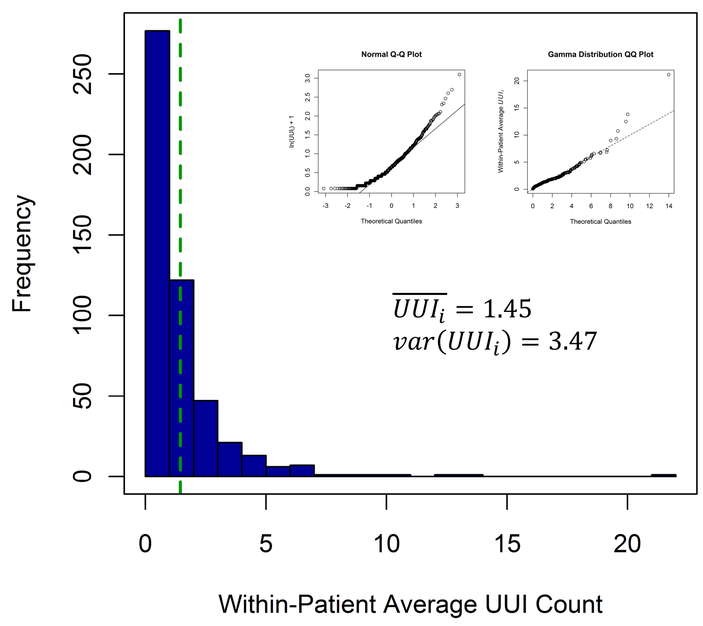
MCMC in WinBUGS was used to estimate the posterior parameter distributions

Model evaluation

Models were compared by :

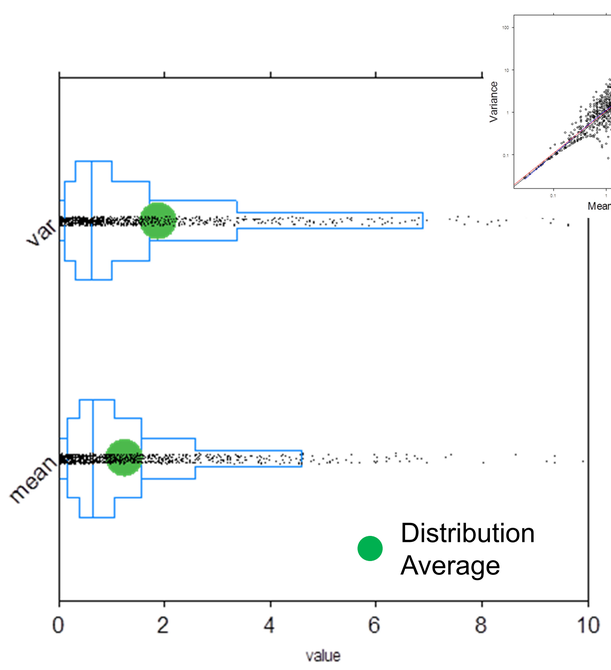
- Deviance Information Criterion (DIC)
- Plausibility and precision of parameter estimates
- Ability to capture individual and aggregate trends and observed variability
- Precision of parameter estimates.

Figure 1. Overall UUI counts are overdispersed



These plots of within-patient mean UUI counts show that the variance between patients is substantially larger than the distribution mean. Even though all patients experienced at least one UUI episode, there is a large proportion of patients with mean UUI counts close to 0.

Figure 2. Within-patient UUI counts are *also* over-dispersed



Here, we compare the within-patient means to the within-patient variances. The inset graphs suggests that, on average, once we appropriately account for the distribution of patient means via a gamma distribution, a Poisson model of daily counts may be appropriate. Closer examination reveals that patient UUI counts are also over-dispersed somewhat.

Figure 3. Model development table

Model	Description	Reference Model	ΔDIC	Comment
00	Random rates between patients	—	—	No distributional constraints on the rates
01	Poisson-Gamma Model	00	-105.2	Use parameterization with random rate parameter. Shape parameter is the overall mean
02	Poisson-Gamma Model	01	3.8	Shape and rate simulataneously fit. Identical fit to Model 01
03	Add effect of time to Model 02	02	-1073.7	Big improvement. Rate constant is ~.055 day^{-1}. Maximal effect is ~66% decline due to placebo
04	Test GP model with average dispersion parameter	03	-54.0	Better fit, per DIC. Dispersion parameter is ~0.16
05	Random dispersion parameter between subjects	04		Did not converge to appropriate parameter values
06	ZIP Model within patients	03, 04	-70.5 -16.5	Similar results to model 04
07	ZIGP Model	06	-4.8	Did not significantly improve the fit

Results:

- Models reported here converged well, with good mixing characteristics, and reasonable final parameter estimates
- Models 01 and 02 represent alternative parameterizations of the Poisson-Gamma Model [4]:

  Model 01:
  $$Y_i \sim Poisson(\lambda u_i)$$
  $$u_i \sim gamma(r_i, r_i)$$

  Model 02:
  $$Y_i \sim Poisson(\lambda_i)$$
  $$\lambda_i \sim gamma(\alpha_i, \beta_i)$$

  Model 01 has the advantage that gamma(r,r) has mean 1, so that λ represents the population mean number of counts
- Treatment with placebo resulted in a pronounced 66% improvement in UUI events (Model 03).
- On average, there was overdispersion within patients, and inclusion of this effect in a GP model improved the fit (Model 04).
- Specification of the dispersion parameter as a random effect in a GP model proved troublesome though there is clearly different behavior between patients (Model 05)
- A ZIP model also accounted for average within-patient overdispersion, while a zero-inflated GP did not improve the model fit substantially

Conclusions:

- Count data in OAB have complex statistical behavior
- Placebo treatment results in substantial improvement in UUI rates with time
- Simple Poisson Regression techniques will result in inaccurate parameter estimates, overestimating small average count rates for UUI events
- Variability between patients could be accounted for with a gamma distribution
- Variation within subjects was over-dispersed on average, though behavior varied between individuals. This behavior could be described by GP or ZIP models. Further work is needed to account for the differences between patients.

Key References

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