# Modeling Adverse Event Rates of Opioids for the Treatment of Osteoarthritis Pain using Literature Data

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## OBJECTIVES

To characterize adverse event (AE) and dropout profiles of opioids for the treatment of Osteoarthritis Pain (OA) using literature data

- **Tools & Methodology:**
  - To use mixed effects models to describe differences in dropout rates and AE's between drug classes/doses
  - Attention was focused on dropout rates due to AE's and proportions reporting events of constipation and nausea

## BACKGROUND

**Data:** The database included close to 40 placebo controlled studies reporting dropouts rates and rates of AE's in over 12000 OA patients

**Definitions:**

- Treatments were classified according to opioid strength as non-opioid (APAP, Ibuprofen, Naproxen), moderate (Codeine, Dextropropoxyphene, Tramadol) and strong (Fentanyl, Hydromorphone, Morphine, Oxycodone, Oxymorphone). In addition to Tapentadol and placebo
- We sought to estimate %attenuation due to active treatment using placebo as a reference

## Model

•Using proportions data together with sample size, the number of events is dealt with as a binomial variable

•A binomial model estimates the probability of an event (p) as a function of influential variables (X), as expressed in equation (1)

•The covariate vector X can be any combination of discrete, categorical, factor and continuous variables

•Treatment dose is normalized by median value, and considered as a continuous variable

$$\log\left(\frac{p_{ij}}{1-p_{ij}}\right) = \sum_{k=1}^{m} X_{ijk}.\beta_{ijk} + \eta_j \qquad (1)$$

$X_{ijk}$ is a vector of $k$ covariate values observed in the *ith* arm of the *jth* study

$\beta_{ijk}$ is a vector of parameter coefficients to be estimated

$\eta_j \sim N(0,\sigma^2)$ is study random effect

## Model Summary and Results

Model for Dropouts due to AE

| Parameter | Value | Std.Error | DF | t-value | p-value |
|---|---|---|---|---|---|
| Placebo | -2.72 | 0.12 | 53 | -21.8 | < 0.0001 |
| Non-Opd | -2.53 | 0.31 | 53 | -8.2 | < 0.0001 |
| Moderate Opd | -2.37 | 0.18 | 53 | -12.8 | < 0.0001 |
| Strong Opd | -1.77 | 0.28 | 53 | -6.3 | < 0.0001 |
| Tapentadol | -1.65 | 0.2 | 53 | -8.4 | < 0.0001 |
| Oxymorphone | 0.91 | 0.24 | 53 | 3.8 | < 0.0001 |
| ose of Moderate Opd | 0.85 | 0.14 | 53 | 5.9 | < 0.0001 |
| Dose of Strong Opd | 0.71 | 0.24 | 53 | 2.9 | 0.005 |
| SD Study RE | 0.37 | - | - | - | - |
| SD Resid Err | 1.36 | - | - | - | - |

# studies=39, # Subjects=12269

Model for Proportion with Consitpation

| Parameter | Value | Std.Error | DF | t-value | p-value |
|---|---|---|---|---|---|
| Placebo | -3.13 | 0.18 | 44 | -17.3 | < 0.0001 |
| Non-Opd | -2.72 | 0.36 | 44 | -7.5 | < 0.0001 |
| Moderate Opd | -2.53 | 0.25 | 44 | -10 | < 0.0001 |
| Strong Opd | -1.09 | 0.18 | 44 | -6.2 | < 0.0001 |
| Tapentadol | -2.15 | 0.21 | 44 | -10 | < 0.0001 |
| Dose of Moderate Opd | 0.58 | 0.16 | 44 | 3.7 | 0.001 |
| SD Study RE | 0.71 | - | - | - | - |
| SD Resid Err | 1.23 | - | - | - | - |

# studies=31, # Subjects=10846

Model for Proportion with Nausea

| Parameter | Value | Std.Error | DF | t-value | p-value |
|---|---|---|---|---|---|
| Placebo | -2.5 | 0.16 | 42 | -15.9 | < 0.0001 |
| Non-Opd | -2.44 | 0.46 | 42 | -5.3 | < 0.0001 |
| Moderate Opd | -1.97 | 0.25 | 42 | -7.8 | < 0.0001 |
| Strong Opd | -0.78 | 0.15 | 42 | -5.3 | < 0.0001 |
| Tapentadol | -1.48 | 0.2 | 42 | -7.4 | < 0.0001 |
| Oxymorphone | 0.56 | 0.27 | 42 | 2 | 0.048 |
| Dose of Moderate Opd | 0.47 | 0.18 | 42 | 2.7 | 0.011 |
| SD Study RE | 0.47 | - | - | - | - |
| SD Resid Err | 1.69 | - | - | - | - |

# studies=30, # Subjects=10726

- The database included about 40 studies on 12 treatments involving over 12000 OA patients.
- A general Linear Mixed Effects Model (glme in Splus) was found suitable in describing the proportions of dropouts and proportions of AE's.
- The large sample size provided high statistical power and produced precise model estimates
- Diagnostic plots indicated adequacy of the model fit. Figure 1 shows plots for the dropout model
- All three models determined that strong opioids increase the chances of constipation, nausea and dropout rates.
- Using placebo as a reference group, strong opioids have odds ratios of 7.7, 5.6 and 5.3, respectively. For moderate opioids, the odds ratios were 3.3, 2.7 and 3.3 and for Non-opioids they were 1.5, 1.1 and 1.2.
- Inference on influence of dose is limited by the dose ranges investigated. However, the dropout model indicated a dose effect for moderate and strong opioids
- Using model predictions, the distribution of "placebo adjusted" proportions are readily available from model estimates. Figure 2 shows increase in dropout rates in different classes.

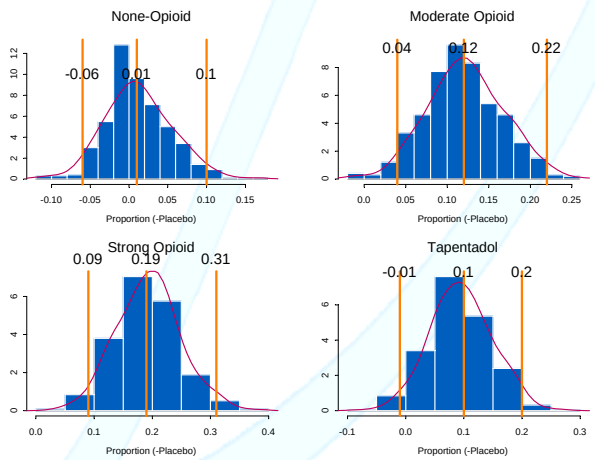
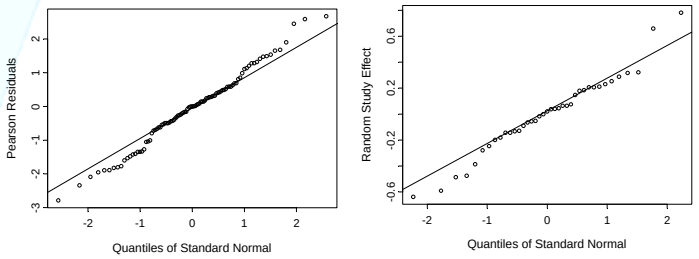



Figure 2: Distribution of predicted dropout rates (placebo subtracted)



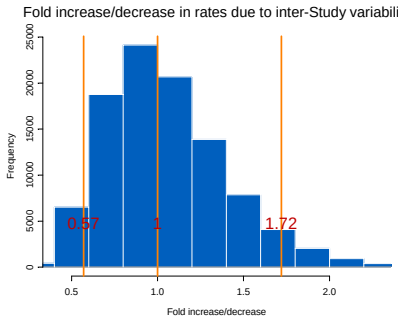




Figure 1:Diagnostic plots of Dropout model: Normal plots of Pearson residuals and random study effect (top) and Distribution of fold increase in rates due to inter-Study variability

## CONCLUSIONS

- The models established that rates of AE's and dropouts increase significantly with the strength of opioids.
- While benefits of Meta analysis using public literature are well established [1,2] , models for proportions have the added advantage of increased statistical power, a consequence of using subject level information.