A Model Based Meta-analysis (MBMA) to Support Development of Medicines for Treatment of DPN, PHN and Fibromyalgia

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GOAL

- To develop a model-based meta-analysis (MBMA) comparator model for neuropathic pain to provide a quantitative framework for comparison of drugs commonly used for the treatment of diabetic peripheral neuropathy (DPN), post-herpetic neuralgia (PHN), and fibromyalgia.

BACKGROUND

Neuropathic Pain

- Neuropathic pain is caused by a lesion or disease of the central or peripheral somatosensory nervous system
- Common peripheral neuropathic pain conditions are DPN (caused by high sugar) and PHN (caused by viral damage to nerve cells after shingles infection)
- Fibromyalgia is an example of central neuropathic pain characterized by widespread musculoskeletal pain accompanied by fatigue, sleep, memory, and mood issues
- Several recommendations for the treatment of neuropathic pain have been proposed[1,2]
- Evidence-based recommendations for the treatment of neuropathic pain are essential, eg, based on meta-analyses of 30% and 50% pain intensity reduction (PID30, PID50) as primary efficacy measure[3]

MBMA

- Model-based meta-analysis (MBMA) was introduced in 2005[4] and has become an increasingly important tool in drug development to inform future study designs and quantitative decision making
- Treatment effects of different drugs across different patient populations are compared by including head-to-head comparisons and indirect comparisons of drugs from randomized controlled trials in a meta-analysis
- MBMA includes dose-response and/or time-course models and allows joint response modeling of multiple correlated endpoints

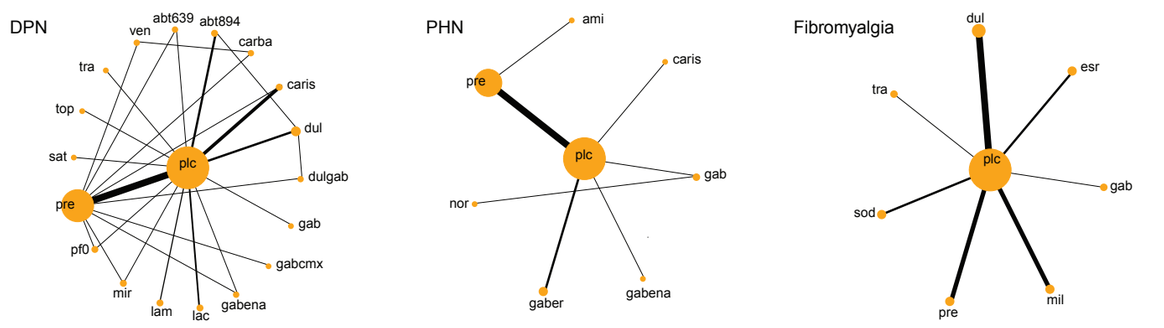
OBJECTIVE

- To develop a joint response MBMA model describing the proportion of patients who achieved ≥30% reduction (PID30) and ≥50% reduction (PID50) from baseline in pain score.

DATA

- The analysis dataset consisted of publicly available, summary-level clinical trial data from 74 randomized controlled trials involving more than 26,000 patients
  - 38 trials in DPN, 15 in PHN, and 21 in fibromyalgia
  - 61 trials with PID30, 66 with PID50, and 53 with both PID30 and PID50
- The dataset included patient and trial characteristics and PID30 and PID50 responder rate for 21 drugs and 3 combined therapies across 9 drug classes
  - Longitudinal PID30 and PID50 data
  - PID30 and PID50 data for a range of doses for 12 of the 21 drugs

Figure 1. Network diagram of the analysis dataset. Each compound is represented by a node. Direct comparisons within a trial are linked by a line. The width of the line is proportional to the number of studies



abt639, abt-639; abt894, abt-894; carba, carbamazepine; caris, carisbamate; dul, duloxetine; dulgab, duloxetine + gabapentin; esr, esreboxetine; gab, gabapentin; gabcmx, gabapentin + b complex; gabena, gabapentin enacarbil; gaber, gabapentin er; lac, lacosamide; lam, lamotrigine; mil, milnacipran; mir, mirogabalin; pf0, pf05089771; plc, placebo; pre, pregabalin; sat, sativex; sod, sodium oxybate; top, topiramate; tra, tramadol + acetaminophen; ven, venlafaxine

MBMA Model Structure

- Joint response model describing the proportion of patients who achieved a reduction from baseline in pain score of at least 30% (PID30) and at least 50% (PID50)
- The number of patients with PID response at time *t* in treatment arm *j* of trial *i* for endpoint *k* (PID30, PID50) is assumed to follow a binomial distribution with probability of response $P(PID)_{ijkt}$ and sample size N_{ijkt}

$$N_{PID,ijkt} \sim binomial\,(N_{ijkt},\ P(PID)_{ijkt})$$

- The probability of response is described as the inverse logit sum of a non-parametric (unstructured) placebo response *eo* and a parametric treatment effect *f(drug, dose, θ, X)*, depending on drug, dose, model parameters θ, and trial covariates X

$$P(PIDk)_{ijkt} = logit^{-1}(eo_{it} + eo_{ik} + f(Drug_{ij}, Dose_{ij}, X_{ij}, \theta) \cdot (1 + et_{ik}))$$

with $logit^{-1}$ the inverse logit transform to keep the probabilities between 0 and 1

  - *f(θ)* is typically a general drug effect or E_{max}-shaped dose-response model
  - eo_{it} is an unstructured placebo model defined by a fixed effect for every trial *i* at time point *t* representing the logit of the PID50 placebo response
  - eo_{ik} and et_{ik} represent a shift in placebo response and drug response on the logit scale from PID50 or PID30 for every trial *i*, respectively
- Trial-to-trial variability in PID response is described by trial-specific random effects ηo_{ik} with mean θo_k and variance ωo_k^2 and ηt_{ik} with mean θt_k and variance ωt_k^2

$$eo_{ik} = eo_k + \eta o_{ik} \quad \text{and} \quad et_{ik} = et_k + \eta t_{ik}$$

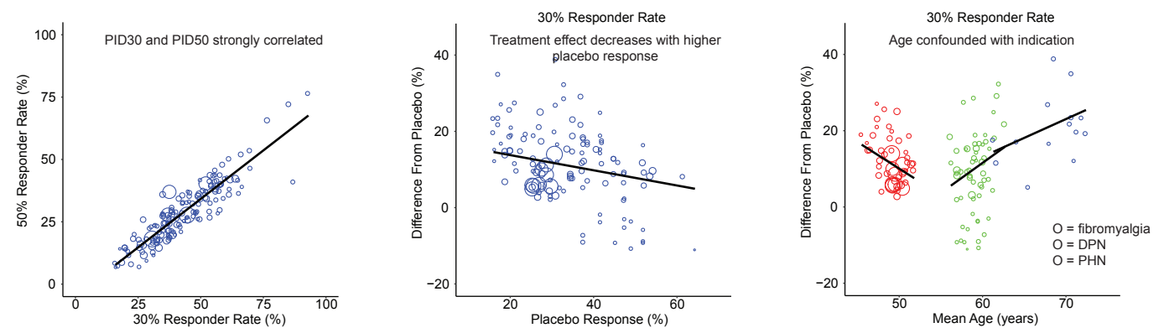
- The correlation between time points is accounted for by assuming a compound symmetry correlation structure for all observations within an endpoint, within one arm within a trial

Final MBMA Model

- MBMA model developed in R (version 3.3.2) using the nlme function
- Drug-specific treatment effects within an indication
  - Described by a constant or E_{max}-shaped dose-response
  - Shared E_{max} within a drug class
  - Drug-specific potency (ED_{50}) across indications
- Onset of treatment effect by drug class was similar to onset of placebo effect or was not estimable
- Additional covariates were evaluated after initial analysis
  - Age had a significant effect on treatment effect (difference from placebo)
    - Common age effect for DPN and PHN: OR (95% CI) = 1.10 (1.05-1.15); age effect not significant for fibromyalgia
    - Age confounded with indication
  - Other covariates were evaluated but were found to be not statistically significant: mean body weight, mean baseline pain score, mean disease duration, sex, race, and imputation method
    - Baseline pain score was not found to be statistically significant based on *P*-value = 0.07 and therefore was not included in the model
- Additional sensitivity analysis to be carried out (ie, imputation method)

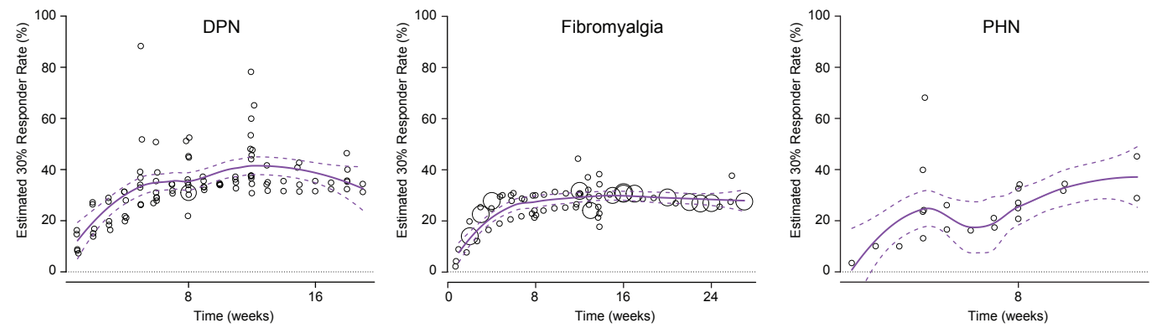
RESULTS

Figure 2. Exploratory plots of the endpoints at primary time point



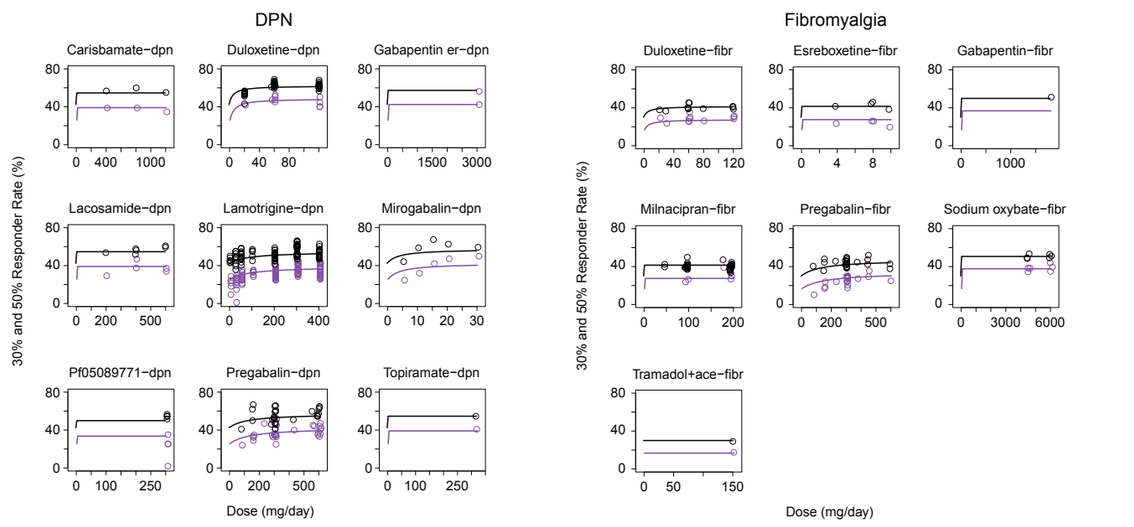
- Magnitude of placebo response is lower for fibromyalgia (29.9%) than for DPN (41.5%) and PHN (37.1%)

Figure 3. Estimated non-parametric placebo response (eo_{it}) of the 30% responder rate with LOESS fit (95% CI)



- Drug potency (ED_{50}) could be estimated for duloxetine, mirogabalin, pregabalin, gabapentin enacarbil, and lamotrigine

Figure 4. Observed and model-predicted dose-response for a subset of drugs included in the analysis dataset

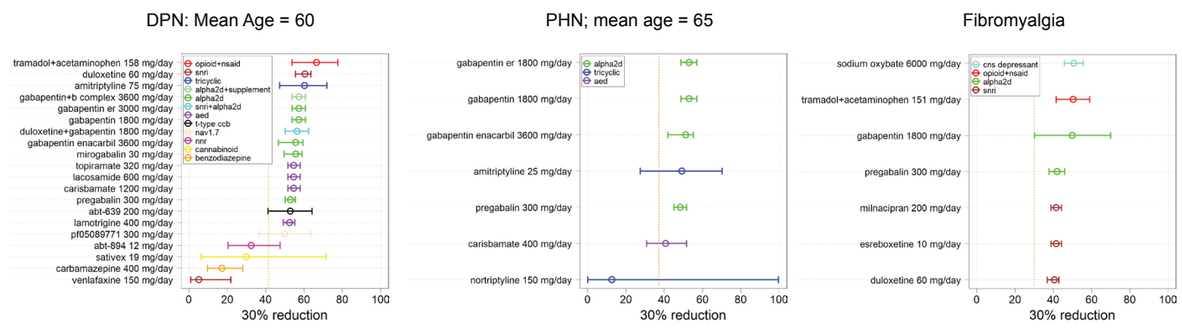


Black and purple curves and markers show 30% and 50% reduction rates, respectively. Estimated placebo response at dose = 0. Symbol size proportional to sample size.

- Forest plots allow the comparison of treatment effect estimates of common drugs in DPN, PHN, and fibromyalgia (shown for PID30 only)

Figure 5. Estimated treatment effect (mean, 95% CI) on an absolute scale for the 30% reduction rate by drug and indication relative to an estimated maximum placebo response of 41.5% for DPN, 37.1% for PHN, and 29.9% for fibromyalgia (orange dotted vertical line)

- Treatment effect estimates with associated 95% confidence intervals were derived as the mean and 2.5th-97.5th percentile intervals across 3,000 simulated data sets with parameter values sampled from the multivariate normal variance-covariance matrix of the estimates
- The estimated mean shift in placebo response and drug response on the logit scale from PID50 to PID30 (eo_k and et_k) inform the treatment effect estimates for the 50% reduction rate



SUMMARY AND CONCLUSIONS

- MBMA provides a quantitative framework for benchmarking new investigational compounds to SOC and improves understanding of drug-response relationship for compounds used in treatment of pain
- The current analysis of the 30% and 50% reduction rates in pain score from baseline shows a lower placebo response for fibromyalgia than for DPN and PHN and a decrease in treatment effect for increasing placebo response
- Age had a statistically significant effect on treatment effect for DPN and PHN. All other tested covariates were not statistically significant

References

1. Dworkin RH, et al. *Pain*. 2007;132(3):237-251.
2. WATAG Advisory Note: Guidelines for the pharmacological treatment of neuropathic pain (2017).
3. Finnerup NB, et al. *Lancet Neurol*. 2015;14(2):162-173.
4. Mandema JW, et al. *Cephalalgia*. 2005;25(9):715-725.

Presented at PAGE: Population Approach Group in Europe; Montreux, Switzerland, May 29-June 1, 2018.