

Concentration-Response Modeling of Adverse Event Data using a Markov Chain Approach

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INTRODUCTION

- An experimental drug, LY, was being evaluated for use as a once weekly subcutaneous injection.
- The most common treatment-emergent adverse events in patients treated with LY were gastrointestinal, consistent with the safety profile of this class. Nausea and vomiting were the most frequently reported.
- The incidence of nausea/vomiting was dose dependent and greatest after the first dose of LY, at approximately the time of maximum concentration (day 2 to 3).
- Incidence of nausea and vomiting declined rapidly after the first 2 weeks of treatment.
- The development team was interested in whether patients would benefit from dose titration to the optimal dose level (20 LY).

OBJECTIVES

The objective of this analysis was to develop an exposure-response model to enable simulations of nausea and vomiting incidence under various dose titration regimens.

The model had to be able to characterize:

- Onset of nausea/vomiting following dose administration.
- Duration and severity of nausea/vomiting events.
- Relationship of LY concentration with onset, duration, and severity.
- Development of tolerance.
- Relationship between nausea and vomiting incidence.

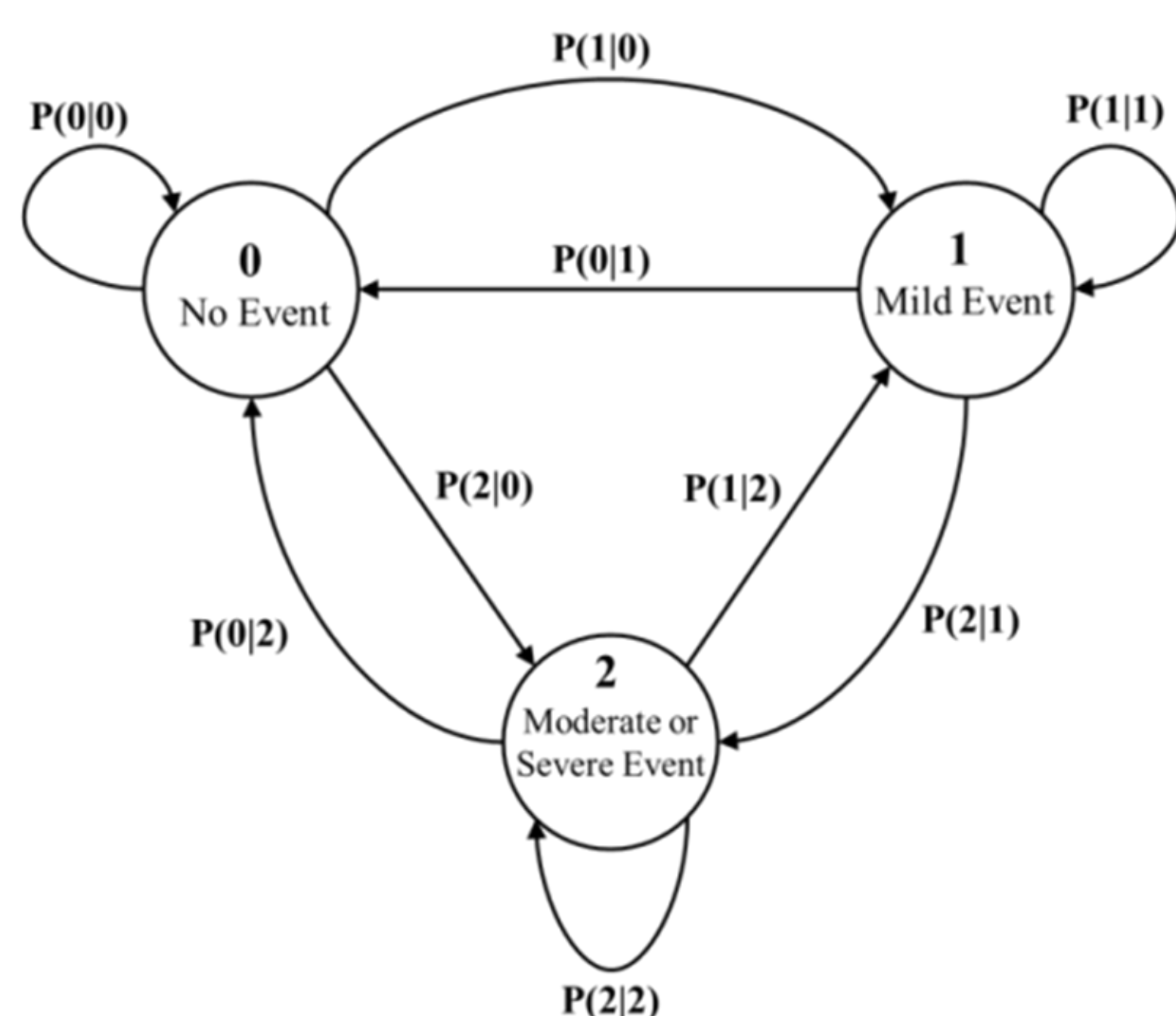
METHODS

- The analysis was conducted using data from 4 clinical pharmacology studies in both healthy subjects and patients.
- Single and multiple dose safety studies were included to capture higher doses with greater incidence rates, and to provide a wide dose range for model development.
- Data from elderly patients was included to capture longer duration of administration with targeted dose levels.

Population	Doses Administered	Duration	N
Healthy subjects	Placebo, 2, 5, 20, 50, 100, and 200	Single dose	20
Japanese Patients	Placebo, 5, 20, 50, and 100	Single dose	40
Patients	Placebo, 0.8, 5, 20, 50, 80, and 100	5 Weeks	43
Patients ≥ 65 years	Placebo, 8, 10, and 20	6 Weeks	37

Markov Chain Approach

- Nausea/vomiting severity was modeled as different states within a Markov Chain.
- Onset and duration of event were governed by transition to a nausea or vomiting state, and how long the system remained in that state.
- The relationship of concentration to onset, duration, and severity was governed by concentration-response on the transition probabilities between states.
- Development of tolerance was included as additional concentration-response relationships.

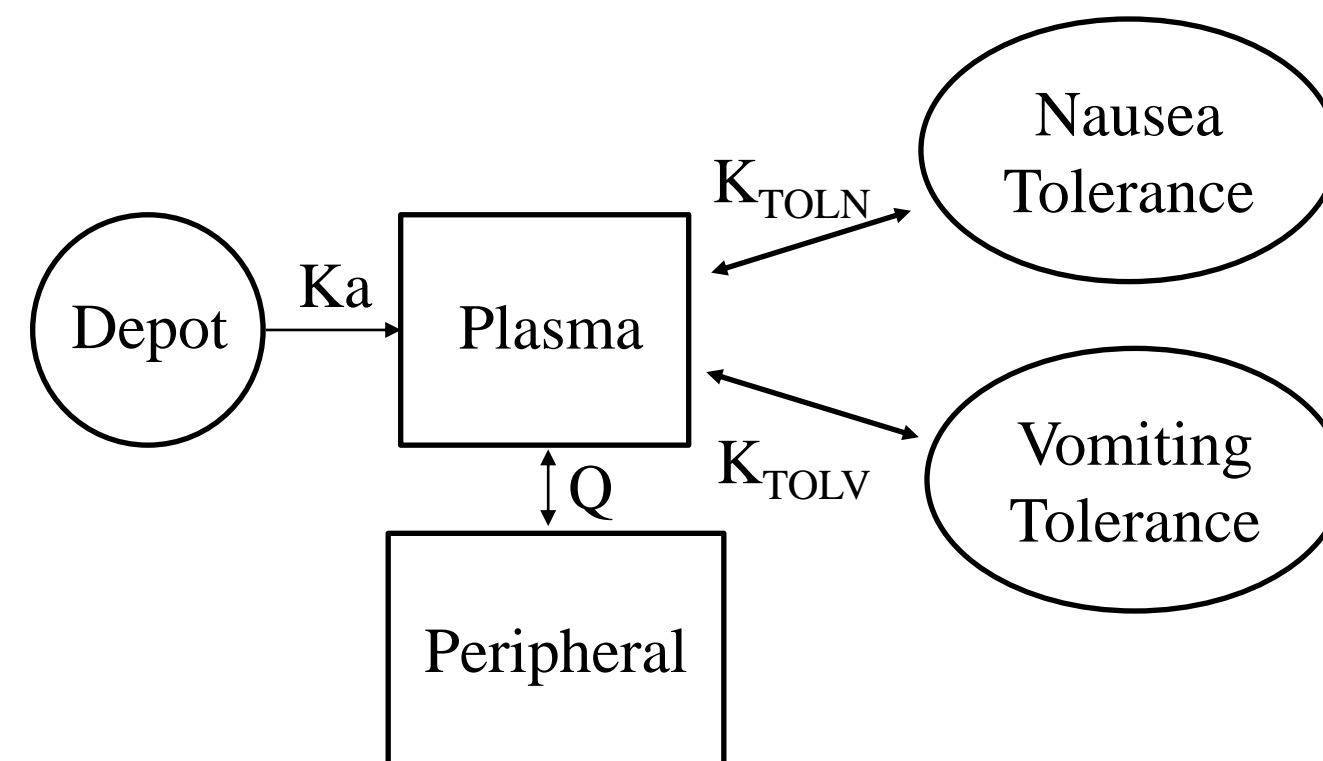


Markov State Diagram

Effect of prior nausea on vomiting, and prior vomiting on nausea tested as additional prior states (not represented on diagram).

Pharmacokinetic Model

- Two-compartment model with first order absorption.
- Separate effect compartments for nausea and vomiting, allowing different rates of tolerance development.



Concentration-Response

- A summary measure of exposure (e.g. AUC or C_{ss}) does not allow characterization of nausea/vomiting in relation to the time-concentration profile.
- LY Concentration at the mid-point of the Markov Chain interval was selected as a concentration measure. This is a good approximation to the mean concentration over an interval when the concentration is monotonically increasing or decreasing.
- A 1-hour time interval was chosen for the MCMC analysis, to follow the concentration profile closely over time and minimize intervals which violate the monotonicity assumption.
- Nausea/vomiting events were incorporated in the dataset at the midpoint of each defined interval, facilitating concentration prediction at those times. This approach simplified both dataset construction and analysis.

Model Form

Increased concentration in plasma (C_p) is assumed to increase the transition probability of the adverse event. Increased concentration in tolerance compartment (C_T) is assumed to decrease the effect of plasma concentration on the transition probability.

For each prior state:

$$XG_1 = A_1 + C_p * Slope_1 * \left[1 - \frac{C_T * T_{MAX}}{TC_{50} + C_T} \right] \quad LG_1 = \frac{e^{XG_1}}{1 + e^{XG_1}}$$

$$XG_2 = A_2 + C_p * Slope_2 * \left[1 - \frac{C_T * T_{MAX}}{TC_{50} + C_T} \right] \quad LG_2 = \frac{e^{XG_2}}{1 + e^{XG_2}}$$

$$P_0 = 1 - LG_1 \quad \text{Probability of no event.}$$

$$P_1 = LG_1 * (1 - LG_2) \quad \text{Probability of mild event.}$$

$$P_2 = LG_1 * LG_2 \quad \text{Probability of moderate/severe event.}$$

Where LG_i is likelihood state ≥ 1; LG₂ is likelihood state =2, given state ≥ 1; A₁ and A₂ are the base logit values for these two likelihoods; Slope₁ and Slope₂ are the concentration-response parameters for these two likelihoods; T_{max} is the maximum developed tolerance; and TC₅₀ is the C_i which corresponds to half-maximal tolerance.

All analyses were conducted using NONMEM 7.2¹. Models were qualified for simulation using visual and numerical predictive checks.

RESULTS

Nausea

- Increased LY concentration was found to increase:
 - the probability of nausea, regardless of prior state.
 - the probability of remaining in a moderate/severe state
- Sustained exposure was found to cause tolerance, decreasing the probability of becoming nauseous.

Vomiting

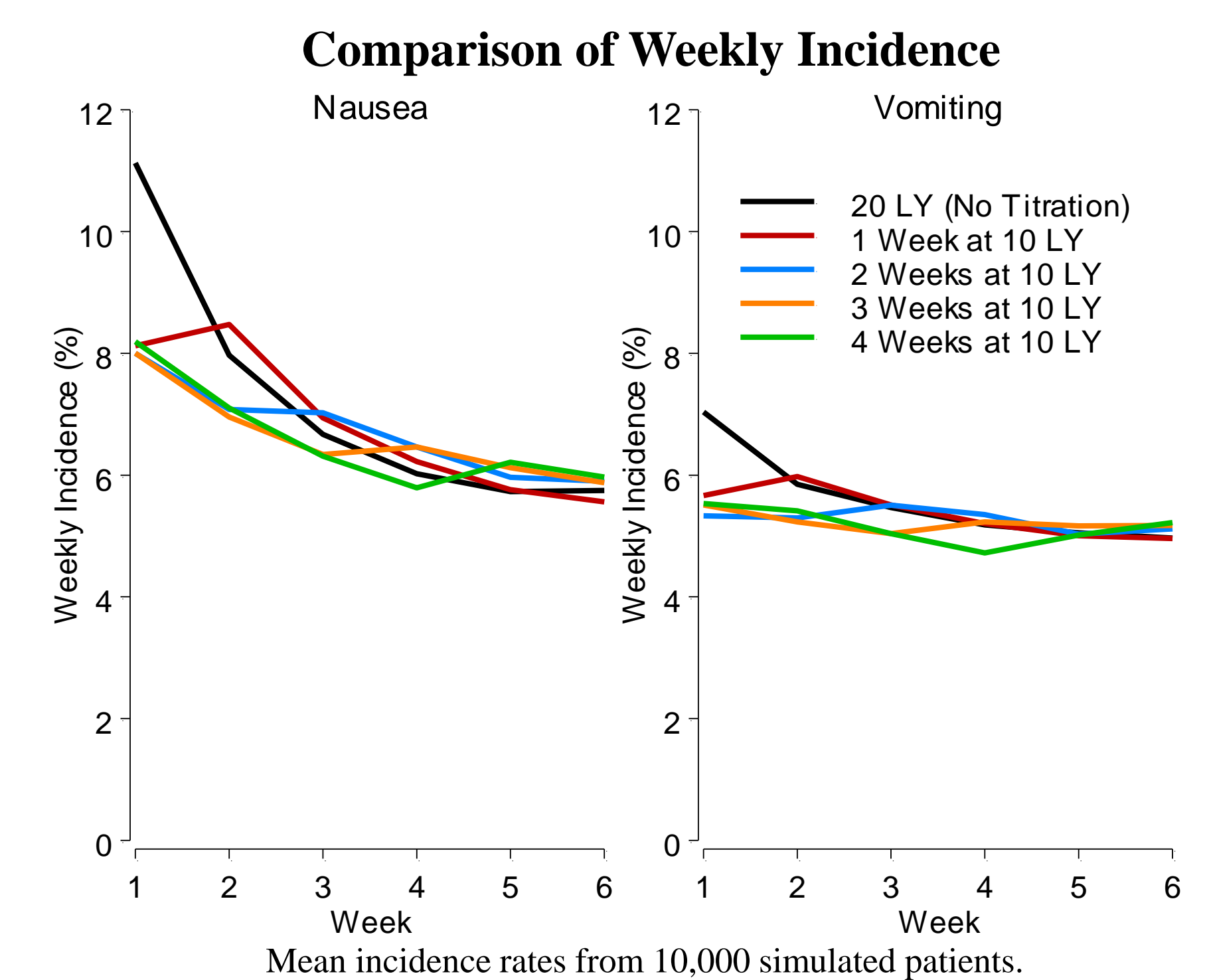
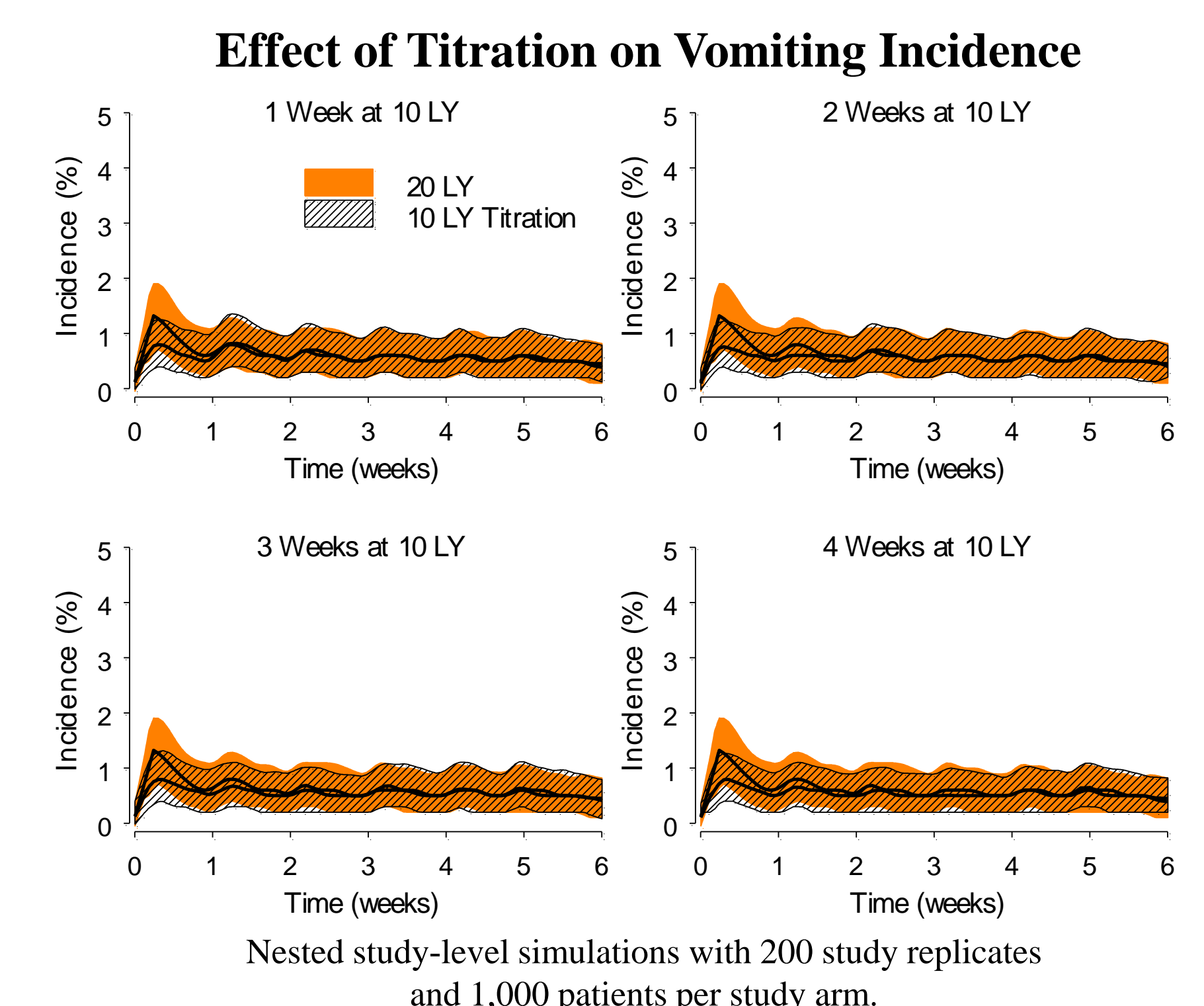
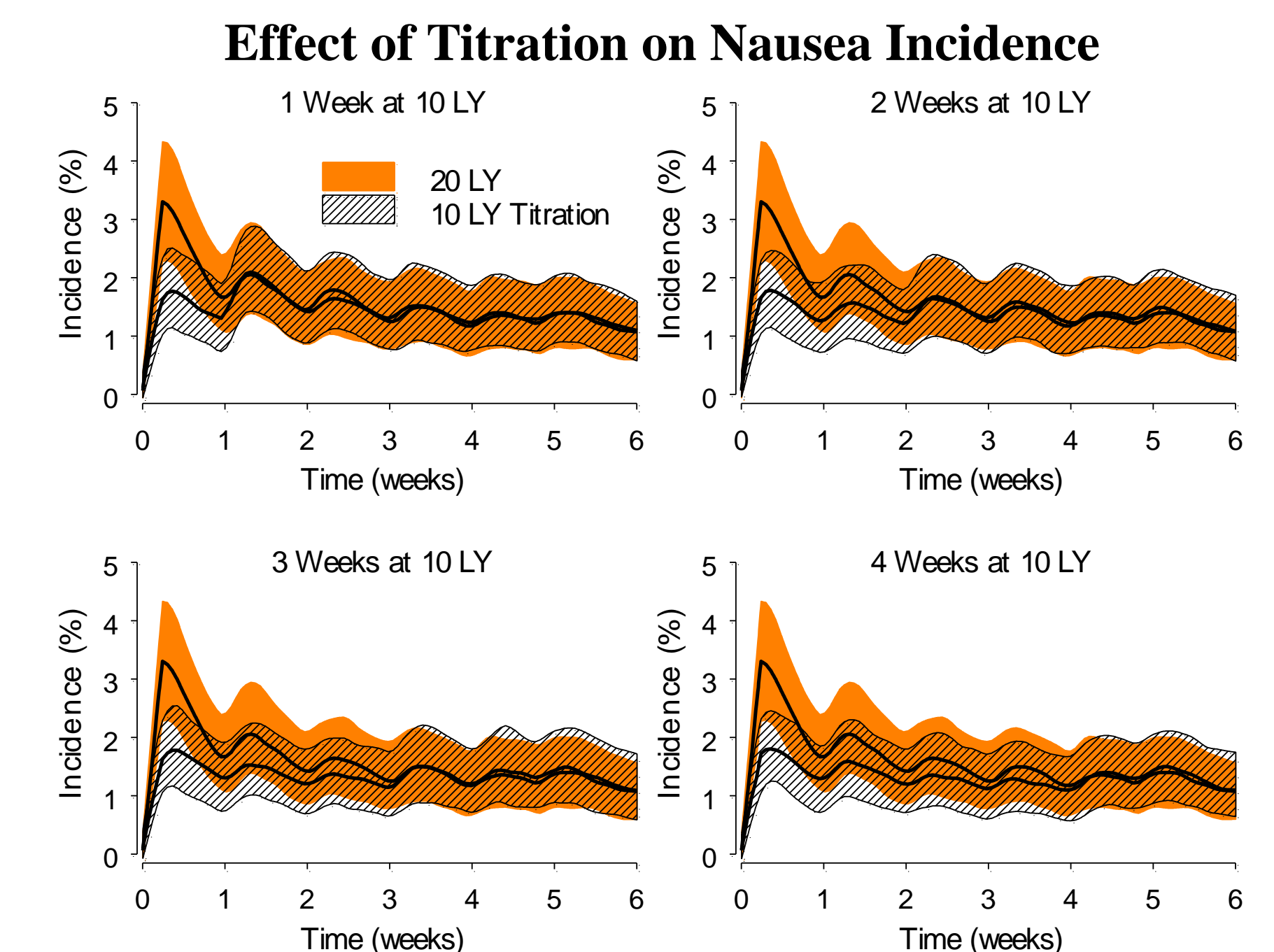
- Probability of vomiting was higher following prior nausea.
- Increased LY concentration was found to increase the probability of entering a vomiting state.
- The probability of continuing to vomit was not affected by LY concentration or previous nausea state.
- Once vomiting commenced, there was no transition between severities.
- Sustained exposure to LY was found to cause tolerance, decreasing the probability of beginning to vomit.

Simulation of Titration Regimens

Different scenarios for the effect of titration on incidence of nausea/vomiting were simulated for the targeted dose levels:

- No titration, 20 LY
- 1-4 weeks of 10 LY, followed by 20 LY.

The linked nausea/vomiting model was recoded into R and imported into the automated simulation system, MuSE².



CONCLUSIONS

The Markov Chain approach has general applicability to the modeling of adverse events, allowing characterization of:

- Onset of nausea/vomiting following dose administration.
- Duration and severity of nausea/vomiting events.
- Relationship of LY concentration with onset, duration, and severity.
- Development of tolerance.
- Relationships between AE endpoints.

The model suggests that titration with 1 week of LY slightly reduces incidence of nausea and vomiting during initial treatment.

The low incidence of both nausea and vomiting and the lack of significant benefit to the patient of a titration approach, support that the 20 LY dose can be administered without need for titration.

References

- Beal, S., Sheiner, L.B., Boeckmann, A., & Bauer, R.J., NONMEM User's Guides. (1989-20013), Icon Development Solutions, Ellicott City, MD, USA, 20013.
- Heathman M, Jennings D, and Lee B. 2010. Interactive Simulation and Visualization of Drug/Disease Models. PAGE; 2010, June 8-11; Berlin, Germany.