

# Pharmacodynamic Differentiation of Lorazepam Sleepiness and Dizziness Using an Ordered Categorical Measure

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**ABSTRACT:** Categorical measures of lorazepam sleepiness and dizziness were modeled to identify differences in pharmacodynamic (PD) parameters between these adverse events (AEs). Differences in data-derived PD parameters were compared with relative incidence rates in the drug label (15.7% and 6.9%, respectively). Healthy volunteers ( $n = 20$ ) received single oral doses of 2 mg lorazepam or placebo in a randomized, double-blind, cross-over fashion. A seven-point categorical scale measuring the intensity of AEs was serially administered over 24 h. The maximum score (MaxS), and area under the effect curve (AUEC) were determined by noncompartmental methods and compared using a paired *t*-test. Individual scores were modeled using a logistic function implemented in NONMEM. AUEC and MaxS for sleepiness were significantly higher than dizziness (20.35 vs. 9.76,  $p < 0.01$ ) and (2.35 vs. 1.45,  $p < 0.01$ ). Model slope estimates were similar for sleepiness and dizziness (0.21 logits  $\times$  mL/ng vs. 0.19 logits  $\times$  mL/ng), but baseline logits were significantly higher for sleepiness ( $-2.81$  vs.  $-4.34$  logits). Data-derived PD parameters were in concordance with label incidence rates. The higher intensity of sleepiness may be directly related to baseline (no drug present) while the increase in intensity as a result of drug was relatively similar for both AEs. © 2010 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 99:3628–3641, 2010

**Keywords:** lorazepam; sleepiness; dizziness; adverse events; ordered categorical; pharmacodynamics

## INTRODUCTION

Ordered categorical scales have been used in a variety of clinical settings to measure subjective effects and feelings, which are clinically relevant yet difficult to measure using objective tests. A good example is pain where several analgesic trials used various categorical scales.<sup>1,2</sup> Such scales have been reported to display high validity and reproducibility<sup>2,3</sup> during repeated assessments and are usually quick and easy to administer.<sup>1</sup>

Pharmacokinetic–pharmacodynamic (PK/PD) modeling of categorical responses may also provide insight into the PD of adverse events (AEs). The

feasibility of using different subjective scales as biomarkers of AEs was investigated in a small clinical pharmacology study.<sup>4</sup> As part of that study, seven-point ordered categorical scales measuring different types of subjective response (e.g., sleepiness, dizziness, etc.) were administered serially after single-dose administration to measure intensity of drug effects over 24 h. Inspection of the effect-time profiles of the more common drug effects showed differential profiles for the different CNS agents, the onset and offset of response as well as the relationship to plasma concentrations.

The current analysis focuses on the categorical measures of two AEs of one of the representative CNS drugs studied,<sup>4</sup> namely lorazepam sleepiness and dizziness, with an aim to identify differences in relevant pharmacodynamic parameters using a PK/PD modeling approach. To date, no pharmacodynamic data, whether being categorical or continuous,

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have been published contrasting lorazepam induced sleepiness and dizziness in the context of population modeling. Their incidence rates in the drug label offer a unique benchmark for comparison. Thus, any differences found in PD measures between sleepiness and dizziness in the current analysis will be compared with differences in incidence rates in the drug label.<sup>5</sup>

From the spectrum of CNS effects measured in the larger study,<sup>4</sup> lorazepam sleepiness and dizziness were selected as the endpoints of interest because: (1) these effects showed a relatively high-scale signal amplitude and highest statistical significance in the time-averaged change from baseline differences with placebo, (2) sleepiness is a more common AE of lorazepam than dizziness according to incidence rates in the label,<sup>5</sup> and (3) their pharmacology is thought to be conferred by benzodiazepine receptor activity in distinctly different areas of the CNS.<sup>6,7</sup> It must be noted that modeling categorical data cannot be performed using conventional nonlinear regression because it has a polynomial distribution which violates the assumption of homogeneity of variance.<sup>8</sup> Therefore, the probabilities of reporting the effect categories as a function of time are typically modeled using logistic regression. The current study employs a logistic function<sup>9,10</sup> to model sleepiness and dizziness categorical scores and assesses model performance using previously published pharmacometric methodology.<sup>11,12</sup>

## METHODS

### Data Collection

Twenty healthy volunteers were randomized in a double-blind, single-dose, five-way crossover design.<sup>4</sup> All subjects gave written informed consent to participate in the study. The study was conducted at the Clinical Pharmacology Unit of Pfizer (Ann Arbor, MI) in accordance with the principles of the Declaration of Helsinki. The study protocol was approved and performed in compliance with the Institutional Review Board/Independent Ethics Committee (IRB/IEC) and International Committee on Harmonization (ICH) Good Clinical Practice guidelines. Each subject received an oral dose of either lorazepam 2 mg, as one of four CNS drugs, or placebo. All study drugs were commonly used marketed compounds within their respective therapeutic indications and were selected to produce different AE profiles which could potentially be measurable after single-dose administration. Each regimen was separated by a 1-week washout period for a total trial period of five consecutive weeks. Based on the half-life of each study drug, this washout period was deemed adequate to ensure lack of any period effect on baseline PD measures. Blood samples were drawn

before dosing and at 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24, 48, and 72 h after the morning dose.

Prior to each blood collection during the first 24 h, a 70-item questionnaire was administered. Items on the questionnaire covered various complaints, symptoms, or feelings the subject experienced. For each statement, the subject was to answer how strongly he or she felt the complaint, symptom, or feeling on a seven-point ordered categorical scale. The seven effect categories were: 0 = none, 1 = minimum, 2 = mild, 3 = moderate, 4 = significant, 5 = severe, and 6 = extreme.

### Analytical Assay

Plasma levels of lorazepam were determined using liquid chromatography tandem mass spectrometry (LC/MS/MS) at PPD Development (Richmond, VA). Briefly, 0.1 mL of human plasma containing sodium heparin was extracted by a liquid-liquid extraction using methyl-*t*-butyl ether. The organic extract was dried and reconstituted in 0.2 mL of formic acid/methanol/5 mM ammonium formate (0.1:50:50, v/v/v), and an aliquot was injected into the LC/MS/MS system. The compounds were separated by reverse phase on a C<sub>18</sub> column (2.0 mm × 50 mm, 5 μm) by gradient elution using a binary mobile phase consisting of formic acid/methanol/water (0.1:10:90, v/v/v) and 0.1% formic acid in methanol (v/v). The analytes were ionized in the mass spectrometer in a Turbo IonSpray source with positive ion atmospheric pressure electrospray ionization and detected with multiple-reaction monitoring modes. The nominal ion transitions monitored were  $m/z = 321 > 275$  for lorazepam and  $m/z = 327 > 281$  for the internal standard (lorazepam-d<sub>4</sub>). These transition ions were selected based on predominant fragmentation pathways of lorazepam and internal standard and their intensity, as observed in their product ion mass spectra. The lorazepam standard curve was linear over the range of 0.5 ng/mL (the lower limit of quantitation) to 50 ng/mL when 0.1 mL plasma was used for the analysis ( $r^2 > 0.998$ ). The intra- and inter-assay variations were less than 15% for the spiked standard curve and quality control samples. The variations for the quality control samples during the long-term study were <12%.

### Data Analyses

#### Pharmacokinetics

A noncompartmental analysis<sup>13</sup> was performed using WinNonLin version 5.2 (Pharsight, Inc., Mountain View, CA) on lorazepam plasma concentration-time profiles to determine maximal concentration ( $C_{\max}$ ), time to maximal concentration ( $T_{\max}$ ), area under the curve from time zero to infinity ( $AUC_{0-\infty}$ ) and the terminal half-life ( $t_{1/2}$ ). Compartmental population

analyses were conducted in NONMEM V<sup>14</sup> using the first-order conditional estimation method with interaction. The general model building strategy is based on modification of different approaches discussed by Beal and Sheiner,<sup>14</sup> Mandema et al.,<sup>15</sup> and Ette and Ludden.<sup>16</sup> During model building, the goodness-of-fit of different models to the data was evaluated using the following criteria: change in the minimum objective function (MOF), visual inspection of concordance and residual plots, precision of the parameter estimates, and decreases in both inter-individual and residual variability. A decrease in the MOF of at least 3.8 upon addition of a parameter was considered statistically significant. This corresponds to a nominal *p*-value of <0.05 and one degree of freedom in the chi-square distribution of the difference of MOF between hierarchical models.

The initial PK model was a one-compartment model defined in terms of the following structural parameters: oral clearance (CL/F), volume of distribution (V1/F), and first-order rate constant for absorption ( $k_a$ ). Other models tested include a term for lag time in absorption (tlag) and/or 2 compartments. Inter-subject variability on mean PK parameters was modeled using an exponential error term and was estimated sequentially on structural parameters such as oral clearance (CL/F), volume of distribution in the central and peripheral compartments (V1/F, V2/F), and on the first-order absorption rate constant ( $k_a$ ). Various models of residual variability were tested including additive, proportional and combined additive/proportional error models. During model building, the off-diagonal elements of the variance-covariance matrix were fixed to 0, that is, it was assumed that there was no correlation between PK parameters. In the final step, the correlation between all parameters was estimated in NONMEM.

Parameter estimates of CL/F and  $t_{1/2}$  were compared with the noncompartmental results to ensure that model was adequate. Confidence intervals around parameter estimates were generated using nonparametric bootstrap procedure ( $n = 1000$  runs) as described by Ette et al.<sup>11</sup>

### Pharmacodynamics

To produce a typical value versus time curve for sleepiness and dizziness categorical scores, the expected value at each time-point was calculated. The expected value or average score of the categorical measure of sleepiness and dizziness at time  $t$  can be defined by the following equation:

$$E(X) = \sum_{X \in M} x_t \times P(x) \quad (1)$$

where  $X$  is the discrete random variable denoting the categorical measure of sleepiness or dizziness,  $x_t$  is

the categorical sleepiness or dizziness score at time  $t$  with a set of possible categorical values  $m$  ranging from 0 to 6, and  $P(x)$  is the probability (obtained as a frequency) of reporting a categorical score  $x$  at time  $t$ . To examine whether or not there were differences in sleepiness and dizziness intensities, a noncompartmental analysis of the time course of average sleepiness and dizziness scores was conducted. Effect intensity endpoints determined were maximum score (MaxS) and area under the effect curve (AUEC) over the entire dosing interval (24 h). A paired  $t$ -test was used to determine whether differences in MaxS and AUEC between sleepiness and dizziness were statistically significant.

Population modeling of the time course of sleepiness and dizziness scores was implemented in NONMEM<sup>14</sup> using a logistic function<sup>9,10</sup> with the second-order Laplacian method of estimation<sup>14</sup> As the intensity of pharmacodynamic effect was self-rated on the seven-point categorical scale (0–6), the logistic function was used to model the probability ( $P$ ) of observing scores  $p \geq m$  ( $m = 0–6$ ) as a function of baseline effect, drug concentrations, and placebo effect. The logistic function used was:

$$gP\{Y_t \geq m_\eta\} = \sum_{i=1}^m \beta_m + \text{drug} + \text{placebo} + \eta \quad (2)$$

where  $g[P\{Y_t \geq m_\eta\}]$  is the function describing the probability of being greater than or equal to a particular effect category,  $m$ ;  $\sum_{i=1}^m \beta_m$  is the sum of baseline parameters ( $\beta_1, \beta_2, \beta_3, \dots, \beta_m$ ) describing the baseline probability of experiencing a particular effect category; 'drug' and 'placebo' are model components describing drug and placebo effects; and  $\eta$  is a subject-specific random effect parameter quantifying inter-individual variability in response assumed to be normally distributed with a mean of 0 and variance  $\omega$ .<sup>2</sup> The logit transform function was used to convert the function  $g[P\{Y_t \geq m_\eta\}]$ , which is in logits, into a probability.

$$P(Y_t \geq m) = \frac{e^{(g)}}{1 + e^{(g)}} \quad (3)$$

Initial inspection of sleepiness data showed the highest reported effect category as 5 (severe). As such, the probabilities modeled over time were ( $p \geq 1, p \geq 2, p \geq 3, p \geq 4, p \geq 5$ ). By definition,  $p \geq 0 = 1$ , and this is not modeled. For the dizziness data, the highest reported category was three, and the probabilities modeled over time were ( $p \geq 1, p \geq 2, p \geq 3$ ). Model building was conducted by adding the model components in Eq. (2) sequentially and observing the change in the MOF.

Modeling was initialized on all data (placebo, baseline, and drug) with incorporation of the baseline

model first followed by the drug model and then the placebo model.

First, baseline probabilities for each effect category were modeled as constants as described by Sheiner.<sup>9</sup> From Eq. (2),  $\beta_1$  is the Y-intercept (in logits) describing the baseline for reporting an effect category of at least minimum intensity (one or more),  $\beta_2$  is the intercept added to  $\beta_1$  to determine the baseline logit contribution for reporting an effect category of at least mild (two or more), and so forth.

The drug component was added by beginning with a simple linear slope function as described below:

$$E = S \times C \quad (4)$$

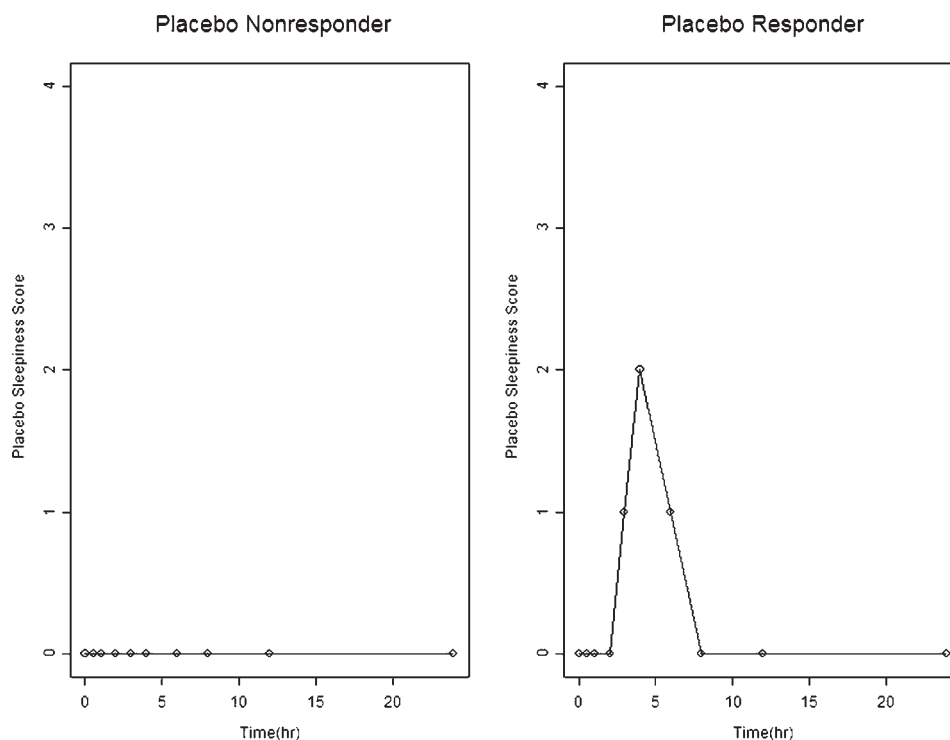
where  $E$  is the drug effect,  $S$  is the slope describing the relationship between drug effect in the logistic domain and drug concentrations  $C$ . Originally  $C$  was tested as concentration in the central compartment determined by *post hoc* individual PK parameter estimates. Addition of an effect compartment,<sup>17</sup> where  $C$  in Equation (4) now represents concentration in the effect compartment, was tested to account for any delay in effect with respect to peak plasma concentrations. This required addition of an extra parameter  $k_{eo}$ , the first-order rate constant describing lag in effect in the biophase<sup>17</sup> compared with central compartment concentrations. A Hill function without

and with a sigmoidicity constant were also tested. Change in the MOF and inspection of the correlation matrix of estimates to ensure model stability was used to select final models.

For the placebo component of Equation (2), several models were tested including a constant modeled as a theta<sup>14</sup> parameter in logits and a Bateman-like function. Incorporation of the placebo component in this manner resulted in the covariance step being aborted. However, inspection of the individual placebo profiles revealed some subjects as nonresponders and others as mild to moderate responders as shown in Figure 1. As such a mixture model<sup>18</sup> on placebo response was tested. A mixture model assumes the population is composed of two or more subpopulations, each having a distinct population mean and random effects. Therefore, if the subject belonged to subpopulation 1 of nonresponders, the placebo response was set to zero. If the subject belonged to subpopulation 2, the placebo response was modeled using a Bateman-like function, with a theta parameter in logits describing the amplitude of placebo effect, and first-order rate constants describing the onset and offset of placebo effect.

#### Assessment of PK/PD Model Performance

Nonparametric bootstrapping<sup>11</sup> and simulation based on bootstrap estimates were performed using SPLUS VI software (Insightful Corp., Seattle, WA). One



**Figure 1.** Representative individual profiles of nonresponder (left) and responder (right) to placebo categorical response.

thousand bootstrap runs were conducted to determine confidence intervals of parameter estimates. This analysis was repeated using successful bootstrap runs only. Simulations were then performed using 500 sets of bootstrap estimates to generate five hundred sets of data as described by Ette et al.<sup>11</sup> Using this simulated data, cumulative probability plots of reporting at least an effect intensity  $m$  ( $p \geq m$ ) as a function of time were constructed to show the performance of the model across effect categories. Ninety percent prediction intervals of the time course of categorical scores were also constructed to visually depict the degree of uncertainty in the models because of random effects and parameter estimate uncertainty. In addition, posterior distributions of relevant PD endpoints were constructed and overlaid on the observed mean values as described by Yano et al.<sup>12</sup> The PD endpoints selected were those determined in the PD noncompartmental analysis (i.e., MaxS and AUEC), as well as the proportion of subjects reporting an AE of at least mild and moderate intensity.

The current logistic model assumes independence of two consecutive categorical observations measured as a function of time. To test that this assumption is reasonable, the posterior distribution of the number of different transitions<sup>19,20</sup> from the logistic model were generated for both lorazepam sleepiness and dizziness and overlaid on the observed mean value.

### Comparison of PD Parameters and Label Incidence

The relative ratio of label incidence of lorazepam sleepiness and dizziness was compared with the relative ratio of various data-derived PD parameters including MaxS, AUEC, and the maximum probability of reporting at least a particular effect category  $m$  ( $p \geq 1$ ,  $p \geq 2$ ,  $p \geq 3$ ). The relative ratio of model-derived PD parameters such as slope was also compared with the ratio of label incidence of sleepiness and dizziness.

## RESULTS

### Pharmacokinetics

Table 1 shows the demographic information of the 20 study subjects. The time course of observed mean  $\pm$  SD, mean predicted, and individual plasma concentrations after single oral dose administration of lorazepam 2 mg are shown in Figure 2. A noncompartmental analysis yielded mean (CV%) estimates for  $C_{\max}$  of 26.8 ng/mL (22.9),  $T_{\max}$  of 1.7 h (40.8),  $t_{1/2}$  of 16.8 h (21.3) and a total systemic exposure or  $AUC_{0-\infty}$  of 551 ng h/mL (31.0). Significant decreases in the MOF, residual and inter-individual variability, and inspection of concordance and residual plots indicated that a two-compartment model

**Table 1.** Subject Demographics ( $n = 20$ )

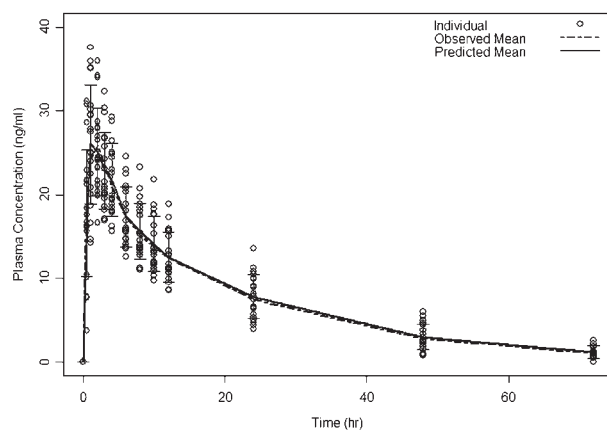
Parameter	Mean (SD)
Gender, $n$	
Male	5
Female	15
Race, $n$	
White	17
Black	3
Age, years	43 (11)
Weight, kg	72 (12)
Creatinine clearance, mL/min	103 (22)

with first-order absorption adequately described the time course of plasma concentrations of 2 mg oral lorazepam.

Table 2 shows the final pharmacokinetic population parameter estimates. The population mean parameter estimates were in good agreement with parameters derived using noncompartmental analysis for both CL/F (3.63 L/h vs. 4.02 L/h) and the derived half-life (16.7 h vs. 16.8 h). Epsilon shrinkage<sup>21</sup> was 45%. Results of the nonparametric bootstrap analysis are included in Table 2. The model was robust with 87% of the runs minimizing successfully. The parameter estimates and confidence intervals obtained from the bootstrap procedure, which included all runs (even those which failed) were generally comparable with the estimates derived from NONMEM. Similar bootstrap estimates and confidence intervals were obtained using only successful runs.

### Pharmacodynamics

Noncompartmental analyses conducted on the effect-time profiles of sleepiness and dizziness scores



**Figure 2.** Observed individual, observed mean  $\pm$  SD, and predicted mean plasma concentrations versus time. Error bars represent 1 standard deviation above and below the observed mean data.

**Table 2.** Pharmacokinetic Parameters in Healthy Volunteers After a 2 mg Oral Dose of Lorazepam ( $n = 20$ )

Parameter	NONMEM Estimate	NONMEM 95% CI	Bootstrap Estimate	Bootstrap 95% CI
CL/F	4.02	3.58–4.46	4.0	3.61–4.49
V1/F	53.6	48.1–59.1	53.3	44.0–59.0
V2/F	37.6	33.3–41.9	37.9	33.4–44.4
K <sub>a</sub>	1.04	0.82–1.26	1.03	0.81–1.28
Q	10.9	9.0–12.8	11	9.06–14.23
Ω-CL/F	25.40%	12.1–38.7	24.44%	16.6–31.18
Ω-V1/F	9.24%	2.08–16.4	9.07%	2.35–17.0
Ω-V2/F	13.10%	3.98–19.1	12.00%	4.3–18.38
Ω-K <sub>a</sub>	35.90%	16.4–55.5	34.21%	18.6–44.4
Residual proportional error	8.34%	5.54–11.1	8.06%	5.76–10.7

CL, systemic clearance; F, bioavailability; V1, central compartment volume; V2, peripheral compartment volume; K<sub>a</sub>, first-order rate of absorption; Q, inter-compartmental clearance; Ω, random effects parameter estimating inter-subject variability.

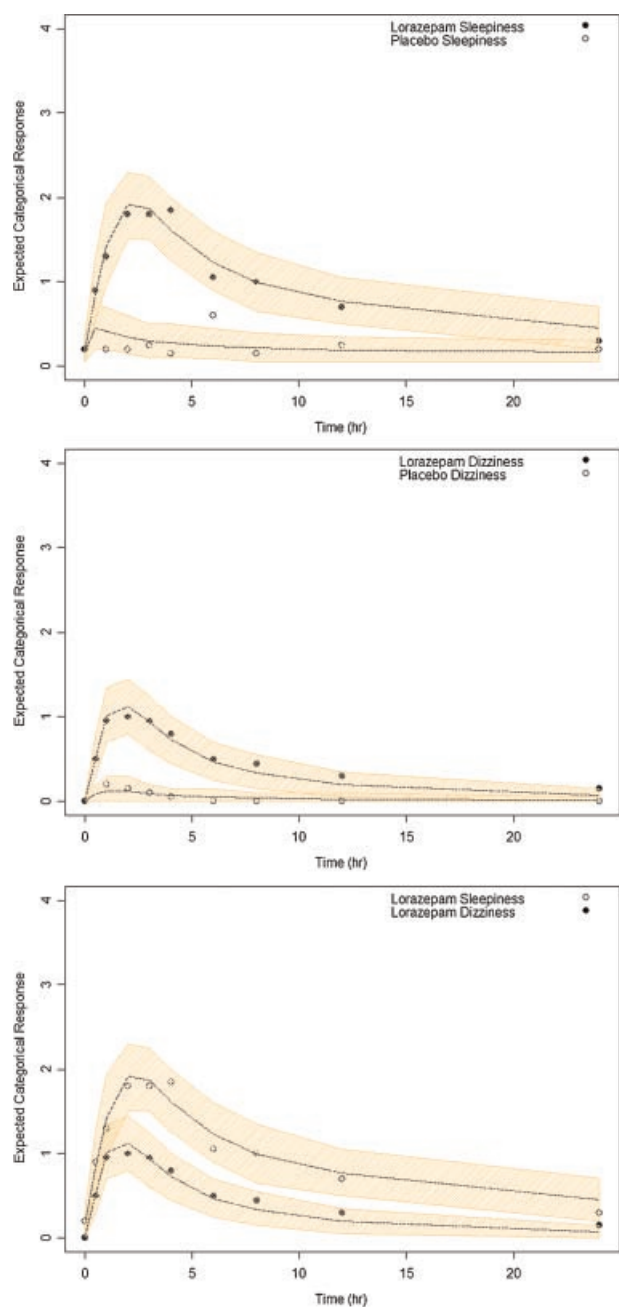
showed significant differences between these AEs in the maximum score (MaxS) and area under the effect curve (AUEC) endpoints. The MaxS of lorazepam sleepiness ( $\pm$ SE) was significantly higher than dizziness ( $2.35 \pm 0.26$  vs.  $1.45 \pm 0.22$ ,  $p < 0.01$ ), as was the AUEC ( $20.35 \pm 3.58$  vs.  $9.76 \pm 2.45$ ,  $p < 0.01$ ). The time to reach MaxS for lorazepam sleepiness scores was delayed (3.98 h, Fig. 3) compared with time of maximal lorazepam concentrations (1.71 h, Fig. 2). This observation justified addition of the effect compartment<sup>17</sup> to describe drug effect in the lorazepam sleepiness model. In contrast, the dizziness effect peaked (2.55 h, Fig. 3) at a time similar to that observed for peak plasma drug concentrations.

Population PD model building was initialized by addition of baseline logit intercepts for each effect category. As indicated in Equation (2), these are added sequentially from  $i = 1$  to  $m$  to quantify the probability of experiencing a score category  $m$  or more in the absence of drug or placebo. Table 3 shows the final PD model estimates. As shown,  $\beta_1$  (which represents the probability in logits of reporting a score of 1 or more at baseline) was significantly higher for sleepiness ( $-2.81$ ) than dizziness ( $-4.34$ ) as indicated by the 95% confidence intervals.  $\beta_4$  and  $\beta_5$  were included in the sleepiness model as they resulted in significant decreases in the MOF. Addition of the drug component of the model as a slope as described in Eq. (4) resulted in a decrease in point reduction in the MOF of 216 and 174 points for sleepiness and dizziness models, respectively, indicating a significant drug effect. As shown in Table 3, slope estimates of sleepiness (0.21 logits/mL ng) and dizziness (0.19) were not significantly different on inspection of the 95% confidence intervals. Addition of an effect compartment was significant for sleepiness but not dizziness, and the final estimate of  $k_{eo}$ , the first-order rate constant describing lag in effect in

the biophase compared with central compartment concentrations, was  $2.44 \text{ h}^{-1}$ .

Placebo effect was modeled as a mixture of nonresponders and responders in the final model, where the responder component was described using a Bateman-like function as shown in Figure 1. Modeling the placebo effect as a mixture, remedied the initial problem encountered with abortion of the covariance step and resulted in stabilization of the final model as indicated by the correlation matrix of estimates being devoid of high correlations ( $>0.8$ ) among parameters. PLAC describes the amplitude of response and, as indicated in Table 3, was similar for sleepiness (3.6 logits) and dizziness (4.3 logits) as was  $k_1$ , the first-order rate constant describing onset of placebo effect. When  $k_2$ , the first-order rate constant describing offset of placebo effect, was modeled for sleepiness placebo, it resulted in over-parameterization as determined by inspection of the correlation matrix of estimates. However, given that the individual responder profiles showed a Bateman pattern of effect and not exponential decay,  $k_2$  was modeled as a fraction of  $k_1$  and the constant used to determine this fraction was determined using a sensitivity analysis. The majority of subjects were nonresponders to placebo effect as indicated by  $P(1)$ , the subpopulation proportion that was nonresponder to placebo, and this estimate was similar between sleepiness (63%) and dizziness (71%). The inter-individual random effects parameter  $\Omega_1$  was significantly higher for sleepiness effect (3.31 logits) compared with dizziness (0.32 logits).

As shown in Table 3, mean population parameter estimates obtained from the bootstrap procedure were generally comparable with the estimates from the final model. The NONMEM confidence intervals were also generally comparable with the bootstrap intervals for most parameters, with the exception of  $\beta_5$ ,  $k_{eo}$ , PLAC, and  $P(1)$  of the sleepiness model; and



**Figure 3.** Ninety percent prediction intervals of sleepiness and dizziness scores in healthy volunteers as a function of time ( $n = 20$ ). Panel one shows lorazepam and placebo sleepiness, panel two lorazepam and placebo dizziness, and panel three lorazepam sleepiness and dizziness. Symbols indicate observed data, middle line indicates mean simulated data, and lower and upper lines indicate lower and upper prediction interval bounds.

PLAC,  $k_1$ , and  $P(1)$ , of the dizziness model, reflecting their asymmetric distribution. The success rate of bootstrap runs was 80% for the lorazepam sleepiness model and 83% for the dizziness model.

Figure 3 shows the observed (points) and overlaid mean simulated scores (lines) and 90% shaded

prediction intervals (PIs) obtained from 500 sets of bootstrap parameter estimates. The mean simulations adequately describe the time course of sleepiness and dizziness scores with the prediction intervals (shaded region) capturing the data and mean simulations. The one exception, however, is a data point of placebo sleepiness (at 6 h), which is not captured by the model and lies slightly outside of the shaded interval. The shaded PI for lorazepam sleepiness is wider than that of lorazepam dizziness indicating the greater model uncertainty of sleepiness.

Figure 4 shows the observed and simulated cumulative probabilities of reporting a sleepiness and dizziness effect greater than or equal to a particular effect category over time ( $p \geq m$ ). The simulations describe the data adequately. As shown, the cumulative probabilities decrease with increasing effect category ( $m$ ). Moreover, peak probabilities of reporting at least an effect category  $m$  at time of maximal effect are higher for lorazepam sleepiness ( $1 = p \geq 1$ ,  $0.45 = p \geq 2$ ,  $0.25 = p \geq 3$ ,  $0.1 = p \geq 4$ ,  $0.05 = p \geq 5$ ) then for lorazepam dizziness ( $0.7 = p \geq 1$ ,  $0.3 = p \geq 2$ ,  $0.15 = p \geq 3$ ) as shown in Figure 4.

Figure 5 shows histograms of the simulated distribution of MaxS, AUEC, and the number of subjects reporting an AE of at least mild and moderate severity obtained from 500 sets of bootstrap parameter estimates, overlaid on the observed mean of these PD endpoints (represented by the vertical black bar). The panels indicate that that proposed models simulate posterior distributions of these parameters, which are centered close to the observed means.

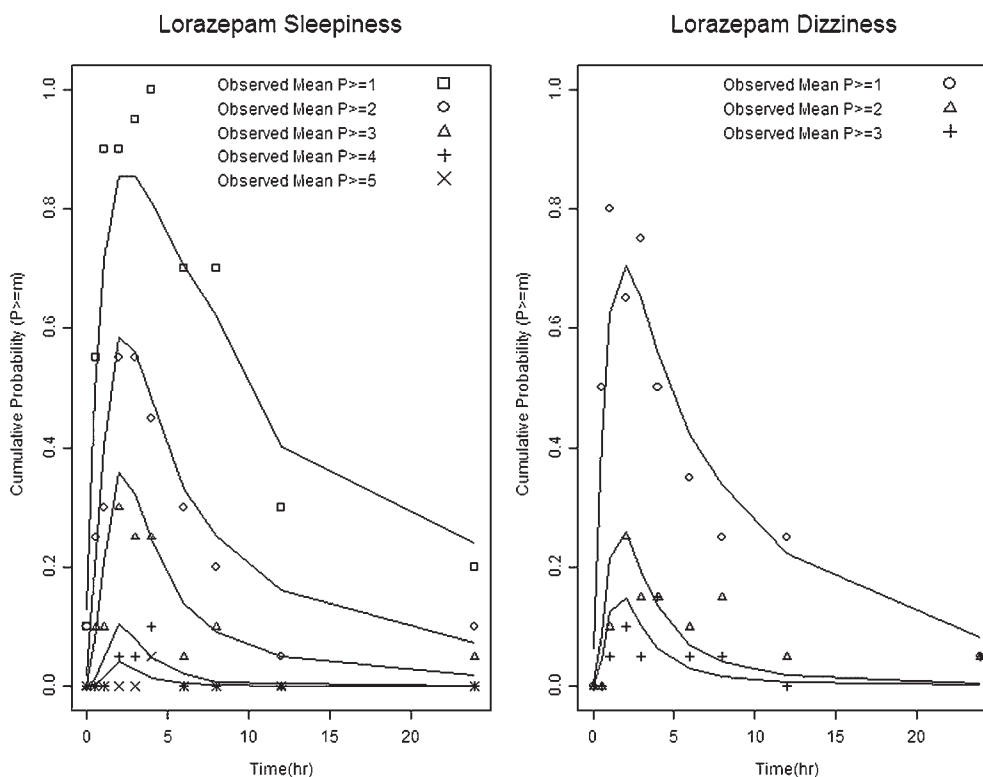
Figure 6a and b shows the posterior distributions of the number of different categorical transitions for lorazepam sleepiness and dizziness, respectively, overlaid on the observed mean. The panels indicate that the observed population mean lies within the posterior distributions of the transitions counts for all simulated transitions. The posterior distributions capture the observed mean adequately overall with the exception of few transitions which lie at the tail of the posterior distribution (transition 1–1 in Fig. 6a and the transitions 1–0, 2–2, 3–1, and 3–0 in Fig. 6b).

Finally, Table 4 relates the various data-derived PD parameters, and the model-derived PD parameter, slope, to the incidence rates of the AEs in the more general population, as reported in the drug label.<sup>5</sup> The ratio of the sleepiness/dizziness endpoints was calculated across these parameters. As shown by the relative ratios, Max ( $p \geq 2$ ), Max ( $p \geq 3$ ), and AUEC, show the greatest concordance to label incidence, followed by MaxS and Max ( $p \geq 1$ ). However, the ratio of sleepiness to dizziness slope parameters

**Table 3.** Pharmacodynamic Parameters in Healthy Volunteers After a 2 mg Oral Dose of Lorazepam or Placebo ( $n = 20$ )

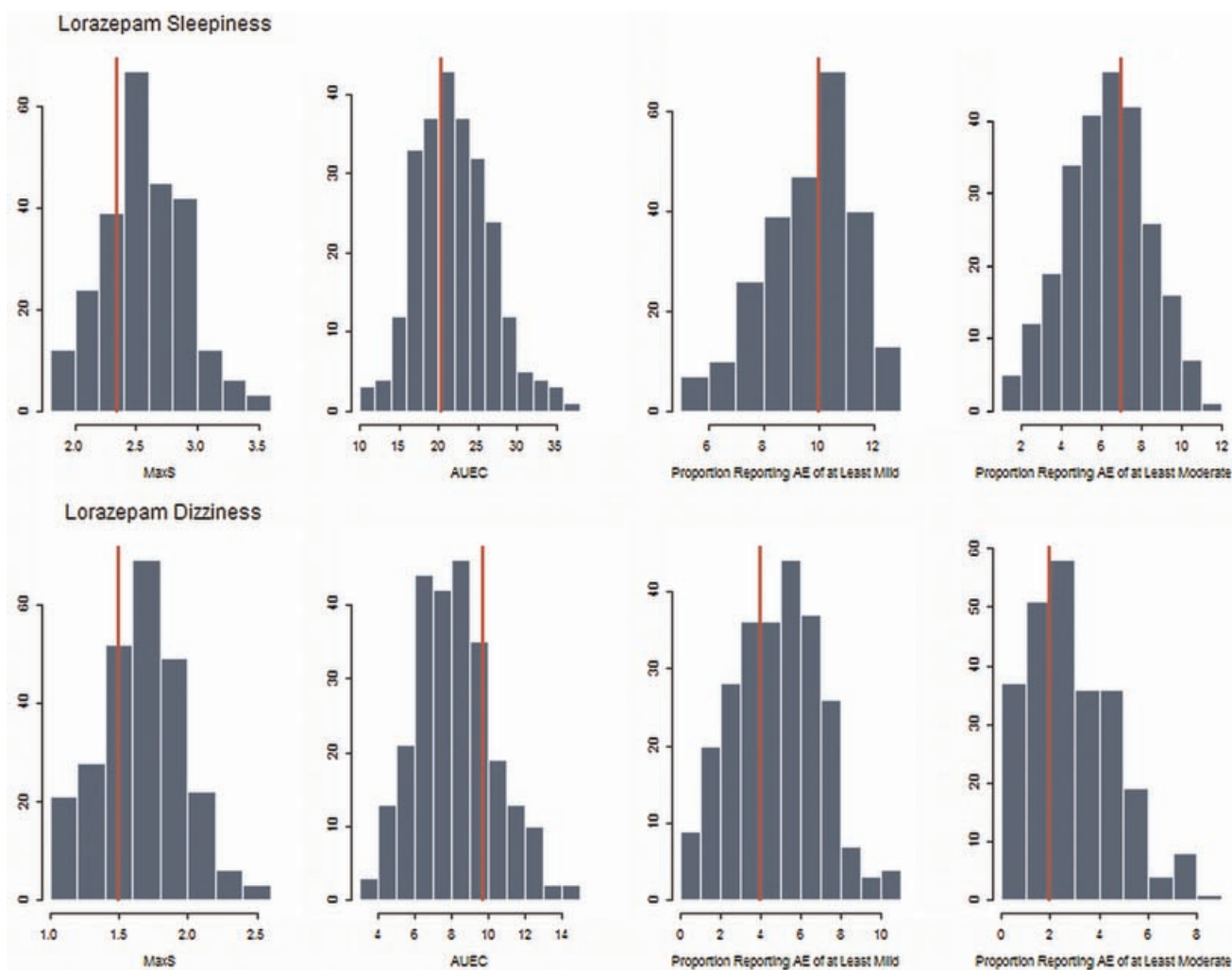
Model Parameter	Lorazepam Sleepiness				Lorazepam Dizziness			
	NONMEM Estimate	NONMEM CI	Bootstrap Estimate	Bootstrap CI	NONMEM Estimate	NONMEM CI	Bootstrap Estimate	Bootstrap CI
<b>Baseline effect</b>								
$\beta_1$ (logits)	-2.81	-4.0 to -1.62	-2.83	-4.5 to -1.71	-4.34	-5.18 to -3.5	-4.51	-6.40 to -3.70
$\beta_2$ (logits)	-2.57	-3.27 to -1.87	-2.58	-3.37 to -1.94	3.17	-4.51 to -1.83	-3.34	-5.49 to -2.26
$\beta_3$ (logits)	-1.79	-2.37 to -1.21	-1.84	-2.5 to -1.29	-1.08	-1.68 to -0.48	-1.08	-2.43 to -0.57
$\beta_4$ (logits)	-2.81	-4.02 to -1.59	-2.86	-4.43 to -1.86	NA	NA	NA	NA
$\beta_5$ (logits)	-1.55	-3.44 to 0.34	-1.6	-64.47 to -6.1E-10	NA	NA	NA	NA
<b>Drug effect</b>								
Slope (logits $\times$ mL/ng)	0.21	0.17 to 0.25	0.21	0.17 to 0.27	0.19	0.15 to 0.23	0.19	0.15 to 0.25
$k_{eo}$ ( $h^{-1}$ )	2.44	0.40 to 4.48	2.59	1.28 to 16.1	NA	NA	NA	NA
<b>Placebo effect</b>								
PLAC (logits)	3.6	1.74 to 5.46	4.00	1.78 to 8.17	4.30	1.65 to 6.95	5.53	3.09 to 13.01
$k_1$ ( $h^{-1}$ )	0.188	0.02 to 0.36	0.175	0.07 to 0.43	0.11	0.07 to 0.29	0.16	0.03 to 1.19
$k_2$ ( $h^{-1}$ )	NA	NA	NA	NA	2.13	0.17 to 4.09	1.93	0.37 to 3.68
$P(1)$	62.80%	39.60 to 96.00	64.60%	14.6 to 94.9	71.00%	43.00 to 99.00	64.80%	16.36 to 89.39
<b>Random effects</b>								
$\Omega_1$	3.31	0.33 to 6.29	3.12	0.60 to 7.00	0.32	-0.62 to 1.25	0.34	0.01 to 2.91

$\beta_1$ - $\beta_5$ , intercept logistic parameters describing the baseline; PLAC, amplitude of placebo effect;  $k_1$  and  $k_2$ , first order rates of onset and offset of placebo response;  $P(1)$ , percentage of nonresponders to placebo; SLOPE, relationship between drug effect and concentrations;  $k_{eo}$ , first-order rate constant describing lag in the effect compartment compared with lorazepam concentrations in the central compartment;  $\Omega_1$ , random effects parameter describing inter-subject variability.



**Figure 4.** Cumulative probability plots of reporting sleepiness and dizziness.  $p \geq 1-5$  is the cumulative probability of reporting an effect of at least minimum, mild, moderate, significant, and severe intensity on the categorical scale. Symbols indicate observed mean data and lines indicate mean simulations.





**Figure 5.** Posterior distributions of MaxS, AUEC, and the proportion reporting an AE of at least mild and moderate intensity for lorazepam sleepiness and dizziness in healthy volunteers after a 2 mg oral dose of lorazepam ( $n = 20$ ). The vertical line in each plot indicates the mean observed value. MaxS is the maximum reported categorical score, AUEC is the area under the effect curve from 0 to 24 h.

was very close to 1 indicating that drug effect may not explain the differences between sleepiness and dizziness across these PD parameters.

## DISCUSSION

The current PK/PD analysis of a seven-point ordered categorical measure aims to differentiate the pharmacodynamics of two of the most common AEs of lorazepam, sleepiness and dizziness. The 2 mg dose of drug selected in this study is within the range of recommended daily doses of lorazepam for maintenance treatment of generalized anxiety disorder. Studies modeling the intensity of drug AEs over time are relatively uncommon,<sup>19,20</sup> and no studies have formally applied population PK/PD analyses in differentiation of AEs.

PK estimates obtained from the noncompartmental and compartmental analysis of the concentration–

time profiles are consistent with previous reports<sup>22</sup> and showed that lorazepam is rapidly absorbed ( $k_a = 1.04 \text{ h}^{-1}$ ), has peak plasma concentrations occurring at about 2 h postdose and that it has relatively moderate steady state volume of distribution (90 L), low systemic clearance (4 L/h), and moderate terminal half-life (16.7 h).

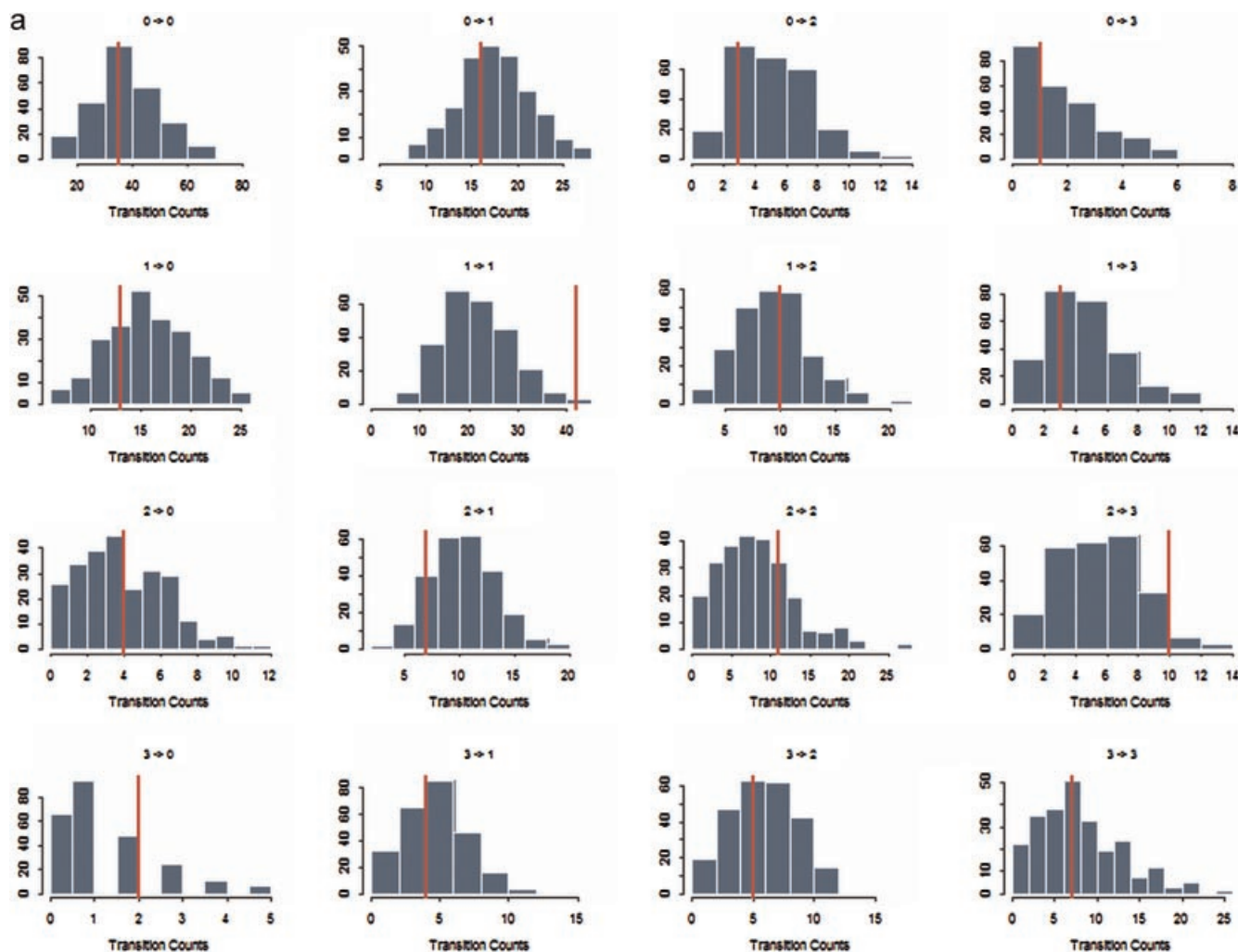
The noncompartmental analysis of the effect-time profiles of sleepiness and dizziness scores indicated that the MaxS of sleepiness was significantly higher than dizziness (2.35 vs. 1.45,  $p < 0.01$ ) as was the AUEC (20.35 vs. 9.76,  $p < 0.01$ ). As shown in Table 4, the ratios of sleepiness/dizziness of these PD parameters are in concordance to the ratio of label incidence, with AUEC showing stronger concordance. While sleepiness and dizziness are the most commonly reported AEs of lorazepam according to the drug label,<sup>5</sup> these effects show minimal to moderate amplitude on the categorical scale as shown in

Figure 3. This observation may underscore the sensitivity of the seven-point categorical scale in discerning small differences between relatively mild to moderate AEs over time.

Differences in reporting various categories of effect intensity between these AEs are seen in the cumulative effect probability plots in Figure 4. Maximum probabilities of reporting at least a minimal effect, Max ( $p \geq 1$ ), are higher for lorazepam sleepiness ( $p = 1$ ) than dizziness ( $p = 0.7$ ). Likewise, maximum probabilities of reporting at least mild and moderate intensity, Max ( $p \geq 2$ ) and Max ( $p \geq 3$ ), are higher for lorazepam induced sleepiness ( $0.45 = p \geq 2$ ,  $0.25 = p \geq 3$ ) than for dizziness ( $0.3 = p \geq 2$ ,  $0.15 = p \geq 3$ ). As these represent the cumulative probabilities (which is a frequency) of

reporting an effect of given intensity in a conceptual population, their relationship to label incidence is more direct than MaxS and AUEC which reflect effect intensity rather than effect frequency. As shown in Table 4, the sleepiness/dizziness ratio across these PD parameters are also in concordance to the ratio of label incidence with Max ( $p \geq 2$ ) and Max ( $p \geq 3$ ) showing the highest concordance followed by Max ( $p \geq 1$ ). The stronger concordance of Max ( $p \geq 2$ ) and Max ( $p \geq 3$ ) to label incidence seems to suggest that the frequency of reporting categorical effects of higher intensity may be better related to incidence in the more general population.

The lack of significant difference between the model estimate of slope for sleepiness (0.21) and dizziness (0.19) at the 95% confidence level suggests that the



**Figure 6.** (a) Posterior distributions of the number of different categorical transitions for lorazepam sleepiness. Transition permutations of the first four of the reported six categories are shown (categories 0, 1, 2, and 3). The vertical line in each plot indicates the mean number of observed transitions. (b) Posterior distributions of the number of different categorical transitions for lorazepam dizziness. Transition permutations of all four reported categories are shown (categories 0, 1, 2, and 3). The vertical line in each plot indicates the mean number of observed transitions.

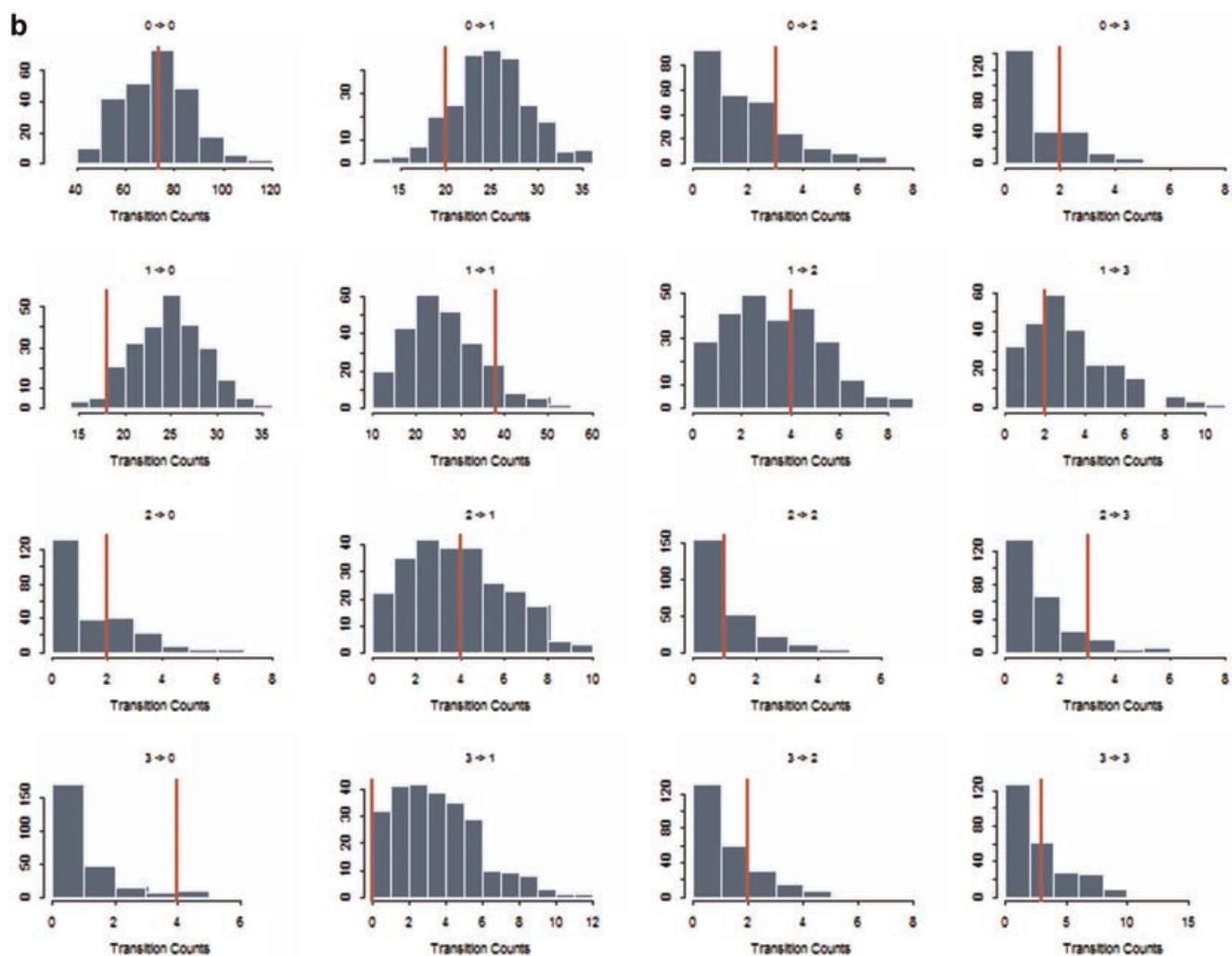


Figure 6. (Continued)

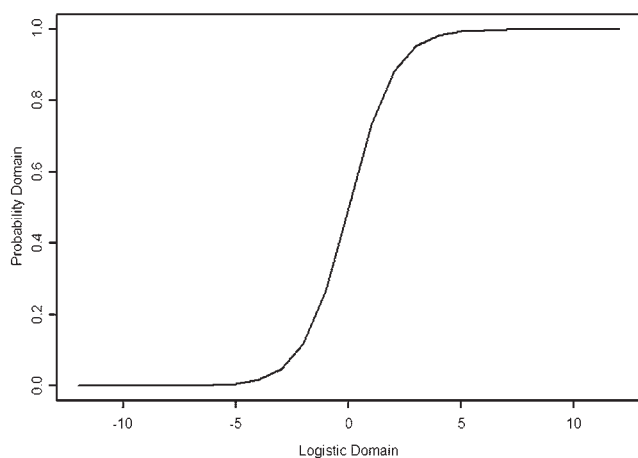
drug does not contribute to the observed differences in intensity of these AEs.  $\beta_1$ , the baseline intercept parameter of effect category 1 (likelihood of having a response of at least minimum intensity), is the only parameter that is significantly different between these AEs at the 95% confidence level. The difference between this estimate for sleepiness and dizziness is 1.5 logits. As shown in Figure 7, which shows the relationship between the probability and logistic domains, the majority of the probability domain ( $0.1 \leq y \leq 0.9$ ) occurs in the logit range  $-3 \leq x \leq 3$ , and 0 logits corresponds to the inflection point at  $y = 0.5$ . In this range, 1.5 logits corresponds to a probability of 0.82. As 0 logits corresponds to  $p = 0.5$ , the difference

$0.32 = p = 0.82 - 0.5$  corresponds to the greater likelihood of reporting sleepiness than dizziness as a result of the baseline difference. From Figure 4, the difference in observed cumulative effect ( $p \geq 1$ ) at  $T_{\max}$  between sleepiness and dizziness is  $1 - 0.7 = 0.3$  equivalent to the value determined above. As ( $p \geq 1$ ) is the cumulative effect across all effect categories, differences in this endpoint between sleepiness and dizziness at  $T_{\max}$  closely resemble differences in Max Score.

It is unclear from a physiological standpoint why the difference in baseline effect exists between sleepiness and dizziness, but one possible explanation may be the time of day in which the data were

Table 4. Relationship of Data-Derived and Model-Derived PD Parameters to the Label Incidence of Sleepiness and Dizziness in Healthy Volunteers After Administration of a 2 mg Oral Dose of Lorazepam

Endpoint/Parameter	Label Incidence	AUEC	MaxS	Max ( $p \geq 1$ )	Max ( $p \geq 2$ )	Max ( $p \geq 3$ )	Slope
Sleepiness	15.7	20.35	2.34	1	0.57	0.35	0.21
Dizziness	6.9	9.76	1.45	0.7	0.25	0.15	0.19
Ratio (sleepiness/dizziness)	2.3	2.1	1.6	1.5	2.3	2.3	1.1

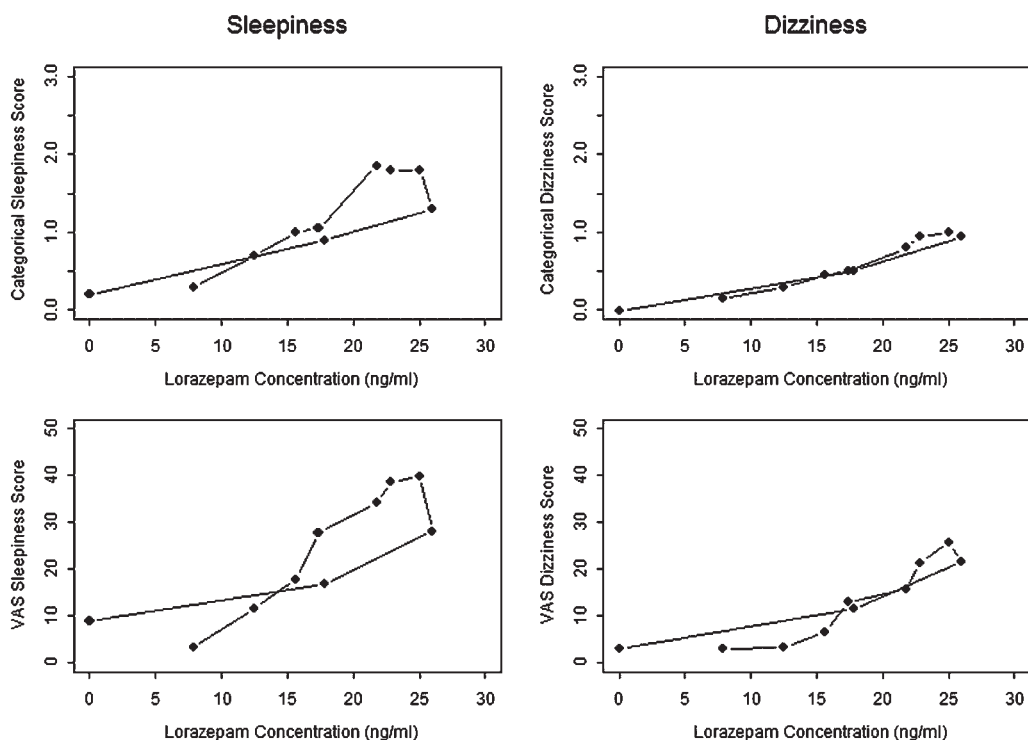


**Figure 7.** Relationship between the probability and logistic domains.

collected. Given that the scale was first applied in the morning, some subjects may have experienced a residual sleepiness in the morning that was reported at baseline. Another explanation may be that subjects may have a greater tendency to report a sleepiness effect than dizziness even in the absence of any drug. However, no placebo response rates of these effects are reported in the lorazepam label to confirm this. Placebo data in the current study, as shown in Figure 3, show a slightly greater sleepiness response at earlier time-points (at 0.5 h postdose administra-

tion), suggesting that differences in reporting sleepiness and dizziness in the absence of drug may be related to time of day.

The PK/PD temporal patterns of sleepiness and dizziness are shown in Figure 8, depicting the counterclockwise hysteresis for lorazepam sleepiness and the closed hysteresis loop for dizziness. The same PK–PD temporal relationships of these AEs were recorded on the Visual Analog Scale<sup>2,3</sup> administered in the same study<sup>4</sup> as shown in Figure 8 further corroborating this finding. Other studies have shown the counterclockwise hysteresis pattern with amnesic,<sup>23</sup> psychomotor,<sup>24,25</sup> and cognitive<sup>24,25</sup> effects after administration of 2 mg oral lorazepam in healthy adults. These studies estimated greater delays with slightly lower  $k_{eo}$  values ( $k_{eo} = 1.3\text{--}1.7\text{ h}^{-1}$ ) compared with the current study ( $2.4\text{ h}^{-1}$ ). However, although correlated to the sedative effect of lorazepam,<sup>26</sup> these amnesic and psychomotor effects are different from sleepiness. On the other hand, in the current study, dizziness showed no such significant delay and the time to MaxS was close to the  $T_{max}$  of lorazepam concentrations. While this temporal difference between AEs is unclear, one pharmacologic explanation may be distributional, that is, lorazepam-induced sleepiness may require traversing of the blood–brain barrier whereas dizziness may not. In fact, if indeed the subjects were reporting vertigo as dizziness,<sup>27</sup> this would require binding to the GABA receptors in the



**Figure 8.** Upper panel: Sleepiness and dizziness scores recorded on the seven-point categorical scale versus lorazepam concentrations. Lower panel: Sleepiness and dizziness scores recorded on the Visual Analog Scale (VAS) versus lorazepam concentrations.

vestibular system of the inner ear which does not require traversing the blood–brain barrier. However, the distributional delay is less likely given the high log  $P$  of lorazepam. Moreover, GABA receptor inhibition of the vestibular axis by lorazepam would actually be therapeutic to vertigo,<sup>28</sup> suggesting that the biophase of lorazepam dizziness is most likely the brain itself and not the inner ear. Another explanation is that these AEs may originate from distinct anatomical locations in the brain. It is known that lorazepam induced sleepiness is the result of binding to and inhibition of benzodiazepine receptors of GABA complexes in the thalamus and sensory cortex of the brain.<sup>6,7</sup> The receptor binding causes downstream inhibition of glucose metabolism,<sup>6,7</sup> which might account for the delayed sensation of sleepiness recorded by the scale. On the other hand, lorazepam-induced dizziness is conferred by benzodiazepine action in receptors of the cerebellum (responsible for maintenance of balance) and these receptors may have a different subunit composition,<sup>29</sup> altering rates of downstream signaling. If such a pharmacologic scenario is indeed valid, this delay may be described using a transduction model.<sup>30</sup>

The performance of the final population models was assessed by a number of diagnostics including the mean simulations in Figure 3, which adequately capture the time course of drug and placebo scores, and the simulations in Figure 4, which capture the observed cumulative probabilities. As a further check to ensure the models simulate realistic data, posterior predictive checks (PPCs)<sup>12</sup> in Figure 5 were performed and show that the simulated distributions of MaxS and AUEC were centered close to the observed mean. These PD parameters were selected based on them being clinically relevant, data-derived parameters, which could be determined using the profile of an individual subject. These parameters condense the PD profiles to a single metric (either AUEC or MaxS) that capture evaluation of peak response and extent of response similar to a PK analysis. Use of analogous metrics (AUC and Cmax) for the PPC is recommended for PK models as discussed by Yano et al.<sup>12</sup> Two other PPC metrics were analyzed: proportion of subjects reporting a categorical effect of at least mild and moderate intensity. As shown in Figure 5, the simulated distributions of these metrics were centered close to the observed mean as well. The 90% PIs in Figure 3 show the model uncertainty conferred by both random effects and uncertainty in estimating the parameter estimates. Typically, the 90% as opposed to 95% PI is assessed, because some confidence to detect a type I error is compromised to compensate for the increased uncertainty incurred by random effects. As shown in Figure 3, the PI of lorazepam sleepiness is wider than dizziness indicating greater model uncertainty. This may be the result

of the greater random effects as shown in Table 3 ( $\Omega$  is higher for sleepiness). As overlaying PIs of these effects shows separation beyond 2 h, one can make the conclusion that, given uncertainty in the model estimates and random effects, the models can detect a difference between the time course (at  $T_{\max}$  and beyond) of these effects at the 90% confidence level.

The current logistic or proportional odds model assumes independence of neighboring consecutive categorical observations as a function of time. The Markov or transition model<sup>19,20</sup> which determines the conditional probability of reporting an observation at time  $t$  given the previous observation, and therefore assumes dependence between these observations, would be a valid model to test because data were collected frequently and longitudinally over time. The PPC analysis of the number of different categorical transitions for both lorazepam sleepiness and dizziness simulated from the logistic models, show that the observed population mean lies within the posterior distributions for the number of the different transitions. The posterior distributions capture the observed mean adequately overall with the exception of few transitions which lie at the tail of the posterior distribution as shown in Figure 6a (lorazepam sleepiness) and 6b (lorazepam dizziness). Although the Markov model may be better suited for simulating individual profiles, the current logistic model appears to predict the general trend of lorazepam sleepiness and dizziness reasonably well as shown in Figure 4.

Finally, certain study caveats should be acknowledged. First, the current study differentiates two AEs of a single drug. It would also be of interest to differentiate the same AE between two drugs in a similar therapeutic class; however, the drugs included in the larger study<sup>4</sup> were of different therapeutic classifications. Second, the low incidence of other AEs observed in this study precluded application of this modeling approach to other AEs (of lower intensity).<sup>4</sup> Nevertheless, the model proposed, may serve as platform to determine the minimal quantifiable categorical signal, given a particular study design and power, by conducting a sensitivity analysis<sup>31</sup> on model parameters. Third, only a single therapeutic dose was investigated. Use of higher doses would better elucidate the maximal categorical response for such AEs. This information would have allowed determination of maximal capacity ( $E_{\max}$ ) of the system and sensitivity ( $EC_{50}$ ) of AEs, enhancing the interpretability of the current analysis. Such an analysis may be feasible in ascending dose studies of compounds under development. Fourth, the study was conducted on healthy volunteers as opposed to patients with anxiety. Extrapolation of adverse event endpoints from healthy volunteers to patients may not be straightforward, as the tolerance of these different populations to AEs

may be quite different. This has been seen in certain CNS indications such as schizophrenia where patients have shown higher tolerance to AEs of antipsychotic medications.<sup>32</sup> Despite the limitations of the study, we believe the current analysis has demonstrated the feasibility of differentiating certain AEs using the pharmacometric approach described and may provide a framework for future studies with a similar aim.

## CONCLUSION

Lorazepam sleepiness and dizziness have shown distinct temporal PK/PD patterns and were recorded with significantly different intensity on the seven-point categorical scale. Differences in the PD endpoints described may be due to differences in baseline parameters. The differences between data-derived PD measures of sleepiness and dizziness were consistent with differences in incidence rates reported in the drug label.

## ACKNOWLEDGMENTS

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