Published in final edited form as:

J Clin Pharmacol. 2016 June ; 56(6): 714–722. doi:10.1002/jcph.646.

Pharmacokinetic-Pharmacodynamic Modeling of Intravenous and Oral Topiramate and Its Effect on the Symbol-Digit Modalities Test in Adult Healthy Volunteers

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Abstract

A sequential pharmacokinetic-pharmacodynamic (PK-PD) modeling approach was used to quantify the effects of a single dose of topiramate (100 or 200 mg) on working memory, attention, and psychomotor speed as measured by the Symbol-Digit Modalities Test (SDMT). Established on data pooled from 3 randomized, crossover studies in healthy subjects (19–55 years of age), using both oral and a novel stable-labeled intravenous (IV) formulation of topiramate, an inhibitory $E_{\max}$ model was found to characterize the topiramate concentration-SDMT score relationship well. At the EC₅₀ of 2.85 $\mu\text{g/mL}$, this topiramate plasma concentration value was estimated to be associated with a 25.5% reduction of SDMT score relative to baseline. Age was an important determinant of the baseline SDMT score, with an estimated decrease of 1.13% in baseline SDMT score with every year of age. Moreover, this approach enabled the quantification of the practice effect observed with repeated administration of the neuropsychological test over shorter testing intervals than have previously been reported in the literature. The finding of a significant effect following a single dose of topiramate in the range widely used to treat migraine and epilepsy needs to be evaluated in a broader patient population undergoing chronic treatment, as the narrow range of resultant concentrations limits the generalizability of the findings.

Keywords

topiramate; SDMT; practice effect; modeling; cognition

Topiramate, a sulfamate-substituted monosaccharide, is a second-generation antiepilepsy drug initially approved by the FDA for partial-onset and primary generalized tonic-clonic seizures. Later, it was approved for migraine prophylaxis, and this is now its major use in the United States. More recently, it was approved for obesity (in combination with phentermine). It is also increasingly prescribed for a wide range of conditions including pain, bipolar disorder, and substance abuse.

Topiramate is associated with cognitive and language adverse effects severe enough to cause a higher rate of discontinuation of therapy when compared to other second-generation antiepilepsy drugs.^{1–4} Reported from studies in patients with epilepsy, the incidence of cognitive complaints associated with topiramate usage is highly variable (3%–44%).^{4–7} Although this variability may be attributed in part to differences in titration rate, maintenance dose, and the underlying etiologies of epilepsy, the relationship between topiramate exposure and cognitive impairment has not been fully investigated.⁸

In both patients and healthy adults, topiramate administration has been shown to produce concentration-related declines in generative and discourse-level verbal fluency, working memory, and attention.^{3,9,10} Given the role of working memory in the production of fluent speech, it is not surprising that, along with measures of verbal fluency, the Symbol-Digit Modalities Test (SDMT), which requires elements of working memory, attention, and psychomotor speed, is one of the neuropsychological tests most sensitive to the cognitive effects of topiramate.^{10–15} For instance, after a single 100-mg dose of topiramate in healthy volunteers, topiramate plasma concentration was found to have the largest impact on both the SDMT as well as tests of verbal fluency.¹⁰ However, there are no studies that provide a quantitative assessment for the exposure-response relationship between topiramate plasma levels and SDMT performance.¹⁰

The objective of this analysis was to quantify the effects of a single dose of topiramate (100 or 200 mg) on working memory, attention, and psychomotor speed as measured by the SDMT. In order to isolate the cognitive effects of topiramate from those possibly arising from an underlying medical condition, subjects were healthy adults. Using both oral and a novel stable-labeled intravenous (IV) formulation of topiramate developed by our group, we utilized a sequential pharmacokinetic-pharmacodynamic (PK-PD) modeling approach to characterize the topiramate plasma concentration–SDMT score relationship and to account for practice effects that occur with repeated administration of the cognitive test.

Methods

The study protocols were approved by the University of Minnesota (UMN) and University of Florida (UF) Institutional Review Boards, and subjects provided written informed consents prior to enrollment.

Subjects

Native English-speaking healthy volunteers between 18 and 65 years of age were recruited from 2 sites, UMN and UF. Exclusion criteria included histories of significant cardiovascular, endocrine, hematopoietic, hepatic, neurological, psychiatric, or renal disease,

current or a history of drug or alcohol abuse within the past 5 years, use of concomitant medications known to affect topiramate or alter cognitive function, use of any investigational drug or device within 30 days prior to screening, a diagnosis of language impairment/disability, uncorrected low vision, and history of intolerance to intravenous administration of medication. Eligible subjects underwent a brief physical and neurological examination. Subjects were expected to have normal renal function as they were healthy, nonelderly adults with no reported history of renal disease.

Study Designs

Data pooled from 3 randomized crossover studies were used to build the PK-PD model. Information about date of birth, race, ethnicity, sex, height, weight, and medical and surgical history was collected at the screening visit. The PD assessment consisted of a neuropsychological battery that included tests of working memory, attention, and psychomotor speed (ie, SDMT) as well as recall and generative and discourse level verbal fluency. This battery was administered to the subjects during all visits. Only the scores from the SDMT were modeled in this paper. Results from the verbal fluency and recall tasks have been previously published.^{9,16}

Study I

Study I (UMN) was a 2-period crossover bioequivalence study of IV and oral topiramate. Two subjects were administered 50 mg of IV topiramate infused over 15 minutes, followed by 50 mg of oral topiramate after a 2-week washout period. The remaining 10 subjects were randomly assigned to receive a single dose of 100 mg IV or oral topiramate in the first period, followed by the alternate route of administration in the second period after a 2-week washout. Blood samples for measurement of topiramate plasma concentration levels were collected predose and at 5, 15, and 30 minutes and 1, 2, 4, 6, 10, 12, 24, 48, 72, 96, and 120 hours postdose. Baseline SDMT scores were collected the day prior to treatment period 1 as well as at the end of treatment period 2 (following a 2-week washout). During periods 1 and 2, SDMT was administered at 0.25, 2, and 6 hours postdose. SDMT scores were available for only the 100-mg dose group, but PK data from the 50-mg group were included in the PK model.

Study II

Study II (UF) was a randomized, double-blind, placebo-controlled 2-period crossover study. Subjects were administered 100 mg oral topiramate or placebo in the first period and the alternate treatment in the second period following a 1-week washout. Baseline SDMT scores were collected 1 week prior to period 1 and 1 week following period 2 dosing. During each dosing period, SDMT was administered approximately 1 to 1.5 hours postdose, and a single blood sample was drawn for measurement of topiramate plasma concentrations immediately after the cognitive function test. Topiramate plasma concentration levels were also measured at baseline visits to ensure complete washout.

Study III

Study III (UMN) was a randomized, double-blind, placebo-controlled, 3-period crossover study with the same pharmacokinetic sampling and SDMT score administration schedule as study II. Either 100 mg or 200 mg oral topiramate was administered during the treatment period. The additional periods consisted of treatment with a single 2-mg dose of a comparator (lorazepam) or placebo.

Plasma Topiramate Measurement

Blood samples from study I were analyzed using a validated liquid chromatography-mass spectrometry (LC-MS) method, with lower limit of quantification of 0.04 $\mu\text{g/mL}$.¹⁷ For studies II and III, topiramate concentrations were quantified by a validated LC-MS developed for simultaneous determination of 9 antiepilepsy drugs. The lower limit of quantification was 0.375 $\mu\text{g/mL}$.¹⁸

Symbol-Digit Modalities Test

The SDMT is a cognitive performance measure of psychomotor speed, working memory, and attention.¹⁹ It consists of a key containing 9 unique symbols corresponding to the numbers 1 to 9, and a list of random symbols, which the subjects are required to match to the numbers according to the key. The number of symbols coded correctly within 90 seconds represents the score. To ensure the subjects understood the instructions prior to the start of the test, a short standardized practice trial was given. Four alternate versions of the SDMT were used in order to minimize the practice effect.

Population Pharmacokinetics-Pharmacodynamics Modeling

Population modeling of topiramate plasma concentrations and SDMT scores was performed using nonlinear mixed-effects modeling with the NONMEM version 7.2 software (ICON Development Solutions, Hanover, Maryland). Diagnostic graphics and exploratory analyses were performed using R (version 3.1.0) and Xpose (version 4.3.2).

The population PK model of oral and IV topiramate used in this analysis has been previously described.¹⁶ Individual empirical Bayesian estimates of the pharmacokinetic parameters from the established PK model were used to model the topiramate plasma concentration–SDMT score relationship. SDMT scores, which consist of the number of correctly coded symbols within the test duration (90 seconds), can be treated as either approximately continuous data or discrete count data, so both distributional assumptions were explored. For the latter, 3 different distributional models were fitted: (1) Poisson, which assumes that the expected number of counts is equal to the variance of the counts within an individual, ie, equidispersion; (2) negative binomial, which allows for overdispersion; and (3) generalized Poisson, which allows for either over- or underdispersion.^{20,21} The relationship between topiramate plasma concentration and SDMT score change was explored using 3 basic functions: (1) linear, (2) exponential/log-linear, and (3) E_{max} as follows:

$$\widehat{E}_{ij} = E0_i - k_i \cdot Cp_{ij} \quad (1)$$

$$\widehat{E}_{ij} = E0_i - \exp(k_i \cdot Cp_{ij}) \quad (2)$$

$$\widehat{E}_{ij} = E0_i \cdot \left(1 - \frac{E_{\max,i} \cdot Cp_{ij}}{EC50_i + Cp_{ij}} \right) \quad (3)$$

where $\widehat{E}_{ij}$ and Cp_{ij} denote the j -th predicted SDMT score and predicted topiramate plasma concentration, respectively, of the i -th individual; k_i is the slope, and $E0_i$, $E_{\max,i}$, and $EC50_i$ are the baseline SDMT score, maximal fractional reduction in SDMT score due to drug effect, and concentration at half of the maximal drug effect, respectively, of the i -th individual.

Individual pharmacodynamic parameters were assumed to be log-normally distributed, and the interindividual random effects were modeled using an exponential error structure. Goodness of fit of the final model was evaluated using graphical assessment, and histograms of the empirical Bayes predictions of the interindividual random effects were also inspected to verify that the statistical assumptions were met (ie, unimodal and symmetrically distributed around 0).

Covariate Assessment

To investigate the potential effect of age, study, and sex on the PD parameters ($E0$, $EC50$, and $E_{\max}$), these covariates were each tested separately to determine if they should be included in the final model using the stepwise forward inclusion and backward elimination approach. The criterion for forward inclusion and backward elimination was an OFV decrease of at least 3.84 for 1 degree of freedom ($P < .05$) and increase of at least 6.63 for 1 degree of freedom ($P < .01$), respectively. The impact of continuous covariates on the PD parameters was explored using linear, exponential, and power models with the covariate scaled/centered by the median value. Categorical covariates were included as discrete indicator variables. To explore practice effect within an individual, the number of prior tests administered (NPT) was included as a dichotomous covariate on baseline SDMT score as shown in equation 4:

$$E0 = TVE0 \times (1 + I_{NPT > n} \times \Theta_{NPT > n}) \quad (4)$$

N is the number of prior tests, $I_{NPT > n}$ is the indicator variable for cutoff at the n -th prior test (ie, comparison of the baseline scores following n prior tests; $n < NPT$ last), compared to the baseline scores from all tests before that ($0 < NPT - n$), and $\Theta_{NPT > n}$ denotes the

proportionality constant for the change in baseline scores. Different cutoff points were explored, starting with a cutoff of $\text{NPT} > 0$, and departure of the 95% confidence interval (CI) of $\Theta_{\text{NPT} > 0}$ from the null value of 1, indicated significant difference.

Model Selection and Assessment

Model selection was based on difference in NONMEM objective function value (OFV) for competing nested models using the likelihood ratio test, graphical diagnostics using goodness-of-fit (GOF) plots, precision of parameter estimates, and plausibility of the parameter estimates. Akaike's information criterion (AIC) was considered for nonnested models. Evaluation of the final model was performed by prediction-corrected visual predictive checks (pc-VPC), using Perlspeaks-NONMEM (PsN) (version 3.6.2), based on 1000 simulations.²²

Precision of the final model parameter estimates was assessed using both the asymptotic standard errors obtained by the covariance routine in NONMEM and nonparametric bootstrap performed using PsN. From the original data set, 1000 bootstrap data sets were constructed by repeated sampling with replacement, and the final model was fitted to each of the bootstrap dataset. The median and the 2.5th and 97.5th percentiles were then obtained for each PD parameter, and 95% CIs based on the percentiles were obtained.

Results

Demographics

The final data set consisted of a total of 189 SDMT scores from 38 healthy volunteers ($n = 30$ for 100 mg and $n = 8$ for 200 mg). Median age across the studies was 26.5 years, ranging from 19 to 55 years. The demographic characteristics of the population included in the PK-PD analysis are summarized in Table 1, stratified by study.

Continuous Distributional Model

The topiramate exposure–SDMT relationship was adequately described by a direct-response inhibitory E_{max} model with treatment of SDMT data as a continuous variable. As shown in Figure 1A, distribution of the observed SDMT scores was approximately normal, indicating adequacy in treatment of the SDMT data as continuous data. The parameters of this final model were also well estimated with RSE of less than 30% and shrinkage values of less than 10%. A summary of the population parameter estimates from the final PK-PD model and the corresponding relative standard errors (RSE) are provided in Table 2.

Of the 3 structural models (linear, exponential, and inhibitory E_{max} function models) that were explored, the E_{max} model provided the best fit, with AIC of 1114.8, compared to the exponential and linear models (1123.4 and 1118.8, respectively). Interindividual random effects for E_{max} and EC_{50} could not be reliably estimated; hence, the base model included only the interindividual random effect on the baseline parameter, E_0 .

With an increase in age, a trend toward a decrease in baseline SDMT score was observed (Figure 2). The inclusion of age as a covariate on baseline SDMT score in the model

improved the fit significantly (decrease in OFV of 18.15; $P < .005$) and explained 24% of the interindividual variability in baseline SDMT relative to the final base model.

When we explored the effect of administering multiple tests on SDMT scores collected under drug-free conditions (pre- and posttreatment baselines and placebo observations), there appeared to be an improvement in test scores (Figure 3). Starting with a cutoff of NPT > 0 , the 95% CI for the estimate of Θ_{NPT} included the null value of 1, indicating no significant difference between the first test score (NPT = 0) and subsequent ones (NPT > 0). At a cutoff of NPT > 1 , a 7% improvement in SDMT score was estimated, with significant departure of Θ_{NPT} from 1 (95% CI: 1.02 to 1.14). This inclusion of NPT > 1 as a covariate also resulted in a significant drop in OFV (6.91; $P < .01$). Subsequent cutoffs (eg, NPT > 2 , NPT > 3 , and so on) were similarly tested, and no clear trend in improvement beyond NPT larger than 1 was observed. Sex, race, and study did not have a significant effect on either the E_0 , EC_{50} , or E_{max} . The final model is represented by equation 5:

$$E_{ij} = E_{0i} \times \Theta_{\text{NPT} > 1} \times (1 + \Theta_{\text{age}} \times (\text{age}_i - \text{median age})) \times \left(1 - \frac{E_{\text{max},i} \times C_{p_{ij}}}{EC_{50,i} + C_{p_{ij}}} \right) \times (1 + \varepsilon_{ij}) \quad (5)$$

where E_{ij} and $C_{p_{ij}}$ are the j -th SDMT score and j -th predicted topiramate plasma concentration, respectively, of the i -th individual, E_{0i} , $E_{\text{max},i}$, and $EC_{50,i}$ are the baseline SDMT score of the i -th individual, $\Theta_{\text{NPT} > 1}$ is the proportionality constant accounting for difference in E_0 for NPT greater than 1, and Θ_{age} is the effect of age on E_0 , and ε_{ij} is the residual error. Fit of this final model is illustrated in Figure 4.

Discrete Distributional Model

Exploration of count data models (Poisson, generalized Poisson, and negative binomial) in this analysis did not yield an improvement of fit to the data, and results were generally similar to those from the model assuming continuous distribution. As shown in Table 2, parameter estimates and their precision were similar for the model assuming continuous data and the Poisson model. For the models that allow for nonequidispersion (generalized Poisson and negative binomial), parameter estimates for baseline and effect of age and NPT on baseline were comparable to those from the model assuming continuous data. However, the dispersion parameter of the generalized Poisson model could not be well estimated ($> 50\%$ RSE), and the overdispersion parameter of the negative Binomial model was near the lower bound of 0. Approximate equidispersion observed from the data (Figure 1B) corroborates the lack of improvement with these 2 models and poor estimation of the dispersion parameter. Based on the lack of improvement in fit for the Poisson model and the lower AIC of the model assuming continuous data compared to Poisson model, the continuous-variable model was selected.

Model Evaluation

The bootstrap analysis results including confidence intervals are summarized in Table 2. All of the 1000 bootstrap analyses successfully converged, indicating model stability, and were included in the summary. The bootstrap showed narrow CIs for all parameters, and the

median values of the parameters from the bootstrap are comparable to the final model estimates from the original dataset, suggesting that these values are reliable.

The results of the visual predictive checks (Figure 5) indicate the adequacy of the final models in describing the central tendency and variability of the observed data.

Discussion

This report provides the first description of the pharmacokinetic-pharmacodynamic relationship between topiramate plasma concentrations and SDMT, a sensitive measure of topiramate-induced impairment of attention, working memory, and psychomotor speed. Established on data pooled from 3 randomized, crossover studies in healthy subjects, an inhibitory $E_{\max}$ model was found to characterize the topiramate concentration–SDMT score relationship well. At the EC50 of 2.85 $\mu\text{g/mL}$, this topiramate plasma concentration value was estimated to be associated with a 25.5% reduction of the SDMT score relative to baseline. Moreover, to our knowledge, this is the first characterization of the practice effect due to repeated administration of the SDMT over intervals as short as 1 week.

In this analysis, age was an important determinant of the baseline SDMT score, with an estimated decrease of 1.13% in baseline SDMT score with every year increase in age. This is consistent with other reports of an SDMT performance decline in normal aging. In particular, a study conducted in older individuals undergoing coronary bypass graft surgery ($n = 239$, mean age 67.2 ± 8.7) reported a similar SDMT score decline rate of approximately 1.26%.²³ Based on normative data from a study in homosexual/bisexual men ranging in age from 25 to 54 years ($n = 733$), a significant association ($P < .0001$) between age and SDMT test performance has also been demonstrated.²⁴ In addition, summary of SDMT data from several studies in healthy subjects also suggests a decrement of SDMT performance in older individuals, with a mean score of 58.2 (SD = 9.1) reported for individuals less than 30 years old, 53.2 (SD = 8.9) for individuals between 30 to 55 years old, and 35.8 (SD = 9.6) for individuals over 55 years old.²⁵

Notably, improvements in SDMT score were observed with multiple administrations of the test when topiramate was not given, indicating the presence of a practice effect, which refers to gains in test scores due to the subject's increasing familiarity with the testing procedure. This practice effect was accounted for in our model by inclusion of NPT as a dichotomous variable on baseline SDMT score, and a significant increase in test scores was found on the third administration of the test. This is consistent with the findings from an earlier study in 54 healthy subjects, which reported a significant increase in SDMT score between the second and third test administration.²⁶ It should be noted that the duration between tests for that study was 18 months, whereas the testing intervals in our studies ranged from hours to 2 months.

Repeated neuropsychological testing over time intervals as short as hours to weeks may be necessary in designs aimed at investigating the acute effect of drug concentration on neurocognitive function within an individual. Although our approach allowed us to characterize the practice effect of SDMT administered multiple times within close temporal

proximity, with the unequal time intervals between drug-free test sessions resulting from the randomization and pooling of data across study designs, modeling of the change in drug-free SDMT score as a function of time may be a preferred approach. However, due to the limited time points for which SDMT scores were collected under drug-free conditions, we were unable to employ a time-dependent approach, which is a limitation of this analysis.

Nevertheless, despite the practice effect that led to improvement of SDMT scores, administration of a single dose of topiramate worsened performance on the SDMT, and the mean SDMT score declined nonlinearly with increasing topiramate plasma concentration. At the typical peak topiramate concentration of 2 $\mu\text{g/mL}$, observed after a dose of 100 mg, an average reduction of 21% in SDMT score relative to the initial baseline is predicted from the model. This decline in attention, working memory, and psychomotor speed, as measured by the SDMT, can be attributed to exposure to topiramate alone because the study population included only healthy subjects, thus eliminating confounding variables such as seizures, drug interactions, and the underlying pathology of epilepsy. In general, these findings are in line with previous reports of the cognitive effects of topiramate in healthy subjects. In a study on healthy volunteers with comparable demographics (mean age [range] = 37 [22 to 58] years) to that in our study, the mean SDMT baseline score was 62.1 compared to the typical score of 59.3 in this study.¹⁴ Interestingly, based on the average topiramate plasma concentration of 9.3 $\mu\text{g/mL}$ reported after titration and multiple dosing to steady state at 300 mg/day topiramate by Meador et al, our model predicts an average drop of 39% in SDMT score, which is higher than the observed average drop of 25.4% in that study.¹⁴ Other than the possibility that the model may be inadequate at predicting the effect on SDMT at high doses, because we have only studied up to 200 mg, it is also possible that tolerance to the cognitive side effects may have developed with slow titration over the 7-week treatment duration in that study. The latter would be consistent with findings of an increase in cognitive side effects with rapid titration schedules in patients with epilepsy.^{26,27} Studies designed to examine acute and chronic effects of topiramate on SDMT score, however, would be needed to verify this.

It is worth mentioning that the narrow range of administered doses and concentrations in our study were limitations to investigating the PK-PD relationship at higher exposures to topiramate. In addition, collection of SDMT data at more time points following placebo treatment is needed for characterization of the time course of the practice effect.

Randomized, placebo-controlled crossover studies using a wider range of topiramate doses and intensive PK-PD sampling are now under way to address these limitations.

In conclusion, we used a PK-PD modeling approach to characterize and quantify the exposure-response relationship of doses (100 or 200 mg) of acutely administered topiramate with SDMT scores in healthy volunteers. Although it is unclear if this relationship can be directly translated to patients with epilepsy, these results may be relevant for patients with migraine or individuals who are taking these doses of topiramate for obesity. Moreover, this approach enabled the quantification of the practice effect observed with repeated administration of neuropsychological tests over shorter testing intervals than have previously been reported in the literature.

Acknowledgments

This study was funded in part by NIH/NINDS R01 NS076665, K01 NS050309, and a grant from the Academic Health Center at the University of Minnesota.

J.C.C. had support from the Epilepsy Foundation New Therapy Grants Program as well as a grant and nonfinancial support from Ligand Pharmaceuticals for the IV TPM study in healthy volunteers; J.C.C. and S.E.M. receive royalty payments as part of a licensing agreement between Ligand Pharmaceuticals and the University of Minnesota; S.E.M., A.K.B., C.N.L., and I.E.L. had support from the National Institutes of Health and the University of Minnesota during the conduct of the study.

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Figure 1.

(A) Histogram of Symbol-Digit Modalities Test (SDMT) score and (B) plot of variance versus mean of SDMT score obtained from raw data. Each observation (open circle) represents 1 subject, solid line represents the line of identity, and the dashed line represents the smoothed loess fit.

Figure 2. Relationship between individual baseline (BL) and age. Open circles represent observations, and the line represents the smoothed loess fit.

Figure 3. Symbol-Digit Modalities Test (SDMT) score change from baseline under drug-free conditions (A) for all studies combined and (B) stratified by study. The boxes represent 25th, 50th, and 75th percentiles, whiskers represent the extreme data within 1.5 times of the interquartile range, and the filled circles represent outliers. Numbers above the median lines denote the number of individuals.

Figure 4.

Symbol-Digit Modalities Test (SDMT) score–topiramate plasma concentration profile. Open circles denote observations, black line denotes final model fit, and black triangles denote baseline/placebo observations from third test administration onward. Inset on top right corner shows topiramate plasma concentration up to 6 $\mu\text{g/mL}$.

Figure 5.

Prediction-corrected visual predictive check for the final model, stratified by (A) placebo and (B) treatment. Open circles represent prediction-corrected observations, lines represent 5th, 50th, and 95th percentiles of prediction-corrected observations, and shaded areas represent 95% confidence intervals of the respective prediction-corrected simulated data.

Table 1

Study Demographics

	Study I	Study II	Study III	Total
N	10	9	11	38
Dose (mg)	100	100	200	-
Body weight (kg) ^a	79.8 (58.30–112.3)	72.27 (54.70–92.3)	78.76 (59.80–111.2)	77.6 (52.2–104.4)
Age (years) ^a	31.5 (19–55)	22 (20–24)	31 (20–50)	30.9 (19–53)
Sex	6 M, 4 F	7 M, 2 F	7 M, 4 F	4 M, 4 F
Race (Caucasian/AA/Others/Unknown)	9/1/0/0	6/1/2/0	7/3/0/1	2/5/1/0
				26/10/3/1

AA, African American; N, number of individuals.

^aMedian (range).

Summary of Continuous and Poisson Population Pharmacokinetic-Pharmacodynamic Model Parameters

Table 2

Parameter	Continuous Model			Poisson Model	
	Estimate (RSE%)	Median From Bootstrap	95%CI From Bootstrap	Estimate (RSE%)	
E0	59.3 (3.2)	59.4	55.7–62.9	59.4 (3.1)	
E _{max}	0.51 (18.3)	0.503	0.26–0.76	0.532 (19.9)	
EC50 (μg/mL)	2.85 (20.7)	2.77	0.43–5.26	3.07 (34.5)	
θ _{NTEST>1}	1.07 (2.7)	1.07	1.02–1.13	1.09 (2.5)	
θ _{N_{age}}	−0.0113 (20.4)	−0.0115	−0.0160–0.00661	−0.0116 (20.0)	
IVV baseline (%CV) ^a	18.3 (13.3)	17.3	12.9–22.5	18.5 (12.7)	
Proportional residual error (%CV) ^b	16.2 (7.6)	15.9	13.5–18.4	–	

E0, baseline SDMT score; EC50, topiramate plasma concentration at half of the maximal drug effect; θ_{NTEST>1}, proportionality constant accounting for difference in E0 for NPT greater than 1; θ_{N_{age}}, effect of age on E0; IVV baseline, interindividual variability on baseline; RSE%, percentage relative standard error.

^aReported as %CV, calculated using equation: $100 \sqrt{\exp(\omega) - 1}$.

^bReported as %CV, calculated using equation: $100 \sqrt{\sigma}$.