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An Innovative Disease-Drug-Trial Framework to Guide Binge Eating Disorder Drug Development: A Case Study for Topiramate

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As with other psychiatric disorders, development of drugs to treat binge-eating disorder (BED) has been hampered by high placebo response and dropout rates in randomized controlled trials (RCTs). Although not approved for use in BED, several RCTs have suggested that topiramate is efficacious for BED in obese individuals. Using data from a positive investigator-initiated RCT of topiramate in 61 obese individuals with BED, the objective of the present study is (i) to develop a quantitative disease-drug-trial framework to inform future BED clinical trial designs, and (ii) to determine the optimal topiramate dose to achieve therapeutic efficacy. Disease-drug-trial models were developed separately for the two efficacy measures, namely, longitudinal normalized weekly binge-eating episode frequency (BEF) and binge day frequency (BDF). Model building consisted of (i) developing a placebo effect model that describes response from the placebo group, (ii) adding a drug effect to the placebo model to describe dose-response relationships, and (iii) developing a parametric time to event model to characterize patient dropout patterns. The placebo effect on normalized BEF and BDF over time demonstrated a maximum decrease of ~ 57% by 5 weeks. Participants had a higher dropout probability if no weight loss occurred during the trial period. The identified dose-response relationship demonstrated a daily dose of 125 mg was needed to exhibit a marked reduction in weekly BEF. The developed comprehensive disease-drug-trial model will be utilized to simulate different clinical trial designs to increase the success for future BED drug development programs.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
☑ Quantitative disease-drug-trial framework has been developed to inform drug development decisions in certain psychiatric disorders, such as schizophrenia and Bipolar disorder. However, no quantitative framework exists to describe symptomatic changes in the response in binge-eating disorder (BED).

WHAT QUESTION DID THIS STUDY ADDRESS?
☑ The objective of this study is to leverage data from a proof-of-concept clinical trial, develop a quantitative framework to describe longitudinal changes in efficacy variables, and determine the optimal dose need to achieve therapeutic efficacy in BED trials using Topiramate as a case study.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
☑ This analysis describes the first disease-drug-trial model in the setting of BED. The quantitative framework suggests that patients with higher baseline severity exhibit a larger placebo response. Patients who demonstrate limited improvement or worsening weight change are at higher risk for dropout.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?
☑ This research proposed a lower dose range for patients with BED receiving topiramate. The developed comprehensive disease-drug-trial model for BED can be utilized to guide BED trial clinical designs and elucidate the success for future BED drug development programs.

Over the past several years, new drug development programs in psychiatry have become sparse due to disinvestment by the pharmaceutical industry.[1] Several challenges have shown to impede drug development success for psychiatric clinical trials. Substantially large placebo response, underexplored exposure-response relationships, and high dropout rates are potential factors that can fail a drug from being marketed.[2,3] One common theme that consistently has shown to "de-risk" drug development is the application of prior knowledge regarding drug-specific properties and disease-specific phenomena using quantitative translational methods. Quantitative disease-drug-trial models

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have been recently used in neuropsychiatry to mathematically represent the time course of a disease, placebo effect, a drug's pharmacologic effect, and trial characteristics to guide drug development and regulatory decision making.[4,5] Examples of the use of disease-drug-trials in psychiatry include the longitudinal evaluation of changes in Positive and Negative Syndrome Scale scores for proper comparison of clinically relevant treatment effects, the development of a placebo-dropout model using Young Mania Rating Scale scores in patients with bipolar disorder to inform future trial design, and the use of the Hamilton Rating Scale for Depression scores to forecast the probability of being a placebo responder.[6–8]

Binge eating disorder (BED) is a psychiatric disorder characterized by recurrent and distressing binge-eating episodes, defined as eating unusually large quantities of food with a sense of lack of control over eating, without inappropriate compensatory weight loss behaviors.[9,10] BED is the most common eating disorder in the United States and occurs in ~ 3% of the general population.[11] Treatment goals include the reduction of binge eating, improvement in emotional well-being, and, for those with obesity, weight loss.[12] The recent recognition of BED as a mental health disorder by Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, has resulted into widespread insurance coverage that consequently incentivizes pharmaceutical companies to develop additional treatment options. However, lisdexamfetamine (Vyvanse; Shire, Wayne, PA) is the only drug with regulatory approval for the treatment of moderate to severe BED. Several pharmacological treatments have been studied and used off-label to treat BED.[13] In particular, three randomized controlled trials have shown that the anticonvulsant, topiramate, is efficacious for reducing binge eating and body weight in obese individuals. Given the presence of other psychiatric comorbidities, high placebo response, heterogeneous treatment responses, and difficulties in retaining patients, the development for newer BED therapies is lackluster.[14]

To take advantage of an untapped market and guide BED drug development, prior knowledge from previous clinical trials can be utilized to improve design and increase the success of future trials.[15] Quantitative approaches have been explored to compare different treatment options and statistical methods in the setting of BED.[16,17] Disease-drug-trial models can serve as a platform to enable simulations of various BED trial design scenarios and to select the design with the highest likelihood of treatment effect to ensure development success. This present study utilizes data from an investigator-initiated clinical trial evaluating topiramate in the treatment of BED in obese individuals.[18] The aims of the current research are to (i) develop a quantitative disease-drug-trial model to describe longitudinal changes in clinical end points and dropouts in patients receiving topiramate or placebo, and (ii) utilize the developed model to determine the optimal topiramate dose needed to achieve therapeutic efficacy in patients with BED.

METHODS
Data
Longitudinal data were obtained from an investigator-led single-center, randomized, double-blind, flexible dose evaluating the efficacy and tolerability of topiramate for BED in obese individuals.[18] Data included participants diagnosed with BED by *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, criteria were randomized to topiramate (*N* = 30) or placebo (*N* = 31). The original trial consisted of a 2–5-week screening period, a 14-week treatment period, and a 2-week treatment taper/discontinuation. The forced titration dosing algorithm (dose range: 25–600 mg/day) used in the study is described in detail in McElroy *et al.*[18] Baseline demographics provided in the analysis data set include: age, age of BED onset, sex, race, comorbid psychiatric disorders, and alcoholism. Laboratory measures, such as vital signs, weight, height, body mass index, body fat percentage, lipid panel, blood pressure, and glucose, were measured at baseline and every visit. Plasma concentrations for topiramate were not collected.

The primary efficacy measure assessed in the trial was the number of binge-eating episodes (binge eating-episode frequency (BEF)) during the 7 days before each visit.[18] Binge-eating episodes, including duration and amount of food consumed, were recorded by participants in take-home diaries, and then evaluated by an investigator to confirm whether they were, in fact, binge-eating episodes. A secondary efficacy measure evaluated in the study was the number of binge-eating days (binge day frequency (BDF)) during the 7 days before each visit. A binge day was defined as a day on which a patient had at least one binge-eating episode. It is also important to note that the US Food and Drug Administration (FDA) considered BDF as an appropriate efficacy measure in the approval for lisdexamfetamine.[19] For visits that occurred greater than or less than 7 days after the previous visit, the number of BEF and BDF were normalized to a weekly frequency.[18] Both efficacy measures were recorded at baseline and 7 additional visits through week 14.

Disease-drug-trial model
Disease-drug-trial models were developed independently to describe the time course (baseline to week 14) for normalized BEF and normalized BDF. Provided data sets lacked any record of daily binge-eating information, which could have been used to model daily binge frequencies as a discrete count variable and derive weekly BEF and BDF. However, for several patients, weekly BEF/BDF was reported in time periods of < 7 days. Therefore, due to normalization and the occurrence of non-integer values, the two response measures were treated as continuous variables.[16] The modeling and simulation approach included the following steps: (i) develop a disease model utilizing information from patients receiving placebo, (ii) develop a disease-drug model utilizing information from patients receiving topiramate and placebo, (iii) develop a dropout model to characterize BED trial attrition trends, (iv) qualify the model using simulations and compare with internal data (internal validation), and (v) qualify the model using simulations and compare with external data (external validation). The rationale for each model component is explained sequentially below:

Disease model. Because patients receiving placebo in clinical trials do not receive active drug, spontaneous changes in BEF or BDF in the placebo group can be viewed

Binge Eating Disorder Disease-Drug-Trial Model
Kalaria et al.

90

as a proxy for the natural course for BED. Hereafter, the placebo effect model will be referred to as the disease model. Therefore, the placebo group data were used to build a disease model that described the trend in the placebo response over time. Several empirical mathematical equations, including the linear, exponential, power, and Weibull models, were first explored as potential models to describe the change in normalized BEF and BDF over time in the placebo group.[20]

Disease-drug model. One of the main goals to incorporate the drug effect on the change in response is to ascertain the optimal dose needed to achieve therapeutic outcomes. Given the flexible dose trial design and the lack of pharmacokinetic data, special attention is needed to discern the dose-response relationship using the disease-drug-trial model framework.[21–23] A major challenge in investigating dose-response relationships in flexible dose titration designs is to avoid attributing a "time effect" as a "dose effect." Delay between drug administration and achievement of steady-state pharmacodynamic response could be related to several reasons, including time to pharmacokinetic steady-state, the presence of a time-varying placebo response, or indication of a delayed drug response. These factors were taken into consideration when developing the dose-response relationship. Both patients randomized to placebo and topiramate were used to build the drug model. Simultaneous analysis of the drug effect model was explored additively and proportionally on the placebo effect using different mathematical functions to describe relationship between dose and change in normalized BEF/BDF.

Dropout model. Missing data due to dropouts could lead to biased interpretations of efficacy and safety. A meta-analysis of eating disorder trials indicated that dropout rates can range upward to 73%, with higher dropouts occurring in the outpatient setting.[24] Dropouts could contain information about the benefits or risks of therapy that may not be evident from clinical end points. To predict the unbiased mean change in BEF and BDF, the probability of patients dropping out was modeled using parametric time-to-event analysis that describes the hazard of dropout over time. Based on exploratory analysis, exponential and Weibull hazard models were tested to determine the predicted dropout probability.[6]

Model development
A nonlinear mixed effect modeling approach was used to develop the disease-drug-trial models using Phoenix NLME version 7 (Certara, St. Louis, MO). First-order conditional estimation method with interaction was used to develop the disease and drug effect models. Dropout patterns were analyzed using the Laplace estimation method. R software version 3.4.1 (www.r-project.org) was used for graphical exploration, data manipulation, and evaluation of the results. Because there were multiple measurements per subject, both between and within subject variability in the parameters were estimated along with the population mean estimates. Variability between subjects for disease and drug model parameters were evaluated assuming random effects following a log-normal or normal distribution (Eq 1):

$$P_i = tvP \cdot \exp^{\eta_i} \text{ or } P_i = tvP + \eta_i \qquad (1)$$

where P_i is the individual parameter, tvP is the population mean parameter estimate, and η_i is the individual-specific random effect that is assumed to be normally distributed with a mean of zero and variance of Ω^2. Correlations among random effects were also tested. Within-subject variability was included using an additive structure to account for any unexplained variability in normalized BEF and BDF. Subject-specific prognostic factors (age, sex, race, comorbid psychiatric illness, alcohol abuse, substance abuse, and age of BED onset) were included into the final model based on statistical significance (decrease in objective function value by 3.84 units at $\alpha = 0.05$), clinical relevance, and model diagnostics.

Model qualification
The final disease-drug-trial model was selected based on the following criteria: successful model minimization, comparison of full vs. reduced models using the Akaike Information Criterion, visual inspection of goodness-of-fit and individual model fit plots, reasonable/plausible parameter estimates and SEs, and a mechanistic understanding of parameter estimates. The precision of final model parameters was obtained using nonparametric bootstrap with replacement using 200 data sets. Five hundred identical replicates of the original data set were used as inputs into the final models to perform in silico clinical trial simulations and to obtain longitudinal normalized BEF, BDF, and probabilities of trial adherence from baseline to week 14 for each patient. Due to the use of an additive error model, it is possible to obtain weekly BEF and BDF that are less than zero and weekly BDF > 7. Therefore, negative frequencies were truncated to zero and weekly binge day frequencies > 7 were reduced to 7. An indicator for the occurrence of a dropout event was recorded if simulated probabilities were less than a randomly generated number from a uniform distribution with bounds between 0 and 1. The 5th, 50th, and 95th percentiles at each week for model predicted and observed total BEF and BDF scores were obtained and visually compared (visual predictive checks (VPCs)). The corresponding 95% confidence bands were used to assess the uncertainty around model predictions. The ability to predict clinical therapeutic outcomes was a major component of model qualification. Responder analysis is typically done to provide clinical relevance to changes in a continuous primary efficacy measure. In the FDA's review of lisdexamfetamine for the treatment of BED, the agency noted that the proportion of subjects with a 4-week cessation of binge eating (zero events of binge eating for at least 4 weeks prior to study end point or end of treatment) is a key secondary end point in evaluating therapeutic success.[25] To qualify the disease-drug-trial model,

quantitative predictive check (QPC) plots were assessed for similarity between simulated vs. observed clinical therapeutic outcomes, as described above.[26]

Dose-response simulations

In order to recommend an optimal topiramate dose, a population average dose-response relationship was simulated using the average parameter estimates from the final model. Optimal dose range selection will be based on the ability achieve a marked response (> 75% change from baseline in binge episodes).

RESULTS

A total of 384 observations from 61 patients were included for model development. Patients receiving topiramate were administered doses in between the range of 50 and 600 mg. Descriptive summary of the baseline demographic characteristics are in **Table S1**. Mean observed BEF and BDF over time for patients taking placebo and topiramate are provided in **Figure S1**. Patients randomized to topiramate experienced a greater reduction from baseline in BEF and BDF than placebo (94% vs. 46% and 93% vs. 46%, respectively). The mean profiles demonstrate that, on average, patients receiving placebo or topiramate reached a steady-state normalized BEF/BDF at ~ 6 weeks. Exploratory analysis suggested that patients with a higher BEF or BDF at baseline experienced a larger absolute reduction in frequency at week 14 in patients taking placebo and topiramate. **Table S2** provides the median and range of topiramate doses by week.

Disease model

An exponential model best described the change in normalized BEF and BDF over time. The impact of the placebo effect was parameterized to be proportional to the baseline frequency based on exploratory findings. The final disease model is described in Eq. 2 where: BASL is the baseline BEF or BDF, P_{max} is the maximum proportional change in placebo response, and k_p is the rate constant associated with the time to achieve maximum placebo effect. The random effect model for the baseline frequency and k_p parameters assumed a log-normal distribution, whereas for the P_{max} parameter, a normal distribution was assumed to allow for a reduction or increased binge frequency at steady-state as compared with baseline.

$$\text{Binge Frequency: } BF(t) = BASL \cdot [1 - P_{max} \cdot (1 - \exp^{-k_p \cdot t})] \quad (2)$$

Table 1 Model parameter estimates with nonparametric bootstrap-based 95% confidence intervals (*N* = 200 replicates)

Parameter	Disease model Estimate (95% CI)	Disease-drug model Estimate (95% CI)	Disease-drug-trial model[a] Estimate (95% CI)
	Normalized weekly binge episodes		
BSL (unit)	5.9 (4.82–7.00)	5.4 (4.75–6.02)	5.4 (4.65–6.12)
P_{max}	0.56 (0.4–0.72)	0.60 (0.48–0.74)	0.57 (0.45–0.81)
k_p (week^{-1})	0.81 (0.21–1.43)	0.57 (0.41–0.74)	0.54 (0.24–0.80)
IIV BSL (CV%)	38 (54–69)	43 (35–50)	45 (33–51)
IIV P_{max} (SD)	0.30 (0.19–0.40)	0.28 (0.20–0.35)	0.31 (0.18–0.37)
IIV k_p (CV%)	94 (81–127)	112 (86–145)	112 (86–145)
ID_{50} (mg/day)	–	155 (104–207)	170 (125–308)
IIV ID_{50} (CV%)	–	159 (95–210)	143 (97–201)
λ_0 (week^{-1})	–	–	0.042 (0.03–0.05)
β_1	–	–	0.16 (0.09–0.27)
RUV (additive)	1.86 (1.31–2.41)	1.53 (1.18–1.87)	1.55 (1.19–1.91)
	Normalized weekly binge day frequency		
BSL (unit)	4.4 (3.97–5.31)	4.4 (4.01–5.00)	4.3 (4.6 5–6.12)
P_{max}	0.55 (0.41–0.69)	0.62 (0.49–0.88)	0.59 (0.49–0.86)
k_p (week^{-1})	0.79 (0.11–1.46)	0.48 (0.17–0.83)	0.55 (0.23–0.94)
IIV BSL (CV%)	39 (31–45)	33 (35–50)	34 (26–40)
IIV P_{max} (SD)	0.29 (0.20–0.35)	0.28 (0.20–0.39)	0.33 (0.22–0.41)
IIV k_p (CV%)	97 (77–128)	116 (70–155)	65 (31–111)
ID_{50} (mg/day)	–	215 (104–350)	227 (125–308)
IIV ID_{50} (CV%)	–	147 (98–207)	81 (37–153)
λ_0 (week^{-1})	–	–	0.044 (0.03–0.06)
β_1	–	–	0.17 (0.06–0.34)
RUV (additive)	1.18 (0.92–1.44)	1.11 (0.92–1.31)	1.10 (0.96–1.27)

β_1, covariate coefficient; BSL, baseline; CI, confidence interval; ID_{50}, dose required to achieve 50% of maximal drug effect; IIV, interindividual variability; k_p, placebo response rate constant; λ_0, baseline hazard; P_{max}, maximum proportional placebo response; RUV, intra-individual variability.
[a]Shrinkage on random effect parameters for BSL, P_{max}, k_p, and ID_{50} ranged from 25–61% and percent relative standard error (%RSE) for all parameters ranged from 6–28% for the final disease-drug-trial models (binge-eating episode frequency and binge day frequency).

Population mean parameter estimates for BASL in the normalized BEF and BDF disease models were 5.88 and 4.6, respectively. The population parameter estimates for P_{max} and k_p were also similar for both models (**Table 1**). Maximum proportional change in placebo response was ~ 55%, and time to reach steady-state placebo response was ~ 4 weeks $(5 \times \frac{0.693}{k_p})$ for both efficacy measures. During model development, no significant covariates were found to influence placebo effect parameters.

Disease-drug model
After adding the topiramate treatment group data to the placebo data, a maximum unbound systemic concentration (I_{max}) drug effect model was found to best characterize the dose-response relationship. An I_{max} model is a nonlinear function that is frequently used in dose-response analysis to describe an increase in response that reaches an asymptotic point with increasing doses. Although pharmacokinetic data was not collected, different exposure metrics, such as previous daily dose and cumulative dose, were tested to best quantify the drug effect. The final disease-drug model is represented Eq. 3: where I_{max} is the maximum proportional change in drug response and ID_{50} is the dose required to achieve 50% of the maximal drug effect. Total daily dose just prior to each weekly visit was found to be the optimal drug exposure metric. The random effect model for ID_{50} was assumed to follow a log-normal distribution.

$$BF(t) = BSL \cdot \left(1 - P_{max} \cdot \left(1 - exp^{-k_p \cdot t}\right)\right) \cdot \left(1 - \left(\frac{I_{max} \cdot DOSE}{ID_{50} + DOSE}\right)\right) \quad (3)$$

Initially, all placebo effect and drug effect parameters were estimated simultaneously, and it was found that the I_{max} parameter was estimated to be ~ 1. Preliminary analysis of the data demonstrated that 81% of patients on topiramate experienced complete remission of binges at study end point. Therefore, model development was continued by fixing the I_{max} parameter to 1. Estimates for ID_{50}, when assessing change in normalized BEF and BDF, were found to be 170 and 228 mg, respectively (**Table 1**). No significant covariates for ID_{50} were identified.

Trial model
Data used for dropout model building indicate that 14 of 30 patients in the topiramate group (46.7%) and 12 of 31 patients in the placebo group (38.7%) did not complete all 14 weeks of treatment. Based on data exploration and model comparison, an exponential time-to-event dropout model was selected to best describe the hazard of dropout (Eq. 4).

$$h(t) = \lambda \cdot exp^{[\beta_1 \cdot \%CFB\ Body\ Weight_{(t)}]} \quad (4)$$

The baseline hazard (λ) is the hazard of a patient dropout without the influence of any predictors. Various predictors of dropouts were evaluated using exploratory Kaplan-Meier plots and Cox proportional hazard models. Time varying predictors including: observed binge frequencies, change from baseline in BEF or BDF, percent change from baseline in BEF or BDF, change from baseline in body weight, and percent change from baseline in body weight were identified as potential predictors for dropout. However, observed percent change from baseline in weight demonstrated the largest reduction in objective function value and an adequate Kaplan-Meier-based VPC plot (**Figure 1**). Parameters for the dropout model were estimated simultaneously with the developed disease-drug model (**Table 1**). The final dropout model suggests that for every unit increase in percent change from baseline in body weight (weight increase), the hazard for dropout increases by 18%.
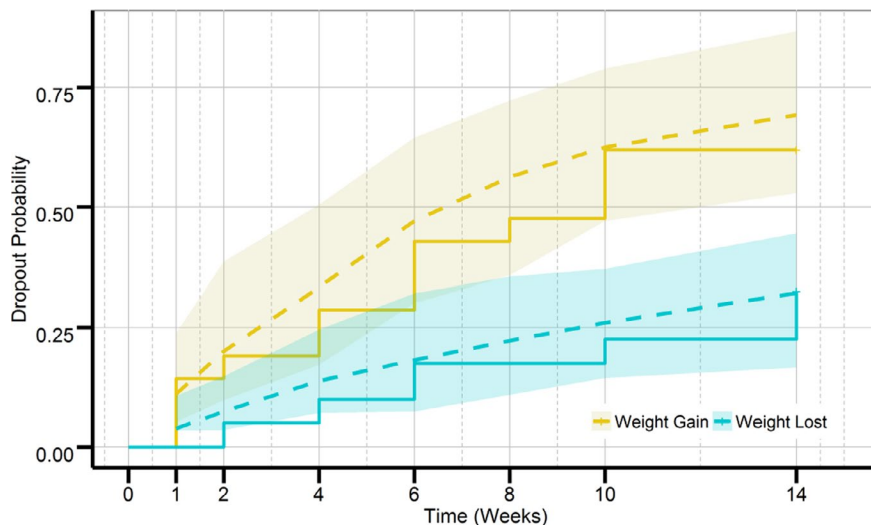

Figure 1 Kaplan-Meier based visual predictive check for final dropout model (*N* = 500 simulations). Solid and dashed lines represent observed and predicted probabilities for dropout. Shaded regions represent the prediction interval for dropout probabilities in each category.
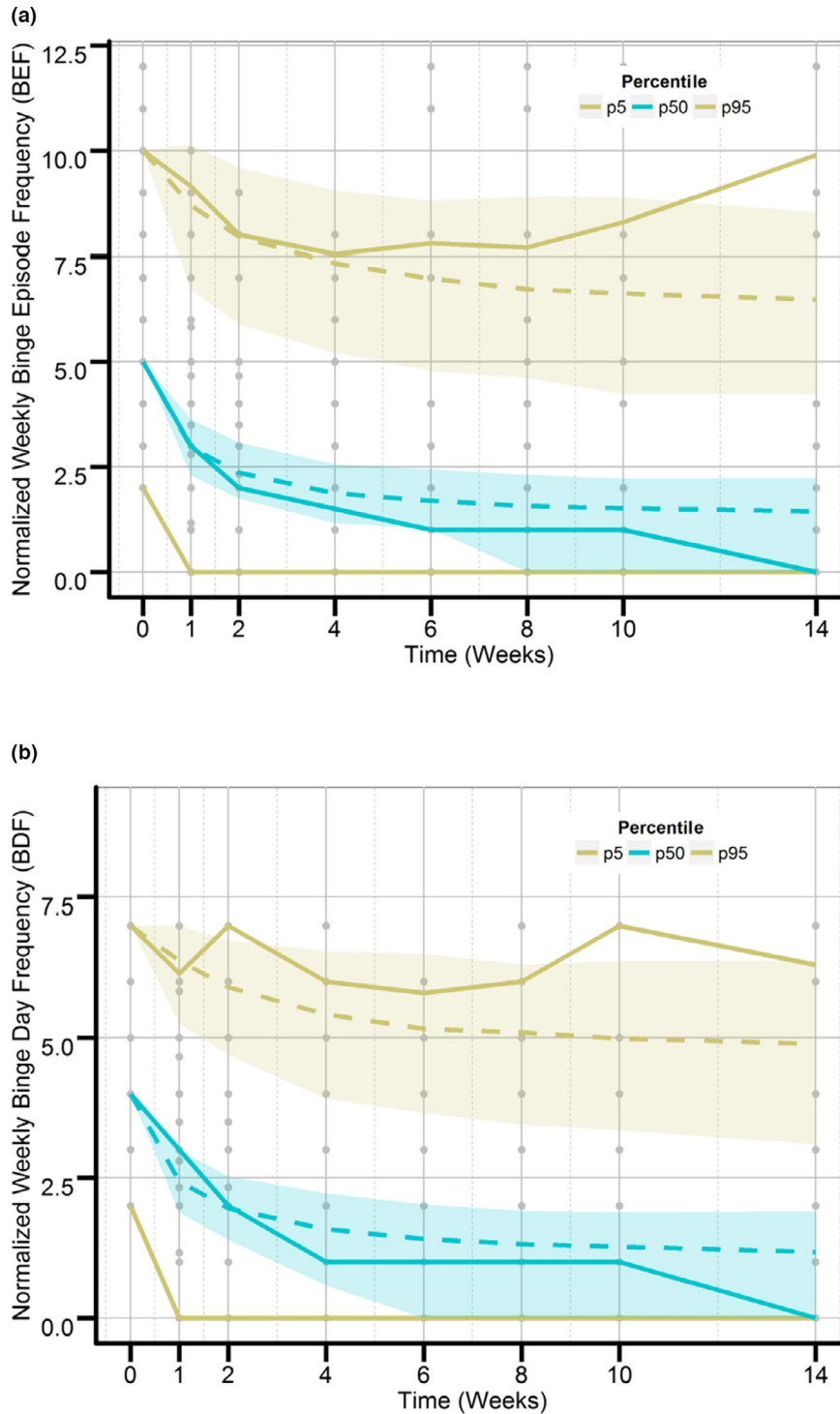
(a)

(b)

Figure 2 Visual predictive check plots. The final disease-drug-trial models characterizing longitudinal normalized weekly binge episodes in patients receiving topiramate and placebo (*N* = 500 simulations) (**a**) and binge day frequency (**b**). Solid and dashed lines represent the observed and model-simulated 5th, 50th, and 95th percentiles. Colored bands demonstrate the 95% confidence interval for the simulated 5th, 50th, and 95th percentiles.

Weight submodel
Because percent change from baseline in weight was found to be a significant time-varying predictor for dropout, a submodel to describe the change in weight over time is needed to simulate BED clinical trials for model qualification. Mean weight loss in patients receiving topiramate was greater than the placebo group (5.9 kg vs. 1.2 kg). Although, no correlation was found between binge frequency and

weight, preliminary analysis suggested that the change in weight over time could be described using a linear relationship. A linear model was developed with treatment arm as the only significant covariate on the slope parameter (Eq. 5). The random effect for the slope parameter was assumed to follow a normal distribution to account for patients who could experience weight loss or weight gain during the trial period.

$$\text{Weight}(t) = \text{WT}_{\text{BSL}} - [\text{slope} \cdot (1 + \beta \cdot (\text{Treatment=Topiramate}))] \quad (5)$$

Parameter estimates for the weight submodel are provided in **Table S3**. Slope parameters for patients taking topiramate and placebo were estimated to be 0.36 kg/week and 0.04 kg/week, respectively. This reflects that patients on topiramate lost an average of nine times more weight per week than patients receiving placebo.

Final model evaluation

Table S4 provides diagnostic comparisons between several investigated structural models. Diagnostic plots for the final combined disease-drug-trial model displayed reasonable agreement between individual predicted vs. observed frequencies and no bias trends in conditional weighted residual vs. population predicted frequencies (**Figure S2**). Individual normalized BEF and BDF vs. time profiles depict adequate fitting by the final disease-drug-trial model. Because of the final model structure, spontaneous increases in BEF or BDF were not captured. Nonetheless, individual predictions were able to describe different trends inherent in the data (**Figure S3**). Median parameter estimates obtained from the bootstrap replicates agreed with the final disease-drug-trial models. VPC plots for the disease-drug-trial model are
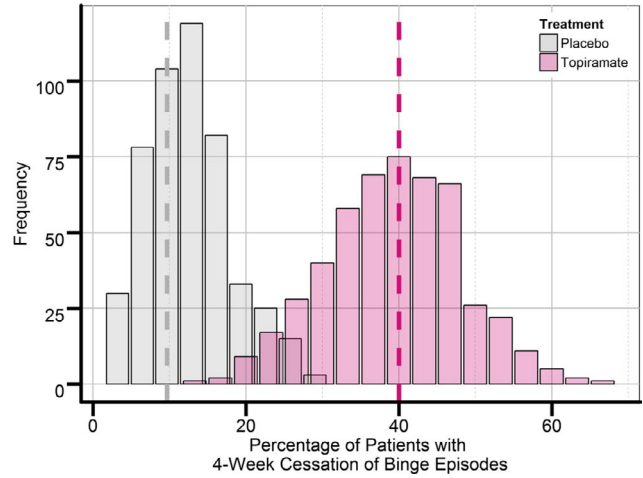

Figure 4 Comparison of percentage of patients with 4-week cessation of binges in patients receiving topiramate vs. placebo based on simulations of binge-eating episode frequency. Dashed lines represent observed percentage of patients with 4-week cessation of binges. The histogram displays the distribution of percentage of patients with 4-week cessation of binges from model-based simulations (*N* = 500 simulations).

shown in **Figure 2**. Simulated median weight over time profiles matched the observed trend in patients taking placebo and topiramate. Model evaluation using QPCs demonstrated the capability of the developed disease-drug-trial model in predicting key clinical outcomes. Clinically meaningful QPCs are presented in **Figures 3-5** demonstrating predictions for categorical response outcomes, percentage of patients exhibiting 4-week binge cessation, and percentage of patients exhibiting clinical meaningful weight loss (≥ 5% reduction in weight) in agreement with the observed outcomes. The population
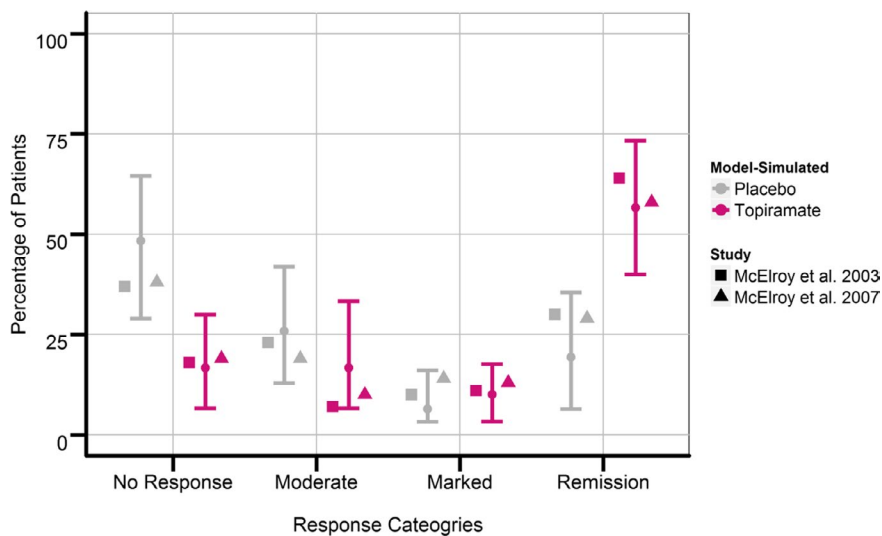

Figure 3 Categorical responder analysis comparing patients receiving placebo vs. topiramate. Response categories based on percent reduction in weekly binge episodes at study end point. Circle point and associated error bars represent model-simulated (*N* = 500 simulations) mean and 95% confidence intervals. Square and triangle points represent observed percentage of patients in each responder category from two randomized controlled trials evaluating topiramate for binge-eating disorder.[18,28] No response: < 50% reduction; moderate response: 50–74% reduction; marked response: 75–99% reduction; remission: cessation of binges.
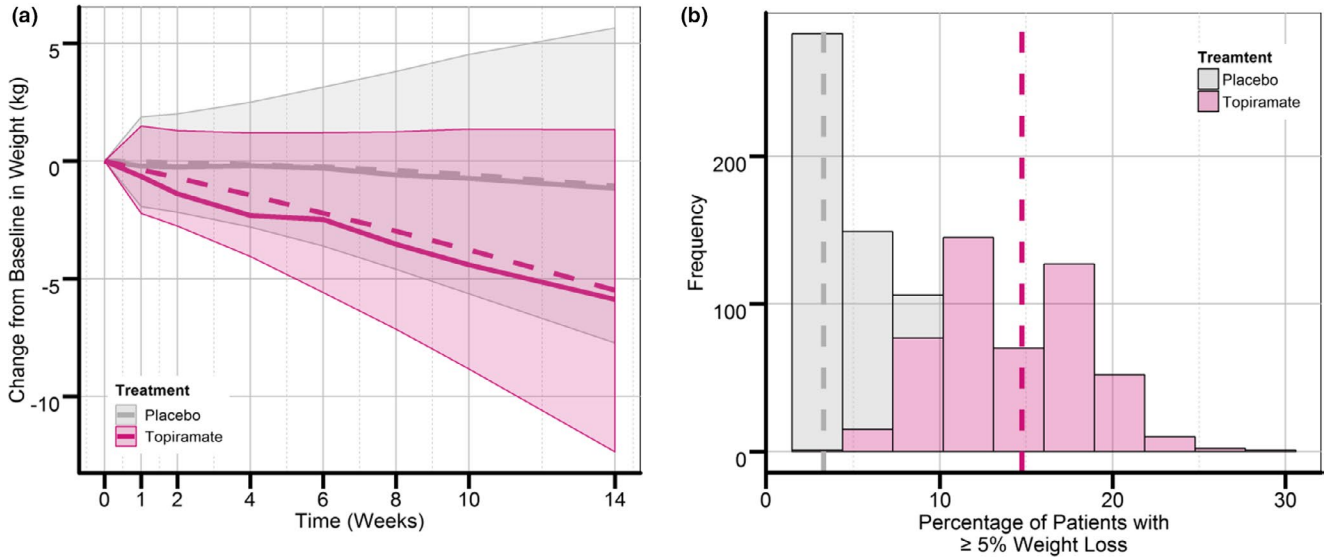
Figure 5 Quantitative predictive check plots for the final weight submodel. (**a**) Longitudinal change from baseline in weight (kg) in patients taking topiramate and placebo. Solid and dashed lines represent the observed mean and model-simulated 50% percentile respectively (*N* = 1,000 simulations). Shaded bands represent 95% confidence intervals. (**b**) Comparison of percentage of patients with clinically meaningful weight loss. Dashed lines represent observed percentage of patients with ≥ 5% weight loss. The histogram displays the distribution of percentage of patients with ≥ 5% weight loss from model-based simulations (*N* = 500 simulations).

average dose-response relationship was derived using the parameter estimates from the disease and drug model (**Figure 6**). Based on the population dose-response relationship illustrated in **Figure 6**, a target daily dose range between 125 and 150 mg should be considered to achieve a marked response (> 75% change from baseline in binge episodes).
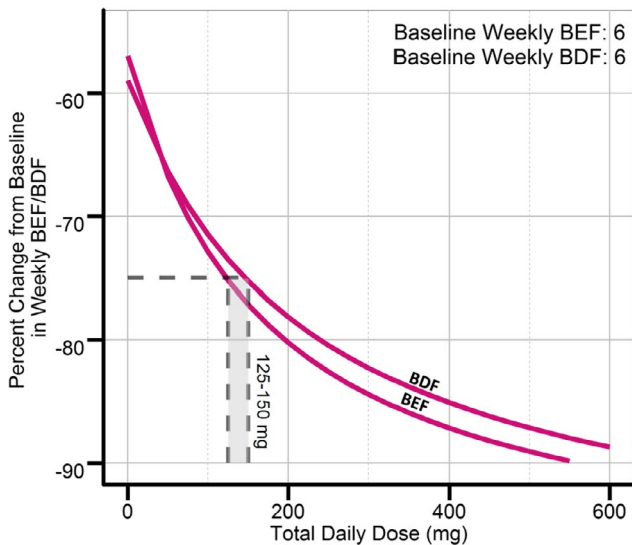

Figure 6 Dose-response curves for assessing percent change from baseline in weekly binge episode frequency (BEF) and weekly binge day frequency (BDF). Dose-response curves were developed using population mean parameter estimates from the final disease-drug-trial model. Dashed lines represent the corresponding dose to achieve a marked reduction (≥ 75%) in weekly binge episodes or BDF.

DISCUSSION

Topiramate in combination with phentermine is currently FDA approved for chronic weight management in adults.[27] Three randomized controlled trials and one open label long-term study have been conducted to evaluate topiramate for the treatment of BED.[18,28–30] Findings from these trials have resulted in off-label use and the inclusion of topiramate as a pharmacologic option in BED treatment guidelines.[31] However, consideration of using topiramate as first-line therapy is limited due to its side effect profile, which includes cognitive dysfunction, paresthesia, taste perversion, metabolic acidosis, and ocular toxicity. Therefore, appropriate dose selection is necessary to maximize the benefit of reducing BED symptoms and limiting risks associated with adverse effects.

One of the many challenges in drug development involves making key "go" or "no-go" decisions after conducting proof-of-concept trials and selecting the optimal design for late-phase clinical trials. The research presented provides the first quantitative approach that leverages existing BED clinical trial data to guide appropriate dose selection for future BED trials. Nonlinear-mixed effect modeling approach was utilized to develop disease-drug-trial models that adequately characterized changes in normalized BEF and BDF over time. In the psychiatry setting, it is very difficult to parse out the natural disease course from the large observed placebo effects due to other contributing factors, such as individual regression toward the mean natural state, external factors leading to symptom fluctuation, and/or concurrent psychological intervention.[32,33] Because underlying mechanisms for placebo response in mental disorders are still unclear, empirical models were explored. Parameter estimates from the disease models suggest that patients experience

96

a similar reduction in normalized weekly BEF and BDF and similar time to steady-state placebo response. Given that weekly BEF and BDF are highly correlated, it is not surprising to see similar parameter estimates. Relative treatment effects seemed to be consistent across both variables based on descriptive analysis and final model development (without fixing the drug effect parameter to 1). The results of this analysis suggest that either weekly BEF or BDF could be used as primary end points. Sample size calculations for future clinical trials should lead to similar results (similar treatment effect sizes and variability) if one were to choose either measure as an end point.

When developing the disease-drug model, several exposure metrics were explored to quantify the drug effect. Cumulative drug effect (cumulative dose) was taken into consideration to account for the impact of prior dosing on current response. However, several patients experienced increases in weekly BEF and BDF after receiving a decreased dose as compared with the week before. In these scenarios, cumulative exposures would not be able to capture the increase in response. In contrast, prior daily dose was found to have the strongest relationship with response. The half-life of topiramate is ~ 21 hours, and to reach a pharmacokinetic steady-state, it would take ~ 4–5 days. Therefore, at each visit, one can assume that a patient has at least reached steady-state drug exposures based on the dose they received. The ID_{50}, dose needed to achieve 50% of drug effect, was found to be similar when using BEF or BDF as the primary outcome. The high between-subject variability on ID_{50} can be potentially attributed to nonresponders and patients who relapsed on treatment during the trial period. The suggested dose range of 125–150 mg falls within recommended topiramate dose ranges for other indications (**Figure 6**).[34] Dose-limiting toxicities prevent patients from starting at the target dose and current practice suggests that patients should be titrated over several weeks. Further research is needed to characterize the exposure-safety relationship in patients with BED treated with topiramate to maximize benefit-risk profiles.

For the purpose of simulating clinical trials for both model validation and future research purposes, patient dropouts were taken into consideration. The inclusion of percent change from baseline in body weight as a significant predictor for patient dropouts led to the development of a submodel to describe longitudinal changes in weight. The majority of patients with BED are known to be overweight and medications used to induce weight loss in patients have been shown as a beneficial treatment strategy.[35] In the current study, patients receiving topiramate experienced an average weight loss of 5.9 kg after 14 weeks as compared with patients receiving placebo who experienced an average weight loss of 1.2 kg.[18] It is noteworthy to discuss that a disconnection between weight loss and reduction in weekly BEF/BDF existed in both studies.[18,28] In patients receiving placebo, even though BEF and BDF decreased, there was no significant reduction in weight at the study end point. For those receiving topiramate, reduction in normalized BEF and BDF was highly correlated with weight loss in the first 4 weeks of treatment, after

which weight loss continues until the end of the study in the presence of a stabilized binge episode/BDFs. This phenomenon was also observed in patients who received cognitive behavioral therapy.[36] Clinical trials assessing maintenance of weight loss have commonly used the benchmark of > 5% reduction in weight to be clinically meaningful.[37] QPC plots demonstrate the ability to predict changes in weight of ≥ 5% in patients undergoing treatment with topiramate and placebo (**Figure 5**). Unlike topiramate, which is known to reduce weight in patients, other treatment options may not have a similar effect.

Limitation of this research includes the inability to determine a population dose-response relationship given the specific flexible-dose titration study design, where a patient's dose at each visit increased unless tolerability concerns were present. In such a scenario, the first challenge in evaluating a dose-response relationship is to ensure that there is no confounding time effect. A follow-up open label, 42-week extension study was conducted for patients who completed the analyzed placebo-controlled trial. At the end of the initial controlled trial and prior to the initiation of the open label study, a taper-off period of 2 weeks was provided for patients receiving topiramate.[29] During this period, patients experienced an increase in weekly BEF of ~ 3.5 units. Furthermore, once patients received topiramate for the 42-week extension, no differences were found between weekly BEF observed at the end of the open label study vs. at the end of the controlled trial (14 weeks). The increase in BEF in a short time frame in patients getting tapered and the sustained drug effect over 56 weeks provides insight into the absence of a delayed drug effect.

The proposed quantitative disease-drug trial modeling framework can be utilized to guide future BED trials by leveraging several pieces of information from the data, such as average time to pharmacodynamic steady-state response, a proportional relationship between baseline binge frequency and placebo response, and correlation between early and later time point efficacy measures, such as change from baseline in BEF and BDF. The developed model could be used to simulate and explore shortened trial durations of 6–8 weeks, which could potentially lead to decreased patient dropouts and trial costs in both fixed and flexible dosing designs. Simulations enrolling patients with a higher baseline binge frequency may demonstrate increased treatment effect sizes and, thus, increase the probability of trial success. The proposed model could also serve to predict responses at later time points based on efficacy measures at early time points. Shortened proof-of-concept studies assessing the primary end point (e.g., 2 weeks) for different therapies could assist with deciding which treatment arms to carry forward to future confirmatory trials. Furthermore, placebo run-in periods have been commonly used to decrease placebo response. Using the model could inform the duration of placebo run-in periods, which may identify placebo responders earlier on for exclusion and clinical trial enrichment.

This case study provides an example of the development of a comprehensive disease-drug-trial model that successfully captures prior information from a single clinical trial. The

derived population dose-response relationship indicates that a lower dose range should be considered for patients with BED receiving topiramate. Although no significant covariates were identified, advanced methodologies are currently under investigation to capture the variability in BED symptoms.

Supporting Information. Supplementary information accompanies this paper on the *Clinical and Translational Science* website (www.cts-journal.com).

Figure S1. Mean normalized weekly binge episodes (**a**) and binge day frequency (**b**) vs. time profiles in patients randomized to topiramate ($N = 30$) and placebo ($N = 31$). *Error bars* represent 95% confidence intervals.
Figure S2. Diagnostic plots for final disease-drug-trial model for weekly binge episodes (**a–d**) and binge day frequency (**e–h**).
Figure S3. Individual prediction fit plots for (**a**) normalized weekly binge episodes and (**b**) normalized weekly binge day frequency from six randomly selected patients.
Table S1. Baseline demographic characteristics.
Table S2. Weekly dosing history.
Table S3. Weight submodel parameter estimates with nonparametric bootstrap-based 95% confidence intervals ($N = 200$ replicates).
Table S4. Model comparisons.

Conflict of Interest. The authors declared no competing interests for this work.

Author Contributions. S.N.K., S.L.M., J.G., and M.G. wrote the manuscript. S.N.K., S.L.M., J.G., and M.G. designed the research. S.N.K. and M.G. performed the research. S.N.K., S.L.M., J.G., and M.G. analyzed the data.

1. Insel, T.R. The NIMH experimental medicine initiative. *World Psychiatry* **14**, 151–153 (2015).
2. Hyman, S.E. Revolution stalled. *Sci. Transl. Med.* **4**, 155–156 (2012).
3. Marder, S.R., Laughren, T. & Romano, S.J. Why are innovative drugs failing in phase III? *Am. J. Psychiatry* **174**, 829–831 (2017).
4. Gobburu, J.V. & Lesko, L.J. Quantitative disease, drug, trial models. *Annu. Rev. Pharmacol. Toxicol.* **49**, 291–301 (2009).
5. Lee, J.Y. & Gobburu, J.V. Bayesian quantitative disease-drug-trial models for Parkinson's disease to guide early drug development. *AAPS* **13**, 508–518 (2011).
6. Reddy, V.P. *et al.* Pharmacokinetic-pharmacodynamic modeling of antipsychotic drugs in patients with schizophrenia part 1: the use of PANSS total score and clinical utility. *Schizophr. Res.* **146**, 144–152 (2013).
7. Sun, W. *et al.* Development of a placebo effect model combined with a dropout model for bipolar disorder. *J. Pharmacokinet. Pharmacodyn.* **40**, 359–368 (2013).
8. Gomeni, R. & Merlo-Pich, E. Bayesian modelling and ROC analysis to predict placebo responders using clinical score measured in the initial weeks of treatment in depression trials. *Br. J. Clin. Pharmacol.* **63**, 595–613 (2007).
9. Diagnostic and Statistical Manual of Mental Disorders: Fifth Edition (DSM-5). (American Psychiatric Association, Falls Church, VA, 2013).
10. Agh, T., Kovacs, G., Pawaskar, M., Supina, D., Inotai, A. & Voko, Z. Epidemiology, health-related quality of life and economic burden of binge eating disorder: a systematic literature review. *Eat Weight Disord.* **20**, 1–12 (2015).
11. Hudson, J.I., Hiripi, E., Pope, H.G. & Kessler, R.C. The prevalence and correlates of eating disorders in the national comorbidity survey replication. *Biol. Psychiatry* **61**, 348–358 (2007).
12. McElroy, S.L. Pharmacologic treatments for binge eating disorder. *J. Clin. Psychiatry* **78**, 14–19 (2017).
13. McElroy, S.L., Guerdjikova, A.I., Mori, N. & Keck, P.E. Psychopharmacologic treatment of eating disorders: emerging findings. *Curr. Psychiatry. Rep.* **17**, 35–42 (2015).
14. Bulk, C.M., Brownley, K.A. & Shapiro, J.R. Diagnosis and management of binge eating disorder. *World Psychiatry* **6**, 142–148 (2007).
15. Bautista, J.R., Pavlakis, A. & Rajagopal, A. Bayesian analysis of randomized controlled trials. *Int. J. Eat. Disord.* **51**, 637–646 (2018).
16. Grotzinger, A., Hilderbrandt, T. & Yu, J. The benefits of using semi-continuous and continuous models to analyze binge eating data: a Monte Carlo investigation. *Int. J. Eat. Disord.* **48**, 746–758 (2015).
17. Vocks, S., Tuschen-Caffier, B., Pietrowsky, R., Rustenbach, S.J., Kersting, A. & Herpertz, S. Meta-analysis of the effectiveness of psychological and pharmacological treatments for binge eating disorder. *Int. J. Eat. Disord.* **43**, 205–217 (2010).
18. McElroy, S.L. *et al.* Topiramate in the treatment of binge eating disorder associated with obesity: a randomized, placebo-controlled trial. *Am. J. Psychiatry* **160**, 255–261 (2003).
19. Vyvanse (lisdexamfetamine) [package insert]: Shire, Wayne, PA. (2017).
20. Reddy, V.P. *et al.* Structural models describing placebo treatment effects in schizophrenia and other neuropsychiatric disorders. *Clin. Pharmacokinet.* **50**, 429–450 (2011).
21. Xu, X., Yuan, M. & Nandy, P. Analysis of dose-response in flexible dose titration clinical studies. *Pharmaceut. Statist.* **11**, 280–286 (2012).
22. Russu, A. *et al.* Joint modeling of efficacy, dropout, and tolerability in flexible-dose trials: a case study in depression. *Clin. Pharmacol. Ther.* **91**, 863–871 (2012).
23. Jacqmin, P. *et al.* Modelling response time profiles in the absence of drug concentrations: definition and performance evaluation of the K-PD model. *J. Pharmacokinet. Pharmacodyn.* **34**, 57–85 (2007).
24. Fassino, S., Piero, A., Tomba, E. & Abbate-Daga, G. Factors associated with dropout from treatment for eating disorders: a compressive literature review. *BMC Psychiatry* **9**, 67–76 (2009).
25. US Food and Drug Administration, Center for Drug Evaluation and Research. Vyvanse (lisdexamfetamine) NDA 021977 Drug Review. January 30, 2015. <https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/021977Orig1s037.pdf>. Accessed August 10, 2018.
26. Jadhav, P.R. & Gobburu, J.V. A new equivalence-based metric for predictive check to qualify mixed effect models. *AAPS J.* **7**, 523–531 (2005).
27. Qsymia (phentermine/topiramate ER) [package insert]. Vivus, Mountain View, CA (2018).
28. McElroy, S.L. *et al.* Topiramate for the treatment of binge eating disorder associated with obesity: a placebo-controlled study. *Biol. Psychiatry* **61**, 1039–1048 (2007).
29. McElroy, S.L. *et al.* Topiramate in the long-term treatment of binge eating disorder associated with obesity. *J. Clin. Psychiatry* **65**, 1463–1469 (2004).
30. Claudino, A.M. *et al.* Double blind, randomized, placebo-controlled trial of topiramate plus cognitive-behavior therapy in binge-eating disorder. *J. Clin. Psychiatry* **68**, 1324–1432 (2007).
31. Aigner, M., Treasure, J., Kaye, W. & Kasper, S. & WFSBP Task Force on Eating Disorders. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the pharmacological treatment of eating disorders. *World. J. Biol. Psychiatry* **12**, 400–433 (2011).
32. Fava, M., Evins, A.E., Dorer, D.J. & Schoenfeld, D.A. The problem of the placebo response in clinical trials for psychiatric disorders: culprits, possible remedies, and a novel study design approach. *Psychother. Psychosom.* **72**, 115–127 (2003).
33. Ernst, E. & Resch, K.L. Concept of true and perceived placebo effects. *BMJ* **311**, 551–553 (1995).
34. Topamax (topiramate) [package insert]. Janssen Pharmaceuticals, Titusville, NJ, 2018.
35. Flegal, K.M., Kit, B.K., Orpana, H. & Graubard, B.I. Association of all-cause mortality with overweight and obesity using body mass index categories: a systematic review and meta-analysis. *JAMA* **309**, 71–82 (2013).
36. Pacanowski, C.R. *et al.* Weight change over the course of binge eating disorder treatment: relationship to binge episodes and psychological factors. *Obesity* **26**, 838–844 (2018).
37. Williamson, D.A., Bray, G.A. & Ryan, D.H. Is 5% weight loss a satisfactory criterion to define clinically significant weight loss? *Obesity* **23**, 2319–2320 (2015).