Predicting Pharmacotherapy Outcome From a Retrospective Chart Study?

Sir: We read with interest the report by Shetti et al.[1] in the December 2005 issue of the *Journal* on predicting nonresponse in obsessive-compulsive disorder (OCD). Though articles on predicting response to pharmacotherapy for OCD should be encouraged, this article gives rise to important methodological questions.

First, the authors plead for a more accurate definition of nonresponse in OCD, but fail to define nonresponse adequately. While they describe nonresponse as having had at least 2 ineffective serotonin reuptake inhibitor (SRI) trials, the mean number of trials in the response group was higher than 1, indicating that some subjects in the response group had had at least 2 ineffective SRI trials as well; they should therefore be qualified as nonresponders. Apart from this, the criterion used in the study to define response was a Clinical Global Impressions scale (CGI) score of 1 or 2, whereas nonresponse was defined as a CGI score of 3 to 7. The gold standard for assessing response in OCD is a decrease on the Yale-Brown Obsessive Compulsive Scale (YBOCS) of 25% to 35%.[2] The authors state that they preferred to use the CGI since the YBOCS lacks sensitivity to measure changes. We believe that not using any OCD scale is even less specific and accurate than using the YBOCS with its limits.

Second, the study is seriously flawed by the retrospective nature of the design. Subjects were included after they completed at least 2 medication trials. At that time, the CGI was administered and the treatment history was reviewed with the subjects with reference to their charts. This retrospective design carries the risk of attrition. Nonresponse is often a reason for not completing a medication trial; nonresponders as well as dropouts due to side effects are not accounted for in this study. The ideal design for identifying predictors would be prospective, which seems to be entirely feasible for this topic. Similarly, one of the inclusion criteria, i.e., after the medication trials, is a YBOCS score higher than 15, or 8 in the case of predominant obsessions or compulsions. This method implies that responders having a YBOCS score less than 15 (or 8) have been excluded beforehand.

Third, crucial aspects from the pharmacotherapy trials have not been presented clearly. All subjects had had at least 10 weeks of any SRI treatment, but the mean duration of treatment is not reported. It is not even clear whether all subjects were still taking the medication at the time of assessment. No information is available on the mean dosages used in the study. It is possible that nonresponders experienced more side effects and therefore received lower mean doses.

Finally, the authors slightly overrate the uniqueness of their study by claiming that they were the first to systematically characterize SRI nonresponders in OCD. A number of previous studies have included subjects with a history of SRI treatment (see Denys et al.[3]). In our own study,[3] 81% of subjects had a history of at least 1 medication trial before entering the study. Moreover, in our study, we presented a prediction model to discriminate response from nonresponse based on a prospective standardized medication trial in 150 patients. We offered an exhaustive review of the literature on response prediction in OCD. It seems that Shetti et al. failed to screen the existing literature on predicting response to pharmacotherapy for OCD, since none of these topics was taken into consideration.

Drs. de Bruijn and Denys report no financial or other affiliation relevant to the subject of this letter.

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Drs. Reddy and Kandavel Reply

Sir: We thank Drs. de Bruijn and Denys for their comments on our recently published article[1] on prediction of drug nonresponse in obsessive-compulsive disorder (OCD). Following are our responses to their comments.

Drs. de Bruijn and Denys claim that our definition of nonresponse is inadequate because some patients in the responder group may have had at least 2 ineffective serotonin reuptake inhibitor (SRI) trials. We would like to clarify here that our sample of responders had 5 subjects who had had more than 2 trials. We classified them as responders because they had responded to later trials. The argument is that they should have been classified as nonresponders. However, it is difficult to classify patients who have responded to treatment as nonresponders simply because, at the time of assessment, they had improved and the ratings also demonstrated that they had responded. It would have been possible for us to classify these 5 patients as nonresponders only if we had performed assessments at the time of nonresponse to 2 trials.

We eliminated these 5 patients from the responder group to see if our results change in any meaningful way. By eliminating the 5 patients, it can be ensured that the sample had no subjects who were once nonresponders but who had later become responders. We performed multiple logistic stepwise forward regression analysis for the same variables to identify predictors of nonresponse using 55 nonresponders and 62 responders. In performing our original regression analysis, we had chosen only those variables that were significant in the univariate analysis. Even with the reduced sample size of responders, variables that were significant in the univariate analysis were the same. Therefore, we used the identical predictors.

The final model resulted in 5 variables with 78% overall correct prediction. The 5 variables that significantly predicted nonresponse were major depressive disorder ($\beta = 3.534$, SE = 1.193, $p = .003$, OR = 34.277), washing compulsions ($\beta = 1.837$, SE = 0.570, $p = .001$, OR = 6.278), sexual obsessions ($\beta = 1.709$, SE = 0.642, $p = .008$, OR = 5.525), the baseline Yale-Brown Obsessive Compulsive Scale (YBOCS) severity score ($\beta = .069$, SE = 0.034, $p = .044$, OR = 1.072), and age ($\beta = –0.071$, SE = 0.032, $p = .027$, OR = 0.932). It is clear that predictors have remained largely similar, with the exclusion of only miscellaneous compulsions from the model. In the univariate analysis, there was a significant difference between

Table 1. Dose and Duration of Adequate Pharmacotherapy Trials for 122 Patients With Obsessive-Compulsive Disorder

Drug	Responders (N = 67), Mean (SD)	Nonresponders (N = 55), Mean (SD)	t	p Value
Fluoxetine				
Dose, mg/d	68.51 (13.66)	70.25 (12.87)	–0.605	.547
Duration, mo	24.55 (17.83)	12.98 (17.18)	3.043	.003
Sertraline				
Dose, mg/d	200.00 (21.32)	207.14 (36.35)	–0.620	.540
Duration, mo	28.79 (55.71)	6.73 (5.60)	1.367	.199
Fluvoxamine				
Dose, mg/d	225.00 (106.06)	250.00 (55.27)	–0.329	.795
Duration, mo	7.50 (6.36)	5.26 (3.26)	0.861	.400
Citalopram				
Dose, mg/d	53.33 (24.22)	68.46 (14.05)	–2.062	.048
Duration, mo	7.33 (3.88)	6.15 (4.25)	0.658	.529
Escitalopram				
Dose, mg/d	…	26.0 (8.94)	…	…
Duration, mo	…	5.1 (2.88)	…	…
Paroxetine				
Dose, mg/d	60.00 (0.00)	61.76 (13.57)	–0.179	.860
Duration, mo	14.00 (5.65)	6.20 (5.34)	1.945	.069
Clomipramine				
Dose, mg/d	185.00 (48.73)	173.86 (48.47)	0.463	.647
Duration, mo	28.00 (29.14)	19.02 (28.49)	0.690	.496

responders and nonresponders with respect to age at onset (22.61 ± 8.79 vs. 18.24 ± 7.56 years; t = 2.861, p = .005) and the prevalence of poor insight (1/59 [2%] vs. 7/53 [13%]; p = .026) and mixed OCD (38/62 [61%] vs. 49/55 [89%]; $\chi^2 = 11.814$, p = .001). Essentially, the major findings of the study remain the same even after excluding the 5 patients from the responder group.

Many researchers believe that the YBOCS is the gold standard for assessing response in OCD. We have clearly explained in our article why we chose the CGI over the YBOCS. The YBOCS may not be sensitive to subtle changes, such as a reduction in rituals from 5 hours to 3 hours per day. Moreover, although the CGI may be lacking in specificity, it is considered effective in capturing the larger clinical picture of psychopathology and subtle changes.[2,3] We have also found that "avoidance," an important clinical dimension in OCD, is not measured by the 10-item YBOCS severity scale. There are many patients who report significant improvement simply because their rituals and avoidance have somewhat decreased; this dimension is not adequately captured in the YBOCS, whereas since the CGI is a global measure of improvement, any change in the clinical status of OCD is represented. In any case, the YBOCS score had fallen significantly in the responder group, whereas in nonresponders the score remained essentially the same.

De Bruijn and Denys also comment that responders having a YBOCS score less than 15 (mixed OCD) or 8 (predominantly obsessive) may have been excluded beforehand. This is not the case. We included only those patients who had clinical OCD at baseline. Baseline score refers to the score at the time of initiating drug treatment and not at the time of assessment for the study. We had baseline scores for the patients since the YBOCS is routinely administered to all the patients in the OCD clinic. Had we excluded those patients whose score was less than 15 or 8 at the time of assessment, our responders' mean score would have been much higher than what is presented in the article.

All of the subjects were still taking treatment with drugs at the time of assessment. The mean dose and duration of adequate trials with various SRIs are given in Table 1. The drug most commonly received among our 122 patients was fluoxetine (N = 86, 70%), followed by sertraline (N = 33, 27%), citalopram (N = 32, 26%), clomipramine (N = 27, 22%), fluvoxamine (N = 21, 17%), paroxetine (N = 19, 16%), and escitalopram (N = 5, 4%). Some responders had improved with less than adequate doses of SRIs, and nonresponders, overall, received somewhat higher, but not statistically significantly higher doses.

Last, de Bruijn and Denys comment on our study design. The study had a retrospective design, treatment was not controlled for, and some attrition could have occurred. There is no debate that a prospectively designed study is superior to a retrospective study. However, there is a paucity of data in this area, and the findings of this study should lead to methodologically more vigorous studies with a prospective design. We do not entirely agree that the review of the literature on drug nonresponse in our study is not extensive. The literature review was more focused simply because the existing data on nonresponse are largely from trials of a particular drug. There are very few data on nonresponse to multiple SRI trials. Our focus, as was mentioned in the article, was to examine predictors of nonresponse to at least 2 adequate trials of SRIs. In the study by Denys et al.,[4] nonresponders were not actually SRI nonresponders. The subjects were nonresponders to either paroxetine or venlafaxine. The authors claim that 81% of their subjects had a history of at least 1 medication trial before entering into their study. However, the nonresponders in their sample cannot be described as SRI nonresponders because (1) there is no evidence in their report to suggest that the subjects had received multiple trials of SRIs in adequate doses and for adequate duration and (2) 40% of the sample had received behavior therapy previously.

Drs. Reddy and Kandavel report no financial or other affiliation relevant to the subject of this letter.

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Quality of Life Among Patients With Depression

Sir: Trivedi et al. are to be congratulated for their recent article describing the relationships between sociodemographic variables and various domains of health-related quality of life (HRQOL) in a large sample of depressed patients.[1] One of the primary findings of this article is that sociodemographic

variables do not have a uniform effect on every HRQOL domain. The authors state that this report "uniquely demonstrates the importance of measurement of multiple domains of HRQOL"[1(p193)]; however, our research group[2] and others[3] have emphasized the importance of measuring multiple domains in depression in earlier articles. For example, our group has reported that advancing age is associated with worse performance in daily living chores but better performance in relationships in a sample of depressed patients.[2] Trivedi et al. also call for new studies to examine the effects of different treatments on HRQOL. We have previously reported evidence that decrements in HRQOL may be relevant in the decision to recommend electroconvulsive therapy (ECT)[4] and that in a nonrandomized design, ECT has greater favorable impact on HRQOL in depressed patients as compared with medication treatment.[5] We are in agreement with Trivedi et al. that HRQOL is important in the evaluation of treatment of depressed patients, perhaps serving as an important driver of clinical decision making and equal in importance to symptoms in judging the overall value of a treatment.

This letter was shown to Dr. Trivedi, who declined to reply. —Editor

Dr. McCall reports no financial affiliations or other relationships relevant to the subject of this letter.

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Galantamine and QTc Prolongation

Sir: This letter is in response to the case report on the use of galantamine 24 mg/day in a 47-year-old schizophrenia patient that was associated with corrected QT interval (QTc) prolongation that resolved upon the discontinuation of galantamine.[1] The report noted that the patient was on a complex medical regimen which included several psychotropic drugs that may affect the QTc interval and that he suffered from hypertension, diabetes, and likely heart disease within the context of syndrome X. The authors also hypothesized about potential risks of QTc prolongation in elderly people suffering from Alzheimer's disease.

Johnson and Johnson Pharmaceutical Research and Development group conducted double-blind placebo-controlled studies in Alzheimer's disease and schizophrenia patients in which the QTc issue is examined directly.[2,3] In neither of these trials was there a statistically significant difference between galantamine and placebo regarding QTc prolongation. The Alzheimer's disease study[2] was a 6-week trial of 139 patients with Holter monitoring and electrocardiogram (ECG) measurements at baseline and 2-week intervals. In this trial, there was no evidence of QTc prolongation with galantamine 24 to 32 mg/day taken in 2 divided doses in comparison with placebo.[2] However, pauses greater than 2 seconds were more common in galantamine-treated than in placebo-treated patients during the titration period. Therefore, caution is advised when using the medication in patients with sick sinus syndrome or known cardiac conduction disturbances.[2] The schizophrenia study[3] was conducted with galantamine extended-release (q.d.) formulation in 104 patients aged 18 to 55 years. ECGs were recorded at baseline and the final visit at week 8. There was no evidence of QTc prolongation in comparison to placebo at doses of 16 to 24 mg/day.

Galantamine is currently indicated for the treatment of mild-to-moderate dementia of the Alzheimer's type and is not approved for the treatment of schizophrenia.

Dr. Brashear is an employee of Johnson & Johnson Pharmaceutical Research and Development, LLC and is a stock shareholder of Johnson & Johnson. Dr. Spivey is an employee of Ortho-McNeil Janssen Scientific Affairs and a stock shareholder of Johnson & Johnson.

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Drs. Nelson and Buchanan Reply

Sir: We appreciate and read with interest the comments by Drs. Brashear and Spivey. In response to our case report,[1] they presented unpublished data from 2 studies performed by Johnson & Johnson Pharmaceutical Research and Development: 1 in subjects with schizophrenia and 1 in subjects with Alzheimer's disease. Because these studies are unpublished, we are unable to evaluate important study sample details, such as subject age and gender, comorbid diseases, and concomitant medications,

and therefore cannot comment on the relevance of their results to the case that we presented. In our case report,[1] we advised caution and monitoring of galantamine use in patients with Alzheimer's disease because of factors such as concomitant medications and medical illnesses that may increase the risk of corrected QT interval (QTc) prolongation. In the cited Alzheimer's disease study,[2] it is unknown whether those subjects were on drug therapy (e.g., antipsychotics or diuretics) or suffered from cardiovascular disease, which one would expect to encounter clinically in this population. Although available data on galantamine monotherapy used in medically stable patients may not demonstrate an effect on QTc interval, its effect when combined with other medications or used in medically compromised patients, as in our case, is not known.

Galantamine-induced QTc prolongation may be a rare event and therefore not captured in studies with a small number of subjects exposed to the drug, such as the unpublished studies cited by Drs. Brashear and Spivey. The fact that they did not find significant mean QTc changes does not undermine the finding of galantamine-associated QTc prolongation in our case report. There remains a strong need for postmarketing surveillance of medication-related adverse events, particularly for rare events, and case reports such as ours serve an important role in updating the safety of drugs when administered in more real-world circumstances.

Dr. Nelson was an employee of the University of Maryland, Baltimore at the time the original case report was submitted.

In the original case report by Drs. Nelson and Buchanan, the study medication was provided by Janssen Pharmaceutica, Titusville, N.J.

Dr. Nelson is an employee and a stock shareholder of Wyeth Pharmaceuticals. Dr. Buchanan has served on a data safety monitoring board for Wyeth; has been a consultant for Pfizer, GlaxoSmithKline, and Organon (non-paid); has received grant/research support from Janssen and Eli Lilly; and has served on an advisory board for Merck.

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Beneficial Effects of the Antiglutamatergic Agent Riluzole in a Patient Diagnosed With Trichotillomania

Sir: Trichotillomania is an impulse control disorder characterized by compulsive hairpulling. While the incidence of hairpulling is quite high in some populations, full criteria for trichotillomania are met by less than 1% of the population.[1–3] Severe cases can lead to bald patches and marked social disability. Although trichotillomania is categorized as an impulse control disorder, some clinicians conceptualize it as being part of a spectrum of disorders characterized by compulsive behavior, including obsessive-compulsive disorder (OCD) and Tourette's syndrome.[4]

The hypothesis that trichotillomania and OCD are etiologically related is based upon phenomenological similarity, high levels of comorbidity,[5] and an increased prevalence of OCD in first-degree relatives of probands with trichotillomania.[6] While the proposition that OCD and trichotillomania are related disorders remains controversial, it has motivated trials of pharmacologic strategies known to be effective in OCD in patients with trichotillomania. Selective serotonin reuptake inhibitor (SSRI) treatment of trichotillomania has shown inconsistent results: 2 double-blind, placebo-controlled studies of fluoxetine have failed to show any consistent benefit,[7,8] but clomipramine, a tricyclic antidepressant with strong serotonin reuptake inhibitory activity, has shown benefit in treating trichotillomania in a few clinical studies.[3,9] Patients who do respond to SSRIs often relapse after weeks or months of continued treatment. Augmentation of SSRI treatment with atypical antipsychotics, which is effective in some cases of SSRI-resistant OCD, has shown a significant decrease in hairpulling in some case reports and small open-label case series.[3]

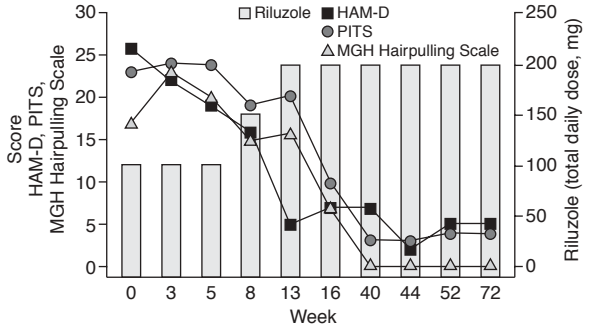
Preclinical and clinical observations suggest that dysregulated glutamate activity may contribute to the pathophysiology of OCD, and we have observed beneficial effects on OCD symptomatology in preliminary studies after treatment with drugs that modulate glutamatergic neurotransmission.[10] In particular, we found the antiglutamatergic drug riluzole, which is thought to reduce synaptic glutamate, to be of benefit to patients with refractory OCD in an initial open-label trial.[11,12] Here, we describe the successful use of riluzole in a patient with severe, chronic trichotillomania.

Case report. Ms. A is a 53-year-old woman with a history of trichotillomania and recurrent major depression, dating back to adolescence. Previous adequate treatment trials without lasting effects included cognitive-behavioral therapy with experienced clinicians, SSRIs (fluoxetine, fluvoxamine, citalopram, escitalopram), and other antidepressants (bupropion, clomipramine, venlafaxine). The longest period of abstinence from hairpulling was a 3-week period in the late 1980s during an early SSRI trial, but the patient's symptoms returned shortly thereafter. When she presented to our clinic in 2005, Ms. A was taking escitalopram 30 mg daily without benefit to her hairpulling or depressive symptoms, and she was able to go, at most, 2 days without pulling.

Ms. A's hairpulling was mainly focused on the scalp, and she wore a hairpiece to cover the resultant frontal alopecia. Ms. A characterized her distress from hairpulling as moderate to severe. Hairpulling at presentation was severe, as quantified by a Psychiatric Institute Trichotillomania Scale[13] score of 23 and a Massachusetts General Hospital Hairpulling Scale[14] score of 17 (Figure 1). She also reported depressed mood, helplessness, hopelessness, decreased concentration, decreased interest in activities, low energy, insomnia, and feelings of extreme guilt and shame. Her Hamilton Rating Scale for Depression (HAM-D)[15] index score at presentation was 26.

After obtaining informed consent for off-label use, we initiated clinical treatment with riluzole at 50 mg twice a day. She experienced an initial decline in hairpulling but then experienced resurgence in symptoms. Over the course of 3 months, her riluzole was titrated upward to 150 mg/day and then to 100 mg twice a day to target her residual trichotillomania and depressive symptoms. Her depressive symptoms improved; at 16 weeks, her HAM-D score had decreased to 7 (see Figure 1). With upward titration of riluzole, her urges to pull her hair vanished entirely, with a corresponding fall in her trichotillomania ratings (see Figure 1).

Figure 1. Changes in Hairpulling and Depressive Symptom Scores in a Patient Treated With Riluzole



Abbreviations: HAM-D = Hamilton Rating Scale for Depression, MGH = Massachusetts General Hospital, PITS = Psychiatric Institute Trichotillomania Scale.

At recent follow-up (72 weeks after initiating riluzole treatment), Ms. A had continued on a stable dose of 100 mg twice a day of riluzole and reported that urges to pull her hair continued to be minimal and readily ignored. Additionally, her improvement in mood persisted. Ms. A's decline in hairpulling behaviors was also readily apparent by significant hair regrowth and continued reduction in trichotillomania and depressive symptom rating scale scores (see Figure 1). Her longtime outpatient clinician reported that Ms. A had previously been unable to maintain such an extended period free of significant hairpulling and found her to be more socially proactive and assertive, insightful, and resilient to external stressors than at any time in the previous 20 years.

This case illustrates the potential utility of antiglutamatergic agents in the treatment of refractory trichotillomania. Our results mirror the apparent utility previously reported in small studies and case series in OCD,[11,12] compulsive skin picking,[16] and compulsive self-injurious behavior.[17] In addition, the improvement in Ms. A's treatment-refractory depression adds to the growing literature on the utility of antiglutamatergic agents in the treatment of depression.[18–21] While the dramatic effect on her previously intractable trichotillomania, in the context of previous studies suggesting a role for riluzole in the treatment of compulsive behavior syndromes, argues in favor of a direct effect of this glutamate-modulating agent on her compulsive hairpulling, it remains possible that the improvement of her trichotillomania was secondary to the marked improvement in her depression (though historically in this patient trichotillomania had persisted even during periods of improved mood). Although generalizations made from single case observations are inherently limited, our observations in this patient suggest that riluzole and other glutamate-modulating agents merit further study in the treatment of refractory trichotillomania.

The authors report no conflict of interest relative to the subject of this letter.

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Correction: Supplement 13, 2006

In the article "Trends in the Pharmacologic Management of Insomnia" by Paul P. Doghramji, M.D., F.A.A.F.P. (2006, Supplement 13, pp. 5–8), an incorrect version of Table 1 was printed. The corrected Table 1, along with corrected references, appears below. The online version of the article has been corrected.

The staff regrets the error.

Table 1. Comparisons of Medications Approved for the Treatment of Insomnia[a]

	Zaleplon	Zolpidem	Zolpidem Extended-Release	Eszopiclone	Ramelteon
Receptor selectivity	BZ_1[4]	BZ_1[5]	BZ_1[6]	BZ_1 and BZ_2[7]	MT_1 and MT_2[8]
Dosage (mg)	5, 10[4]	5, 10[5]	6.25, 12.5[6]	1, 2, 3[7]	8[8]
Schedule	IV[4]	IV[5]	IV[6]	IV[7]	Not scheduled[8]
Restricted to short-term usage	Yes[4]	Yes[5]	No[6]	No[7]	No[8]
Sleep latency	↓[4]	↓[5]	↓[6]	↓[7]	↓[8]
Number of awakenings	…[20–22]	↓[5]	↓[11]	↓[12]	…[16]
Wake after sleep onset	…[b]	…[10,23]	↓[6]	↓[7]	…[13]
Total sleep time	↑[9]	↑[5]	↑[11]	↑[7]	↑[13]

[a]Data from Sonata [prescribing information],[4] Ambien [prescribing information],[5] Ambien CR [prescribing information],[6] Lunesta [prescribing information],[7] Rozerem [prescribing information],[8] Ancoli-Israel et al.,[9] Perlis et al.,[10] Erman et al.,[11] Halas,[12] Erman et al.,[13] Roth et al.,[16] Elie et al.,[20] Ancoli-Israel et al.,[21] Hedner et al.,[22] and Scharf et al.[23]

[b]Zaleplon is known to have no effect on wake after sleep onset because of its short half-life.

Symbols: ↑ = increased, ↓ = decreased, … = no consistent effect.

Abbreviations: BZ = benzodiazepine, MT = melatonin.

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Correction: December 2006

In the article "Zonisamide in the Treatment of Binge Eating Disorder With Obesity: A Randomized Controlled Trial" by Susan L. McElroy, M.D., et al. (December 2006 issue, pp. 1897–1906), there should be no lines connecting week 16 to endpoint in Figures 1 and 2. The corrected figures are shown below, and the online version of the article has been corrected.

The staff regrets the error.

Figure 1. Mean Binge Frequency Over 16 Weeks of Treatment in Patients With Binge Eating Disorder Randomly Assigned to Zonisamide or Placebo

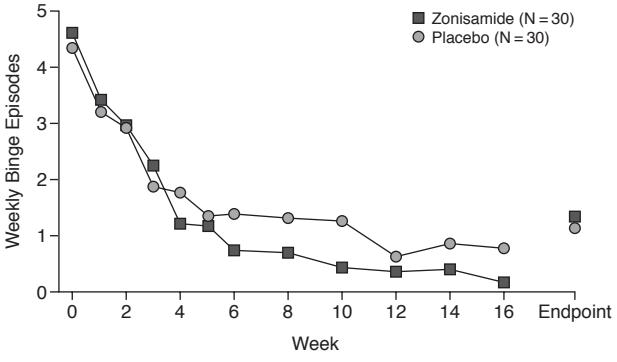

Figure 2. Weight Loss in Patients With Binge Eating Disorder Randomly Assigned to 16 Weeks of Double-Blind Treatment With Zonisamide or Placebo