Memantine in the Treatment of Binge Eating Disorder: An Open-Label, Prospective Trial

Brian P. Brennan, MD[1,2]*
Jacqueline L. Roberts, BA[1]
Kate V. Fogarty, RN[1]
Karina A. Reynolds, BS[1]
Jeffrey M. Jonas, MD[3]
James I. Hudson, MD, ScD[1,2]

ABSTRACT

Objective: To assess preliminarily the efficacy of memantine in binge eating disorder.

Method: This was an open-label, 12-week, flexible-dose (5–20 mg/day) trial of memantine in binge eating disorder. The primary outcome was frequency of binge days. Secondary outcomes included frequency of binge episodes, body-mass index (BMI), weight, Clinical Global Impressions Severity (CGI-S), Three Factor Eating Questionnaire (TFEQ), Montgomery–Asberg Depression Rating Scale (MADRS), Hamilton Anxiety Rating Scale (HAM-A), and Sheehan Disability Scale (SDS). Longitudinal random regression analysis was performed for frequency of binge days and episodes, BMI, weight, and CGI-S; analysis of baseline to endpoint change was performed for all outcomes.

Results: Sixteen individuals received memantine; 15 completed at least one postbaseline evaluation, 9 completed the study. Mean dose at endpoint was 18.3 mg/day. Memantine was associated with significant reductions in frequency of binge days and episodes, severity of illness ($p < .001$ for both analyses), disinhibition on the TFEQ ($p = .015$), and disability on the SDS ($p < .05$ for three subscales). There was no significant change in BMI, weight, MADRS, HAM-A, and TFEQ cognitive restraint and hunger.

Conclusion: In this open-label trial, memantine was well tolerated and effective in reducing binge eating, severity of illness, and disability, but had little effect on BMI and weight.

Keywords: memantine; binge eating disorder; obesity; BMI

(Int J Eat Disord 2008; 41:520–526)

Introduction

Binge eating disorder is characterized by recurrent episodes of binge eating that are associated with impaired control and significant distress, but are not associated with any of the inappropriate compensatory weight loss behaviors characteristic of bulimia nervosa or anorexia nervosa (e.g., self-induced vomiting, misuse of laxatives, fasting, or excessive exercise).[1] Recent epidemiological data suggest that the lifetime prevalence of binge eating disorder in the general population is 2.8%, making it more prevalent than a combination of anorexia nervosa and bulimia nervosa.[2] In addition, binge eating disorder exhibits substantial comorbidity with other psychiatric disorders[2,3] and is strongly associated with severe obesity.[2] Collectively, these findings underscore the importance of binge eating disorder as a significant public health problem.

Currently, there is no FDA-approved pharmacological treatment for binge eating disorder. Several agents have demonstrated benefit in reducing both binge episodes and body weight in placebo-controlled studies, including the selective serotonin reuptake inhibitors (SSRIs) fluvoxamine,[4] sertraline,[5] and citalopram[6]; the dual serotonin norepinephrine reuptake inhibitor and appetite suppressant sibutramine[7,8]; the selective norepinephrine reuptake inhibitor atomoxetine[8,9]; and the antiepileptics topiramate,[10,11] and zonisamide.[12] However, many of these agents are associated with adverse

Accepted 25 February 2008

Dr. Hudson has received research grant support from Forest Laboratories, Eli Lilly and Company and Ortho-McNeil Neurologics. He has served on advisory boards for Eli Lilly and Pfizer. Dr. Brennan has received research grant support from Eli Lilly. Dr. Jonas is currently an employee of Isis Pharmaceuticals; however, at the time of study design and initiation, he was an employee of Forest Laboratories. The other authors have no relevant disclosures.

Supported by Forest Laboratories (Investigator-Initiated Trial).

Correspondence to: Brian P. Brennan, McLean Hospital, 115 Mill Street, Belmont, MA 02478. E-mail: bbrennan@partners.org

[1] Biological Psychiatry Laboratory, McLean Hospital, Belmont, Massachusetts

[2] Department of Psychiatry, Harvard Medical School, Boston, Massachusetts

[3] Isis Pharmaceuticals, 1896 Rutherford Road, Carlsbad, California

Published online 23 April 2008 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/eat.20541

effects that limit their use, most notably sexual side effects with the SSRIs, increased blood pressure with sibutramine, and cognitive dysfunction with topiramate and zonisamide. Psychological treatments, particularly cognitive–behavioral therapy and interpersonal therapy, while reducing the frequency of binge episodes in controlled studies have not demonstrated a significant reduction in body weight, limiting their effectiveness.[13–17] As a result, evaluation of novel agents for binge eating disorder is warranted.

There has been increasing evidence that the hypothalamus, specifically the ventromedial and lateral regions and the arcuate nucleus, plays a significant role in the regulation of appetite.[18] It is theorized that elevated serum levels of glutamate disrupt appetite regulation in the arcuate nucleus through glutamate-induced neurotoxic effects mediated by *N*-methyl-D-aspartate (NMDA) receptors.[19] Animal studies have also shown that stimulation of the lateral hypothalamus by glutamate and glutamate agonists causes an intense, rapid, dose-dependent increase in food intake.[20,21]

Memantine is a low-to-moderate-affinity noncompetitive NMDA receptor antagonist that is used in the treatment of Alzheimer's disease.[22] It is generally well tolerated and does not produce the psychotomimetic effects characteristic of other NMDA receptor antagonists such as ketamine. Preliminary data from a recent small open-label trial of five individuals with binge eating disorder and obesity found memantine to be effective in reduction of binge episodes and weight.[23] As a result, we sought to replicate these findings by conducting an open-label trial of memantine in 16 individuals with binge eating disorder.

Method

Study Design

This study was a 12-week, single-center, open-label, flexible-dose study. Participants that met eligibility criteria after a 2-week, medication-free, pretreatment phase entered the 12-week treatment phase. Memantine was dispensed in 5- and 10-mg tablets at an initial dose of 5 mg/day. Participants remained on 5 mg/day for a period of 7 days, following which the dose was increased by 5 mg/day every 7 days as tolerated to a maximum dose of 20 mg/day. In cases where 20 mg/day was not well tolerated, the dose of study medication could be lowered to a minimum daily dose of 10 mg. Participants who completed the 12-week treatment phase and demonstrated a response to the study medication were eligible to continue into a 12-week, open-label extension phase. Those who were not eligible or elected not to continue into the extension phase were tapered off of study medication over the course of 7 days. A medication taper was not required for participants on the minimum daily dose of 10 mg.

Participant Selection Criteria

Participants were individuals recruited through advertisements for a medication trial of binge eating disorder. Participants were eligible for the study if they met DSM-IV criteria for binge eating disorder, and reported three or more binge episodes per week during the 2 weeks prior to screening and the 2 week period between screening and baseline (pretreatment phase). Additionally, eligible participants had a body mass index (BMI) of 30–50 and were between the ages of 18 and 65, inclusively.

Participants were excluded if they had a current diagnosis or lifetime history of bipolar disorder, schizophrenia, or other lifetime psychotic disorder; demonstrated clinically significant depression as defined by a score of greater than 24 on the Montgomery–Asberg Depression Rating Scale (MADRS)[24]; were, in the opinion of the investigator, at serious homicidal or suicidal risk; had a diagnosis of substance abuse or dependence in the 3 months prior to the start of study medication; had a diagnosis of current organic mental disorder, factitious disorder, or malingering; had a history of a personality disorder that may interfere with assessment or adherence to study procedures; had initiated formal psychotherapy (including cognitive–behavioral, interpersonal, dietary behavioral, or self-guided cognitive behavioral therapy) for binge eating disorder or any other psychiatric disorder within 6 months prior to screening; had a positive urine drug screen at screening; had previously been treated with memantine for any reason and discontinued due to adverse effect or a hypersensitivity reaction; were pregnant or lactating; or had a clinically significant medical condition including a progressive or degenerative neurological disorder.

Participant Evaluation

The McLean Hospital Institutional Review Board approved the protocol, and all participants provided written informed consent prior to the initiation of any study procedures. All participants underwent a screening evaluation in which the following information was obtained: medical and psychiatric history, the Structured Clinical Interview for DSM-IV[25] to establish binge eating disorder and any other comorbid Axis I diagnoses, physical examination, height and weight, vital signs, an electrocardiogram, and clinical laboratory tests (including a basic chemistry profile, complete blood count with differentials, thyroid stimulation hormone level, urinalysis, urine drug screen, and urine pregnancy test). At screening and all subsequent visits, participants were given diary cards

on which to record on a daily basis the number of binge eating episodes, time spent binge eating, foods eaten during binge, and the number of study medication tablets taken. Following the 2-week, pretreatment phase, study visits were conducted on a weekly basis for the first month and every other week thereafter for the remainder of the study.

At each visit following screening, participants were assessed for number of binge days since the previous visit, number of binge eating episodes since the previous visit, medication dose, medication compliance ascertained by tablet count, adverse effects, use of any concomitant medications, vital signs, weight, and other outcome measures (described later).

Outcome Measures

The primary efficacy measure was the number of binge days per week during the treatment phase. Binge days were defined as those in which a participant reported one or more binge episodes. The following criteria were used to qualify a binge episode: (1) eating in a certain period of time (e.g., within a 2-h period), an amount of food that is definitely larger than most people would eat in a similar period of time under similar circumstances and (2) experiencing a lack of control over eating during the eating episode (e.g., a feeling that one cannot stop eating or control what or how much one is eating). Binges were assessed through clinical interview and review of diary cards by physician investigators (B.P.B. or J.I.H.). The frequency of days was defined as the mean number of binge days per week in the interval between visits (total number of binges divided by number of days in the interval, and then multiplied by seven).

Secondary outcome measures were frequency of binge episodes (calculated in a similar manner to the frequency of binge days), BMI, weight, the Clinical Global Impressions Severity (CGI-S) and Improvement (CGI-I) scales,[26] the Yale-Brown Obsessive-Compulsive Scale[27] modified for Binge Eating (Y-BOCS-BE) to measure obsessiveness of binge eating thoughts and compulsiveness of binge eating behaviors,[10] the Three Factor Eating Questionnaire (TFEQ)—measures three dimensions of eating behavior (cognitive restraint, disinhibition, and hunger)[28]—the MADRS,[24] the Hamilton Anxiety Rating Scale (HAM-A),[29] the Barratt Impulsiveness Scale-Version 11 (BIS-11),[30] the Sheehan Disability Scale (SDS),[31] and response categories. To determine response categories, we tabulated categories based on percentage decrease in weekly frequency of binges from baseline (the 2-week, pretreatment phase) to endpoint (the final week of treatment) and defined the categories as follows: remission = cessation of binges, marked (75–99%) decrease, moderate (50–74%) decrease, and none = <50% decrease. These response categories have been used in previous pharmacologic treatment studies of binge eating disorder.[4–6,9–12,32,33]

The following safety measures were assessed: adverse events, routine blood chemistry and hematology laboratory values, urinalysis, physical examination findings, and an electrocardiogram.

Statistical Analysis

The analysis employed is similar to a previous open-label study that we conducted for the treatment of binge eating disorder.[33] The primary analysis for each outcome that was assessed at every visit (frequency of binges, frequency of binge days, BMI, weight, CGI-S, and YBOCS-BE) was a longitudinal repeated-measures random regression analysis, using modifications of analyses we used in previous placebo-controlled studies of binge eating disorder.[5,6,9–12,32–34] This longitudinal analysis was our primary analysis and assessed the rate of change of each outcome measure during the treatment period. We used a model for the mean of the outcome variable that included a term for time. We modeled time as a continuous variable, with weeks ranging from 0 at baseline to 12 at the week 12 visit after beginning treatment with memantine, using the logarithmic transformation log(weeks +1), because the response of most outcome measures was approximately linear on the logarithmic scale. The measure of effect was the estimated change in the outcome at week 12. For the analysis of binge day frequency and binge frequency, we used the logarithmic transformation log ([binges/week] +1) to normalize the data and stabilize variance. To account for the correlation of observations within individuals in the random regression analysis, we used PROC MIXED in SAS software (version 9.1, Cary, NC) to calculate the standard errors of the parameter estimates using first-order antedependence as the covariance structure. The random regression analysis is intent-to-treat, using available observations on all participants who completed a baseline evaluation.

The primary analysis for outcome measures not assessed at every visit (TFEQ, MADRS, BIS, and SDS, and response categories) and for the CGI-I, and a secondary analysis of the outcomes assessed at every visit was an endpoint analysis of the change from baseline, applying a one-sample t test to the last observation carried forward, with the null hypothesis being no change from baseline.

We set α at 0.05, two-tailed, for statistical significance.

Results

Twenty-four participants signed informed consent documents for the study from July 17, 2006 to March 29, 2007. Of these, eight withdrew prior to receiving treatment (did not meet full criteria for BED [$N = 1$]; positive urine drug screen [$N = 1$]; and patient decision or lost to follow up [$N = 6$]), and 16 received treatment with memantine. Of those

TABLE 1. Outcome measures before and after 12 weeks of treatment with memantine and analysis of change in outcome measures

	Mean			Longitudinal Analysis		Endpoint Analysis	
				12-Week Change		Change from Baseline to Final Visit	
Outcome Measure	Baseline ($N = 16$)	Last Observation ($N = 15$[a])	Week 12 ($N = 9$[b])	Estimate	p Value	Estimate	p Value
Binges/wk	5.5 (1.6)[c]	1.3 (1.1)	1.2 (1.1)	−2.4[d] [−3.5, −1.5][e]	<.001	−2.1[d] [−3.4, −1.1]	<.001
Binge days/wk	4.4 (1.0)	1.2 (1.0)	1.1 (1.0)	−1.8[d] [−2.5, −1.1]	<.001	−1.7[d] [−2.7, −0.9]	<.001
BMI	37.4 (4.7)	37.5 (5.2)	38.3 (5.4)	0.03 [−0.46, 0.53]	.89	0.14 [−0.26, 0.54]	.47
Weight (kg)	100.1 (19.9)	100.4 (21.7)	103.0 (23.8)	0.13 [−1.2, 1.4]	.85	0.4 [−0.7, 1.5]	.44
CGI-S score	4.4 (0.5)	2.7 (1.2)	2.9 (1.3)	−1.9 [−2.5, −1.3]	<.001	−1.7 [−2.3, −1.1]	<.001
YBOCS-BE							
Total	16.9 (4.8)	7.7 (5.2)	8.2 (4.7)	−9.5 [−12.6, −6.4]	<.001	−8.4 [−10.7, −6.1]	<.001
Obsessions	7.9 (3.5)	3.7 (2.7)	3.7 (2.6)	−5.0 [−6.7, −3.3]	<.001	−3.9 [−5.2, −2.6]	<.001
Compulsions	8.9 (2.8)	4.0 (2.9)	4.6 (2.7)	−4.5 [−6.1, −2.8]	<.001	−4.5 [−5.9, −3.1]	<.001
TFEQ score							
Cognitive restraint	23.3 (4.4)	24.2 (7.3)	26.0 (8.0)			0.7 [−2.1, 3.5]	.60
Disinhibition	20.0 (2.9)	18.4 (3.6)	18.9 (2.8)			−1.3 [−2.3, −0.3]	.015
Hunger	15.9 (4.7)	14.2 (3.6)	13.6 (3.7)			−1.9 [−4.0, 0.2]	.07
MADRS score	7.3 (4.4)	6.1 (4.4)	7.2 (5.1)			−1.2 [−2.6, 0.1]	.07
HAM-A score	4.9 (3.3)	6.0 (4.9)	7.0 (5.8)			0.6 [−1.3, 2.5]	.48
Barrett Impulsivity Scale							
Motor	23.6 (4.3)	24.8 (4.8)	23.0 (3.9)			1.2 [−1.2, 3.7]	.30
Cognitive	19.9 (2.4)	20.8 (2.1)	20.0 (2.0)			0.5 [−0.8, 1.9]	.39
Nonplanning	29.1 (3.6)	30 (4.1)	28.4 (3.5)			0.1 [−2.0, 2.2]	.93
Sheehan Disability Scale							
Work	1.3 (1.6)	0.3 (0.6)	0.4 (0.8)			−0.9 [−1.5, −0.2]	.013
Social	1.6 (1.5)	0.4 (0.7)	0.4 (0.7)			−1.0 [−1.5, −0.5]	<.001
Family	2.5 (2.6)	0.2 (0.6)	0.2 (0.7)			−1.9 [−3.0, −0.8]	.003

Notes: BMI, body mass index (weight in kilograms divided by height in m^2); CGI-S, Clinical Global Impression-Severity; CI, confidence interval; HAM-A, Hamilton Rating Scale for Anxiety; MADRS, Montgomery–Asberg Depression Rating Scale; TFEQ, Three-Factor Eating Questionnaire; YBOCS-BE, Yale-Brown Obsessive–Compulsive Scale Modified for Binge Eating.

[a] $N = 14$ for MADRS and HAM-A; $n = 13$ for Barrett Impulsiveness Scale and TFEQ scores.

[b] $N = 8$ for Barratt Impulsiveness Scale and TFEQ scores.

[c] Values in parentheses indicate SDs.

[d] Statistical analysis was performed on the logarithmic scale; for ease of interpretation, the estimate and confidence intervals were back-transformed and are shown on the original scale.

[e] Values in square brackets indicate 95% CIs.

receiving medication, there were 13 women and three men; 15 were non-Hispanic white and one was Hispanic; and the mean age (SD) was 42.7 (15.0) years. Baseline clinical features are presented in **Table 1**. Thirteen participants had no lifetime psychiatric diagnosis other than BED on the SCID; one participant had current social anxiety disorder and generalized anxiety disorder; and two participants had a past history of major depressive disorder.

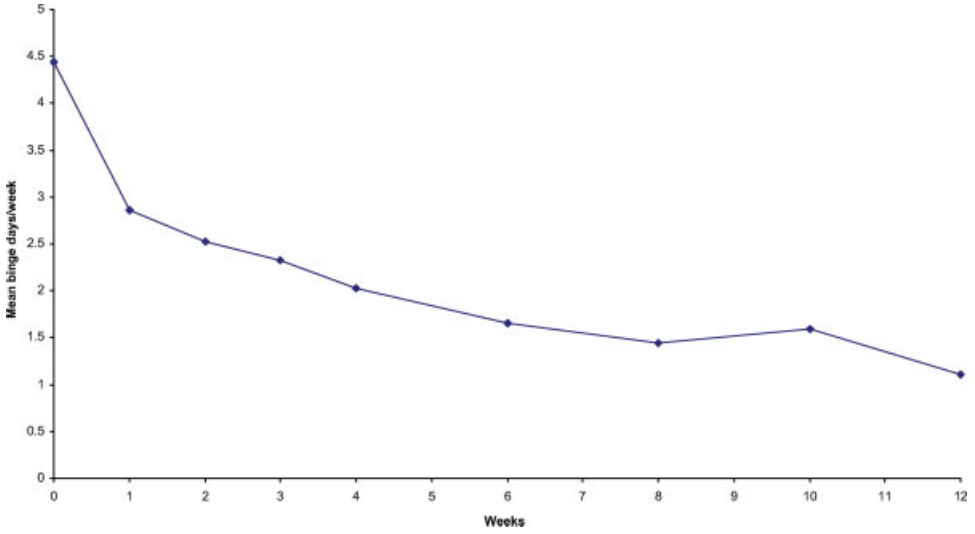
Of the 16 participants who received memantine, nine completed 12 weeks of treatment and seven withdrew prematurely, including one participant who did not have any postbaseline evaluations. The reasons for withdrawal were lack of efficacy ($N = 1$), adverse event ($N = 1$), moved out of state ($N = 1$), lack of time due to illness in relative ($N = 1$), and lost to follow-up ($N = 3$).

All 15 participants who had one postbaseline visit were titrated to 10 mg of memantine daily, and all but two of the 14 participants continuing in the study past 2 weeks were titrated to 20 mg daily and remained at that dose for the remainder of their time in the study. The mean (SD) dose at endpoint was 18.3 (3.6) mg daily.

The observed mean values for the outcome measures at last observation (for the 15 who had at least one postbaseline visit) and at 12 weeks (for the nine completers) are presented in **Table 1**, along with the analysis of change in outcome measures. The frequency of binges decreased steadily over the course of the study (see **Fig. 1**). In both the longitudinal and endpoint analysis, there was a highly significant decrease in frequency of binges, frequency of binge days, severity of illness, and scores on the YBOCS-BE (total, obsessions, and compulsions) ($p < .001$ for all measures).

Weight and BMI showed no significant change on either of these two analyses. However, there was a significant association between weight loss and decrease in frequency of binges ($\rho = .005$). The four participants who had a remission of binge eating at endpoint lost weight, whereas the three participants with a less than 50% reduction in frequency of binge eating gained weight.

FIGURE 1. Mean weekly frequency of binge days over 12 weeks of memantine treatment. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]



On the endpoint analysis, there was a significant decrease in TFEQ disinhibition (but not cognitive restraint or hunger), and in impairment on all three subscales of the SDS (work, social, and family). There was no significant change from baseline to endpoint on the MADRS, HAM-A, and Barrett Impulsiveness Scale.

The great majority of participants had a greater than 50% reduction in the frequency of binge eating at last observation, with 4 of 15 (27%) achieving a moderate response, 4 (27%) a marked response, and 4 (27%) remission of binge eating. On the CGI-improvement scale, 9 of 15 (60%) participants were rated as much improved or very much improved ($p < .001$ for one-sample t-test of improvement category equal to no change).

Adverse events reported by more than one participant were decreased libido, diarrhea, facial swelling, fatigue, headaches, and nausea ($N = 2$ for each). No participant experienced a serious adverse event. There were no changes in vital signs or clinical laboratory values suggestive of drug-related toxicity.

Conclusion

Open-label treatment with memantine in 16 individuals with binge eating disorder was associated with a marked and statistically significant reduction in frequency of binges, frequency of binge days, obsessive–compulsive features of binge eating, and severity of illness. There was also significant improvement in clinical global improvement, and in work, social, and family functioning on the SDS, as well as a decrease in TFEQ subscale of disinhibition. However, there was no significant change in BMI, weight, level of depressive symptoms on the MADRS, level of anxiety symptoms on the HAM-A, TFEQ subscales of cognitive restraint and hunger, or subscales of the Barrett Impulsiveness Scale. It should be noted that levels of depressive and anxiety symptoms were low at baseline, making it difficult to assess potential improvement on these measures.

These findings provide preliminary evidence for the effectiveness of memantine in reducing binge eating, obsessive–compulsive features of binge eating, severity of illness, and disability in binge eating disorder. Despite improvements in these domains, there is little evidence that memantine reduces body weight in binge eating disorder. Nevertheless, it is possible that memantine induces modest weight loss or prevents weight gain via its effect on binge eating, since nonresponders all gained weight and those who ceased binge eating all lost weight. By contrast, Hermanussen and Tresguerres[23] found a large reduction in body weight, in addition to a reduction in binge eating, associated with memantine treatment of binge eating disorder. Randomized controlled trials in Alzheimer's disease showed either no change in body weight[35,36] or modest weight gain[37] in subjects treated with memantine.

Because the present study did not include a placebo condition, it is unclear to what extent the improvement observed was due to placebo response versus drug response. Binge eating disor-

der is associated with moderately high levels of placebo response in clinical trials.[38] However, the response in this study would appear to be larger than that observed in most clinical trials; for example, the mean percentage of those rated as much improved or very much improved on the CGI-improvement scale was 33% in four trials of SSRIs in binge eating disorder,[38] whereas it was 60% in this trial. Nevertheless, only a placebo-controlled study can fully address this issue.

The mechanism of action whereby memantine might benefit binge eating disorder is not known. One possibility is that memantine recalibrates appetite regulation through a reduction in NMDA-receptor-mediated neuronal excitotoxicity in the arcuate nucleus. However, it is also interesting to note that subjects had a significant decrease in the obsessive–compulsive features of binge eating, which are prominent in binge eating disorder.[39] Interestingly, there is growing neuroimaging evidence that obsessive–compulsive disorder is associated with glutamatergic hyperactivity in several brain regions including the caudate nucleus[40] and anterior cingulate.[41] Therefore, it is also possible that memantine acts to reduce both the obsession to binge and the compulsive act of binge eating by reducing glutamatergic neurotoxicity in these brain regions. Notably, memantine and the potent antiglutamatergic agent riluzole have both demonstrated benefit in the treatment of obsessive–compulsive disorder,[42,43] and riluzole showed benefit in the treatment of obsessive–compulsive disorder with disordered eating in one case study.[44]

Memantine was well tolerated in this study. The adverse events reported were generally mild and consistent with known side effects of memantine; only one participant withdrew because of adverse events.

The main limitation of the study, in addition to the absence of a placebo treatment group, is the potential for lack of generalizability. Factors that limit our findings may include a treatment of only 12 weeks, a sample that was predominantly female and non-Hispanic Caucasian, and the fact that several forms of psychopathology were excluded.

In summary, in an open-label prospective, 12-week trial, memantine 10–20 mg daily in individuals with binge eating disorder was associated with improvements in binge eating, severity of illness, functioning, and several other measures, but not with weight loss. Memantine was relatively well tolerated. Because this study used an open-label design, these results should be considered preliminary, pending replication in a placebo-controlled trial.

References

1. de Zwaan M, Mitchell JE, Raymond NC, Spitzer RL. Binge eating disorder: Clinical features and treatment of a new diagnosis. Harv Rev Psychiatry 1994;1:310–325.
2. Hudson JI, Hiripi E, Pope HG Jr, Kessler RC. The prevalence and correlates of eating disorders in the National Comorbidity Survey Replication. Biol Psychiatry 2007;61:348–358.
3. Javaras KN, Pope HGJ, Lalonde JK, Roberts JL, Nillni YI, Laird NM, et al. Co-occurrence of binge eating disorder with psychiatric and medical disorders. J Clin Psychiatry 2008;69:266–273.
4. Hudson JI, McElroy SL, Raymond NC, Crow S, Keck PEJ, Carter WP, et al. Fluvoxamine in the treatment of binge-eating disorder: A multicenter placebo-controlled, double-blind trial. Am J Psychiatry 1998;155:1756–1762.
5. McElroy SL, Casuto LS, Nelson EB, Lake KA, Soutullo CA, Keck PEJ, et al. Placebo-controlled trial of sertraline in the treatment of binge eating disorder. Am J Psychiatry 2000;157:1004–1006.
6. McElroy SL, Hudson JI, Malhotra S, Wlege JA, Nelson EB, Keck PEJ. Citalopram in the treatment of binge-eating disorder: A placebo-controlled trial. J Clin Psychiatry 2003;64:807–813.
7. Appolinario JC, Bacaltchuk J, Sichieri R, Claudin AM, Godoy-Matos A, Morgan C, et al. A randomized, double-blind, placebo-controlled study of sibutramine in the treatment of binge-eating disorder. Arch Gen Psychiatry 2003;60:1109–1116.
8. Wilfley DE, Crow SJ, Hudson JI, Mitchell JE, Berkowitz RI, Blakesley V, Walsh BT. The Sibutramine Binge Eating Disorder Research Group. Efficacy of sibutramine for the treatment of binge eating disorder: A randomized multi-center placebo-controlled double-blind study. Am J Psychiatry 2008;165:51–58.
9. McElroy SL, Guerdjikova A, Kotwal R, Welge JA, Nelson EB, Lake KA, et al. Atomoxetine in the treatment of binge-eating disorder: A randomized placebo-controlled trial. J Clin Psychiatry 2007;68:390–398.
10. McElroy SL, Arnold LM, Shapira NA, Keck PEJ, Rosenthal NR, Karim MR, et al. Topiramate in the treatment of binge eating disorder associated with obesity: A randomized, placebo-controlled trial. Am J Psychiatry 2003; 160:255–261.
11. McElroy SL, Hudson JI, Capece JA, Beyers K, Fisher AC, Rosenthal NR. Topiramate for the treatment of binge eating disorder associated with obesity: A placebo-controlled study. Biol Psychiatry 2007;61:1039–1048.
12. McElroy SL, Kotwal R, Guerdjikova AI, Welge JA, Nelson EB, Lake KA, et al. Zonisamide in the treatment of binge eating disorder with obesity: A randomized controlled trial. J Clin Psychiatry 2006;67:1897–1906.
13. Wilfley DE, Welch RR, Stein RI, Spurrell EB, Cohen LR, Saelons BE, et al. A randomized comparison of group cognitive-behavioral therapy and group interpersonal psychotherapy for the treatment of overweight individuals with binge-eating disorder. Arch Gen Psychiatry 2002;59:713–721.
14. Wonderlich SA, de Zwaan M, Mitchell JE, Peterson C, Crow S. Psychological and dietary treatments of binge eating disorder: Conceptual implications. Int J Eat Disord 2003;34 (Suppl):S58–S73.
15. Grilo CM, Masheb RM. A randomized controlled comparison of guided self-help cognitive behavioral therapy and behavioral weight loss for binge eating disorder. Behav Res Ther 2005;43: 1509–1525.

16. Grilo CM, Masheb RM, Wilson GT. Efficacy of cognitive behavioral therapy and fluoxetine for the treatment of binge eating disorder: A randomized double-blind placebo-controlled comparison. Biol Psychiatry 2005;57:301–309.
17. Devlin MJ, Goldfein JA, Petkova E, Jiang H, Raizman PS, Wolk S, et al. Cognitive behavioral therapy and fluoxetine as adjuncts to group behavioral therapy for binge eating disorder. Obes Res 2005;13:1077–1088.
18. Bouret SG, Draper SJ, Simerly RB. Formation of projection pathways from the arcuate nucleus of the hypothalamus to hypothalamic regions implicated in the neural control of feeding behavior in mice. J Neurosci 2004;24:2797–2805.
19. Hermanussen M, Tresguerres JA. Does high glutamate intake cause obesity? J Pediatr Endocrinol Metab 2003;16:965– 968.
20. Stanley BG, Willett VL III, Donias HW, Ha LH, Spears LC. The lateral hypothalamus: A primary site mediating excitatory amino acid-elicited eating. Brain Res 1993;630:41–49.
21. Stanley BG, Ha LH, Spears LC, Dee MG II. Lateral hypothalamic injections of glutamate, kainic acid, D,L-alpha-amino-3-hydroxy-5-methyl-isoxazole propionic acid or *N*-methyl-D-aspartic acid rapidly elicit intense transient eating in rats. Brain Res 1993;613:88–95.
22. Möbius HJ, Stöffler A, Graham SM. Memantine hydrochloride: Pharmacological and clinical profile. Drugs Today 2004;40: 685–695.
23. Hermanussen M, Tresguerres JAF. A new anti-obesity drug treatment: First clinical evidence that antagonizing glutamate-gated Ca^{2+} ion channels with memantine normalizes binge eating disorders. Econ Hum Biol 2005;3:329–337.
24. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry 1979;134:382–389.
25. First MB, Spitzer RL, Gibbon M, Williams JB. Structured Clinical Interview for DSM-IV Axis I Disorders (Research Version, 2/96 Final). New York, NY: Biometrics Research, New York State Psychiatric Institute, 1996.
26. Guy W. (Ed). ECDEU Assessment Manual for Psychopharmacology–Revised (DHEW Publ No ADM 76-388). In: Rockville, MD: U.S. Department of Health, Education, and Welfare, Health Administration, NIMH Psychopharmacology Research Branch, Division of Extramural Research Programs; 1976, pp. 218–222.
27. Goodman WK, Price LH, Rasmussen SA, Mazure C, Fleishmann RL, Hill CL, et al. The Yale-Brown Obsessive Compulsive Scale. I. Development, use, and reliability. Arch Gen Psychiatry 1989;46: 1006–1011.
28. Stunkard AJ, Messick S. Eating Inventory Manual. San Antonio, TX: The Psychological Corporation, Harcourt Brace & Company, 1988.
29. Hamilton M. The assessment of anxiety states by rating. Br J Med Psychol 1959;32:50–55.
30. Patton JH, Stanford MS, Barratt ES. Factor structure of the Barratt impulsiveness scale. J Clin Psychol 1995;51:768–774.
31. Leon AC, Olfson M, Portera L, Farber L, Sheehan DV. Assessing psychiatric impairment in primary care with the Sheehan Disability Scale. Int J Psychiatry Med 1997;27:93–105.
32. Arnold LM, Hess EV, Hudson JI, Welge JA, Berno SE, Keck PEJ. A randomized, placebo-controlled, double-blind, flexible-dose study of fluoxetine in the treatment of women with fibromyalgia. Am J Med 2002;112:191–197.
33. McElroy SL, Kotwal R, Hudson JI, Nelson EB, Keck PE. Zonisamide in the treatment of binge-eating disorder: An open-label, prospective trial. J Clin Psychiatry 2004;65:50–56.
34. Hudson JI, Pope HG Jr, Wurtman J, Yurgelun-Todd D, Mark S, Rosenthal NE. Bulimia in obese individuals. Relationship to normal-weight bulimia. J Nerv Ment Dis 1988;176:144–152.
35. Reisberg B, Doody R, Stoffler A, Schmitt F, Ferris S, Mobius HJ. Memantine treatment in moderate-to-severe Alzheimer's disease. N Engl J Med 2003;348:1333–1341.
36. Peskind ER, Potkin SG, Pomara N, Ott BR, Graham SM, Olin JT, et al. Memantine treatment in mild to moderate Alzheimer disease: A 24-week randomized, controlled trial. Am J Geriatr Psychiatry 2006;14:704–715.
37. van Dyck CH, Tariot PN, Meyers B, Malca-Resnick E. A 24-week randomized, controlled trial of memantine in patients with moderate-to-severe Alzheimer disease. Alzheimer Dis Assoc Disord 2007;21:136–143.
38. Carter WP, Hudson JI, Lalonde JK, Pindyck L, McElroy SL, Pope HGJ. Pharmacologic treatment of binge eating disorder. Int J Eat Disord 2003;34 (Suppl):S74–S88.
39. McElroy SL, Phillips KA, Keck PE Jr. Obsessive compulsive spectrum disorder. J Clin Psychiatry 1994;55 (Suppl):33–51; discussion 2–3.
40. Rosenberg DR, MacMaster FP, Keshavan MS, Fitzgerald KD, Stewart CM, Moore GJ. Decrease in caudate glutamatergic concentrations in pediatric obsessive-compulsive disorder patients taking paroxetine. J Am Acad Child Adolesc Psychiatry 2000;39: 1096–1103.
41. Rosenberg DR, Mirza Y, Russell A, Tang J, Smith JM, Banerjee SP, et al. Reduced anterior cingulate glutamatergic concentrations in childhood OCD and major depression versus healthy controls. J Am Acad Child Adolesc Psychiatry 2004;43:1146–1153.
42. Coric V, Taskiran S, Pittenger C, Wasylink S, Mathalon DH, Valentine G, et al. Riluzole augmentation in treatment-resistant obsessive-compulsive disorder: An open-label trial. Biol Psychiatry 2005;58:424–428.
43. Pasquini M, Biondi M. Memantine augmentation for refractory obsessive-compulsive disorder. Prog Neuropsychopharmacol Biol Psychiatry 2006;30:1173–1175.
44. Sasso DA, Kalanithi PS, Trueblood KV, Pittenger C, Kelmeni B, Wayslink S, et al. Beneficial effects of the glutamate-modulating agent riluzole on disordered eating and pathological skin-picking behaviors. J Clin Psychopharmacol 2006;26: 685–687.