Current Topics in Pharmacology
Vol. 20, 2016

Short Communication

Effect of topiramate in Japanese patients with binge eating disorder

Eiji Kirino*

Department of Psychiatry, Juntendo University Shizuoka Hospital, 1129 Nagaoka Izunokunishi, Shizuoka, 4102211, Japan.

ABSTRACT

Treatment options for binge eating disorder are limited in Japan. Thus, a small exploratory study was conducted to assess the efficacy of topiramate in Japanese patients with binge eating behavior. This was a prospective, open-label, single-arm, observational study conducted at a single hospital. Patients included in this study were outpatients. Topiramate was administered up to 14 months or until loss of follow-up. Initial dose of topiramate was 25 mg/day, and then the dose was gradually increased to optimal dose. The maximum allowed dose was 200 mg/day. The primary outcomes were the changes in the mean scores of Clinical Global Impression-Severity (CGI-S) scale for binge eating behavior from baseline, the frequency of binge eating and binge days per week. A total of 22 patients (4 males and 18 females) were included in this study. The mean duration of topiramate administration was 7.0 months. The mean score of CGI-S scale for binge eating behavior was significantly decreased from 3.68 ± 0.65 at baseline to 2.23 ± 1.02 ($p < 0.001$). Both frequency of binge eating and binge days per week were significantly decreased from 8.29 ± 8.07 times/ week at baseline to 1.95 ± 2.57 times/week ($p = 0.002$), and 4.80 ± 2.61 days/week to 1.98 ± 2.38 days/week ($p = 0.001$), respectively. The present study showed the potential of topiramate for the treatment of binge eating behavior. The efficacy and safety of topiramate in the treatment of binge eating disorder in the Japanese population should be confirmed in a large scale study.

KEYWORDS: topiramate, eating disorder, binge eating disorder, bulimia nervosa

1. INTRODUCTION

Eating disorder is one of the important public health issues. Particularly in Japan, eating disorder has been recognized as one of the intractable disorders [1]. The core symptoms of the two types of eating disorders, bulimia nervosa and binge eating disorder, include recurring episodes of binge eating, eating in a discrete period of time, an amount of food that is definitely larger than what most people would eat, and lack of control in eating behavior. Bulimia nervosa, compared with binge eating disorder, is further defined by the features of recurrent inappropriate compensatory behaviors to prevent weight gain, and self-evaluation unduly influenced by body shape and weight [2]. Mental disorders are common in both but not the only comorbidities of concern. Obesity is especially a concern in binge eating. Obesity causes numerous complications, including type 2 diabetes, hyperlipidemia, hypertension, and renal dysfunction, which increase the risk of cardiovascular disease. Controlling binge eating behavior is essential for preventing such complications.

As treatments for bulimia nervosa and binge eating disorder, specialty psychological therapies such as cognitive behavior therapy (CBT) and interpersonal therapy are available; however, their

*Email id: ekirino@juntendo.ac.jp

efficacy is still limited [3, 4]. Alternatively, several guidelines have recently discussed the benefits of the pharmacotherapy option [5-7]. Only fluoxetine is currently approved by the United States Food and Drug Administration (FDA) for treatment of bulimia nervosa; no drug has been approved for treatment of binge eating disorder. In Japan, unfortunately, no drug has been approved yet for either disorder.

Topiramate, originally approved by the FDA as an anticonvulsant drug in 1996, has been investigated for the treatment of bulimia nervosa and binge eating disorder outside Japan. To date, there have been five placebo-controlled randomized clinical trials (RCTs) of topiramate in binge eating populations: two trials in patients with bulimia nervosa and three trials in patients with binge eating disorder [8-12]. All five trials showed that topiramate significantly reduced binge eating behavior compared to placebo. As there is no evidence for the use of topiramate in the treatment of binge eating behavior in Japan, we conducted a small, open-label exploratory study to assess its efficacy in the Japanese population.

2. MATERIALS AND METHODS

This is a prospective, open-label, single-arm, observational study conducted at a single hospital. Patients recruited in this study were outpatients at the Juntendo University Hospital, who were 18 years of age or older and had been diagnosed with bulimia nervosa or binge eating disorder based on the Diagnostic and Statistical Manual of Mental Disorders (5^{th} Ed.) [2]. Patients who had a history of pharmacotherapy for bulimia nervosa or binge eating disorder and who were taking any medication that might adversely interact with or obscure the action of topiramate were excluded. The study protocol was approved by the Juntendo University Hospital, and the study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. All patients provided written informed consent after the study procedures were fully explained.

Information on the baseline characteristics of the patients, including age, gender, body weight, duration of eating disorder, pre-existing mental disease, the number of binge eating and binge days during the previous week, the number of vomiting during the previous week, and medical history, were collected at screening. Eligible patients received topiramate at Juntendo University Hospital. Topiramate was administered for 14 months or until loss of follow-up. Initial dose of topiramate was 25 mg/day, and then the dose was gradually increased to optimal dose. The maximum allowed dose was 200 mg/day.

The primary outcomes were the changes in the mean scores of Clinical Global Impression-Severity (CGI-S) scale for binge eating behavior from baseline, the frequency of binge eating and binge days per week. As secondary outcomes, the changes in the mean scores of CGI-S scale for pre-existing mental disease, Clinical Global Impression-Improvement (CGI-I) scale for binge eating, the frequency of vomiting, administration of diuretics or laxatives, and body weight were also evaluated. For safety, adverse events, clinical laboratory data, physical examination findings, and vital signs were assessed.

The primary and secondary outcomes were assessed by paired-t test. For all statistical analyses, probability values of <0.05 were considered to indicate a significant difference.

3. RESULTS

A total of 22 patients (4 males and 18 females) were included in this study between July 1, 2011 and August 31, 2011. Among them, three patients were diagnosed with bulimia nervosa and nineteen patients were diagnosed with binge eating disorder. The characteristics of these patients are summarized in table 1. The mean age (± SD) was 37.8 ± 13.0 years. The mean duration of the topiramate administration was 7.0 ± 3.0 months, and mean dose of topiramate was 102.3 ± 40.0 mg/day.

The mean score of CGI-S scale for binge eating behavior was significantly decreased from 3.68 ± 0.65 at baseline to 2.23 ± 1.02 at post-treatment ($p < 0.001$) (Figure 1). Both frequency of binge eating and binge days per week were significantly decreased from 8.29 ± 8.07 times/week at baseline to 1.95 ± 2.57 times/week ($p = 0.002$), and from 4.80 ± 2.61 days/week to 1.98 ± 2.38 days/week ($p = 0.001$), respectively. The mean score of CGI-I scale for binge eating behavior at the end of

Table 1. Baseline characteristics of patients.

Variables	N = 22
Age (years), mean ± SD	37.8 ± 13.0
Male/female, (n)	4/18 (18.2%/81.8%)
Body weight (kg), mean ± SD	67.9 ± 21.6
Duration of eating disorder (years), mean ± SD	3.8 ± 7.1
Pre-existing mental disease (n)	
Schizophrenia	7 (27.3%)
Depression	6 (27.3%)
Mental retardation	2 (9.1%)
Dysthymia	1 (4.5%)
Bipolar disorder	1 (4.5%)
Post-traumatic stress disorder	1 (4.5%)
Social anxiety disorder	1 (4.5%)
Pervasive developmental disorder	1 (4.5%)
None	3 (13.6%)
Duration of main mental disease (years), mean ± SD	8.72 ± 6.69
CGI-S scale, mean ± SD	
CGI-S scale for binging behavior	3.68 ± 0.65
CGI-S scale for pre-existing mental disease	4.16 ± 0.83
Binge eating	
Binge eating (times/week)	3.8 ± 8.1
Binge eating (days/week)	4.8 ± 2.6
Vomiting (times/week)	2.3 ± 4.6
Medical history	
Administration of diuretics (times/week)	0.0 ± 0.0
Administration of laxatives (times/week)	1.3 ± 2.5

CGI-S, Clinical Global Impression-Severity.

follow-up was 2.18 ± 0.91. The frequency of vomiting was also significantly decreased from 2.30 ± 4.64 times/week to 0.43 ± 1.81 times/week. On the other hand, mean body weight was changed from 67.91 ± 21.60 kg at baseline to 68.04 ± 18.83 kg; no significant change was observed. The frequencies of administration of diuretics and laxatives were changed from 0.00 ± 0.00 times/week at baseline to 0.33 ± 1.53 times/week, and from 1.32 ± 2.50 times/week to 1.41 ± 2.58 times/week, respectively; no significant changes were observed. The mean score of CGI-S scale for pre-existing mental disease was slightly, but not significantly, improved from 4.16 ± 0.83 at baseline to 3.95 ± 0.71 ($p = 0.41$). The mean score of CGI-I scale at the end of follow-up was 3.11 ± 0.81. Regarding safety, no adverse events or abnormal laboratory data were observed during the study.

4. DISCUSSION

The present study is the first prospective study known to investigate the efficacy of topiramate in patients with bulimia nervosa and binge eating disorder in Japan. In the treatment of naive patients

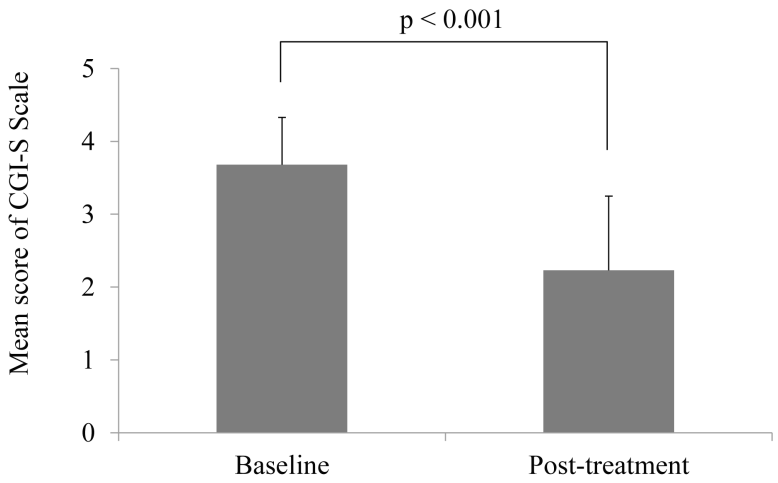

Figure 1. Mean score of CGI-S scale for binge eating at baseline and post-treatment.

with mean treatment duration of 7 months, topiramate demonstrated a significant improvement in the score of CGI-S scale for binge eating behavior as well as in the frequency of binge eating and binge days per week. Body weight was not significantly changed. The findings of the present study were comparable to previously conducted placebo-controlled RCTs outside Japan. In patients with bulimia nervosa, Hoopes *et al*. reported a significant decrease in the frequency of binge days per week in the topiramate group compared with the placebo group within 10 weeks [12]. Similar findings on the efficacy of topiramate in patients with bulimia nervosa were also reported by Nickel *et al*. [11]; patients taking topiramate had a significant decrease in the frequency of binging/purging as well as body weight. The efficacy of topiramate in patients with bulimia nervosa is not limited to just the reduction of binge eating behavior, but appears to also improve psychological and psychiatric symptoms, including self-esteem, eating attitudes, anxiety, and body image [13]. Interestingly, topiramate has even been shown to significantly improve the quality of life of these patients [11].

McElroy *et al*. also reported efficacy of topiramate in obese patients with binge eating disorder [9, 10]. In both RCTs [9, 10], topiramate significantly decreased the frequency of binge eating and binge days, as well as body mass index and body weight within 10 weeks and 14 weeks; the score of the CGI-S scale was also significantly improved in the topiramate group compared with the placebo group [10]. In both trials, significantly more patients treated with topiramate responded to the treatment compared to patients treated with placebo. Furthermore, Claudino *et al*. reported the efficacy of combining topiramate with CBT on binge eating disorder in obese patients [8]. Compared with placebo + CBT, topiramate + CBT demonstrated a significant reduction in body weight within 21 weeks. Although the frequency of binge eating did not differ between groups, significantly more patients attained remission in the topiramate + CBT group compared with the placebo + CBT group. Taken together, pharmacotherapy with topiramate appears to be beneficial for the treatment of binge eating behavior in obese patients, and combination with CBT could improve the remission rate.

Although the mechanism of action of topiramate for binge eating behavior has yet to be clarified, topiramate is considered to reduce binge eating behavior through glutamate receptor antagonism. In rat models, lateral hypothalamic injections of glutamate, kainic acid, D,L-alpha-amino-3-hydroxy-5-methyl-isoxazole propionic acid (AMPA) or N-methyl-D-aspartic acid rapidly elicits intense transient eating in a dose-dependent manner [14]. In another study with rat models, fourth ventricle injection of 1,2,3,4-tetrahydro-6-nitro-2,3-dioxo-benzo[f]quinoxaline-7-sulfanomide (NBQX), an antagonist of AMPA/kainate receptor antagonist, suppresses the intake of food and water, as well as

sucrose [15]. More recently, Hettes *et al.* reported that selective stimulation of lateral hypothalamic kainate receptors containing glutamate receptor 5 (GluR5) is sufficient to elicit feeding behavior [16]. Taken together, topiramate appears to control binge eating behavior *via* its selective antagonistic effect on GluR5 [17].

Although the present study showed essential clinical evidence for topiramate efficacy in Japanese patients with binge eating behavior, there are some limitations. The number of patients included in the present study is small, only 22. In addition, there is no control arm, and the mean follow-up period of 7 months is considered relatively short. No adverse events were observed during the study, which could be due to the small cohort and short follow-up period. Based on the results of the present study, safety information is limited and further investigation on the safety profile of topiramate in binge eating populations is desirable.

5. CONCLUSION

In conclusion, the present study was a preliminary investigation on the efficacy of topiramate on binge eating behavior in the Japanese population. The study shows the potential of topiramate for the treatment of binge eating disorders. However, a randomized controlled study with a large cohort is strongly warranted to confirm the efficacy and safety of topiramate on binge eating disorder in the Japanese population.

ACKNOWLEDGMENTS

The author would like to express his deepest gratitude to the patients and staff members at the institution for their contribution to this study.

This work was not supported by any industry funding, nor requested by any organization. Medical writing was supported by Koki Yamashita, PhD., of Maxwell International, Inc. (Chiba, Japan).

CONFLICT OF INTEREST STATEMENT

The author declares no conflict of interest.

REFERENCES

1. Japan Intractable Diseases Information Center: A list of 130 Tokutei Shikkan (specified rare and intractable diseases), 2016.
2. American Psychiatric Association. 2013, Diagnostic and statistical manual of mental disorders (5th Ed.). Arlington, VA, American Psychiatric Publishing.
3. Hay, P. P., Bacaltchuk, J., Stefano, S. and Kashyap, P. 2009, Cochrane Database Syst. Rev., CD000562.
4. Wilson, G. T. 2011, Psychiatr. Clin. North Am., 34, 773.
5. National Institute for Health and Care Excellence. 2004, Clinical Guideline No 9. London.
6. American Psychiatric Association. 2006, Am. J. Psychiatry, 163, 4.
7. Aigner, M., Treasure, J., Kaye, W., Kasper, S. and Disorders W. T. F. O. E. 2011, World J. Biol. Psychiatry, 12, 400.
8. Claudino, A. M., de Oliveira, I. R., Appolinario, J. C., Cordas, T. A., Duchesne, M., Sichieri, R. and Bacaltchuk, J. 2007, J. Clin. Psychiatry, 68, 1324.
9. McElroy, S. L., Hudson, J. I., Capece, J. A., Beyers, K., Fisher, A. C., Rosenthal, N. R., and Topiramate Binge Eating Disorder Research G. 2007, Biol Psychiatry, 61, 1039.
10. McElroy, S. L., Arnold, L. M., Shapira, N. A., Keck, P. E. Jr., Rosenthal, N. R., Karim, M. R., Kamin, M. and Hudson, J. I. 2003, Am. J. Psychiatry, 160, 255.
11. Nickel, C., Tritt, K., Muehlbacher, M., Pedrosa Gil, F., Mitterlehner, F. O., Kaplan, P., Lahmann, C., Leiberich, P. K., Krawczyk, J., Kettler, C., Rother, W. K., Loew, T. H. and Nickel, M. K. 2005, Int. J. Eat Disord., 38, 295.
12. Hoopes, S. P., Reimherr, F. W., Hedges, D. W., Rosenthal, N. R., Kamin, M., Karim, R., Capece, J. A. and Karvois, D. 2003, J. Clin. Psychiatry, 64, 1335.
13. Hedges, D. W., Reimherr, F. W., Hoopes, S. P., Rosenthal, N. R., Kamin, M., Karim, R. and Capece, J. A. 2003, J. Clin. Psychiatry, 64, 1449.
14. Stanley, B. G., Ha, L. H., Spears, L. C. and Dee, M. G. 1993, Brain Res., 613, 88.
15. Zheng, H., Patterson, C. and Berthoud, H. R. 2002, Am. J. Physiol. Regul. Integr. Comp. Physiol., 282, R147.
16. Hettes, S. R., Heyming, T. W. and Stanley, B. G. 2007, Brain Res., 1184, 178.
17. Gryder, D. S. and Rogawski, M. A. 2003, J. Neurosci., 23, 7069.