Abstract. – BACKGROUND: Binge-eating disorder (BED) is a relatively new disorder characterized by binge eating without purging.

AIM: The purpose of this article is to review the potential use of the recently proposed compounds for the treatment of BED.

MATERIALS AND METHODS: A medline of published articles from 1980 to December 2012 was carried out using the following keywords: BED and treatment, topiramate, zonisamide, ghrelin.

RESULTS: The pharmacological treatment of BED is still heterogeneous and poorly established, mainly for the lack of controlled studies in large samples of patients.

CONCLUSIONS: The data on serotonin and noradrenaline reuptake inhibitors and on novel anticonvulsants seem quite promising in terms of efficacy and tolerability. In addition, the preliminary findings on the possibility of modulating appetite through the interference with the ghrelin system suggest new and intriguing ways of intervention in BED.

Key Words: BED, Topiramate, Zonisamide, Ghrelin.

Introduction

Binge-eating disorder (BED) is characterized by binge eating without purging, often, but not necessarily, associated with obesity. The Diagnostic and Statistical Manual for Mental Disorders, fourth edition, (DSM-IV) provides the research criteria for BED which include: eating very rapidly, eating until feeling uncomfortably full, eating large amounts of food when not hungry, eating alone because of embarrassment about how much one is eating, and feeling disgust, guilt, or depression after overeating. The marked distress required for the diagnosis includes unpleasant feelings during and after the binge episodes, as well as concerns about the long-term effect of the recurrent binge episodes on body weight and shape. Binge episodes must occur, on average, at least 2 days a week for a period of at least 6 months.

BED was recognized in 1959 through the identification of its core that are the following: a rapid consuming of a large quantities of food in a relatively short period of time with a sense of loss of control over eating, guilt after the binge, and presence of these features in some obese patients. Epidemiological studies suggest that between 1.5% and 3.0% of women meet full criteria for BED, while the prevalence in men is estimated to be about two-thirds of that in women.

Comorbidity is common amongst BED patients, in particular with major depression, anxiety and personality disorders.

BED has been related to impulse control disorders (ICDs), as its most salient feature is represented by the loss of control over eating.

The treatment of patients suffering from BED is multidimensional and includes both pharmacotherapy and cognitive-behavioral therapy (CBT). Currently, the literature supports the use of three categories of medications: antidepressants, anticonvulsants and anti-obesity agents. Amongst antidepressants, selective serotonin (5-HT) reuptake inhibitors (SSRIs) are the most studied drugs: in particular, fluoxetine, fluvoxamine, sertraline, citalopram and escitalopram have been shown to reduce significantly the binge eating frequency and body weight in BED patients.

A similar efficacy has been described for some of the classical anticonvulsants. Other anticonvulsants, such as topiramate and zonisamide, are now under investigation for the treatment of BED and obesity.

Further, the research on the pharmacotherapy of BED is now focusing on other compounds, including modulators of peptide hormones.

The purpose of this article was to review the rationale, as well as the evidence, for the potential use of novel pharmacological treatments in BED.
Materials and Methods

We conducted a Medline search of English-language articles from 1980 to December 2012 using the following keywords: BED and treatment, topiramate, zonisamide. Single case reports, observational studies, opinion articles, and studies concerning adults or adolescents with syndromes resulting in BED (i.e., night eating syndrome) were reviewed.

Results and Discussion

Newer Anticonvulsants: Topiramate and Zonisamide

Topiramate and zonisamide, two novel anticonvulsants, seem to be able to suppress appetite and increase the control on eating 11,14,15. Topiramate, a sulfamate-substituted monosaccharide which shows anticonvulsant properties, more recently has been used in the treatment of migraine, bipolar disorder and bulimia nervosa (BN) 16-20. Animal models suggest that stimulation of the lateral hypothalamus, by glutamate agonists (like kainate/AMPA agonists), provokes an intense rapid dose-dependent increase in food intake 20. Therefore, it has been hypothesized that antagonists of kainate/AMPA glutamate receptors, like topiramate, might contribute to suppress appetite and to regain control over eating 20. In a first open trial, 9 out of 13 BED patients with obesity responded to topiramate with a moderate reduction in binge eating and the weight loss correlating with the drug dose 21. A second open-label trial 22, too, reported a decreased frequency of binge episodes and a significant weight loss. These findings were subsequently supported by data coming from a randomized, double blind trial 23. Sixty-one patients with obesity were assessed for 14 weeks and topiramate was administered (mean dosage: 212 mg/day), while leading to a significant reduction and remission of purge days, body mass index (BMI) and weight (5.9 kg for topiramate versus 1.2 kg for placebo). Topiramate showed a higher efficacy than placebo on both the primary and secondary outcome measures of frequency of binge episodes. At the last assessment, 64% of topiramate-treated patients had stopped binge eating, as compared with 30% of patients receiving placebo. In two subsequent case reports 24,25, obese BED women with no psychiatric comorbidity who failed to respond to other agents, were successfully treated with topiramate. A 22-year-old woman who had failed to lose weight by several treatments was treated with topiramate 24. The patient reached the target dose of 75 mg/day after two weeks and, since then, showed a marked reduction of binge-eating episode per week (from 4 to 1 day). After four months of treatment, there were no longer binge-eating episodes and the weight was 98.6 kg (BMI=38.5 kg/m²). An initial hypersomnia was the only side effect reported 24. In the other above-mentioned case report, a female patient did not show any substantial change after a nutritional counselling associated with a treatment with fluoxetine 60 mg/day and quetiapine 400 mg/day. After three weeks of topiramate administration (mean dosage 100 mg/day) a significant improvement in eating habits was reported, as assessed by Eating Disorder Test (EAT), Eating disorder Intuitive (EDI) and Yale Brown Obsessive and Compulsive Scale (Y-BOCS) total scores 25. In another study 21, the response of 13 female outpatients with BED was evaluated in a naturalistic, open-label treatment with topiramate (100-1400 mg/day, mean dosage 492.3±467.8 mg/day). After the beginning of the treatment, 9 patients displayed a moderate or good response and maintained this result for periods ranging between 3 and 30 months (mean±SD = 18.7±8.0 months). Two patients showed a moderate or good response and two had a mild or no response. The mean±SD weight of the 13 patients significantly decreased from 99.3±26.4 kg to 87.5±20.4 kg, but only 7 patients lost ≥ 5 kg of weight. Seven women and one man with a diagnosis of BED and a BMI above 30 were enrolled in another study 22. Four patients displayed a complete remission of the binge eating episodes, and two had a marked reduction in binge frequency. Two patients discontinued the study for mild side effects and lack of efficacy. The dosage of topiramate started from 25 mg to 75 mg twice daily until the end of the study. All patients who completed the trial showed a reduction in binge eating at the end of treatment. The mean measure of binge eating episodes per week decreased significantly from 4.3 at baseline to 1.1 at the end of the study, as did the binge eating scale scores, which decreased from 31.8 to 15.3 26.

In another placebo-controlled study, 195 patients were treated with topiramate and 199 patients with placebo and topiramate was observed to induce binge eating remission in 58% of patients (placebo, 29%; p < .001). In particular, topiramate reduced binge eating days/week (~3.5 ±
1.9 vs. –2.5 ± 2.1), binge episodes/week (–5.0 ± 4.3 vs. –3.4 ± 3.8), weight (–4.5 ± 5.1 kg vs. .2 ± 3.2 kg), and BMI (–1.6 ± 1.8 kg/m² vs. .1 ± 1.2 kg/m²), compared with placebo (p < .001).

Some Authors underlined a possible mechanism of action of topiramate as antidepressant and mood stabilizer when BED is in comorbidity with mood disorders and impulsive personality. However, the remission of binge eating in subjects without comorbidity may be ascribed more likely to a direct effect on eating control. In a 3-month study, topiramate was used to treat 16 patients who underwent adjustable gastric banding (AGB) and showed difficulty losing weight due to, amongst other factors, the development or maintenance of BED. There was a mean increase in weight loss from 20.4% to 34.1%, without the need for band readjustment and only two patients showed intolerance to topiramate and were shifted to fluoxetine 40 mg per day. Other cases about recurrent binge eating and weight gain in patients with BED after bariatric surgery have been reported. In three patients topiramate was administered for an average period of 10 months. In the first case a woman was prescribed topiramate 25 mg up to 1000 mg/day. Subsequently, fluoxetine 20 mg was added for depressive symptoms, but after 2 months it was discontinued for mood shifts. After one year and six months, she reported a decrease of appetite and of the weekly frequency of binge episodes from 14 to 0. In the second case, topiramate was administered up to 450 mg/day, and after 9 months the patient reported a significant decrease on Clinical Global Impression (CGI) and BMI with no binge per week. Finally, in the last case the topiramate maximum dosage was 175 mg/day, with similar results. These findings seem to support the use of topiramate in case of a recurrence of binge eating and weight gain (1 to 3 years in the average) after bariatric surgery.

Zonisamide, a benzisoxazole derivative, is another anticonvulsant which has been found to be associated with weight loss. In fact, a reduction of the normal appetite and weight loss has been demonstrated in patients with epilepsy. In an open-label 12-week study, the Authors evaluated this treatment in 15 BED patients. Patients started a dosage of 100 mg up to 600 mg/day of zonisamide and binge frequency, weekly frequency of binge days, BMI, CGI, weight and YBOCS-BE scores were measured. Eight patients completed the study. The analyses found a significant decrease of binge behavior and frequency, BMI, YBOCS-BE scores and CGI, while providing a preliminary evidence for the effectiveness of zonisamide in BED. A controlled open study evaluated the efficacy and safety of zonisamide as augmentation to individual cognitive behavioral therapy (CBT) in the treatment of binge eating disorder patients. Twenty-four threshold and subthreshold binge eating disorder patients were enrolled in the CBT alone group and twenty-eight patients in the CBT plus zonisamide group. In the two groups the BMI was measured at the beginning (T0), at the end (T1) of treatment, one year after the end of treatment (T2), the symptoms were assessed by the Eating Disorder Examination-Questionnaire, the Binge Eating Scale, the Beck Depression Inventory and State-Trait Anxiety Inventory. At T1, the CBT plus zonisamide group showed a higher mean reduction of all the assessed parameters and rating scale scores. At T2, the CBT alone group regained weight, while the CBT plus zonisamide group reduced their body mass and showed a higher reduction in binge eating frequency.

Several mechanisms of action had been suggested for the efficacy of this drug, the most likely seem to be the possible enhancement of dopamine, or the inhibition of glutamate transmission.

In conclusion, the use of two newer anticonvulsants, topiramate and zonisamide, seems to be very promising for the treatment of BED. However, further studies in larger samples of patients are needed to better explore their efficacy and safety.

**Peptide Modulators**

Much attention has been directed towards the manipulation of some peptide systems as potential targets for eating disorder treatment on the basis of different findings derived from preclinical studies on appetite control. It has been shown that leptin, insulin, cholecystokinin, glucagon-like peptide-1 mediate hunger, satiety and general metabolism, while ghrelin is the only appetite-stimulating hormone discovered up to now. Ghrelin is a 28-aminoacid peptide hormone, released by the human fundus mucosa and rat stomach, and represents the endogenous ligand for the growth hormone secretagogue receptor (GHR-S). Ghrelin influences gastroentero-pancreatic functions and has orexigenic, metabolic, cardiovascular, and antiproliferative effects. GHR-S receptors have been found in different hypothalamus nuclei. In adults, plasma ghrelin concentrations increase two-folds before a meal and decrease within 1 h after eating. Ghrelin concentrations are reported to be high in patients on diets, while stomach-by-
pass surgery decreased ghrelin concentrations. This suggests that the size of the stomach may be directly correlated to ghrelin concentrations. In addition, a series of observations suggested that ghrelin is a strong gastrokinetic agent. Changes in ghrelin concentrations have been explained as part of complex compensatory efforts of the neuroendocrine system to counteract negative energy balance.33,35 Nevertheless, the relation between plasma ghrelin concentrations and eating patterns in patients with eating disorders remains unclear. In a study carried out in bulimia nervosa (BN) subjects, the presence of abnormal eating behaviors with habitual binge eating and purging was found to influence circulating ghrelin level. The Authors concluded that the presence of binge-eating/purging may influence fasting plasma ghrelin concentrations. In contrast with these data, no difference was reported in ghrelin concentrations between anorectic patients suffering from the binge-eating/purging subtype and those from the restrictive subtype. In a sample of bulimic women, no significant association was found between circulating ghrelin and the severity of binge/vomiting frequency. Plasma ghrelin concentrations were negatively related with the BMI, the plasma concentrations of TSH, free T3 and free T4, whereas they were positively related to plasma cortisol concentrations. Ghrelin plasma levels of women with binge-eating and purging behavior were significantly lower than those of women with anorexia nervosa (AN), restricting type. These data suggest that ghrelin concentrations reflect more nutritional status rather than specific patterns of disordered eating behavior. In another study, 30 obese patients were enrolled and divided in three groups: 12 non-bingeing, 11 subthreshold and 14 with full fledged syndrome. After 2 baseline blood draws, a nutritional meal was provided and blood samples were drawn. As compared with the others, BED subjects showed lower baseline ghrelin concentrations prior to the meal, a lower area under the curve (AUC), with lower levels at 5, 15, 30, 90, and 120 min, and a smaller decline in ghrelin postmeal. This ghrelin pattern in BED patients may be due to down regulation by binge eating, and the smaller decline in ghrelin after meals may then provide a weaker satiety signal. Interesting results also came from association studies on ghrelin and ghrelin receptor gene polymorphism with BN and obesity. The 171T/C polymorphism of the ghrelin receptor was explored in 228 Japanese patients with eating disorders. One hundred thirty-one patients with anorexia restrictor, 97 with anorexia binge-purging and 108 bulimic patients, and 300 healthy control subjects participated in the study. The results showed that the CC type of GHSR gene polymorphism (171T/C) is a risk factor for BN, but not for AN. Genotyping was performed to determine the presence of polymorphisms; with this information, linkage disequilibrium (LD) between the markers was analyzed and the distributions of the genotypes, the allele frequencies, and the haplotype frequencies were compared between the groups. The Leu72Met (408 C > A) (rs696217) polymorphism in exon 2 and the 3056 T > C (rs2075356) polymorphism in intron 2 were in LD (D = 0.902, r² = 0.454). Both polymorphisms were significantly associated with bulimia nervosa, purging subtype (BN-P). In addition, a significant increase in the frequency of the haplotype Met72-3056 C in BN-P patients was observed. These findings suggest that the Leu72Met (408 C > A) and the 3056 T > C polymorphisms of the preproghrelin gene are associated with susceptibility to BN-P.

Conclusions

Obesity is one of the mayor problem in Western societies related to the large availability of food followed by the rapidly escalating incidence of eating disorders, whose therapeutic management is still disappointing. BED is a relatively new condition characterized by binge eating without purging that often, but not necessarily, is associated with obesity. In this paper, we reviewed some of the available studies on novel pharmacological treatment of BED.

Evidence suggested that certain pharmacological treatments might represent significant advantages over placebo to achieve short-term remission from binge eating and weight loss. The most investigated compounds are represented by the newer anticonvulsants, topiramate and zonisamide. Preliminary findings would suggest that also the modulation of ghrelin, the only appetite-stimulating hormone discovered up-to now, may be beneficial. In any case, although intriguing, data in this field are limited.

In conclusion, the pharmacological treatment of BED is still problematic due to the multifunctional causality of the disorder and the little information on its pharmacological mechanisms.
References


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Novel treatments for binge eating disorder


