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Role of Antiepileptic Drugs in the Management of Eating Disorders

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Abstract

Growing evidence suggests that antiepileptic drugs (AEDs) may be useful in managing some eating disorders. In the present paper, we provide a brief overview of eating disorders, the rationale for using AEDs in the treatment of these disorders and review the data supporting the effectiveness of specific AEDs in the treatment of patients with eating disorders. In addition, the potential mechanisms of action of AEDs in these conditions are discussed.

Of the available AEDs, topiramate appears to have the broadest spectrum of action as an anti-binge eating, anti-purging and weight loss agent, as demonstrated in two placebo-controlled studies in bulimia nervosa and three placebo-controlled studies in binge-eating disorder (BED) with obesity. Topiramate may also have beneficial effects in night-eating syndrome and sleep-related eating disorder, but controlled trials in these conditions are needed. The results of one small controlled study suggest that zonisamide may have efficacy in BED with obesity. However, both topiramate and zonisamide are associated with adverse effect profiles that may limit their use

in patients with eating disorders. Phenytoin may be effective in some patients with compulsive binge eating, particularly if co-morbid EEG abnormalities are present, but available data are too varied to allow definitive conclusions to be made. Carbamazepine and valproate may be effective in treating patients with bulimia nervosa or anorexia nervosa when they are used to treat an associated psychiatric (e.g. mood) or neurological (e.g. seizure) disorder; otherwise, both agents, particularly valproate, are associated with weight gain.

In conclusion, AEDs have an emerging role in the management of some eating disorders.

Eating disorders are important public health problems,[1-4] but a substantial number of afflicted patients do not respond adequately to the available treatments.[5,6] Growing evidence suggests that antiepileptic drugs (AEDs), compounds marketed primarily to prevent epileptic seizures, may be useful in managing some of these conditions.[7-9] In the present paper, we provide a brief overview of eating disorders, the rationale for using AEDs in the treatment of these disorders, review the data supporting the effectiveness of specific AEDs in treating patients with eating disorders and discuss the potential mechanisms of action of AEDs in these conditions. We conclude that AEDs have an emerging role in the management of some eating disorders.

To explore the role of AEDs in eating disorders, we surveyed the literature for available first- and second-generation AEDs in the treatment of all recognized and potential eating disorders. A MEDLINE search of the English language literature from January 1966 to April 2008 was performed using the following terms: 'eating disorders', 'anorexia nervosa' (AN), 'bulimia nervosa' (BN), 'binge eating disorder' (BED), 'eating disorder not otherwise specified' (NOS), 'pica', 'rumination', 'night eating syndrome' (NES), 'sleep-related eating disorder' (SRED) and 'weight', as well as 'antiepileptic', 'anticonvulsant', 'barbiturate', 'benzodiazepine', 'carbamazepine', 'clonazepam', 'diphenylhydantoin', 'felbamate', 'gabapentin', 'lamotrigine', 'levetiracetam', 'oxcarbazepine', 'phenytoin', 'pregabalin', 'tiagabine', 'topiramate', 'valproate', 'vigabatrin' and 'zonisamide'.

1. Overview of Eating Disorders

Eating disorder nosology is an evolving field.[2,10,11] The two major psychiatric classification systems, namely the International Statistical Classification of Diseases, 10th edition (ICD-10)[12] and DSM-IV,[13] each list eating disorders under two broad categories, one for eating disorders only (see table I) and the other for conditions with onset usually in infancy, childhood and/or adolescence (see table II). Both ICD-10

Table I. Eating disorders as defined in the International Statistical Classification of Diseases, 10th edition (ICD-10)[12] and the DSM-IV[13]

ICD-10	DSM-IV
Anorexia nervosa	Anorexia nervosa
Atypical anorexia nervosa	Bulimia nervosa
Bulimia nervosa	Eating disorder NOS[a]
Atypical bulimia nervosa[b]	
Overeating associated with other psychological disturbances[c]	
Vomiting associated with other psychological disturbances[d]	
Other eating disorders[e]	
Eating disorder, unspecified	

a Includes subthreshold anorexia nervosa, subthreshold bulimia nervosa, self-induced vomiting without binge eating, repeatedly chewing and spitting out large amounts of food and binge-eating disorder.

b Includes bulimia NOS and hyperorexia nervosa.

c Includes overeating due to stressful events, such as bereavement, accident, childbirth etc., and psychogenic overeating.

d Includes psychogenic vomiting.

e Includes pica in adults and psychogenic loss of appetite.

NOS = not otherwise specified.

Table II. Eating disorders as defined in the International Statistical Classification of Diseases, 10th edition (ICD-10)[12] and the DSM-IV,[13] with onset usually occurring in infancy, childhood and/or adolescence

ICD-10	DSM-IV
Pica of infancy and childhood	Pica
	Rumination disorder
	Feeding disorder of infancy or early childhood

and DSM-IV recognize AN, BN and pica, and define these syndromes similarly. Key defining features of AN are deliberate weight loss, a fear of fatness, disturbed body image and amenorrhoea. Defining features of BN are recurrent episodes of binge eating with inappropriate compensatory behaviours aimed at preventing weight gain. Pica is defined as the repetitive or persistent eating of non-nutritive substances. Both classification systems also include categories for sub-syndromal or atypical presentations of AN and BN, which are categorized in the DSM-IV as eating disorder NOS.[14,15] Examples include AN without amenorrhoea and purging without binge eating. Unlike ICD-10, DSM-IV includes rumination disorder and BED. Rumination is defined as the repeated regurgitation and re-chewing of food, and is listed under disorders with onset usually in infancy, childhood or adolescence, although it may occur at any age.[16] BED is proposed to be a possible new diagnostic entity and is given as an example of eating disorder NOS. BED is defined by recurrent, distressing episodes of binge eating that are not accompanied by regular inappropriate compensatory weight loss behaviours.

Several other eating disorders have been proposed but are not mentioned in either the ICD-10 or DSM-IV. For example, NES is characterized by morning anorexia, evening hyperphagia and sleep disturbance.[17,18] Some definitions include or focus on nocturnal ingestions after waking from sleep, such as the nocturnal eating (drinking) syndrome proposed by the International Classification of Sleep Disorders (ICSD).[3,19] SRED is characterized by nocturnal eating after waking from sleep, and may meet DSM-IV and ICSD criteria for parasomnia NOS, where there is reduced awareness during the nocturnal eating.[3,20,21] The relationship between NES and SRED is presently unclear. Although some authorities have argued that these two conditions are separate entities, others have proposed that NES and SRED are related along a continuum of altered awareness during the nocturnal ingestions.[3] Finally, although eating disorders resulting from general medical conditions and substances have been described in the literature, neither is listed as a category in the DSM-IV or ICD-10.[22,23]

Of note, neither obesity nor drug-induced weight gain are categorized as eating disorders in either the ICD-10 or DSM-IV, even though both conditions may be associated with disturbed eating behaviour, including binge eating.[23-26] In addition, neuropsychiatric syndromes characterized by polyphagia are usually not categorized as eating disorders.[27-29] Although all these conditions have been investigated in some studies as potential targets for intervention with AEDs, these topics will not be the focus of the present paper.[9]

No single study has evaluated the epidemiology of all potential eating disorders. However, growing evidence indicates that eating disorder NOS may be more common than BN and AN.[14] In particular, BED may be more common than BN and AN combined, with the lifetime prevalence estimates of DSM-IV BED, BN and AN from the National Comorbidity Survey Replication (NCS-R) being 2.8%, 1.0% and 0.6%, respectively.[1] In addition, 4.5% of the population had any lifetime binge eating, defined as binge-eating episodes occurring at least twice weekly for at least 3 months. Although it is not known whether prevalence rates of eating disorders are changing over time, data from the NCS-R suggest that the incidence of BN and BED has increased with successive birth cohorts.[1] Less is known about the epidemiology of pica, rumination disorder, feeding disorder of infancy or early childhood, NES or SRED, but some of these disorders may be more common than once thought. Pica is frequently observed in children, as well as in pregnant women and patients of lower socioeconomic status.[30] The prevalence of

NES and SRED in the general adult population has been estimated to be 1–1.5% each.[31,32]

AN, BN and BED are associated with medical morbidity, other psychiatric disorders (particularly mood, anxiety and substance use disorders), reduced quality of life, and impairment.[1,2,33,34] Pica is similarly associated with medical complications and other psychiatric disorders, as well as developmental disorders and iron deficiency anaemia.[30] AN, by definition, is associated with low bodyweight, whereas BED is associated with obesity, including severe obesity.[1,34,35] NES, and possibly SRED, may also be associated with overweight and obesity.[17] Both genetic and environmental factors are thought to contribute to the pathophysiology of AN, BN and BED.[35-39] Less is known about the pathophysiology of the other eating disorders.

Psychological treatments are thought to be extremely important in the management of most eating disorders,[2,5,6,40] but many patients with these conditions receive psychotropic medications, particularly antidepressants.[41] Several guidelines[5,40] and reviews[2,42-48] suggest that SSRIs are reasonable first- or second-line pharmacological treatments for BN or BED based on controlled studies showing that these drugs are superior to placebo in reducing binge eating, at least over the short term. Indeed, the only medication approved by the US FDA for the treatment of an eating disorder is fluoxetine, which is used for the treatment of BN. Preliminary placebo-controlled data suggest that SSRIs may also be effective in NES.[49]

Several other types of antidepressants have been shown to be effective in treating BN, including TCAs, MAOIs, trazodone and bupropion.[5,42,46] As with fluoxetine, these agents reduce purging and binge-eating behaviour. However, bupropion is contraindicated for BN because of an elevated risk of seizures.[50] Although TCAs have been shown to be effective in the treatment of the binge eating of BED, these medications, like the SSRIs, are less satisfactory in inducing weight loss.[43,44,47] Moreover, antidepressants have been shown to be ineffective in promoting weight gain or in preventing weight loss in AN.[51,52]

Several drugs other than antidepressants show promise in the treatment of eating disorders.[45] Three placebo-controlled studies, including one large multicentre trial with 304 participants, have shown that sibutramine reduces both binge eating and excessive bodyweight in BED.[53-55] Small, placebo-controlled studies suggest beneficial results for the serotonin 5-HT_3 receptor antagonist ondansetron in the treatment of BN,[56] the selective noradrenaline reuptake inhibitor atomoxetine in the treatment of BED[57] and the dopamine D_3 receptor agonist pramipexole in the treatment of SRED;[58] however, these findings need to be replicated in larger controlled trials. In some case reports, open-label trials and, more recently, in a small, randomized, placebo-controlled trial, atypical antipsychotics, particularly olanzapine, have been reported to be effective in the treatment of AN, including in treatment-resistant patients.[48,59] Further placebo-controlled studies are needed to confirm these findings.

However, many patients with eating disorders who undergo pharmacotherapy exhibit inadequate responses to treatment with antidepressants and other available agents. Overall, the available pharmacotherapeutic armamentarium for eating disorders is still less than adequate; therefore, new medical treatments for eating disorders are needed.

2. Rationale for Using Antiepileptic Drugs (AEDs) in Eating Disorders

There are several rationales for AEDs being useful in the treatment of eating disorders.[7,8,43,44] First, individual AEDs have diverse molecular targets and combinations of actions.[60-63] AEDs have been found to be efficacious in a variety of neuropsychiatric conditions beyond epilepsy, including some that are likely to be related to eating disorders.[64] Examples of these conditions include those for which AEDs have regulatory approval but whose co-occurrence with eating disorders is underrecognized, such as bipolar disorder[65] and migraine,[66] as well as those whose co-occurrence with eating disorders is well established and for which emerging placebo-controlled data suggest

that AEDs have efficacy, such as anxiety disorders, substance use disorders, personality disorders and obesity.[9,64,67-72] AEDs that are effective in treating conditions related to eating disorders may also be effective in treating the eating disorders themselves, or at least be useful in managing co-occurring conditions in patients with eating disorders.

The second rationale for the use of AEDs in the treatment of eating disorders is that many AEDs have effects on weight and appetite,[73] as well as on neural systems important in regulating eating and weight control.[74-77] For example, valproate, gabapentin and pregabalin are associated with weight gain and increased appetite, whereas topiramate, zonisamide and felbamate are associated with weight loss and decreased appetite. The neural systems involved in the regulation of feeding behaviour and weight control that are affected by AEDs include the glutamatergic (e.g. felbamate, topiramate and phenobarbital [phenobarbitone]), GABAergic (e.g. valproate, felbamate, topiramate, gabapentin, levetiracetam, phenobarbital, benzodiazepines, vigabatrin and tiagabine), serotonergic (e.g. zonisamide), dopaminergic (e.g. zonisamide) and neuropeptide Y (e.g. topiramate, valproate and zonisamide) systems.[78-84] Furthermore, valproate has been shown to modulate the extracellular signal-regulated kinase (ERK) signalling pathway.[80] Although some of the effects of AEDs on appetite and weight are problematic in certain clinical situations (e.g. weight gain from valproate in obese patients), they could translate into therapeutic effects on eating behaviour and bodyweight in patients with eating disorders. For example, AEDs with anorectic or weight loss effects have been shown to be helpful in patients with eating disorders who binge eat and are overweight.[85-87] In contrast, AEDs associated with weight gain may be useful in the treatment of patients with AN, particularly if this effect is accompanied by anxiolytic or mood stabilizer effects, such as is seen with pregabalin or valproate, respectively.[8,88,89]

A third rationale for the use of AEDs in the treatment of eating disorders is that a number of new AEDs are currently in development and may come to market.[90] Some of these new agents may prove to have beneficial psychotropic properties and/or useful effects on appetite or weight regulation, and may therefore have therapeutic effects in patients with eating disorders.

3. First-Generation AEDs in the Treatment of Eating Disorders

3.1 Phenytoin

Phenytoin is a classical AED that is still widely used to treat a broad range of epilepsies. The primary mechanism of action of the drug is thought to be antagonism of voltage-gated sodium channels.[60,63] Phenytoin is generally weight neutral and has no psychiatric indications, but preliminary placebo-controlled data suggest that it may be effective in the treatment of bipolar mania.[62]

There are two small, placebo-controlled trials of phenytoin in patients with compulsive or binge eating in the literature that report contrasting results.[91,92] In the negative trial, four obese patients with compulsive eating received phenytoin in a crossover design.[91] No significant differences were found between phenytoin and placebo on any outcome measure, and none of the patients showed a marked response to phenytoin. In the positive study, 19 of 20 women with 'binge-eating syndrome' completed a 12-week crossover trial comparing phenytoin with placebo.[92] Ten women were of normal weight, nine were overweight or obese and one had active AN. All subjects received phenytoin or placebo for 6 weeks each. Final serum phenytoin concentrations were 10–20 μg/mL in 12 subjects, 5–10 μg/mL in another five subjects and <3 μg/mL in the remaining 2 subjects who completed the trial. Subjects who were treated with phenytoin first reported a 37% decrease in the frequency of binge eating ($p < 0.01$). However, when these subjects switched to placebo, no further changes in the frequency of binge eating were observed. Conversely, subjects who were treated with placebo first reported no change in the frequency of binge eating but, after switching to phenytoin, a 39% decrease in the

frequency of binge eating was observed ($p < 0.01$). Eight of 19 (42%) subjects who completed the study displayed a moderate or better response (a >50% reduction in the frequency of binge episodes) while receiving phenytoin. One subject experienced a remission of binge eating and five others had a marked response (defined as a >75% reduction in the frequency of binge episodes). When the two groups were compared, there were significantly fewer episodes of binge eating in the phenytoin–placebo group than in the placebo–phenytoin group ($p < 0.02$), indicating a carryover effect for the phenytoin–placebo sequence.

These two controlled studies were accompanied by mostly positive reports of open-label phenytoin treatment reducing compulsive eating in patients of various weights.[93-97] In the first report, Green and Rau[93] presented ten patients with compulsive eating binges, nine of whom responded to treatment with phenytoin. Four patients were underweight and diagnosed with AN, two were of normal weight and four were obese. The authors observed that nine of the patients had EEG abnormalities and hypothesized that binge eating may be related to epilepsy. These authors ultimately expanded their investigation to a series of 47 patients,[96] of whom 27 (57%) showed a 'good' response to phenytoin treatment, with 20 (43%) showing an 'uncertain' or 'poor' response. Moreover, patients with abnormal EEGs were significantly more likely to exhibit a good response to phenytoin (21/30 [70%]) compared with patients with a normal EEG (6/17 [35%]; $p < 0.001$). Green and Rau[93] concluded that the findings of their expanded study supported their theory that binge eating may be related to epilepsy.

There are two further reports in the literature of open-label trials of phenytoin in the treatment of patients with AN.[98,99] In one report, a subset of 42 patients receiving phenytoin along with psychotherapy and other medications exhibited an improvement in their attitude towards food, eating behaviour, hostility and fear; however, quantitative results were not provided.[98] In the other report, a 16-year-old girl with 'classical' AN beginning simultaneously with partial complex seizures showed both weight gain and seizure control when treated with phenytoin.[99]

3.2 Carbamazepine

Carbamazepine is a widely used AED that, like phenytoin, is thought to exert its antiepileptic effects in part through sodium channel blockade.[60,63] Carbamazepine is approved for use in trigeminal neuralgia, as well as for the treatment of manic and mixed episodes in bipolar I disorder.[61] Placebo-controlled data suggest that carbamazepine may be beneficial in treating alcohol withdrawal[71] and borderline personality disorder.[72]

One randomized, placebo-controlled study of carbamazepine in the treatment of an eating disorder was located in the literature.[100] In this study, 16 subjects with DSM-III-defined[101] BN and at least one binge per week and no binge-free intervals of longer than 3 weeks during the previous year, received the drug in a crossover design.[7,8,100] The first six subjects were treated at 6-weekly intervals over a period of 18 weeks in a placebo–carbamazepine–placebo or a carbamazepine–placebo–carbamazepine sequence. The next ten subjects were treated over a period of 12 weeks in two 6-weekly intervals of placebo–carbamazepine or carbamazepine–placebo. No significant differences were seen in response to carbamazepine and placebo. One subject had complete remission of binge eating, one subject exhibited a marked response and another three subjects improved while receiving carbamazepine compared with baseline, but showed no difference on drug compared with placebo. Of note, the subject who had the remission also had co-morbid cyclothymic disorder; this subject showed a marked improvement in mood, as well as in bulimic symptoms, while receiving carbamazepine.

In addition, two case reports of carbamazepine in the treatment of AN were found in the literature. In one report, a patient with AN and cyclothymia experienced remission of binge eating and mood symptoms while receiving a combination of carbamazepine and lithium.[8,102] In the other report, a patient with AN receiving

carbamazepine developed fulminant hepatic failure in response to paracetamol (acetaminophen).[103]

Finally, there are two reported cases of the use of carbamazepine in pica.[104,105] In one report, coprophagia due to a glioblastoma in a 46-year-old man was treated successfully with carbamazepine.[104] In the other report, the pica of a severely mentally handicapped man with depression responded to the antidepressant lofepramine after not responding to treatment with carbamazepine.[105]

3.3 Valproate

Valproate is a very commonly used AED that is approved for use in the treatment of several types of epilepsy in children and adults, to prevent migraines in adults and for the treatment of manic and mixed episodes in bipolar I disorder in adults.[61,62,64] The numerous actions of valproate include blockade of sodium channel activity, facilitation of GABA transmission and effects on various intracellular signalling pathways such as ERK.[60-63,80]

The only reports in the literature concerning the use of valproate in eating disorders are case studies. Valproate was found to be effective in the treatment of three hospitalized young women (aged 17, 17 and 20 years) with BN and co-morbid rapid-cycling bipolar disorder.[8,88,89] All three patients were previously unresponsive or only partially responsive to lithium and antipsychotics, and had mildly abnormal EEGs. Two patients were treated with valproate alone and one was treated with valproate in combination with lithium. All three patients responded well to valproate, with marked improvement in both bulimic and mood symptoms. In one of the patients,[8,88] bulimic and mood symptoms recurred on two occasions when plasma concentrations of valproic acid fell below 50 μg/mL. In another case, a combination of valproate and clonazepam was effective in treating both eating disorder symptoms and seizures in a 13-year-old girl with AN and epilepsy.[106]

However, valproate has been reported to worsen binge eating and enhance weight gain in patients with BED and co-morbid bipolar disorder.[107]

3.4 Other Agents

There are isolated reports in the literature of the use of clonazepam, administered as monotherapy or adjunctively with dopamine agonists, in the treatment of SRED, with mixed results.[108,109] No other reports on the use of first-generation AEDs in treating eating disorders were found, with the exception of descriptions of two patients who did not respond to treatment with primidone and barbiturates, but who did respond to treatment with phenytoin. The patient who did not respond to treatment with primidone was in the original report by Green and Rau[93] regarding the effectiveness of phenytoin in treating compulsive eating disorders. The patient who did not respond to treatment with barbiturates had AN and a seizure disorder.[99]

4. Second-Generation AEDs in the Treatment of Eating Disorders

4.1 Topiramate

Topiramate is approved for the treatment of epilepsy in children and adults, as well as for the prevention of migraine in adults. The use of topiramate is associated with anorexia and weight loss in a wide range of conditions.[110] Placebo-controlled data suggest that topiramate may be effective in the treatment of obesity, psychotropic-associated weight gain, alcohol dependence, borderline personality disorder, cocaine dependence and major depression, but not bipolar mania.[9,68-70,110-113] Topiramate has a number of pharmacodynamic effects, but its mechanism of action in epilepsy, and possibly substance abuse, is thought to be related to its dual effects of enhancing GABAergic inhibition and reducing glutamatergic excitation.[63,68,69]

Five randomized, placebo-controlled studies of topiramate in 640 subjects with DSM-IV-defined eating disorders were found in the literature: two monotherapy trials in a total of 99 subjects with BN,[114-116] two monotherapy trials in 468 subjects with BED and obesity[85,86] and one

adjunctive trial of topiramate plus CBT in 73 subjects with BED and obesity.[117] In all five trials, topiramate was superior to placebo on the primary outcome measure.

The first study of topiramate in BN was a 10-week trial in 69 subjects.[114,115] Topiramate (median dosage 100 mg/day; range 25–400 mg/day) was found to be superior to placebo in reducing the frequency of binge and purge days (i.e. days during which at least one binge eating or purging episode occurred [p = 0.004]); the bulimia/uncontrollable overeating (p = 0.005), body dissatisfaction (p = 0.007) and drive for thinness (p = 0.002) subscales of the Eating Disorder Inventory;[118] the bulimia/food pre-occupation (p = 0.019) and dieting (p = 0.031) subscales of the Eating Attitudes Test;[119] and bodyweight (mean decrease of 1.8 kg for topiramate vs 0.2 kg increase for placebo [p = 0.004]).[112,113] Remission rates from binge eating and purging were 32% for topiramate and 6% for placebo (p = nonsignificant). The topiramate-treated group exhibited a significantly greater reduction in mean Hamilton Rating Scale for Anxiety (HAM-A)[120] score than did the placebo-treated group (p = 0.046). In addition, the reduction in the Hamilton Rating Scale for Depression (HAM-D) score tended to be greater in the topiramate-treated group, but the difference did not reach statistical significance (p = 0.069). Significantly more topiramate-treated subjects compared with placebo-treated subjects reported an improvement on the Patient Global Improvement scale[121] (p = 0.004). Withdrawal rates from the study were 34% for the topiramate-treated group compared with 47% for the placebo-treated group. One subject discontinued treatment with topiramate because of nausea. The most common adverse effects associated with topiramate were fatigue, influenza-like symptoms and paraesthesias.

The second study was a 10-week trial in 60 subjects who had had BN for at least 12 months.[116] Thirty subjects received topiramate (titrated to 250 mg/day by the sixth week, with the dosage then held constant) and 30 received placebo. Topiramate was associated with significant decreases in the frequency of binging and/or purging (defined as a >50% reduction; 37% for topiramate and 3% for placebo), bodyweight (difference in weight loss between the two groups = 3.8 kg) and all scales on the SF-36 Health Survey (SF-36)[122] [all p < 0.001]. Five subjects (17%) receiving topiramate and six subjects (20%) receiving placebo were considered to have dropped out of the study. All subjects tolerated topiramate well.

In the first controlled study in BED, 61 subjects with DSM-IV-defined BED and obesity (defined as a body mass index [BMI] >30 kg/m^2) received topiramate (n = 30) or placebo (n = 31) for 14 weeks.[85] Topiramate was significantly superior to placebo in reducing the frequency of binge episodes, the global severity of illness, obsessive-compulsive features of binge-eating symptoms, as assessed by the Yale-Brown Obsessive Compulsive Scale modified for binge eating (YBOCS-BE),[85,123] bodyweight and BMI. Topiramate-treated subjects exhibited a 94% reduction in the frequency of binge episodes and a mean weight loss of 5.9 kg, whereas placebo-treated subjects had a 46% reduction in the frequency of binge episodes and a mean weight loss of 1.2 kg. However, the withdrawal rate was high: 14 subjects (47%) receiving topiramate and 12 subjects (39%) receiving placebo did not complete the trial. Six patients in the topiramate group discontinued treatment because of adverse events (headache [n = 3], paraesthesias [n = 2] and amenorrhoea [n = 1]). The most common adverse effects associated with topiramate were paraesthesias, dry mouth, headache, dyspepsia, dizziness, taste perversion and confusion.

The patients who completed that study (n = 35) were offered the opportunity to participate in a 42-week open-label extension trial of topiramate.[124] Forty-four patients (31 who received topiramate in the open-label trial plus 13 who received topiramate in the double-blind study only) received at least one dose of topiramate; 43 patients provided outcome measures at a median final dosage of 250 mg/day. The mean weekly frequency of binge episodes declined significantly from baseline to final visit for all 43 patients (–3.2; p < 0.001), for the 15 patients who received

topiramate during the controlled and open-label studies (–4.0; $p < 0.001$) and for the 15 patients who received topiramate only during the open-label trial (–2.5; $p = 0.044$). There was also a significant reduction in bodyweight in all patients. However, 21 of 31 patients (68%) who entered the extension trial did not complete the 42 weeks of open-label treatment. Eight patients in the topiramate group discontinued treatment because of adverse events. The most common adverse events associated with topiramate were paraesthesias, dry mouth, headache, taste perversion, cognitive problems and dizziness.

The second controlled study of BED was a multicentre trial in which 407 subjects with BED and three or more binge-eating days/week, a BMI of between 30 and 52 kg/m^2 and no current psychiatric disorders or substance abuse were randomized to receive topiramate or placebo for 16 weeks.[86] Thirteen subjects did not meet the study's inclusion criteria, resulting in 195 topiramate- and 199 placebo-treated subjects who were evaluated for efficacy. Compared with placebo, topiramate significantly reduced binge-eating days/week (mean ± SD -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 vs 0.2 ± 3.2 kg) and BMI (-1.6 ± 1.8 vs 0.1 ± 1.2 kg/m^2) [all $p < 0.001$]. Topiramate also significantly decreased obsession, compulsion and total scores on the YBOCS-BE; overall, motor and nonplanning impulsiveness scores of the Barratt Impulsiveness Scale, Version II;[125] cognitive restraint, disinhibition and hunger subscores of the Three Factor Eating Questionnaire (TFEQ);[126] and overall, social and family life disability scores of the Sheehan Disability Scale.[127] Significantly more topiramate-treated subjects (58%) achieved remission compared with placebo-treated subjects (29%; $p < 0.001$). Discontinuation rates were 30% in each group, with adverse events being the most common reason for discontinuation of topiramate (16% vs 8% in the placebo-treated group). The most common adverse events resulting in discontinuation of topiramate were difficulty with memory NOS (3% for topiramate vs 1% for placebo) and depression (2% for topiramate vs 1.5% for placebo). Treatment-emergent adverse events that occurred significantly more often with topiramate than placebo were paraesthesias, upper respiratory tract infection, taste perversion, difficulty with concentration/attention and difficulty with memory NOS.

The third controlled study of topiramate in the treatment of BED was another multicentre trial in which 73 subjects with BED and obesity (defined as a BMI ≥30 kg/m^2) were randomized to 19 sessions of CBT in conjunction with topiramate ($n = 37$) or placebo ($n = 36$) for 21 weeks.[117] Compared with subjects receiving placebo, subjects receiving topiramate showed a significantly greater rate of reduction in weight (the primary outcome measure) over the course of treatment ($p < 0.001$). Subjects taking topiramate also exhibited clinically significant weight loss (–6.8 kg) compared with those taking placebo (–0.9 kg). Rates of reduction in the frequency of binge eating, Binge Eating Scale[128] scores and Beck Depression Inventory (BDI)[129] scores did not differ between the two groups during treatment, but a greater number of subjects in the topiramate group (31 of 37) attained remission of binge eating compared with those in the placebo group (22 of 36; $p = 0.03$). No difference in completion rates was seen between the two groups, although one subject receiving topiramate withdrew from the study because of an adverse effect. Paraesthesias and taste perversion were more frequent with topiramate, whereas insomnia was more frequent with placebo ($p < 0.05$).

Consistent with these controlled studies, there are a number of open-label reports in the literature of topiramate reducing binge eating, purging and/or overweight in patients with BN or BED, including those with treatment-resistant conditions, those with co-morbid depressive and bipolar disorders, and those receiving the drug as monotherapy or in combination with antidepressants and/or mood stabilizers.[107,130-135] These include reports of topiramate successfully reducing binge eating and weight loss difficulties after adjustable gastric banding or gastric bypass surgery.[136,137] In addition, there are reports of topiramate reducing binge eating in patients with epilepsy, including in one woman with BN[138]

and in six patients with BED and traumatic brain injury.[139] In the woman with BN, her BN antedated her epilepsy and had not responded to 5 years of treatment with phenytoin, which had been effective in preventing her seizures.[138]

There are also reports of topiramate successfully reducing night-time eating in patients with NES[140,141] and reducing nocturnal eating episodes in patients with SRED.[140,142,143] Improvements in weight and sleep were also described. One of these reports was a retrospective chart review of 30 patients with SRED who were treated with topiramate in a sleep disorders clinic.[142] Of the 25 patients with at least one post-baseline follow-up appointment, 17 (68%) were considered topiramate responders, receiving a Clinical Global Impression (CGI)-Improvement[121] rating of 'much improved' or 'very much improved'. Seven patients (28%) lost >10% of their baseline bodyweight. The mean (±SD) dose of topiramate was 135 ± 62 mg (range 25–300 mg) over a mean period of 11.6 ± 11.4 months (range 1–42 months). Seven of the 17 patients who were classed as topiramate responders (41%) had discontinued topiramate after a mean of 12.4 months.

There are only two case reports of therapeutic topiramate use in AN, with mixed results.[144,145] In one report, topiramate significantly improved the concurrent AN of a patient with bipolar disorder.[144] In the other report, topiramate possibly 'triggered' a recurrent episode of AN in a woman with an extensive psychiatric history who was being treated with the drug for epilepsy.[145] There are also isolated reports regarding the abuse of topiramate by patients with eating disorders in order to lose weight.[146,147]

4.2 Zonisamide

Zonisamide is a broad-spectrum AED that is approved for the treatment of epilepsy in adults. Zonisamide is associated with anorexia, weight loss and possible therapeutic effects in obesity.[148] The multiple pharmacodynamic actions of zonisamide include antagonism of sodium and calcium channels, effects on serotonin, dopamine and acetylcholine metabolism, and neuroprotective properties.[81]

We found one open-label study[149] and one randomized, placebo-controlled study[87] in the literature of zonisamide in BED. In the open-label study, 15 outpatients with BED and obesity (mean ± SD BMI = 40.0 ± 6.8 kg/m^2) received flexible-dose zonisamide (100–600 mg/day) for up to 12 weeks.[149] Seven patients discontinued zonisamide prematurely because of an inadequate response (n = 1), protocol nonadherence (n = 2) and adverse events (n = 4). Significant decreases were found in the frequency of binge-eating episodes, the frequency of binge days, BMI, bodyweight, and scores on the CGI-Severity (CGI-S),[121] YBOCS-BE total and TFEQ hunger and disinhibition scales.

In the controlled study, 60 outpatients with DSM-IV-defined BED and obesity (BMI >30 kg/m^2) received flexible-dose zonisamide (100–600 mg/day; n = 30) or placebo (n = 30) for 16 weeks.[87] Compared with placebo, zonisamide was associated with a significantly greater rate of reduction in the frequency of binge-eating episodes ($p = 0.021$), bodyweight ($p < 0.0001$), BMI ($p = 0.0001$) and scores on the CGI-S ($p < 0.0001$), YBOCS-BE ($p < 0.0001$) and TFEQ disinhibition ($p < 0.0001$) scales. The mean (±SD) daily dose of zonisamide at endpoint evaluation was 436 ± 159 mg/day. Plasma leptin levels did not change significantly with weight loss. In contrast, plasma ghrelin levels (which are thought to be decreased in obesity and BED) increased with zonisamide, but decreased with placebo ($p = 0.0001$).

However, the attrition rate was high: 18 patients (60%) receiving zonisamide and 12 patients (40%) receiving placebo did not complete the 16-week treatment period.[87] Twelve patients (eight receiving zonisamide and four receiving placebo) discontinued treatment because of adverse events. The most common reasons for discontinuing zonisamide were cognitive complaints (n = 2), psychological complaints (n = 2) and bone fracture (n = 2). The most common adverse effects associated with zonisamide were a dry mouth, somnolence, headache, nausea, nervousness and taste perversion.

4.3 Other Agents

There is a report in the literature of two patients with BN whose co-occurring self-mutilating behaviour responded to oxcarbazepine, a keto analogue of carbamazepine.[150] However, the patient whose eating disorder was not in remission when oxcarbazepine was added continued to purge by vomiting. We also found several reports describing a small subset of patients receiving levetiracetam for epilepsy who developed substantial, sometimes clinically significant, weight loss requiring drug discontinuation.[151,152] The weight loss was sometimes accompanied by a 'decrease in pleasure with food'.[152] One patient was reported to develop pica.[151]

No reports of other second-generation AEDs, including felbamate, gabapentin, lamotrigine, levetiracetam, pregabalin, tiagabine or vigabatrin, in patients with eating disorders were located. This is despite the fact that felbamate is associated with anorexia and weight loss (and could thus be of possible benefit in the treatment of BED); lamotrigine is approved for use in bipolar disorder, with preliminary evidence for its effectiveness in obesity[153] and borderline personality disorder[154] (thus being of possible use in the treatment of BN or BED); and gabapentin and pregabalin are associated with weight gain and are effective in the treatment of several anxiety disorders[67,73] (thus having possibly beneficial effects in AN).

5. Conclusion

The efficacy of AEDs in eating disorders based on controlled studies is summarized in table III. At the time of writing, the available data suggest that topiramate, and possibly zonisamide, may have beneficial effects in at least one of the eating disorders. Of these AEDs, topiramate appears to have the broadest spectrum of action as an anti-binge eating, anti-purging and weight loss agent, with efficacy (at least over the short term) in BN and BED. One small open-label study suggests that the anti-binging and weight loss effects of topiramate in BED may persist for up to 1 year; however, the attrition rate may be high, due, in part, to adverse events, including those involving cognitive impairment.[124] Examples are difficulty with memory, confusion and attention/concentration. Topiramate may also have beneficial effects in the treatment of NES and SRED; however, further controlled trials investigating the utility of topiramate in the treatment of these conditions are needed. Zonisamide may have efficacy in the treatment of BED associated with obesity; however, like topiramate, its usefulness may be limited by its adverse effect profile. Phenytoin may be effective in the treatment of some patients with compulsive binge eating and/or AN, particularly if co-morbid EEG abnormalities or epilepsy are present; however, available data are too mixed to enable definitive conclusions to be made. Carbamazepine and valproate may be effective in the treatment of patients with BN or AN when they are used to treat an associated psychiatric (e.g. bipolar) or neurological (e.g. seizure) disorder; otherwise, both agents, particularly valproate, are associated with weight gain. Moreover, the results of a controlled study of carbamazepine in BN, although small, were negative.[100] Valproate has been associated with

Table III. Summary of antiepileptic drugs (AEDs) studied in randomized, placebo-controlled trials of eating disorders

AED	Disorder			
	anorexia nervosa	bulimia nervosa	binge-eating disorder	binge/compulsive eating
Topiramate	NT	++	+++	NT
Zonisamide	NT	NT	+	NT
Carbamazepine	NT	†	NT	NT
Phenytoin	NT	NT	NT	±

NT = not tested; + = efficacy in at least one randomized, placebo-controlled trial; ++ = efficacy in ≥2 randomized, placebo-controlled trials; +++ = efficacy in ≥3 randomized, placebo-controlled trials; † = at least one negative randomized, placebo-controlled trial; ± = one positive and one negative randomized, placebo-controlled trial.

a worsening of binge eating and weight gain in patients with BED and co-morbid bipolar disorder.[107]

The potential mechanisms of action of AEDs in these conditions are unknown. One possibility is that topiramate or zonisamide may reduce binge eating in patients with BED and/or BN by decreasing appetite or enhancing satiety. By reducing binge eating (and possibly other forms of pathological overingestion, such as compulsive eating, grazing, subjective overeating, emotional eating, night eating and eating induced by craving), topiramate and zonisamide may cause beneficial weight loss.[85-87] In fact, topiramate has been shown to induce weight loss and decrease weight gain in rodent models of obesity in part by reducing caloric intake, although the mechanism by which it does this is unknown.[155-159] As noted earlier in section 2, topiramate and zonisamide each potentially affect neural systems that regulate eating behaviour. Both these AEDs affect glutamate transmission.[60,63,78,79] Furthermore, topiramate upregulates neuropeptide Y immunoreactivity in the hypothalamus[83] and zonisamide affects central serotonin and dopamine function.[81]

A second possibility is that topiramate and/or zonisamide reduce forms of eating motivated by the rewarding or hedonic properties of food (i.e. nonhomeostatic ingestion[26,160]), consistent with the concept that some eating disorders may represent food addictions.[161] Supporting this possibility are the findings that topiramate inhibits nicotine-induced increases in dopamine in rodent brain[162] and is efficacious in the treatment of alcohol, and possibly cocaine, dependence.[68-70]

A third possibility is that topiramate, and perhaps zonisamide, reduces disordered eating via a general effect on pathological impulsivity, rather than having specific effects on feeding behaviour or reward. Supporting this proposed mechanism of action are findings that eating disorders, particularly BN and BED, are characterized by features of pathological impulsivity[163,164] and that topiramate may decrease other pathological impulsive behaviours. Thus, in addition to decreasing alcohol and cocaine use in patients with substance use disorders,[68-70] topiramate has been shown to be superior to placebo in reducing aggression and/or anger in men and women with borderline personality disorder[111,112] and in women with major depression.[113] Therefore, topiramate, and possibly zonisamide, may benefit these conditions via an anti-impulsivity effect that spans diagnostic categories.

A fourth possibility is that certain AEDs may benefit disordered eating behaviour through direct metabolic actions. For patients with BED or BN, it may be that direct weight loss induced by topiramate or zonisamide leads to a secondary reduction in binge eating. Support for this proposed mechanism of action comes from rodent models of obesity showing that topiramate induces weight loss or prevents weight gain in part by stimulating energy expenditure,[155-159] as well as from other rodent models showing that topiramate has direct effects on glucose and lipid metabolism.[165-168] It has also been hypothesized that carbonic anhydrase inhibitors, including topiramate and zonisamide, induce weight loss by inhibiting carbonic anhydrase-mediated *de novo* lipogenesis.[169]

Yet another possible mechanism by which AEDs reduce symptoms of eating disorders is through their therapeutic effects in any co-morbid neurological or psychiatric condition that may be related aetiologically to the eating disorder. Although a clear link between eating disorders and epilepsy has not been demonstrated, the two may co-occur and symptoms of eating disorders have been reported to respond to the removal of epileptogenic foci.[22] In addition, as noted earlier, there may be a link between eating disorders and migraine[66] and perinatal evidence suggests that neurological factors may sometimes contribute to the aetiology of eating disorders.[22,38,39]

With respect to AEDs and their psychotropic properties, substantial research indicates a relationship between eating disorders and other psychiatric disorders, including mood, anxiety and substance use disorders. However, just as there are case reports suggesting that valproate has anti-binge-eating effects in BN when it effectively

treats a co-morbid bipolar disorder,[130-132,159,160] there are reports suggesting that the drug may make the binge-eating in BED worse, even when stabilizing an associated bipolar disorder.[107] Thus, the relationships between neurological function, psychiatric function, eating behaviour and weight regulation clearly need further investigation, as do the roles that AEDs may play in treating patients who have a dysfunction in several of these domains. Controlled trials of AEDs in patients with eating disorders and specific co-occurring neurological or psychiatric disorders are needed to evaluate the efficacy, tolerability and safety of these agents in explicit co-morbid conditions (i.e. valproate in AN with bipolar disorder or topiramate in BN or BED with migraine, substance abuse or borderline personality disorder).

In summary, the present review suggests that AEDs have an emerging role in the management of eating disorders, particularly the use of topiramate in the treatment of BED and possibly BN. Further studies are needed to clarify the patient subgroups in which specific agents may be most useful. In addition, future AEDs, particularly those with psychotropic benefits and those with effects on appetite and weight, should be considered as potential therapeutic agents for eating disorders.

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References

1. Hudson JI, Hiripi E, Pope Jr HG, et al. The prevalence and correlates of eating disorders in the National Comorbidity Survey Replication. Biol Psychiatry 2006; 61: 348-58
2. Yager J, Powers PS, editors. Clinical manual of eating disorders. Washington (DC): American Psychiatric Publishing, 2007
3. Winkelman JW. Sleep-related eating disorder and night eating syndrome: sleep disorders, eating disorders, or both? Sleep 2006; 29: 876-7
4. MacClancy J, Macbeth H, Henry J, et al. Consuming the inedible: cross-disciplinary approaches. Oxford: Berghahn, 2007
5. American Psychiatric Association. Treatment of patients with eating disorders. 3rd ed. Am J Psychiatry 2006; 163 Suppl. 7: 4-54
6. Berkman ND, Bulik CM, Brownley KA, et al. Management of eating disorders. Evid Rep Technol Assess (Full Rep) 2006; 135: 1-166
7. Kaplan AS. Anticonvulsant treatment of eating disorders. In: Garfinkel PE, Garner DM, editors. The role of drug treatments for eating disorders. New York: Brunner/Mazel, 1987: 96-123
8. Hudson JI, Pope Jr HG. The role of anticonvulsants in the treatment of bulimia. In: McElroy SL, Pope Jr HG, editors. Use of anticonvulsants in psychiatry. New York: Oxford University Press, 1988: 141-53
9. McElroy SL, Guerdjikova A, Keck Jr PE, et al. Antiepileptic drugs in obesity, psychotropic-induced weight gain, and eating disorders. In: McElroy SL, Keck Jr PE, Post RM, editors. Antiepileptic drugs to treat psychiatric disorders. New York: Informa Healthcare, 2008; 283-309

10. Bulik CM, Sullivan PF, Kendler KS. An empirical study of the classification of eating disorders. Am J Psychiatry 2000; 157: 886-95
11. Wilfley DE, Bishop ME, Wilson GT, et al. Classification of eating disorders: toward DSM-V. Int J Eat Disord 2007; 40 Suppl.: S123-9
12. World Health Organization. International statistical classification of diseases. 10th ed. Geneva: World Health Organization, 2007
13. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 4th ed. Washington, DC: American Psychiatric Association, 1994
14. Machado PP, Machado BC, Goncalves S, et al. The prevalence of eating disorders not otherwise specified. Int J Eat Disord 2007; 40: 212-7
15. Rockert W, Kaplan AS, Olmsted MP. Eating disorder not otherwise specified: the view from a tertiary care treatment center. Int J Eat Disord 2007; 40 Suppl.: S99-103
16. Papadioiykis V, Mimidis K. The rumination syndrome in adults: a review of the pathophysiology, diagnosis and treatment. J Postgrad Med 2007; 53: 203-6
17. O'Reardon JP, Peshek A, Allison KC. Night eating syndrome: diagnosis, epidemiology and management. CNS Drugs 2005; 19: 997-1008
18. Streigel-Moore RH, Franko DL, May A, et al. Should night eating syndrome be included in the DSM? Int J Eat Disord 2006; 39: 544-9
19. American Academy of Sleep Medicine. The international classification of sleep disorders: diagnostic and coding manual, 2nd ed. Westchester (IL): American Academy of Sleep Medicine, 2005
20. Winkelman JW. Clinical and polysomnographic features of sleep-related eating disorder. J Clin Psychiatry 1998; 59: 14-9
21. Plante DT, Winkelman JW. Parasomnias. Psychiatr Clin North Am. 2006; 29: 969-87
22. Uher R, Treasure J. Brain lesions and eating disorders. J Neurol Neurosurg Psychiatry 2005; 76: 852-7
23. Theisen FM, Linden A, König IR, et al. Spectrum of binge eating symptomatology in patients treated with clozapine and olanzapine. J Neural Transm 2003; 110: 111-21
24. Stunkard AJ. Eating patterns and obesity. Psychiatr Q 1959; 33: 284-95
25. Volkow ND, O'Brien CP. Issues for DSM-V: should obesity be included as a brain disorder? Am J Psychiatry 2007; 164: 708-10
26. Devlin MJ. Is there a place for obesity in DSM-V? Int J Eat Disord 2007; 40 Suppl.: S83-8
27. Gilmour J, Skuse D, Pembrey M. Hyperphagic short stature and Prader-Willi syndrome: a comparison of behavioral phenotypes, genotypes and indices of stress. Br J Psychiatry 2001; 179: 250-4
28. Arnulf I, Zeitzer JM, File J, et al. Kleine-Levin syndrome: a systematic review of 186 cases in the literature. Brain 2005; 128: 2763-76
29. Daousi C, Dunn AJ, Foy PM, et al. Endocrine and neuroanatomic features associated with weight gain and obesity in adult patients with hypothalamic damage. Am J Med 2005; 118: 45-50
30. Rose EA, Porcerelli JH, Neale AV. Pica: common but commonly missed. J Am Board Fam Pract 2000; 13: 353-8
31. Rand CS, Macgregor AM, Stunkard AJ. The night eating syndrome in the general population and among postoperative obesity surgery patients. Int J Eat Disord 1997; 22: 65-9
32. Winkelman JW, Herzog DB, Fava M. The prevalence of sleep-related eating disorder in psychiatric and nonpsychiatric populations. Psychol Med 1999; 29: 1461-6
33. Hay P. Quality of life and bulimic eating disorder behaviors: findings from a community based sample. Int J Eat Disord 2003; 33: 434-42
34. Grucza RA, Przybeck TR, Cloninger CR. Prevalence and correlates of binge eating disorder in a community sample. Comp Psychiatry 2007; 48: 124-31
35. Hudson JI, Lalonde JK, Berry JM, et al. Binge eating disorder as a distinct familial phenotype in obese individuals. Arch Gen Psychiatry 2006; 63: 313-9
36. Slof-Op't Landt MC, van Furth EF, Meulenbelt I, et al. Eating disorders: from twin studies to candidate genes and beyond. Twin Res Hum Genet 2005; 8: 467-82
37. Javaris KN, Laird NM, Reichborn-Kjennerud T, et al. Familiality and heritability of binge eating disorder: results of a case-control family study and a twin study. Int J Eating Disord 2008; 41: 174-9
38. Cnattingius S, Hultman CM, Dahl M, et al. Very preterm birth, birth trauma, and the risk of anorexia nervosa among girls. Arch Gen Psychiatry 1999; 56: 634-8
39. Favaro A, Tenconi E, Santonastaso P. Perinatal factors and the risk of developing anorexia nervosa and bulimia nervosa. Arch Gen Psychiatry 2006; 63: 82-8
40. National Institute for Clinical Excellence (NICE). Eating disorders: core interventions in the treatment and management of anorexia nervosa, bulimia nervosa and related eating disorders. Clinical guideline no 9. London: National Institute for Clinical Excellence, 2004 Jan
41. Mond JM, Jay PJ, Rodgers B, et al. Health service utilization for eating disorders: findings from a community-based study. Int J Eat Disord 2007; 40: 399-408
42. Hudson JI, Pope Jr HG, Carter WP. Pharmacologic therapy of bulimia nervosa. In: Goldstein E, editor. The management of eating disorders and obesity. Totowa (NJ): Humana Press, 1999: 19-32
43. Carter WP, Hudson JI, Lalonde JK, et al. Pharmacologic treatment of binge eating disorder. Int J Eat Disord 2003; 34 Suppl.: 74-88S
44. Appolinario JC, McElroy SL. Pharmacological approaches in the treatment of binge eating disorder. Curr Drug Targets 2004; 5: 301-7
45. Steffen KJ, Roerig JL, Mitchell JE, et al. Emerging drugs for eating disorder treatment. Expert Opin Emerg Drugs 2006; 11: 315-36
46. Shapiro JR, Berkman ND, Brownley KA, et al. Bulimia nervosa treatment: a systematic review of randomized controlled trials. Int J Eat Disord 2007; 40: 321-36
47. Brownley KA, Berkman ND, Sedway JA, et al. Binge eating disorder treatment: a systematic review of randomized controlled trials. Int J Eat Disord 2007; 40: 337-48
48. McElroy SL, Guerdjikova AI, O'Melia A, et al. Pharmacotherapy of the eating disorders. In: Agras WS, editor.

Oxford handbook of eating disorders. New York: Oxford University Press. In press

49. O'Reardon JP, Allison KC, Martino NS, et al. A randomized, placebo-controlled trial of sertraline in the treatment of night eating syndrome. Am J Psychiatry 2006; 163: 893-8
50. Horne RL, Ferguson JM, Pope Jr HG, et al. Treatment of bulimia with bupropion: a multicenter controlled trial. J Clin Psychiatry 1988; 49: 262-6
51. Walsh BT, Kaplan AS, Attia E, et al. Fluoxetine after weight restoration in anorexia nervosa: a randomized controlled trial [published errata appear in JAMA 2006; 296: 934 and JAMA 2007; 298: 2008]. JAMA 2006; 295: 2605-12
52. Bulik CM, Berkman ND, Brownley KA, et al. Anorexia nervosa treatment: a systematic review of randomized controlled trials. Int J Eat Disord 2007; 40: 310-20
53. Appolinario JC, Bacaltchuk J, Sichieri R, et al. A randomized, double-blind, placebo-controlled study of sibutramine in the treatment of binge-eating disorder. Arch Gen Psychiatry 2003; 60: 1109-16
54. Milano W, Petrella C, Casella A, et al. Use of sibutramine, an inhibitor of the reuptake of serotonin and noradrenalin, in the treatment of binge eating disorder: a placebo-controlled study. Adv Ther 2005; 22: 25-31
55. Wilfley DE, Crow SJ, Hudson JI, et al. Efficacy of sibutramine for the treatment of binge eating disorder: a randomized multicenter placebo-controlled double-blind study. Am J Psychiatry 2008; 165: 51-8
56. Faris PL, Kim SW, Meller WH, et al. Effect of decreasing afferent vagal activity with ondansetron on symptoms of bulimia nervosa: a randomized, double-blind trial. Lancet 2000; 355: 792-7
57. McElroy SL, Guerdjikova A, Kotwal R, et al. Atomoxetine in the treatment of binge-eating disorder: a randomized placebo-controlled trial. J Clin Psychiatry 2007; 68: 390-8
58. Provini F, Albani F, Vetrugno R, et al. A pilot double-blind placebo-controlled trial of low-dose pramipexole in sleep-related eating disorder. Eur J Neurol 2005; 12: 432-6
59. Bissada H, Tasca GA, Barber AM, et al. Olanzapine in the treatment of low body weight and obsessional thinking in women with anorexia nervosa: a randomized, double-blind, placebo-controlled trial. Am J Psychiatry 2008; 165: 1281-8
60. Rogawski MA, Löscher W. The neurobiology of antiepileptic drugs. Nat Rev Neurosci 2004; 5: 553-64
61. Rogawski MA, Löscher W. The neurobiology of antiepileptic drugs for the treatment of nonepileptic conditions. Nat Med 2004; 10: 685-92
62. Johannessen Landmark C. Antiepileptic drugs in nonepilepsy disorders: relations between mechanisms of action and clinical efficacy. CNS Drugs 2008; 22: 27-47
63. White HS, Smith MD, Wilcox KS. Mechanisms of action of antiepileptic drugs. Int Rev Neurobiol 2007; 81: 85-110
64. McElroy SL, Keck Jr PE, Post RM, editors. Antiepileptic drugs to treat psychiatric disorders. New York: Informa Healthcare, 2008
65. McElroy SL, Kotwal R, Keck Jr PE, et al. Comorbidity of bipolar and eating disorders: distinct or related disorders with shared dysregulations? J Affect Disord 2005; 86: 107-27
66. Brewerton TD, George MS. Is migraine related to the eating disorders? Int J Eat Disord 1993; 14: 75-9
67. Mula M, Pini S, Cassano GB. The role of anticonvulsant drugs in anxiety disorders: a critical review of the evidence. J Clin Psychopharmacol 2007; 27: 263-72
68. Johnson BA, Ait-Daoud N, Bowden CL, et al. Oral topiramate for treatment of alcohol dependence: a randomized controlled trial. Lancet 2003; 361: 1677-85
69. Johnson BA, Rosenthal N, Capece J, et al. Topiramate for treating alcohol dependence: a randomized controlled trial. JAMA 2007; 298: 1641-51
70. Kampman KM, Pettinati H, Lynch KG, et al. A pilot trial of topiramate for the treatment of cocaine dependence. Drug Alcohol Depend 2004; 75: 233-40
71. Polycarpon A, Papanikolaou P, Ioannidis JP, et al. Anticonvulsants for alcohol withdrawal. Cochrane Database Syst Rev 2005; (3): CD005064
72. Zanarini M. Antiepileptic drugs in personality disorders. In: McElroy SL, Keck Jr PE, Post RM, editors. Antiepileptic drugs to treat psychiatric disorders. New York: Informa Healthcare, 2008: 343-8
73. Biton V. Effect of antiepileptic drugs on body weight: overview and clinical implications for the treatment of epilepsy. CNS Drugs 2003; 17: 781-91
74. Gao O, Horvath TL. Neuronal control of energy homeostasis. FEBS Lett 2008; 582: 132-41
75. Meister B. Neurotransmitters in key neurons of the hypothalamus that regulate feeding behavior and body weight. Physiol Behav 2007; 92: 263-71
76. Clifton PG, Kennett GA. Monoamine receptors in the regulation of feeding behaviour and energy balance. CNS Neurol Disord Drug Targets 2006; 5: 293-312
77. Uevama E, Morikawa Y, Yasuda T, et al. Attenuation of fasting-induced phosphorylation of mitogen-activated protein kinases (ERK/p38) in the mouse hypothalamus in response to refeeding. Neurosci Lett 2004; 371: 40-4
78. Okada M, Kawata Y, Mizuno K, et al. Interaction between Ca2+, K+, carbamazepine and zonisamide on hippocampal extracellular glutamate monitored with a microdialysis electrode. Br J Pharmacol 1998; 124: 1277-85
79. Ueda Y, Doi T, Tokumaru J, et al. Effect of zonisamide on molecular regulation of glutamate and GABA trasporter proteins during epileptogenesis in rats with hippocampal seizures. Brain Res Mol Brain Res 2003; 116: 1-6
80. Rosenberg G. The mechanisms of action of valproate in neuropsychiatric disorders: can we see the forest for the trees? Cell Mol Life Sci 2007; 64: 2090-103
81. Biton V. Clinical pharmacology and mechanism of action of zonisamide. Clin Neuropharmacol 2007; 30: 230-40
82. Brill J, Lee M, Zhao S, et al. Chronic valproic acid treatment triggers increased neuropeptide y expression and signaling in rat nucleus reticularis thalami. J Neurosci 2006; 26: 6813-22
83. Husum H, Van Kammen D, Termeer E, et al. Topiramate normalizes hippocampal NPY-LI in flinders sensitive line 'depressed' rats and upregulates NPY, galanin, and CRH-LI in the hypothalamus: implications for

mood-stabilizing and weight loss-inducing effects. Neuropsychopharmacol 2003; 28: 1292-9

84. Kwak SE, Kim JE, Kim DS, et al. Differential effects of vigabatrin and zonisamide on the neuropeptide Y system in the hippocampus of seizure prone gerbil. Neuropeptides 2005; 39: 507-13
85. McElroy SL, Arnold LM, Shapira NA, et al. Topiramate in the treatment of binge eating disorder associated with obesity: a randomized, placebo-controlled trial [published erratum appears in Am J Psychiatry 2003; 160: 612]. Am J Psychiatry 2003; 160: 255-61
86. McElroy SL, Hudson JI, Capece JA, et al. Topiramate for the treatment of binge eating disorder associated with obesity: a placebo-controlled study. Biol Psychiatry 2007; 61: 1039-48
87. McElroy SL, Kotwal R, Guerdjikova AI, et al. Zonisamide in the treatment of binge eating disorder with obesity: a randomized controlled trial. J Clin Psychiatry 2006; 67: 1897-906
88. Herridge PL, Pope Jr HG. Treatment of bulimia and rapid-cycling bipolar disorder with sodium valproate: a case report. J Clin Psychopharmacol 1985; 5: 229-30
89. McElroy SL, Keck Jr PE, Pope Jr HG. Sodium valproate: its use in primary psychiatric disorders. J Clin Psychopharmacol 1987; 7: 16-24
90. Rogawski MA. Diverse mechanisms of antiepileptic drugs in the development pipeline. Epilepsy Res 2006; 69: 273-94
91. Greenway FL, Dahms WT, Bray GA. Phenytoin as a treatment of obesity associated with compulsive eating. Curr Ther Res 1977; 21: 338-42
92. Wermuth BM, Davis KL, Hollister LE, et al. Phenytoin treatment of binge eating syndrome. Am J Psychiatry 1977; 134: 1249-53
93. Green RS, Rau JH. Treatment of compulsive eating disturbances with anticonvulsant medication. Am J Psychiatry 1974; 131: 428-32
94. Rau JH, Green RS. Compulsive eating: a neuropsychologic approach to certain eating disorders. Compr Psychiatry 1975; 16: 223-31
95. Weiss T, Levitz L. Diphenylhydantoin treatment of bulimia [letter]. Am J Psychiatry 1976; 133: 1093
96. Rau JH, Green RS. Soft neurological correlates of compulsive eaters. J Nerv Ment Dis 1978; 166: 435-7
97. Moore SL, Rakes SM. Binge eating: therapeutic response to diphenylhydantoin [case report]. J Clin Psychiatry 1982; 43: 385-6
98. Parsons JM, Sapse AT. Significance of hypercortisolism in anorexia nervosa. J Orthomolecular Psychiatry 1985; 14: 13-8
99. Szyper MS, Mann JD. Anorexia nervosa as an interictal symptom of partial complex seizures [abstract]. Neurology 1978; 28: 335
100. Kaplan AS, Garfinkel PE, Darby PL, et al. Carbamazepine in the treatment of bulimia. Am J Psychiatry 1983; 140: 1225-6
101. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 3rd ed. Washington, DC: American Psychiatric Association, 1980
102. Hudson JI, Pope Jr HG, Jonas JM, et al. Treatment of anorexia nervosa with antidepressants. J Clin Psychopharmacol 1985; 5: 17-23
103. Young CR, Mazure CM. Fulminant hepatic failure from acetaminophen in an anorexic patient treated with carbamazepine [letter]. J Clin Psychiatry 1998; 59: 622
104. Stewart JT. Treatment of coprophagia with carbamazepine [letter]. Am J Psychiatry 1995; 152: 295
105. Jawed SH, Krishnan VH, Prasher VP, et al. Worsening of pica as a symptom of depressive illness in a person with severe mental handicap. Br J Psychiatry 1993; 162: 835-7
106. Tachibana N, Sugita Y, Teshima Y, et al. A case of anorexia nervosa associated with epileptic seizures showing favorable responses to sodium valproate and clonazepam. Jpn J Psychiatry Neurol 1989; 43: 77-84
107. Shapira NA, Goldsmith TD, McElroy SL. Treatment of binge-eating disorder with topiramate: a clinical case series. J Clin Psychiatry 2000; 61: 368-72
108. Schenck CH, Hurwitz TD, O'Connor KA, et al. Additional categories of sleep-related eating disorders and the current status of treatment. Sleep 1993; 16: 457-66
109. Yeh SB, Schenck CH. Sleep-related eating disorder in a 29 year-old man: a case report with diagnostic polysomnographic findings. Acta Neurol Taiwan 2007; 16: 106-10
110. McElroy SL, Keck Jr PE. Topiramate. In: Schatzberg AF, Nemeroff CB, editors. The American Psychiatric Press textbook of psychopharmacology. 3rd ed. Washington, DC: American Psychiatric Press. In press
111. Nickel MK, Nickel C, Kaplan P, et al. Treatment of aggression with topiramate in male borderline patients: a double-blind, placebo controlled study. Biol Psychiatry 2005; 57: 495-9
112. Nickel MK, Nickel C, Mitterlehner FO, et al. Topiramate treatment of aggression in female borderline personality disorder patients: a double-blind placebo-controlled study. J Clin Psychiatry 2004; 65: 1515-9
113. Nickel C, Lahman C, Tritt K, et al. Topiramate in treatment of depressive and anger symptoms in female depressive patients: a randomized double-blind, placebo-controlled study. J Affect Disord 2005; 87: 243-52
114. Hoopes SP, Reimherr FW, Hedges DW, et al. Treatment of bulimia nervosa with topiramate in a randomized, double-blind, placebo-controlled trial, part 1: improvement in binge and purge measures. J Clin Psychiatry 2003; 64: 1335-41
115. Hedges DW, Reimherr FW, Hoopes SP, et al. Treatment of bulimia nervosa with topiramate in a randomized, double-blind, placebo-controlled trial, part 2: improvement in psychiatric measures. J Clin Psychiatry 2003; 64: 1449-54
116. Nickel C, Tritt K, Muehlbacher M, et al. Topiramate treatment in bulimia nervosa patients: a randomized, double-blind, placebo-controlled trial. Int J Eat Disord 2005; 38: 295-300
117. Claudino AM, de Oliveira IR, Appolinario JC, et al. Double-blind, randomized, placebo-controlled trial of topiramate plus cognitive-behavior therapy in binge-eating disorder. J Clin Psychiatry 2007; 68: 1324-32
118. Garner DM, Olmsted MP. Scoring the eating disorder inventory. Am J Psychiatry 1986; 143: 680-1

119. Garner DM, Garfinkel PE. The Eating Attitudes Test: an index of the symptoms of anorexia nervosa. Psychol Med 1979; 9: 273-9
120. Hamilton M. The assessment of anxiety states by rating. Br J Med Psychol 1959; 32: 50-5
121. Guy W. ECDEU assessment manual for psychopharmacology. Rockville (MD): US Department of Health, Education, and Welfare (ADM), 1976: 76-338
122. Ware Jr JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36): I. Conceptual framework and item selection. Med Care 1992; 30: 473-83
123. Goodman WK, Price LH, Rasmussen SA, et al. The Yale-Brown Obsessive Compulsive Scale: I. Development, use, and reliability. Arch Gen Psychiatry 1989; 46: 1006-11
124. McElroy SL, Shapira NA, Arnold LM, et al. Topiramate in the long-term treatment of binge-eating disorder associated with obesity [published erratum appears in J Clin Psychiatry 2005; 66: 138]. J Clin Psychiatry 2004; 65: 1463-9
125. Barrat E, Stanford M. Impulsiveness: impulsiveness in personality characteristics of the personality disordered client. New York (NY): Wiley, 1995
126. Stunkard A, Messick S. Eating inventory manual. San Antonio (TX): The Psychological Corporation, Harcourt Brace & Company, 1988
127. Sheehan DV, Harnett-Sheehan K, Raj BA. The measurement of disability. Int Clin Psychopharmacol 1996; 11 Suppl 3: 89-95
128. Gormally J, Black S, Daston S, et al. The assessment of binge eating severity among obese persons. Addict Behav 1982; 7: 47-55
129. Beck AT, Ward CH, Mendelson M, et al. An inventory for measuring depression. Arch Gen Psychiatry 1961; 4: 561-71
130. Appolinario JC, Coutinho W, Fontenelle L. Topiramate for binge-eating disorder. Am J Psychiatry 2001; 158: 967-8
131. Appolinario JC, Fontenelle LF, Papelbaum M, et al. Topiramate use in obese patients with binge eating disorder: an open study. Can J Psychiatry 2002; 47: 271-3
132. Schmidt do Prado-Lima PA, Bacaltchuck J. Topiramate in treatment-resistant depression and binge eating disorder. Bipolar Disord 2002; 4: 271-3
133. Felstrom A, Blackshaw S. Topiramate for bulimia nervosa with bipolar II disorders. Am J Psychiatry 2002; 159: 1246-7
134. Barbee JG. Topiramate in the treatment of severe bulimia nervosa with comorbid mood disorders: a case series. Int J Eat Disord 2003; 33: 456-72
135. De Bernardi C, Ferraris S, D'Innella P, et al. Topiramate for binge eating disorder. Prog Neuropsychopharmacol Biol Psychiatry 2005; 29: 339-41
136. Zilberstein B, Pajecki D, Garcia de Brito AC, et al. Topiramate after adjustable gastric banding in patients with binge eating and difficulty losing weight. Obes Surg 2004; 14: 802-5
137. Guerdjikova AI, Kotwal R, McElroy SL. Response of recurrent binge eating and weight gain to topiramate in patients with binge eating disorder after bariatric surgery. Obes Surg 2005; 15: 273-7
138. Knable M. Topiramate for bulimia nervosa in epilepsy. Am J Psychiatry 2001; 158: 322-3
139. Dolberg OT, Barkai G, Gross Y, et al. Differential effects of topiramate in patients with traumatic brain injury and obesity: a case series. Psychopharmacol (Berl) 2005; 179: 838-45
140. Winkelman JW. Treatment of nocturnal eating syndrome and sleep-related eating disorder with topiramate. Sleep Med 2003; 4: 243-6
141. Tucker P, Masters B, Nawar O. Topiramate in the treatment of comorbid night eating syndrome and PTSD: a case study. Eat Disord 2004; 12: 75-8
142. Winkelman JW. Efficacy and tolerability of open-label topiramate in the treatment of sleep-related eating disorder: a retrospective case series. J Clin Psychiatry 2006; 67: 1729-34
143. Martinez-Salio A, Soler-Algarra S, Calvo-Garcia I, et al. Nocturnal sleep-related eating disorder that responds to topiramate [in Spanish]. Rev Neurol 2007; 45: 276-9
144. Guille C, Sachs G. Clinical outcome of adjunctive topiramate treatment in a sample of refractory bipolar patients with comorbid conditions. Prog Neuropsychopharmacol Biol Psychiatry 2002; 26: 1035-9
145. Rosenow F, Knake S, Hebebrand J. Topiramate and anorexia nervosa. Am J Psychiatry 2002; 159: 2112-3
146. Colom F, Vieta E, Benabarre H, et al. Topiramate abuse in a bipolar patient with an eating disorder. J Clin Psychiatry 2001; 62: 475-6
147. Chung AM, Reed MD. Intentional topiramate ingestion in an adolescent female. Ann Pharmacother 2004; 38: 1439-42
148. Gadde KM, Franciscy DM, Wagner II HR, et al. Zonisamide for weight loss in obese adults: a randomized controlled trial. JAMA 2003; 289: 1820-5
149. McElroy SL, Kotwal R, Hudson JI, et al. Zonisamide in the treatment of binge eating disorder: an open-label, prospective trial. J Clin Psychiatry 2004; 65: 50-6
150. Cordas TA, Tavares H, Calderoni DM, et al. Oxcarbazepine for self-mutilating bulimic patients. Int J Neuropsychopharmacol 2006; 9: 769-71
151. Hadjikoutis S, Pickersgill TP, Smith PE. Drug points: weight loss associated with levetiracetam. BMJ 2003; 327: 905
152. Gelisse P, Juntas-Morales R, Genton P, et al. Dramatic weight loss with levetiracetam. Epilepsia 2008; 49: 308-15
153. Meredith CH. A single-center, double-blind, placebo-controlled evaluation of lamotrigine of obesity in adults. J Clin Psychiatry 2006; 67: 258-62
154. Tritt K, Nickel C, Lahmann C, et al. Lamotrigine treatment of aggression in female borderline-patients: a randomized, double-blind, placebo-controlled study. J Psychopharmacol 2005; 19: 287-91
155. York DA, Singer L, Thomas S, et al. Effect of topiramate on body weight and body composition of Osborne-mendel rats fed a high-fat diet: alterations in hormones, neuropeptide, and uncoupling-protein mRNAs. Nutrition 2000; 16: 967-75
156. Picard F, Deshaies Y, Lalonde J, et al. Topiramate reduces energy and fat gains in (Fa/?) and obese (fa/fa) Zucker rats. Obes Res 2000; 8: 656-63

157. Richard D, Ferland J, Lalonde J, et al. Influence of topiramate in the regulation of energy balance. Nutrition 2000; 16: 961-6

158. Richard D, Picard F, Lemieux C, et al. The effects of topiramate and sex hormones on energy balance of male and female rats. Int J Obes Relat Metab Disord 2002; 26: 344-53

159. Lalonde J, Samson P, Poulin S, et al. Additive effects of leptin and topiramate in reducing fat deposition in lean and obese ob/ob mice. Physiol Behav 2004; 80: 415-20

160. Batterham RL, Ffytche DH, Rosenthal JM, et al. PYY modulation of cortical and hypothalamic brain areas predicts feeding behaviour in humans. Nature 2007; 450: 106-9

161. Avena NM. Examining the addictive-like properties of binge eating using an animal model of sugar dependence. Exp Clin Psychopharmacol 2007; 15: 481-91

162. Schiffer WK, Gerasimov MR, Marsteller DA, et al. Topiramate selectively attenuates nicotine-induced increases in monoamine release. Synapse 2001; 42: 196-8

163. Nasser JA, Gluck ME, Geliebter A. Impulsivity and test meal intake in obese binge eating women. Appetite 2004; 43: 303-7

164. McElroy S, Kotwal R. Binge eating. In: Hollander E, Stein DJ, editors. Clinical manual of impulse-control disorders. Washington, DC: American Psychiatric Publishing, 2006: 115-48

165. Wilkes JJ, Nguyen MT, Bandyopadhyay GK, et al. Topiramate treatment causes skeletal muscle insulin sensitization and increased Acrp 30 secretion in high-fat-fed male Wistar rats. Am J Physiol Endocrinol Metab 2005; 289: E1015-22

166. Liang Y, Chen X, Osborne M, et al. Topiramate ameliorates hyperglycaemia and improves glucose-stimulated insulin release in ZDF rats and db/db mice. Diabetes Obes Metab 2005; 7: 360-9

167. Wilkes JJ, Nelson E, Osborne M, et al. Topiramate is an insulin-sensitizing compound in vivo with direct effects on adipocytes in female ZDF rats. Am J Physiol Endocrinol Metab 2005; 288: E617-24

168. Ha E, Yim SV, Jung KH, et al. Topiramate stimulates glucose transport through AMP-activated protein kinase-mediated pathway in L6 skeletal muscle cells. Pharmacogenomics J 2006; 6: 327-32

169. De Simone G, Supuran CT. Antiobesity carbonic anhydrase inhibitors. Curr Top Med Chem 2007; 7: 879-84

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