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Polaprezinc (Zinc–L-Carnosine Complex) as an Add-on Therapy for Binge Eating Disorder and Bulimia Nervosa, and the Possible Involvement of Zinc Deficiency in These Conditions

A Pilot Study

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Abstract:

Background: Zinc plays an important role in appetite regulation. L-Carnosine, an endogenous dipeptide, may also regulate eating behavior via its histaminergic and antilutamatergic properties. Polaprezinc (zinc–L-carnosine complex) is a medication for gastric ulcers. A small case series reported successful treatment of binge eating with add-on polaprezinc.

Methods: This was an open trial of add-on polaprezinc in patients with binge eating disorder (BED; n = 22) or bulimia nervosa (BN; n = 7) receiving antidepressants. A 4-week baseline period was followed by a 16-week polaprezinc treatment at 150 mg/d (containing 34 mg zinc and 116 mg L-carnosine) in addition to ongoing psychotropic medications. We also assessed their zinc status via a laboratory index and zinc deficiency–related symptoms.

Results: At the study end, both conditions showed a significant reduction in the 4-week frequency of combined objective and subjective binge eating episodes, the 4-week frequency of days when at least 1 such episode occurred (only in BED), several aspects of eating disorder psychopathology (rated by the Eating Disorder Examination–Questionnaire), and comorbid depressive symptoms (rated by the 16-item Quick Inventory of Depressive Symptomatology [Self-Report]). Serum copper/zinc ratio decreased from 1.4 to 1.1 on average in both conditions. All patients had multiple zinc deficiency–related symptoms at baseline that substantially improved after polaprezinc treatment. Overall, the effectiveness of polaprezinc was greater in BED patients than in BN patients, with minor adverse effects.

Conclusions: These findings offer preliminary evidence for the effectiveness of polaprezinc in treating BED and BN and suggest the involvement of zinc deficiency in these conditions.

Key Words: polaprezinc, zinc, carnosine, binge eating disorder, bulimia nervosa

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Psychopharmacologic treatment options for binge eating disorder (BED) and bulimia nervosa (BN) are limited to lisdexamfetamine and fluoxetine, respectively. Moreover, these treatments are only

approved in some countries.¹ Here we focus on 2 nutrients, zinc and L-carnosine, as potential therapies for these conditions. Zinc plays an important role in appetite regulation.² In rats, reduced food intake and a cyclic feeding pattern are indicative of zinc deficiency.² Individuals who binge eat also often show cyclic up-and-down appetite with episodes of either binge eating or almost no eating. This similarity with rat models led us to hypothesize that individuals who binge eat have a zinc deficiency. Zinc deficiency has been reported in BN patients^{3,4} but not in BED patients.

L-Carnosine is an endogenous dipeptide composed of β -alanine and L-histidine.⁵ The latter is a precursor of histamine. The central histaminergic system is implicated in the regulation of eating behavior.⁶ The administration of histamine, L-histidine, and L-carnosine has reduced food intake in certain animal studies.^{7,8} The central glutamatergic system also participates in food intake regulation, and increased glutamate neurotransmission has been associated with appetite enhancement.⁹ L-Carnosine can reduce the extracellular glutamate level in the brain and protect against its excitotoxicity.¹⁰

Polaprezinc is a zinc–L-carnosine complex that is prescribed in Japan for the treatment of gastric ulcers.¹¹ It is given at a daily dose of 150 mg that contains 34 mg zinc and 116 mg L-carnosine. Thus, a synergistic effect of zinc and L-carnosine on binge eating is anticipated. Previously, a small case series reported successful treatment of binge eating with add-on polaprezinc to ongoing antidepressant treatment.¹²

We conducted an open trial of polaprezinc in 29 patients with BED or BN to investigate (1) its effectiveness and safety, and (2) their zinc status via a laboratory index and zinc deficiency–related symptoms. As in the previous study, we recruited patients receiving antidepressants (regardless of the presence/absence of other concomitant psychotropic medications) and added polaprezinc to their regimen.

MATERIALS AND METHODS

Design

This was a prospective, open-label study with a 4-week baseline period followed by 16 weeks of adjunct polaprezinc (Zeria Pharmaceutical Co, Ltd, Tokyo, Japan) at 150 mg/d (divided into 2 doses) to the ongoing treatment regimen at the initial dose. Some patients were given polaprezinc at 75 mg/d (once per day) for 4 weeks, which was then increased to 150 mg/d for the remaining study period. Use of benzodiazepine receptor agonists as required was permitted. Furthermore, only minimal supportive psychotherapy was administered.

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Participants

We recruited outpatients attending Keieikai Yashio Hospital or Keieikai Yuai Clinic (both in Saitama, Japan) between March 2016 and July 2018. The inclusion criteria included the following: meeting the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)* criteria for BED or BN; treatment with antidepressants at a stable dose for a minimum of 8 weeks; and aged between 18 and 65 years. Exclusion criteria included the following: a history of a personality disorder that might interfere with assessment or adherence to study procedures; serious suicidal risk; clinically unstable medical illness; pregnancy, pregnancy plans, or lactating during the study period; receiving cognitive-behavioral or interpersonal therapy; and having received polaprezinc within the past 6 months.

The study was approved by the Ethics Committee of the Jikei University School of Medicine (Tokyo, Japan) and the Institutional Review Boards of Keieikai Yashio Hospital and Keieikai Yuai Clinic. All patients provided written informed consent after the study procedures were fully explained. The study was conducted in accordance with the Declaration of Helsinki and is registered in the Clinical Trials Registry of the University Hospital Medical Information Network (identifier: UMIN000021368).

Definition of Binge Eating

“Objective binge eating” is a form of binge eating defined by the *DSM-5* as eating of an unusually large amount of food in a discrete period with a sense of loss of control while doing so. Among BED and BN patients, “subjective binge eating” is also commonly experienced, where the patient experiences a loss of control during eating but the amount of food consumed is not large, although the patient views it as excessive.¹³ Because of its clinical significance, subjective binge eating has been included in the diagnostic criteria for BED and BN in the new *International Classification of Diseases, 11th Revision*.¹⁴ In addition to objective binge eating, we included subjective binge eating in the measurement of binge eating episodes.

Schedule of Assessments and Study Instruments

The patients were receiving antidepressants for their different psychiatric disorders for at least 8 weeks before study enrollment. At the initial visit (visit 1), interested patients were evaluated for study eligibility. Binge eating disorder or BN diagnosis was first assessed, followed by assessment for comorbid psychiatric diagnoses, both based on information obtained from the Mini-International Neuropsychiatric Interview for *DSM-IV*,¹⁵ additional unstructured interviews, chart reviews, and, if applicable, the Conners' Adult ADHD Diagnostic Interview for *DSM-IV*.¹⁶ Each diagnosis was finally made according to the *DSM-5* criteria. We made this choice because the Mini-International Neuropsychiatric Interview and Conners' Adult ADHD Diagnostic Interview for *DSM-5* were unavailable.

A total of 34 patients were tentatively eligible at this point. We then asked them to record the number of binge eating episodes on a take-home diary. A binge eating episode was defined as (1) eating a large amount of food in a discrete period (ie, within a 2-hour period) and (2) a sense of loss of control over eating during the episode (ie, a feeling that you cannot stop eating or control what or how much you are eating). An episode was considered completed when 30 minutes or more passed without the patient eating. Whether the amount of food was large was determined by the patient; that is, binge eating episodes included both objective and subjective binge eating. Finally, they underwent a physical examination and were interviewed for zinc deficiency-related symptoms, including hair loss, dermatitis, acne, nail fragility, dysgeusia,

stomatitis, glossitis, diarrhea, and dysphagia.¹⁷ We included dysphagia because it is often associated with iron deficiency, and because zinc participates in iron metabolism,¹⁷ it may also appear in zinc deficiency.

We observed the patients every 4 weeks during the 20-week study period (visits 1–2 during the baseline period; visits 2–6 during the adjunct polaprezinc period). At visit 2, we reassessed whether the patient met the BED or BN diagnostic criteria through clinical interviews and reviewing their diaries. In addition, we administered the Eating Disorder Examination–Questionnaire (EDE-Q)¹⁸ to confirm the BED or BN diagnosis and to rate the severity of the eating disorder psychopathology. Consequently, of the 34 tentatively eligible patients at visit 1, 2 were excluded based on an insufficient frequency of objective binge eating to satisfy criteria for BED or BN diagnosis. Other 3 patients withdrew consent before visit 2. The remaining 29 patients were formally enrolled and entered the adjunct polaprezinc period. During visit 2, the enrolled patients also completed the 16-item Quick Inventory of Depressive Symptomatology (Self-Report; QIDS-SR₁₆)¹⁹ to rate the severity of their depressive symptoms.

Polaprezinc treatment was begun after visit 2. At visit 2 and the following visits, we assessed the number of binge eating episodes and binge eating days (days when at least 1 binge eating episode occurred) since the previous visit through clinical interviews and reviewing the patients' diaries. We also assessed the EDE-Q and QIDS-SR₁₆ scores, body mass index (BMI) and weight, adverse events, and performed routine hematologic and biochemical tests, as well as assessments for serum levels of zinc, copper, iron, and ferritin. Blood samples were collected in the fasting state between 8 and 9 A.M. and assessed in a commercial laboratory (LSI Medience Corporation, Tokyo, Japan). At the final visit, we interviewed the patients on whether their zinc deficiency-related symptoms had improved, deteriorated, or were unchanged.

EDE-Q and QIDS-SR₁₆

The EDE-Q is a self-report measure that assesses attitudes, feelings, and behaviors related to eating and body image over the prior 28 days. Based on the EDE-Q, the baseline period and assessment interval were set at 4 weeks in the present study design. The EDE-Q provides a Global score and 4 subscale scores (Restraint, Eating Concern, Shape Concern, and Weight Concern). Each score ranges from 0 to 6, with higher scores indicating greater severity. The validity of EDE-Q for BED and BN has been previously reported.^{20,21}

The QIDS-SR₁₆ is a self-report measure of depressive symptoms over the prior 7 days. The score ranges from 0 to 27, with higher scores indicating more severe symptoms. For patients with a QIDS-SR₁₆ score of 11 or higher at baseline (indicating moderate or more severe depression), treatment response and remission for depression were defined as follows: response, a 50% or more reduction in the QIDS-SR₁₆ score from baseline at final visit; and remission, a QIDS-SR₁₆ score of 5 or less at 2 consecutive scheduled follow-up visits.

Outcome Measures

The primary outcome measure was the 4-week frequency of binge eating episodes. Secondary outcome measures were the 4-week frequency of binge eating days, EDE-Q and QIDS-SR₁₆ scores, BMI, weight, serum levels of zinc and copper, and the serum copper/zinc ratio. In addition, we calculated the baseline prevalence of zinc deficiency-related symptoms and traced their alterations with polaprezinc treatment. Safety parameters were assessed for detailed self-reports on adverse events and clinical laboratory data.

Statistical Analysis

We statistically evaluated changes in the outcome measures during the follow-up period through the Friedman test. We quantified the effect sizes for its test using eta squared (η^2).²² A *P* value of less than 0.05 was considered statistically significant. All analyses were performed using PROC FREQ in SAS software (version 9.1; Cary, NC).

RESULTS

All the 29 enrolled patients successfully completed the 16-week polaprezinc treatment. Table 1 shows their baseline characteristics, mean imipramine-equivalent daily antidepressant dose, and current psychiatric comorbidities, by the type of eating disorder. Most of the BED and BN patients had multiple comorbidities. Only 2 patients had no comorbidity (1 BED and 1 BN). The frequent comorbidities were a cluster of bipolar and related disorders that comprised bipolar I, bipolar II, cyclothymic, and other specified bipolar and related disorders (73% in BED, 86% in BN); panic disorder (77% in BED, 86% in BN); and social anxiety disorder (55% in BED, 57% in BN).

Table 2 presents the observed mean values for the outcome measures (shown only at baseline, weeks 8 and 16). For the BED patients, there was a highly significant and steady decrease in the 4-week frequency of binge eating episodes, the 4-week frequency of binge eating days, EDE-Q scores, and QIDS-SR₁₆ score over the course of treatment (*P* < 0.001 for all measures), except for the EDE-Q Restraint score (*P* = 0.361). Of the 22 BED patients, 19 (86%) had a 75% or more reduction in the 4-week frequency of binge eating episodes, and 5 (23%) achieved remission (no episodes) at week 16. Based on the QIDS-SR₁₆ scores, of the 19 BED patients who had a baseline QIDS-SR₁₆ score of 11 or higher, 8 (42%) responded to treatment for depression and none were remitted.

TABLE 1. Baseline Characteristics and Psychiatric Comorbidities of the 29 Patients, Classified by Type of Eating Disorder

Variable	BED (n = 22)	BN (n = 7)
Mean age (SD), y	37.6 (9.5)	31.0 (11.0)
Male/female ratio	5/17	3/4
Mean duration of illness (SD), y	7.9 (9.0)	9.9 (10.7)
Mean daily dose of antidepressants (SD), mg*	55.3 (46.6)	100.4 (128.5)
Comorbidity (current), n (%)		
Bipolar I disorder	2 (9)	—
Bipolar II disorder	7 (32)	4 (57)
Cyclothymic disorder	—	1 (14)
Other specified bipolar and related disorder	7 (32)	1 (14)
Major depressive disorder	2 (9)	—
Panic disorder	17 (77)	6 (86)
Social anxiety disorder	12 (55)	4 (57)
Generalized anxiety disorder	2 (9)	—
Posttraumatic stress disorder	1 (5)	1 (14)
Alcohol use disorder	3 (14)	—
Borderline personality disorder	6 (27)	3 (43)
ADHD	7 (32)	2 (29)

*Imipramine-equivalent dose.

ADHD, attention-deficit/hyperactivity disorder.

Among the BN patients, there was a significant and almost steady decrease in the 4-week frequency of binge eating episodes (*P* = 0.048), EDE-Q Eating Concern (*P* = 0.032) and Weight Concern (*P* = 0.044) scores, and QIDS-SR₁₆ score (*P* = 0.010); however, the 4-week frequency of binge eating days and the remaining EDE-Q scores did not improve. Of the 7 BN patients, 3 (43%) had a 75% or more reduction in the 4-week frequency of binge eating episodes and 1 (14%) achieved remission at week 16. For depression, of the 6 BN patients who had a baseline QIDS-SR₁₆ score of 11 or higher, 1 (17%) responded to treatment and was remitted.

There was no change in the BMI and weight among the BED and BN patients. Serum zinc levels increased significantly in the BED patients (*P* < 0.001) and numerically, but not significantly, in the BN patients (*P* = 0.243). Serum copper levels remained unchanged in both patient groups. Consequently, the serum copper/zinc ratio decreased significantly in the BED patients (*P* < 0.001) and numerically, but not significantly, in the BN patients (*P* = 0.108). Serum ferritin (in both patient groups) and iron (in BN patients) levels remained unchanged; serum iron levels in the BED patients fluctuated significantly (*P* = 0.036), but without a regular direction.

Table 3 presents 9 zinc deficiency-related symptoms observed in our patients. At baseline, all patients had 3 or more of the 9 symptoms (mean, 6.5). Notably, almost all patients had hair loss (91% in BED, 86% in BN) and dermatitis (95% in BED, 86% in BN). Only 1 patient (in BN) had neither hair loss nor dermatitis. Instead, the patient had acne, dysgeusia, stomatitis, glossitis, diarrhea, and dysphagia. Table 3 also shows the responses of these symptoms to the 16-week polaprezinc treatment; a substantial number of the symptoms improved in both patient groups, especially in BED patients, whereas none deteriorated.

The reported adverse events were drowsiness (n = 2), nausea (n = 2), dizziness (n = 1), constipation (n = 1), and stomachache (n = 1), and were all mild and transient without requiring treatment. For laboratory indices, 2 patients showed mild to moderate elevation of liver enzymes and thus were given ursodeoxycholic acid (UDCA). In the moderate case, aspartate aminotransferase, alanine aminotransferase, and γ -glutamyl transferase decreased from 82 to 49 U/L, 182 to 101 U/L, and 78 to 46 U/L, respectively, after 12 weeks on 300 mg/d of UDCA, whereas those enzyme levels changed little after 8 weeks on 150 mg/d of UDCA in the mild case. No significant changes were observed in the other laboratory parameters.

DISCUSSION

In this open-label study on BED and BN patients, adjunct polaprezinc treatment was associated with a significant reduction in the frequency of binge eating episodes, the frequency of binge eating days (only in BED patients), several aspects of eating disorder psychopathology (rated by EDE-Q), and depressive symptoms (rated by QIDS-SR₁₆) (Table 2). It should be noted that the “overeating with a sense of loss of control” measured in this study denoted the characteristic compulsive overeating observed in the BED and BN patients, and included both objective and subjective binge eating. Therefore, the recorded number of binge eating episodes was probably greater than those specified by *DSM-5*, which limits only to objective ones. For EDE-Q in the BED patients, only the Restraint subscale score did not show a significant change; however, unlike the other subscale scores, it was low at baseline, indicating it as a differential feature between BED and BN. For EDE-Q in the BN patients, only the Eating Concern and Weight Concern subscale scores showed a significant improvement. Changes in the QIDS-SR₁₆ score indicated that 42% of the BED patients and 17% of the BN patients who had moderate or more severe depression at baseline achieved a treatment

TABLE 2. Outcome Measures at Baseline and After Polaprezinc Treatment in the 29 Patients, Classified by Type of Eating Disorder

Outcome Measure	Baseline, Mean (SD)	Week 8, Mean (SD)	Week 16, Mean (SD)	<i>P</i> *	η^2 †
BED (n = 22)					
Binge eating episodes/4 wk‡	57.7 (48.5)	27.7 (24.1)	11.2 (19.7)	<0.001	0.742
Binge eating days/4 wk‡	21.2 (6.7)	15.4 (9.1)	6.4 (9.6)	<0.001	0.681
EDE-Q score					
Global	3.1 (1.0)	2.1 (1.1)	1.9 (1.2)	<0.001	0.375
Restraint	0.8 (1.0)	0.9 (1.0)	0.9 (1.1)	0.361	0.049
Eating concern	3.4 (1.6)	1.3 (1.0)	1.0 (0.9)	<0.001	0.574
Shape concern	4.2 (1.3)	3.1 (1.7)	3.0 (1.8)	<0.001	0.279
Weight concern	4.0 (1.4)	2.9 (1.6)	2.7 (1.7)	<0.001	0.255
QIDS-SR ₁₆ score	16.8 (5.4)	11.5 (4.7)	9.5 (6.0)	<0.001	0.483
BMI, kg/m ²	25.9 (5.2)	25.8 (5.3)	25.6 (5.2)	0.250	0.061
Weight, kg	68.2 (19.0)	68.2 (19.7)	67.6 (19.3)	0.250	0.061
Biochemical variables					
Zinc, µg/dL	90.6 (9.5)	114.6 (19.4)	108.3 (24.3)	<0.001	0.265
Copper, µg/dL	119.5 (32.8)	118.1 (39.9)	119.1 (35.5)	0.556	0.035
Copper/zinc ratio	1.3 (0.4)	1.1 (0.5)	1.2 (0.5)	<0.001	0.310
Ferritin, ng/mL	81.52 (79.62)	75.24 (73.95)	79.38 (93.85)	0.647	0.029
BN (n = 7)					
Binge eating episodes/4 wk‡	34.9 (19.4)	27.6 (26.6)	17.6 (17.7)	0.048	0.342
Binge eating days/4 wk‡	19.1 (6.6)	15.6 (9.4)	12.4 (11.0)	0.093	0.285
EDE-Q score					
Global	3.3 (0.9)	2.9 (1.3)	2.6 (1.4)	0.102	0.276
Restraint	1.6 (1.0)	2.5 (1.7)	2.0 (1.8)	0.516	0.116
Eating concern	4.2 (1.4)	2.9 (1.6)	2.5 (1.7)	0.032	0.378
Shape concern	3.8 (1.6)	3.3 (1.9)	3.1 (1.9)	0.508	0.118
Weight concern	3.5 (1.9)	3.0 (2.1)	2.5 (1.9)	0.044	0.349
QIDS-SR ₁₆ score	17.6 (4.8)	11.7 (5.1)	12.6 (7.2)	0.010	0.475
BMI, kg/m ²	21.4 (2.7)	21.3 (2.8)	20.8 (3.0)	0.167	0.231
Weight, kg	60.0 (10.2)	59.8 (10.3)	58.3 (9.5)	0.167	0.231
Biochemical variables					
Zinc, µg/dL	86.0 (10.6)	108.2 (47.1)	118.4 (42.8)	0.243	0.214
Copper, µg/dL	117.4 (40.5)	106.5 (33.0)	105.9 (23.1)	0.460	0.141
Copper/zinc ratio	1.4 (0.5)	1.2 (0.6)	1.0 (0.5)	0.108	0.296
Ferritin, ng/mL	109.16 (68.90)	86.25 (61.31)	111.60 (79.46)	0.714	0.083

For simplicity, only the results at baseline, weeks 8 and 16 are listed.

*Data on changes over the study period, including the data at nonlisted time points, were statistically analyzed by the Friedman test.

†Effect size was calculated as eta squared (η^2).

‡Includes both objective and subjective binge eating.

response for depression. These findings offer preliminary evidence for the effectiveness of polaprezinc in treating BED and BN.

The adverse events were minor, of which only elevated liver enzymes required treatment. Furthermore, results from a Japanese large clinical trial of polaprezinc for gastric ulcers have reported an incidence of elevated liver enzymes of 0.1% to less than 1% and few significant adverse events.²³

There were no significant changes in the BMI and weight in both patient groups, with only slight weight loss (−0.6 kg [0.9%] in BED, −1.7 kg [2.8%] in BN) (Table 2). Nevertheless, given the likely occurrence of weight gain as a natural course, weight maintenance is still a positive outcome in both BED and BN.²⁴ Moreover, the 5 BED patients who achieved binge eating remission lost more weight (−2.1%) compared with the nonremitted BED patients (−0.6%). This is consistent with findings from other studies that reported more weight loss in remitted BED patients.^{25,26} The baseline mean BMI of the BED patients was 25.9 kg/m², with a

minority being obese (4 of 22 [18%], as defined by a BMI of ≥ 30 kg/m²). Many BED patients have been reported to be of a healthy weight or overweight but not obese (obesity rate, ~40%).²⁷ Japanese BED patients are reported to have a mean BMI of approximately 24 kg/m² and an obesity rate of only 7.3%.^{28,29} Thus, the observed modest weight loss effect of polaprezinc indicates that it could be safely applied to the high proportion of nonobese BED patients. Unfortunately, we did not collect data on the purging episodes for the BN patients, and thus could not determine whether these behavioral changes affected the weight outcome.

Based on all the outcomes, the magnitude of the effectiveness of polaprezinc was smaller in the BN patients than in the BED patients. To explore the factors contributing to this difference, we analyzed baseline differences between the BED and BN patients regarding age, duration of illness, number of psychiatric comorbidities, frequency of binge eating episodes and days, EDE-Q and QIDS-SR₁₆ scores, and biochemical variables. The

TABLE 3. Baseline Prevalence of Zinc Deficiency–Related Symptoms and the Responses After 16-Week Polaprezinc Treatment in the 29 Patients, Classified by Type of Eating Disorder

Symptom	BED (n = 22)		BN (n = 7)	
	Baseline	Week 16	Baseline	Week 16
	n (%)	IM/UC ratio	n (%)	IM/UC ratio
Hair loss	20 (91)	17/3	6 (86)	3/3
Dermatitis	21 (95)	20/1	6 (86)	6/0
Acne	14 (64)	13/1	6 (86)	6/0
Nail fragility	15 (68)	13/2	5 (71)	3/2
Dysgeusia*	15 (68)	15/0	6 (86)	5/1
Stomatitis	13 (59)	12/1	5 (71)	3/2
Glossitis	12 (55)	12/0	4 (57)	2/2
Diarrhea	12 (55)	9/3	5 (71)	3/2
Dysphagia	17 (77)	16/1	6 (86)	4/2

At baseline, all patients exhibited ≥ 3 of the 9 symptoms (mean, 6.5).

No symptoms deteriorated.

*Only subjective, not including objective dysgeusia.

IM, improved; UC, unchanged.

results showed that only EDE-Q Restraint score was significantly high in the BN patients. Besides, there was no significant difference in the elevated serum zinc levels at study end between the BED and BN patients; thus, loss of polaprezinc in BN patients through vomiting was unlikely. Therefore, one reason for the effectiveness difference might be because of intense dietary restraint in the BN patients. The effectiveness difference is similar to that observed for other treatments in previous studies,³⁰ which is also noted in the *DSM-5*. It possibly results from severity differences between the 2 disorders. That is, BN has been characterized by more disordered eating behaviors (greater amount of food consumed by binge eating, fewer calories consumed when eating but not binge eating),³¹ more intense dietary restraint that increases the risk for binge eating,³² higher severities in clinical and psychopathological variables,^{33,34} poorer prognosis,^{24,33} and lower placebo response rate.^{35,36}

Notably, our patients had a high frequency of psychiatric comorbidity (Table 1). This could be attributed to the naturalistic design of the study, the setting of minimal inclusion and exclusion criteria to enhance generalization of the results, and the recruitment of patients already receiving treatment for different psychiatric disorders. Generally, both BED and BN patients have a reported broad range of psychiatric comorbidities, especially mood and anxiety disorders.²⁷ Regarding mood disorders, the presence of hypomanic symptoms has been associated with binge eating.^{37–39} Also among our patients, bipolar spectrum (ie, bipolar I, bipolar II, or subthreshold bipolar disorder) frequently co-occurred with a severe degree of depression (as expressed by a baseline mean QIDS-SR₁₆ score of 17). Despite their mood/emotional instability possibly causing binge eating, a limited number of the patients took mood stabilizers. Instead, antidepressants were used at a relatively low dose to prevent manic switch or activation syndrome. Reportedly, BED and BN patients with multiple comorbidities like ours may be less responsive to treatment than those without comorbidities.^{40,41}

We detected high rates of zinc deficiency–related symptoms in both BED and BN patients (Table 3). There is no sensitive biomarker of zinc status, and therefore, the most reliable diagnostic method for zinc deficiency is confirming its deficiency based on the clinical response to a zinc load.⁴² Baseline serum zinc level of our patients was relatively high (89.5 $\mu\text{g}/\text{dL}$ vs reference range

of 80–130 $\mu\text{g}/\text{dL}$, in the morning and fasting⁴³). However, we left our blood samples at room temperature from the morning of blood collection until the evening of measurement. Therefore, because erythrocytes contain approximately 10 times more zinc than serum, it is possible that microhemolysis elevated serum zinc levels by approximately 20%.⁴⁴ Zinc and copper antagonize each other's intestinal absorption, and the balance between them is more important than their actual levels in zinc deficiency diagnosis.⁴⁵ A previous study indicated that a serum copper/zinc ratio of 1.1 or greater might be an effective marker for the diagnosis of taste disorders derived from zinc deficiency (under the same measurement condition as the present study).⁴⁵ According to this value, 21 of our 29 patients (16 of 22 in BED, 5 of 7 in BN) were zinc deficient at baseline. However, upon polaprezinc addition, all patients (regardless of baseline serum copper/zinc ratio) showed high treatment response rates (50%–100%; mean, 87%) for their zinc deficiency–related symptoms, when the rate was calculated as the ratio of the number of improved symptoms to the total number of improved and unchanged symptoms. This suggests that zinc deficiency existed even in patients with a baseline serum copper/zinc ratio of less than 1.1. Overall, the decrease in serum copper/zinc ratio from 1.4 at baseline to 1.1 at the study end suggests an improvement in zinc deficiency. Incidentally, iron deficiency often coexists with zinc deficiency, and iron-deficiency symptoms partially overlap with those of zinc deficiency.¹⁷ Therefore, we hypothesized that some of our patients might have had an iron deficiency. We found 4 of all 29 patients to be iron deficient, defined as a serum ferritin level of less than 12 ng/mL at baseline.⁴⁶ Thus, to some extent, iron deficiency might have contributed to our patients' symptoms.

Zinc and L-carnosine have potentially common mechanisms of action against binge eating, for example, by modulating glutamate neurotransmission and reducing oxidative stress and inflammation. The glutamate system plays an important role in the regulation of food intake.⁹ Animal studies have shown that central injection of glutamate or its receptors agonists rapidly elicits a feeding response⁴⁷ and that centrally injected mGluR5 agonists stimulate feeding, whereas its receptor antagonists inhibit food intake.⁴⁸ Thus, this system could be a treatment target for binge eating. Indeed, glutamate-modulating agents (topiramate, memantine, and acamprostate) have offered promise against BED or BN.^{49–51}

Zinc binds with the glutamate *N*-methyl-D-aspartate receptor and serves as its inhibitory modulator.⁵² L-Carnosine exists in glial cells throughout the brain.³ L-Carnosine has been reported to reduce glutamate excitotoxicity by upregulating the glutamate transporter 1,¹⁰ the primary controller of extracellular glutamate levels located on astrocyte membranes. Oligodendrocytes release L-carnosine in a process mediated by their own glutamate receptor,⁵³ indicating that L-carnosine interacts with glutamate in neuron-to-glia communication. Thus, L-carnosine plays a putative role in glutamate modulation via glial cells.

Meanwhile, both zinc and L-carnosine have antioxidant and anti-inflammatory properties.^{54,55} Because oxidative stress and inflammation can induce glutamate excitotoxicity,^{56,57} zinc's and L-carnosine's ability in reducing these conditions may benefit binge eating. In addition, zinc is essential for the immune system as its deficiency results in multiple immunologic dysfunctions.⁵⁴ Recently, eating disorders have been linked to immunologic abnormalities, as shown by abnormal cytokine production⁵⁸ and a link with autoimmune disease in cohort studies.⁵⁹ Thus, balancing the immune function by zinc supplementation could lead to eating disorders alleviation.

Our patients' emotional improvement may reflect a positive psychological effect secondary to their binge eating improvement or might be directly because of polaprezinc as demonstrated by supporting evidence. Zinc deficiency induces depression, irritability, and mood lability,⁶⁰ with zinc supplementation improving these symptoms. L-Carnosine induces glial cells to secrete neurotrophins that activate neuronal cells,⁶¹ and can inhibit monoamine oxidase in the brain,⁶² indicating its potential for mood improvement. L-Carnosine also ameliorates amygdaloid-kindled seizures via its histaminergic action,⁶³ which could be beneficial for inhibiting trauma-related fear memory that occurs in binge eating patients. So far, L-carnosine has shown antidepressant-like activity in rats⁶⁴ and improved mood in healthy individuals,⁶⁵ and its therapeutic potential for depression has been proposed.⁶⁶ Finally, because glutamatergic hyperactivity, oxidative stress, and inflammation are implicated in mood disorders,^{57,67} the counteractive activity of zinc and L-carnosine may have a potential application against these disorders.

Our study has several limitations. First, because of its uncontrolled open-label design, our findings should be interpreted cautiously. The simple act of recording binges is a means of psychological accountability that could reduce binge frequency. Binge eating disorder is particularly associated with a substantial placebo response rate (38% in a pooled analysis, as defined by a $\geq 75\%$ reduction in binge eating episodes).³⁶ The higher proportion (86%) of our BED patients achieved a response, although we are unable to directly compare the 2 studies because of our inclusion of subjective binge eating. Second, the small sample size, relatively short treatment duration, and few obese BED patients limit our findings. Third, we did not have data on the food consumed during binge eating and the number of objective binge eating episodes. Fourth, our patients are not representative of the general patient population because of their relatively severe psychopathology requiring psychiatric treatment. Fifth, although no patients receiving polaprezinc dropped out and treatment-emergent adverse events were minimal and acceptable, the established doctor-patient relationship before study enrollment may have operated advantageously to the absence of dropouts. Sixth, the use of benzodiazepine receptor agonists as required and supportive psychotherapy could be confounding factors, although the frequency of medication use did not change significantly and psychotherapy was minimal during the study period. Seventh, we did not assess dysgeusia using the taste test but instead assessed it based on its awareness; therefore, its prevalence

(21 of 29 patients) may have been underestimated. Finally, treatment response rate for zinc deficiency-related symptoms did not correlate with a baseline zinc-deficient state determined by the serum copper/zinc ratio. Thus, there is still a possibility that the symptoms are nonspecific.

In summary, this open-label trial found add-on polaprezinc to be effective and well-tolerated in reducing the frequency of combined objective and subjective binge eating, some eating disorder psychopathology, and comorbid depressive symptoms in BED and BN patients. Despite its limitations, this is the first study to formally examine the effectiveness and safety of polaprezinc for BED and BN by focusing on its 2 components, that is, zinc for appetite regulation and L-carnosine for histaminergic and antiglutamatergic properties. In addition, it indicated the possible involvement of zinc deficiency in these conditions and the need for zinc supplementation for their improvement. Because of its benign adverse effect profile and low cost, polaprezinc merits further exploration as a novel therapy for BED and BN. Future studies should evaluate the effectiveness of polaprezinc as a monotherapy and the effectiveness of zinc and L-carnosine alone.

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AUTHOR DISCLOSURE INFORMATION

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