Continuing Weight-Loss Effect after Topiramate Discontinuation in Obese Persons with Schizophrenia: a Pilot Open-Label Study

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Abstract
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Introduction: Few studies have investigated the likelihood of weight maintenance in obese persons with schizophrenia after their initial successful weight loss. This pilot open-label study examined the efficacy of topiramate in weight loss and the trajectory of weight changes after topiramate discontinuation.
Methods: This study enrolled 10 obese persons with schizophrenia. A 4-month treatment phase was started, followed by a 12-month discontinuation phase. Body weight was measured as the primary outcome every month. Secondary outcomes included leptin levels, fasting glucose, lipid profiles, and insulin resistance index.

Results: After the 4-month addition of topiramate, participants lost 1.79 kg of their body weight (95 % CI = −3.03 to −0.56, p = 0.005). The maximum weight reduction was 4.32 kg, occurring when topiramate had been discontinued for 12 months (95 % CI = −6.41 to −2.24, p < 0.001).
Discussion: The continuing weight-loss effect after topiramate discontinuation might have resulted from topiramate's potential to improve leptin functioning. These findings demonstrate that topiramate's weight-loss effect could not only persist during its administration, but also continue to improve after its discontinuation.

Introduction
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Topiramate is an anticonvulsant approved for the treatment of epilepsy and migraine prophylaxis [1]. The proposed pharmacological mechanisms of topiramate include a decrement of neuronal excitation, an enhancement of γ-aminobutyric acid (GABA) activity at a non-benzodiazepine site on $GABA_A$ receptors, an increase in GABA-mediated chloride channels, a modulation of voltage-dependent sodium and calcium channels, a blockade of kainate/AMPA glutamate receptor, and an increase in the potassium conductance [2]. The efficacy of topiramate has been reported in several psychiatric conditions, such as psychotic disorders [3,4], bipolar disorder [3], and substance-related disorders [3,5]. Appetite suppression and weight loss are common adverse effects in persons treated with topiramate [1–3]. In this sense, the pursuit of whether topiramate is a potential weight-loss drug for overweight persons has been the focus of many investigations.

The prevalence of metabolic syndrome in persons with schizophrenia is as much as 2-fold higher than that in the general population [6,7]. Obesity, among the components of metabolic syndrome, has been clearly demonstrated to be the major driving force leading not only to insulin resistance but also to cardiovascular disease risk [8]. Attention has been paid to the efficacy of topiramate in the management of overweight persons with schizophrenia, and the preliminary data are promising both in the prevention of weight gain [9,10] and in weight reduction [11,12].
Nevertheless, in addition to the extent of weight loss that the weight-loss agents could bring about, clinicians are interested to know whether the improved body weight could be sustained, and how long these agents need to be taken. Few studies so far have explored the likelihood of these weight-loss drugs in the maintenance of weight loss. Most of all, it is unknown whether weight regain would occur after discontinuing these drugs. A previous study found that in

persons with schizophrenia receiving olanzapine therapy, the improved body weight could not be sustained after discontinuing sibutramine, an approved weight-loss drug [13]. Recently, another study addressing metformin discontinuation reported similar negative findings in non-diabetic patients with schizophrenia treated with clozapine [14]. Indubitably, the challenge to find an appropriate approach for maintenance of weight loss in schizophrenia remains.

So far there are no studies investigating whether and over how long a period weight loss could be sustained after topiramate discontinuation. Only one case report suggested weight rebound after topiramate cessation [15]. This pilot study aimed to evaluate the overall efficacy of topiramate for weight management in non-diabetic, overweight individuals with schizophrenia. The study investigating the effects of metformin discontinuation recorded body weight only 24 weeks after metformin discontinuation [14], rendering the trajectory of weight changes unclear. In our study the primary outcome was the monthly weight changes during topiramate addition and after topiramate discontinuation. The secondary outcome measures included fasting leptin, lipid profiles, insulin resistance index, and adverse effects. The null hypothesis of the study was that weight loss produced by topiramate could not be sustained after discontinuing topiramate intervention.

Methods
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Participants
From January 2011 to March 2012 a total of 10 individuals with schizophrenia were judged eligible. Participants were recruited from the long-stay ward of the Beitou Branch, Tri-Service General Hospital, National Defense Medical Center, a psychiatric teaching hospital in Taiwan. The Institutional Review Board for the Protection of Human Subjects at the Tri-Service General Hospital approved the protocol. All participants were informed about the aims and other details of the study, and gave written informed consent in accordance with the National Health and Medical Research Council guideline. They were free to withdraw their participation at any time.

All participants were older than 20 years of age with a body mass index (BMI) exceeding $27 \, kg/m^2$, were diagnosed with schizophrenia according to DSM-IV criteria, had been stable on current psychotropics for at least 6 months, and were non-diabetic and normotensive. Additionally, all participants were fully capable of comprehending the study's purpose, procedure, treatment, risk and possible benefits, alternative treatment, and their right to refuse to participate in this study.

Individuals were excluded if they had a history of another significant medical disorder (e.g., epilepsy); if they met criteria for substance-related disorders; if they had a history of suicidality (attempt or current ideation); if they were involved in a special diet or special physical exercise program for weight reduction; and/or if they had a history of exposure to topiramate, or were currently taking topiramate or other weight-loss drugs. Importantly, individuals who lost more than 5% of body weight within 3 months were excluded because these persons might be suitable for non-pharmacological interventions for their weight management.

Study design
An open-label, fixed-dose design was used. This pilot study consisted of 2 stages. The first stage was a 4-month treatment phase (M_0, M_1, M_2, M_3, and M_4), and the second stage was a 12-month follow-up phase (M_5, M_6, M_7 to M_{16}), during which topiramate was discontinued and body weight was investigated every month. To ensure tolerance to gastrointestinal adverse effects, such as nausea and vomiting, a 4-week titration schedule was used. An initial daily dose of 25 mg of topiramate was increased weekly, and if well-tolerated, increased to reach the target dose of 50 mg of topiramate twice a day. The participants were withdrawn if intolerable adverse effects occurred or if the dose of the psychotropic was changed. Tobacco use and alcohol consumption were not allowed.

The study was implemented in the chronic ward, and all participants stayed in the hospital for more than 6 months. The daily caloric intake was around 2 000 calories, and the ward menus were predesigned by a nutritionist. In our chronic ward, there was a daily routine of 30 min of moderate intensity physical activity. It has been suggested that compared with non-hospitalized patients or patients in acute care settings, chronically hospitalized patients had more consistent activities of daily living, more reliable adherence to medications, more similar diet content, and more limited access to their favorite foods or foods external to the hospital – all of which could eliminate confounders [16].

Assessment
Outcome measures included body weight, glucose, leptin, insulin, lipid profiles, and insulin resistance. Insulin resistance was calculated using the homeostasis model assessment insulin resistance (HOMA-IR: fasting glucose [mmol/L] × fasting insulin [mU/L]/22.5) [17]. Serum leptin levels were determined with a sensitive radioimmunoassay and were set into relationship to the BMI-adjusted reference range (log_{10}-scaled) of healthy men and women [18]. Venous blood samples were collected after an overnight fast, between 07.30 h and 09.00 h. Scales for safety included the Udvalg for Kliniske Undersogelser Side Effect Rating Scale [19] and the 17-item Hamilton Depression Rating Scale [20]. Laboratory measures and scales for safety were assessed at baseline, 4 months after topiramate administration (M_4), and 3 months after topiramate discontinuation (M_7). All participants underwent measurements of height and weight by a digital weighing scales with height rods. Height was measured to the nearest 0.1 cm (shoes and socks removed). Body weight was measured to the nearest 0.1 kg every month with the participant wearing only a standard T-shirt (double extra large). A trained nurse blinded to the study protocol completed these measurements.

Statistical analyses
All statistical analyses were conducted with the Statistical Package for the Social Science software for Windows (Chicago, IL). Paired sample *t*-tests were used to evaluate each continuous variable for pre- to post-treatment change. Given that body weight was measured repeatedly on the same individual across time, generalized estimating equations (GEE) were employed, and the first-order autoregressive working correlation structure was chosen. GEE could accommodate the correlation of repeated measurements, account for within-subject dependence effects, use all available data points, and be sensitive to patterns of change over time. In the GEE model body weight measured every

Table 1 Demographic and clinical characteristics in nondiabetic, overweight persons with schizophrenia.

Case	Age	Sex	Education[a]	Duration[a]	BW[a]	BMI[b]	MS[c]	Daily dose of medications	Dose[d]
1	63	M	12	47	77.0	29.7	yes	risperidone 6 mg, clotiapine 40 mg, benzhexol 4 mg, lorazepam 1 mg	840
2	58	M	8	28	89.6	30.3	yes	flupentixol 6 mg, benzhexol 5 mg, estazolam 2 mg	360
3	37	M	12	22	88.3	29.2	yes	quetiapine 800 mg, chlorpromazine 500 mg, lithium 900 mg, flurazepam 60 mg	1500
4	44	F	7	16	78.1	32.1	yes	clozapine 400 mg, lithium 1 200 mg, benzhexol 5 mg, lorazepam 2 mg	600
5	52	F	12	26	66.6	27.5	no	zotepine 150 mg, benzhexol 10 mg	300
6	50	F	6	10	83.2	33.3	no	clozapine 400 mg	600
7	46	F	12	29	69.1	27.7	yes	risperidone 6 mg, estazolam 2 mg, flurazepam 60 mg	600
8	54	F	9	34	92.7	39.1	no	chlorpromazine 100 mg, clonazepam 4 mg, flurazepam 30 mg	100
9	36	F	6	21	77.1	30.5	yes	quetiapine 600 mg, haloperidol 5 mg, benzhexol 5 mg, flurazepam 60 mg	1 050
10	51	F	9	34	92.7	36.7	yes	risperidone 4 mg, benzhexol 5 mg, clonazepam 4 mg	400
Mean	49.1 (8.6)	na	9.3 (2.5)	26.9 (10.5)	81.5 (9.4)	31.6 (3.8)	na	na	635 (407.6)

BW = body weight; BMI = body mass index; MS = metabolic syndrome

[a] Education and duration of illness were recorded in years, and body weight was measured in kilograms

[b] Body mass index was calculated as body weight divided by the square of the height (kilograms per square meter)

[c] The diagnosis of metabolic syndrome was made according to International Diabetes Federation Task Force Criteria

[d] The dose of each antipsychotic was converted to chlorpromazine equivalents

[e] The mean and the standard deviation of each variable were presented

month was the dependent variable. Independent variables that were entered in the final model included a time effect, the baseline body weight, and the dose of antipsychotic that were converted to chlorpromazine equivalents [21]. Other laboratory measures not identified as covariates were not included in the GEE model, such as age, sex, the dose of lithium and anticholinergic, and the diagnosis of metabolic syndrome according to International Diabetes Federation Task Force Criteria [22]. The time effect implied each month investigation, including 4-month treatment phase (M_0, M_1, M_2, M_3, and M_4) and 12-month follow-up phase (M_5, M_6, M_7 to M_{16}).

In addition to the first GEE model examining changes in body weight, a second GEE model was conducted to explore the effect of leptin on topiramate-associated weight loss. In the second GEE model, the dependent variable was the body weight, and the independent variables included a time effect, leptin levels, baseline body weight, and an interaction effect ([time] × [leptin]). The working correlation was first-order autoregression. Body weight changes in the second GEE model included only M_0, M_1, M_2, M_3, M_4, and M_7, as leptin levels were obtained only in these months.

Results

Monthly body weight changes

Overall, topiramate was well tolerated. There were no serious adverse events, and no one discontinued medication due to adverse effects. No subject developed suicidal ideation. Of the 10 persons recruited in this pilot study, one patient dropped out on

M_3 because of changes in the psychotropics. All participants' demographic and clinical characteristics are shown in ◉ **Table 1**. For controlling the dose of antipsychotic in the GEE model, the dose of each antipsychotic was converted to chlorpromazine equivalents [21]. ◉ **Table 2** and ◉ **Fig. 1** display the monthly weight changes from baseline. Participants significantly reduced their body weight from the second month (B = −1.04, S.E. = 0.43, 95 % CI = −1.89 to −0.19, p = 0.016), and after the 4-month addition of topiramate, the body weight differed significantly from baseline body weight (B = −1.79, S.E. = 0.63, 95 % CI = −3.03 to −0.56, p = 0.005). Topiramate was discontinued at the end of M_4, and importantly, participants sustained the reduced body weight throughout the 12-month follow-up period (from M_5 to M_{16}), with the exception of M_{10} (B = −1.17, S.E. = 0.69, 95 % CI = −2.51 to −0.17, p = 0.088) and M_{12} (B = −1.55, S.E. = 0.87, 95 % CI = −3.25 to 0.15, p = 0.074). Notably, the maximum weight loss occurred on M_{16} (B = −4.32, S.E. = 1.06, 95 % CI = −6.41 to −2.24, p < 0.001).

Secondary outcome measures

◉ **Fig. 2** illustrates the secondary outcome measures. As noted, high-density lipoprotein levels were significantly improved from 38.44 ± 7.23 mg/dL to 43.44 ± 7.18 mg/dL after 4-month treatment with topiramate (95 % CI = 1.762 to 8.238, t = 3.56, df = 8, p = 0.007). The improved high-density lipoprotein levels could be sustained after 3 months of topiramate discontinuation (45.11 ± 5.89 mg/dL, 95 % CI = 2.636 to 10.698, t = 3.814, df = 8, p = 0.005). The other secondary measures on M_4 and M_7, including fasting glucose, low-density lipoprotein, cholesterol, triglyceride, and HOMA-IR, did not significantly differ from those on baseline.

Table 2 Monthly weight changes in 10 persons with schizophrenia receiving 4-month adjunctive therapy of topiramate.[a]

Parameter	B	SE	95 % Wald CI		Wald χ^2	df	p
			Lower	Upper			
(Intercept)	13.63	2.12	9.47	17.79	41.17	1	<0.001
Month 0[b]	0						
Month 1	−0.89	0.52	−1.92	0.14	2.89	1	0.089
Month 2	−1.04	0.43	−1.89	−0.19	5.76	1	0.016
Month 3	−1.75	0.46	−2.65	−0.85	14.4	1	<0.001
Month 4	−1.79	0.63	−3.03	−0.56	8.07	1	0.005
Month 5	−1.74	0.51	−2.73	−0.74	11.67	1	0.001
Month 6	−1.35	0.54	−2.41	−0.3	6.37	1	0.012
Month 7	−1.38	0.7	−2.75	−0.01	3.89	1	0.049
Month 8	−1.45	0.65	−2.72	−0.18	5	1	0.025
Month 9	−1.74	0.76	−3.23	−0.26	5.27	1	0.022
Month 10	−1.17	0.69	−2.51	0.17	2.91	1	0.088
Month 11	−1.83	0.68	−3.16	−0.5	7.25	1	0.007
Month 12	−1.55	0.87	−3.25	0.15	3.2	1	0.074
Month 13	−1.96	1	−3.93	0.004	3.83	1	0.05
Month 14	−3.79	1.15	−6.04	−1.54	10.9	1	0.001
Month 15	−4.13	1.03	−6.12	−2.11	16.03	1	<0.001
Month 16	−4.32	1.06	−6.41	−2.24	16.51	1	<0.001
Baseline BW	0.87	0.02	0.82	0.91	1722.38	1	<0.001
Dose[c]	−0.001	0.0006	−0.002	2.6×10^{-5}	4.34	1	0.055
Age	−0.04	0.02	−0.08	0.003	3.3	1	0.069

CI = confidence interval; SE = standard error; BW = body weight

[a] General estimating equations, with controlling for baseline body weight, the dose of antipsychotic, and age, were conducted to evaluate monthly weight changes in ten participants with schizophrenia

[b] Month 0 is the beginning of topiramate treatment, and Month 5 is the first month after topiramate discontinuation

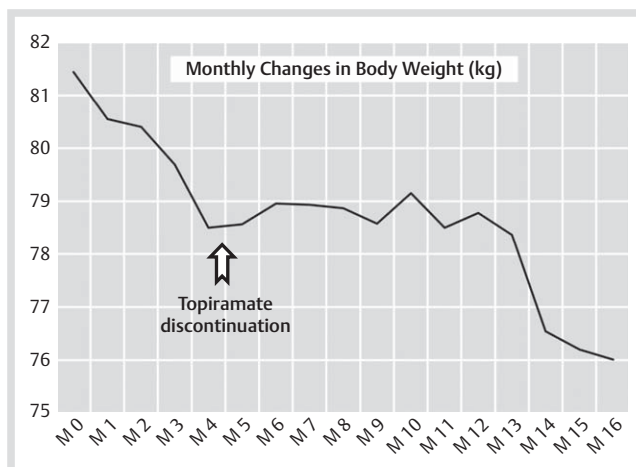[c] The dose of each antipsychotic was converted to chlorpromazine equivalents

Fig. 1 Monthly changes in body weight in obese persons with schizophrenia treated with topiramate. M 0 is the baseline body weight, and M 5 is the first month after topiramate discontinuation. After the 4-month addition of topiramate, the participants significantly lost 1.79 kg of their body weight (B = −1.79, S.E. = 0.63, 95 % CI = −3.03 to −0.56, p = 0.005). The reduced body weight was successfully sustained throughout the 12-month follow-up period, with the exception for M 10 (B = −1.17, S.E. = 0.69, 95 % CI = −2.51 to −0.17, p = 0.088) and M 12 (B = −1.55, S.E. = 0.87, 95 % CI = −3.25 to 0.15, p = 0.074). The maximum weight loss occurred on M 16 (B = −4.32, S.E. = 1.06, 95 % CI = −6.41 to −2.24, p < 0.001).
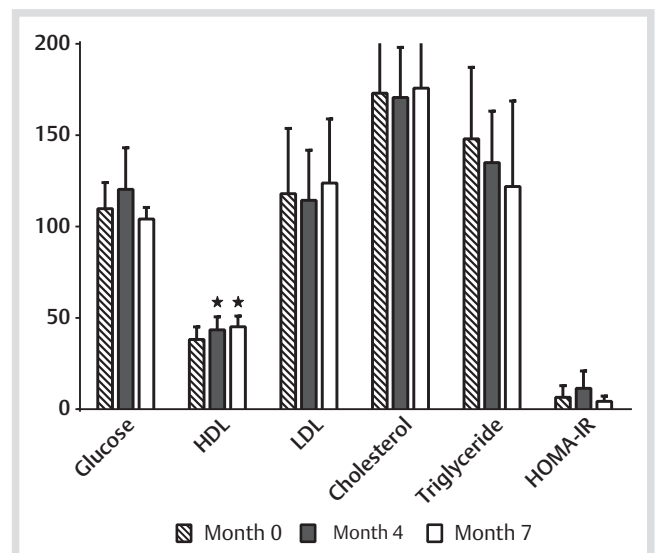

Fig. 2 Secondary outcomes were evaluated at baseline (Month 0), 4-month after topiramate administration (Month 4), and 3-month after topiramate discontinuation (Month 7). Compared with the baseline levels, only HDL levels at Month 4 (t = 3.56, df = 8, p = 0.007) and Month 7 (t = 3.814, df = 8, p = 0.005) reached statistical significance. Abbreviations: HDL = high-density lipoprotein; LDL = low-density lipoprotein; HOMA-IR = homeostasis model assessment insulin resistance.

Interaction between topiramate discontinuation and leptin levels

The second GEE model that evaluates the main effect of leptin on weight loss is shown in ⊙ **Table 3**. If the interaction effect ([time] × [leptin]) was not included in the GEE model, leptin itself could exert the main effect (B = 0.032, S.E. = 0.008, 95 % CI = 0.016 to 0.047, Wald χ^2 = 15.45, p < 0.001). Nevertheless, when the interaction effect was included, as noted in the ⊙ **Table 3**, the main effect of leptin did not reach statistical significance (B = 0.004, S.E. = 0.01, 95 % CI = −0.02 to 0.003, Wald χ^2 = 0.11, p < 0.739). The interaction effect was statistically

Table 3 General estimating equations assessing the effect of leptin on topiramate-associated weight loss in 10 persons with schizophrenia.[a]

Parameter	B	SE	95% Wald CI		Wald χ^2	df	p
			Lower	Upper			
(Intercept)	6.06	1.5	3.11	9	16.23	1	<0.001
Month 0[b]	0						
Month 1	−0.83	1.05	−2.89	1.21	0.64	1	0.425
Month 2	−1.91	0.63	−3.16	−0.67	9.12	1	0.003
Month 3	−3.19	0.62	−4.41	−1.97	26.12	1	<0.001
Month 4	−3.89	0.84	−5.55	−2.24	21.28	1	<0.001
Month 7	−2.07	0.63	−3.3	−0.85	10.97	1	0.001
Baseline BW	0.92	0.02	0.89	0.96	2 840.02	1	<0.001
Leptin	0.004	0.01	−0.02	0.03	0.11	1	0.739
Leptin * Month 0	0						
Leptin * Month 1	−0.002	0.02	−0.05	0.04	0.01	1	0.916
Leptin * Month 2	0.02	0.02	−0.02	0.05	1.03	1	0.31
Leptin * Month 3	0.04	0.01	0.01	0.07	8.43	1	0.004
Leptin * Month 4	0.06	0.02	0.02	0.09	9.08	1	0.003
Leptin * Month 7	0.18	0.03	0.13	0.24	45.37	1	<0.001

CI = confidence interval; SE = standard error; BW = body weight

[a]The general estimating equations included baseline body weight and leptin levels as covariates

[b]Month 0 is the beginning of topiramate treatment, and Month 7 is the 3-month follow-up after topiramate discontinuation
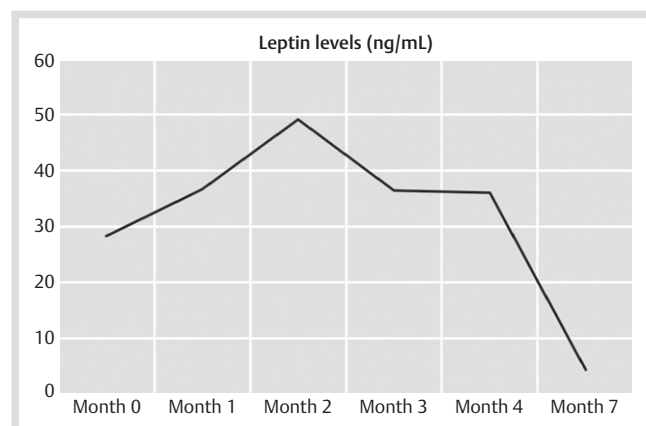

Fig. 3 Leptin levels were measured at baseline (Month 0), during the 4-month addition of topiramate (Month 1 to Month 4), and at 3-month follow-up after topiramate discontinuation (Month 7). Only at Month 2 ($t = -3.08$, df = 9, $p = 0.013$) and Month 7 ($t = 3.727$, df = 8, $p = 0.006$) did leptin levels significantly differ from those at baseline.

significant on M_3, M_4, and M_7. ○ **Fig. 3** depicts the trends of leptin levels on M_0, M_1, M_2, M_3, M_4, and M_7. Leptin levels on M_7 were significantly different from those on M_4 (95% CI = −53.467 to −9.889, $t = -3.535$, df = 8, $p = 0.01$) and M_0 (95% CI = −36.08 to −8.5, $t = -3.727$, df = 8, $p = 0.006$), but leptin levels on M_4 did not differ significantly from those on M_0 (95% CI = −3.161 to 21.94, $t = 1.725$, df = 8, $p = 0.007$). The Cohen's d effect size of the change in leptin levels from M_0 to M_7 is 1.85.

Discussion

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One of the major difficulties with treating obesity is that even after initial successful weight loss, most persons relapse into their previous unhealthy eating habits, thereby leading to weight regain. This study represents an attempt to explore, after the discontinuation of topiramate, how long the overweight persons with schizophrenia would maintain their body weight. After the

4-month addition of topiramate 100 mg/d, the participants significantly lost 1.79 kg of their body weight (95% CI = −3.03 to −0.56), and the weight-loss effect could be observed from the second month. This finding is somewhat similar to those derived from studies addressing the efficacy of topiramate in the management of overweight persons with schizophrenia [9–11]. However, an intriguing, and important, finding emerged – even though topiramate had been discontinued, the weight-loss effect persisted. The maximum weight reduction was 4.32 kg, occurring when topiramate had been discontinued for 12 months. These findings clearly suggest that weight-loss effect could not only persist during topiramate administration but also continued to improve despite topiramate discontinuation. The mechanisms of topiramate-associated weight loss have been discussed in detail elsewhere [2,11]; in this paper, therefore, we emphasize the possible mechanisms contributing to continuing weight-loss effect after topiramate discontinuation.

The first mechanism might be attributed to the improvement in leptin resistance. Leptin is the primary adipose hormone that provides adiposity signal to brain, which could result in reducing food intake and increasing energy expenditure [23,24]. Nevertheless, obese persons generally have markedly elevated, rather than decreased, leptin levels. The coexistence of obesity and an unusually high circulating concentration of leptin has been linked to leptin resistance [23–25], a condition similar to insulin resistance. Leptin resistance is an important component in the development and maintenance of obesity [23–25]. Additionally, leptin resistance and obesity may aggravate each other, causing a vicious cycle to develop. In this scenario, restoration of leptin functioning might be a therapeutic target to successfully cut off this vicious cycle. An animal study published recently reported the efficacy of topiramate in improving leptin functioning [26]. The involved molecular mechanisms are to enhance leptin signaling to the brain and increase hypothalamic expression of anorexigenic neuropeptides. Given leptin resistance as a consequence of defects in leptin signaling and impairment in the hypothalamic neural circuitry [23,25], topiramate theoretically improves leptin resistance, thereby leading to continued weight loss.

The second mechanism of topiramate responsible for continuing weight-loss effect might be related to the modulation of cortico-mesolimbic dopamine function [27]. Like alcoholism in which decreased dopamine D_2 receptor availability correlates with cue reactivity and craving [28], obese individuals are found to have decreased striatal D_2 receptor availability [29, 30]. The reduced basal activity of mesolimbic dopamine system might predispose them to attribute greater incentive salience to food cues, leaving them at more risk for compulsive eating. Several lines of evidence have supported the efficacy of topiramate in alcohol dependence [31, 32], and regulating cortico-mesolimbic dopamine function is one of the proposed mechanisms [27]. Therefore, after 4-month treatment with topiramate, the restored mesolimbic dopamine tone might theoretically abate the hyperreactivity of the mesolimbic system toward reward-predicting cues, thus adapting our patient's motivation to eat palatable food.

In our study, after 3 months of topiramate discontinuation, leptin levels were decreased by 84.5% (4.4 ± 6.7 ng/mL) from a baseline value of 43.3 ± 17 ng/mL. The second GEE model indicated that in addition to baseline body weight, the interaction effect of [Month 7] × [leptin] contributed to the main proportion of variance of weight changes. The significant interaction effect clear suggests that after topiramate was discontinued for 3 months, the remarked reduction in leptin levels significantly affects weight changes. A previous study has reported the association between leptin levels and the percentage of weight decrease in persons with epilepsy taking topiramate [2]. Namely, persons who reduced more body weight had a more significant reduction of leptin levels after topiramate administration. In this study, the effect size for change in leptin levels is large (1.85). Taking the above points together, continuing weight-loss effect after topiramate discontinuation may be associated with the improvement of leptin resistance, the restoration of mesolimbic dopamine function, and the remarked changes in leptin levels.

Data from previous studies addressing weight changes after discontinuation of weight-loss agents appear to stand in contrast to our findings. Either sibutramine [13] or metformin [14] demonstrates weight regain in obese persons with schizophrenia after their discontinuation. In this study, we hypothesize that topiramate discontinuation-associated continuing weight-loss effect results from the potential of topiramate to improve leptin functioning, decrease leptin levels, and restore mesolimbic dopamine function. One may question why metformin or sibutramine could not have continuing weight-loss effects after their discontinuation if both drugs do affect leptin in a similar way. Evidence suggests that metformin could decrease serum leptin levels [33], restore leptin sensitivity [34], and increase hypothalamic leptin receptor expression [35]. In the case of sibutramine, post-treatment leptin levels were decreased in some studies [36, 37], but increased in the other one [38]. Until now, research has not explored how these 2 weight-loss agents influence mesolimbic dopamine system. Moreover, few head-to-head studies have compared the extent to which these 2 drugs affect leptin functioning and leptin levels, not to mention the other molecular mechanisms contributing to weight-controlling properties. It is clear that further studies designed in a head-to-head manner into the differences among weight-loss agents would be interesting and provide a hint to solve the puzzle.

We advise to exercise caution while interpreting the findings from this study. First, our sample size was small, which may have reduced the stability of estimates and led to wide confidence intervals. Based on an alpha of 0.05, a power of 0.8, an effect size of 0.665 for weight changes, and a 2-sided paired t-test, a sample size of 20 was determined. In the same manner with an effect size of 1.85 for leptin changes, a sample size of 5 was obtained. Evidently, further study using a sample size larger than 20 could confirm our findings.

Second, weight loss was observed from the second month; however, at that time leptin levels were still so high, and the interaction effect ([time] × [leptin]) reached significance from the third month. Thus, there may be other underinvestigated mechanisms in this study leading to topiramate's weight-loss effect. Indeed, diverse pharmacological mechanisms have been associated with topiramate-induced weight loss [2, 11], such as its antagonistic effect on kainite/AMPA glutamate receptor.

The third limitation is the fact that although the dose of the antipsychotic had been controlled, the liability among antipsychotics to induced weight gain is distinctly different [39]. In other words, it remains to be established which kinds of antipsychotic-associated weight gain are most manageable by topiramate. This study included 2 patients treated with the high potential weight gain antipsychotic, clozapine. Fourth, although chronically hospitalized patients might have more consistent activities of daily living and more similar diet contents, this study could be improved if we used eating scale, such as the 3-Factor Eating Questionnaire-R18 [40]. Assessing the aspects of eating behavior, including cognitive restraint, uncontrolled eating, and emotional eating, provides another approach to disentangle the mechanisms underlying continuing weight loss after topiramate discontinuation.

Fifth, leptin levels were obtained until 3-month follow-up after topiramate discontinuation; hence, it is unknown, since that time point, whether the interaction effect between topiramate discontinuation and leptin levels could have an impact on weight changes. Finally, the subjects in this study were non-diabetic and normotensive, so the efficacy of topiramate on weight reduction should be generalized with caution to other populations, such as obese individuals with well-established diabetes. Maintaining the weight loss is difficult to achieve for most persons, and in this respect, it may be even more difficult to do for persons with schizophrenia, consisting of negative symptoms and cognitive deficits as intrinsic parts of illness. This study demonstrates a sustained benefit of topiramate to reduce body weight in obese persons with schizophrenia. Above all, subjects revealed continued reductions in body weight and leptin levels even after topiramate had been discontinued for 12 months. We suggest, based on previous evidence and our present findings, that continuing weight-loss effect after topiramate discontinuation might have resulted from topiramate's potential to improve leptin functioning, decrease leptin levels, and restore mesolimbic dopamine function.

We acknowledge that the small sample size and the lack of control group limit the generalizability of the findings. However, this study provides new evidence that in obese persons with schizophrenia, maintenance of weight loss after the discontinuation of weight-loss agents might be possible. To put this in perspective, a better understanding toward the overall mechanisms of topiramate and their interactions with leptin is thus of significant importance. We believe that this pilot study should be replicated because of the encouraging results. Further investigation is necessary to determine the efficacy of higher doses of topiramate in weight management and its impact on leptin functioning, and to evaluate the potential continuing weight-loss effect in different populations.

Acknowledgements
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Conflict of Interest
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The authors declare no conflicts of interest.

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