

## Topiramate의 신경성 폭식증 치료효과: 국내외 보고된 임상연구결과 및 치험사례 중심으로

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### Topiramate for the Treatment of Binge Eating Disorder or Bulimia Nervosa : A Systemic Review of Human Clinical Studies and Case Reports

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지난 20 여 년 간 서구 선진사회에서는 식사장애(Eating disorder) 중에서 신경성 폭식증(Bulimia nervosa)의 발병률이 급격히 상승하였고, 우리나라는 특히 젊은 여성층에서 발병률이 빠르게 상승하고 있다. 치료약물로는 주로 항우울제가 선택되지만, 치료효과가 미흡한 바, 항경련제인 topiramate가 효과가 있다는 보고들이 있어 이를 신경성 폭식증 치료에 적극 사용할 수 있는가에 관심이 고조되었다. 본 연구는 topiramate가 지닌 신경성 폭식증 치료효과에 대한 최신 지견을 얻고자, 1990년부터 2006년 사이 MEDLINE과, 한국의학논문데이터베이스에 등재된 국내외 자료를 binge eating disorder, bulimia nervosa, topiramate라는 3개의 주요어휘로 검색하여 추출한 자료중에서, 대조군이 사용된 무작위 배정, 이중맹검 임상연구 및 치험사례만을 선별하여 임상적유효성을 평가하였다. 국외 임상연구 및 치험사례에 따르면, topiramate가 신경성 폭식증에 수반되는 유해한 증상의 발생빈도를 경감시키는데 유효함을 나타내었다. 국내에는 아직 topiramate의 신경성 폭식증 치료효과를 검증한 체계화된 임상연구나 치험사례가 보고된 바 없었다. 피험자의 규모가 작다는 한계에도 불구하고, 일일 투여량 25 mg로 시작하여 점차 증량후 최대 600 mg까지 투여한 국외의 연구결과는, topiramate가 신경성 폭식증 치료에 유효한 결과를 보인다고 사료되므로, 국내 신경성 폭식증 임상치료와 연구에 반영되기를 기대한다.

□ Key words – binge eating disorder, bulimia nervosa, topiramate

Binge eating disorder (BED) is characterized by recurrent, uncontrollable, and distressing episodes of excessive food consumption, identified as 'binge', without compensatory inappropriate weight loss behaviors.<sup>1,2)</sup> Bulimia nervosa (BN) is a chronic disorder involving repeated episodes of uncontrolled binge eating, followed by inappropriate compensatory behaviors such as self-induced purging, fasting, inappropriate use of diuretics or laxatives, and excessive exercise, on average, at least twice weekly for 3 months.<sup>2-4)</sup> The

prevalence of BED in the general population is estimated to be 1.5 to 2.0%,<sup>1)</sup> and the incidence of BN peaks during adolescence and young adulthood affecting up to 5% of adolescent females in the United States<sup>3)</sup>, and these trends are similar in Korea recently.<sup>5-8)</sup> The etiology of BED and BN is complex and includes distinct factors such as genetic, physiologic, biochemical, developmental and psychological factors.<sup>4,9)</sup> Persons with BN are overly sensitive about their weight and have a distorted body image.<sup>4,6)</sup> Many persons with BN have chaotic and troubled personal relationships, and substance abuse are common.<sup>4,5)</sup>

Numerous studies have examined the utility of drugs such as tricyclic antidepressants and selective serotonin reuptake inhibitors in the treatment of BED or BN, and

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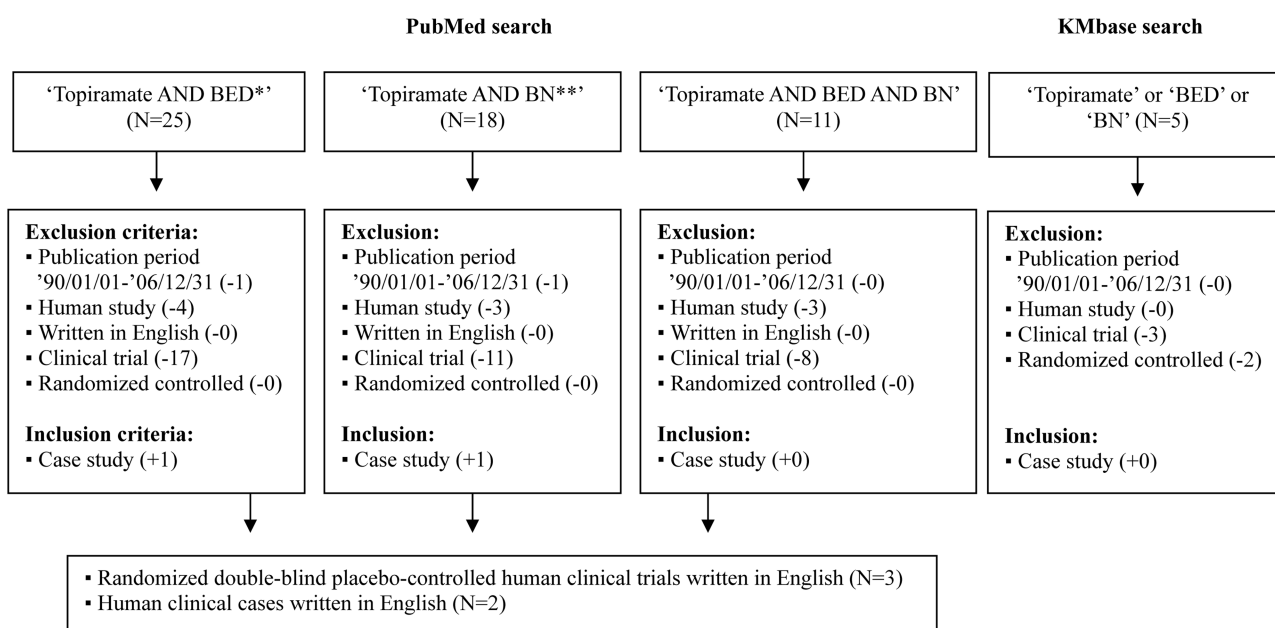
many of these trials found the study drug superior to placebo.<sup>10,11)</sup> However, most of the patients treated with these drugs rarely achieve disease remission.<sup>9)</sup> For this reason, interest in topiramate as a treatment for eating disorders has increased.<sup>9,12)</sup>

Topiramate, a broad-spectrum antiepileptic drug or anticonvulsant currently approved as adjunctive therapy in various forms of seizure, has shown potential efficacy in the treatment of eating disorders.<sup>3,9,13,14)</sup> In patients with bipolar disorder, treatment with topiramate was associated with appetite suppression and weight loss.<sup>3)</sup> Topiramate has also demonstrated efficacy in pilot and controlled studies for the treatment of BED and BN.<sup>3,9,12)</sup> The purpose of this article is to review literature concerning the use of topiramate for BED or BN by evaluating the primary literatures retrieved via both a MEDLINE (January 1990-December 2006) and a Korean Medical Database (KMbase) search using three keywords such as binge eating disorder, bulimia nervosa, and topiramate.

The combination of keywords in the MEDLINE were ‘topiramate AND binge eating disorder’ and ‘topiramate AND bulimia nervosa’ at each searching. The limit conditions were ‘human study’, ‘written in English’, ‘clinical trial’, ‘randomized controlled trial’, ‘case study’, ‘words in all fields’, and the publication period of ‘January 1, 1990 – December 31, 2006’. We retrieved a total of 5 articles from a 3 different subset of keywords in the PubMed. Three articles were the randomized, double-blind, controlled clinical trial studies and the rest 2 were case studies. However, we could not find any article including both the keyword set and the limitations in the KMbase (Scheme 1).

McElroy et al.<sup>1)</sup> conducted a 14-week, single-center, randomized, double-blind, placebo-controlled study in 61 patients with DSM-IV (Diagnostic and Statistical Manual of Mental Disorders; Version IV, published in 1994) BED and obesity (BMI≥30 kg/m<sup>2</sup>). The study was followed by an open-label, 42-week extension study for patients who completed the placebo-controlled trial. Topiramate was titrated from an initial dose of 25 mg/day up to 600 mg/day. During the extension trial, patients were evaluated every 4 weeks. A 1-sample paired t-test

### Literature Review



\* BED (binge eating disorder); \*\* BN (bulimia nervosa)

Scheme 1. Search flow of the data sources and the limitations in retrieving

was used to evaluate the weekly frequency of binge-eating episodes before each clinic visit. Thirty one patients entered the open-label extension trial. Fifteen patients received topiramate during the double-blind study and 16 patients received placebo. In total, 44 patients (31 patients described above and 13 patients on topiramate in the double-blind study only) took at least 1 dose of topiramate. Forty three patients completed the trial at a median final dose of 250 mg/day. Topiramate therapy was statistically significantly associated with a reduction in the mean binge frequency and the mean weight. For all patients receiving at least 1 dose of topiramate either in the double-blind study or the open-label extension trial (n=43), the mean reduction of binge frequency was 3.2 binges/week ( $p<0.001$ ) and the mean weight loss was 6.0 kg ( $p<0.001$ ). For the patients who completed the open-label extension trial (n=10), the mean reduction of binge frequency was 5.0 binges/week ( $p=0.002$ ) and the mean weight loss was 14.2 kg ( $p<0.001$ ). The study has several limitations, i.e., an uncontrolled, open-label trial with a small sample size and high attrition rate. Despite these limitations, the study suggests that topiramate may be effective for patients with BED and obesity.

A 10-week, randomized, double-blind, placebo-controlled trial assessed the efficacy of topiramate in patients with BN.<sup>3)</sup> Patients 16 to 50 years old with DSM-IV BN were randomly assigned to receive topiramate (n=35) or placebo (n=34). Topiramate treatment was initiated at 25 mg/day for the first week, and patients were then titrated by 25 to 50 mg/week until the maximum tolerated dose, complete or near-complete efficacy, or the maximum daily dose of 400 mg was achieved. Patients were seen weekly for 10 weeks and then tapered from study medication. The primary efficacy measure was the mean weekly number of days in which a patient binged, purged, or both binged and purged. A 2-group t test with a 5% significance level was used to analyze the efficacy of topiramate. The researchers found that topiramate was associated with a greater percent reduction in mean weekly number of binge and/or purge days (44.8% from baseline with

topiramate versus 10.7% with placebo,  $p=0.004$ ). The mean weekly number of binge days decreased 48.2% with topiramate versus 17.7% with placebo ( $p=0.015$ ). Topiramate decreased the mean weekly number of purge days (43.4% with topiraate versus 16.6% with placebo,  $p=0.016$ ) and mean purge frequency (49.8% with topiramate versus 21.6% with placebo  $p=0.016$ ). The mean binge frequency decreased 49.2% with topiramate versus 28.0% with placebo ( $p=0.071$ ), although that did not meet statistical significance. The limitations of the study were the small sample size and short treatment period. According to the results of the study, topiramate may be potential for the treatment of BN. However, larger and longer studies are needed to confirm these results.

Another study assessed the effect of topiramate on bingeing and purging behavior, body weight, and the health-related quality of life (HRQOL) in patients with BN.<sup>9)</sup> The researchers conducted a 10-week randomized, double-blind, placebo-controlled study. One hundred two women aged 18 years or older who had been suffering from DSM-IV BN for at least 12 months were included in the study. Sixty patients were randomly assigned to receive topiramate (topiramate group [TG]; n=30) or a placebo (control group [CG]; n=30). The nonparametric Mann-Whitney U test was performed to evaluate the primary outcome measures of changes in the frequency of bingeing/purging, in body weight, and in the HRQOL by using the SF-36 Health Survey (SF-36) scales. The SF-36 consists of a questionnaire with 36 items that are categorized according to several subject areas. The items record eight dimensions of subjective health. The items and scales of the SF-36 were calculated so that a higher score corresponds to a better state of health. The topiramate group experienced a significantly greater difference of change than the placebo group in the frequency of bingeing/purging (-3.3 in a week, 95% confidence interval [CI]= -4.3 to -2.1;  $p<0.001$ ), body weight (-3.8 kg, 95 % confidence interval [CI]= -5.4 to -2.1;  $p<0.001$ ), and SF-36 (1.9 to 9.6; all 8 dimension  $p<0.001$ ). No serious side effects were reported during the study. The study suggests that topi-

ramate is a safe and effective agent for improving the bingeing/purging behavior and the HRQOL in patients with BN, but there are limitations in the study. The sample size was relatively small and only women were included in the study. Thus, additional study is needed to establish the effects of topiramate in both men and women with BN and how long-lasting the benefits are (Table 1).

Bernardi et al.<sup>15)</sup> reported the case of a 27 year old female suffering from BED, without psychiatric or neuroendocrine comorbidity. Symptoms of BED had not improved by nutritional counselling and pharmacological therapy with fluoxetine 60 mg/day and quetiapine 400 mg/day. Topiramate was given 25 mg twice daily for 3 weeks followed by a 25 mg increase every 3 weeks up to 100 mg twice daily without concomitant treatment. After a 3-week period, improvements were seen in eating habits and obsessive and compulsive behavior. After 28 weeks of therapy, her weight decreased from 75 kg (BMI= 26.57) to 63 kg (BMI= 22.32). In this case, topiramate was associated with improvement in the treatment of binge eating disorder associated obesity.

A case series by Barbee<sup>16)</sup> which described 5 cases demonstrated that topiramate was associated with the reduction of bingeing and purging behavior in patients with comorbid mood disorders. In 3 out of the 5 cases in the series, topiramate almost completely eliminated bingeing and purging behavior. One of the patients discussed was a 36-year-old woman with BN and depression. She was prescribed citalopram 120 mg, gabapentin 800 mg, olanzapine 30 mg, lamotrigine 150 mg (all given at bedtime), and dextroamphetamine, 10 mg twice daily. Despite this regimen, she was still bingeing and purging five to six times daily. Topiramate at a dose of 30 mg at bedtime was initiated, and titrated upward to a dose of 200 mg. Bingeing and purging episodes stopped completely within 4 weeks. The efficacy of topiramate for BN in the absence of other psychiatric diagnoses should be further researched, as all patients in these case series suffered from at least one other psychiatric illness. In cases, almost patients with BED or BN who were unresponsive to antidepressants, antipsychotics, or

anticonvulsants showed improvement in bingeing and purging behavior with topiramate (Table 1).

## Summary

The clinical investigations above suggest that topiramate may be an effective agent in the treatment of BED or BN by reducing bingeing/purging episodes, improving the HRQOL, and decreasing weight. The case report and case series also support these findings. However, there are several limitations in the above studies and cases. All these had relatively small sample size, and two of them were only 10-week-period studies. Optimal duration of treatment with topiramate in patients with BED or BN is unknown. As most clinicians treat the patient with BED or BN for 6 to 12 months and then reassess, at least 6 months period is needed to show its efficacy. One of studies included only women in the patient group. In the case series, all patients had severe comorbid mood disorders such as major depression and bipolar disorder besides BN. Therefore, notwithstanding its clinical usefulness, additional researches are needed to define the role and the benefits of topiramate in the treatment of BED or BN more thoroughly.

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Table 1. The summary of the retrieved study data to evaluate the therapeutic efficacy of topiramate on patients with bulimia nervosa

Investigator, Year of publish	Type of study	Methods	Results	Remarks
McElroy et al. <sup>1)</sup> 2004	Single-center, randomized, double-blind, placebo-controlled study	<ul style="list-style-type: none"> <li>• 61 patients with DSM-IV BED and obesity (<math>BMI \geq 30 \text{ kg/m}^2</math>) were chosen.</li> <li>• After 14-week placebo-controlled trial, 42-week, open-label, extension study followed.</li> <li>• Titrated from an initial dose of 25 mg/day up to 600 mg/day. Evaluated every 4 weeks</li> <li>• 44 patients took at least 1 dose of topiramate. 43 patients completed this trial at a median final dose of 250 mg/day.</li> </ul>	<p><i>Topiramate may be effective for patients with BED and obesity:</i></p> <ul style="list-style-type: none"> <li>• At least 1 dose of topiramate (n=43), the mean reduction of binge frequency was 3.2 binges/week (<math>p &lt; 0.001</math>) and the mean weight loss was 6.0 kg (<math>p &lt; 0.001</math>).</li> <li>• Completed the extension trial (n=10), the mean reduction of binge frequency was 5.0 binges/week (<math>p = 0.002</math>) and the mean weight loss was 14.2 kg (<math>p &lt; 0.001</math>).</li> </ul>	<ul style="list-style-type: none"> <li>• Study limitations: Uncontrolled, open-label trial, small sample size, and high attrition rate</li> </ul>
Hoopes et al. <sup>3)</sup> 2003	Randomized, double-blind, placebo-controlled trial	<ul style="list-style-type: none"> <li>• For 10 weeks, patients of 16-50 years old with DSM-IV BN received topiramate (n=35) or placebo (n=34).</li> <li>• Topiramate was initiated at 25 mg/day for the first week, titrated by 25 to 50 mg/week until the maximum tolerated dose, complete or near-complete efficacy, or the maximum daily dose of 400 mg was achieved.</li> </ul>	<p><i>Topiramate may be a potential treatment for BN:</i></p> <ul style="list-style-type: none"> <li>• Reduction in mean weekly number (MWN) of binge and/or purge days (44.8% from baseline with topiramate vs 10.7% with placebo, <math>p = 0.004</math>). The MWN of binge days decreased 48.2% with topiramate vs 17.7% with placebo (<math>p = 0.015</math>). Topiramate decreased the MWN of purge days (43.4% with topiramate vs 16.6% with placebo, <math>p = 0.016</math>)</li> <li>• Mean purge frequency (49.8% with topiramate vs 21.6% with placebo <math>p = 0.016</math>). The mean binge frequency decreased 49.2% with topiramate vs 28.0% with placebo (<math>p = 0.071</math>)</li> </ul>	<ul style="list-style-type: none"> <li>• Study limitations: Small sample size and short treatment period</li> </ul>
Nickel et al. <sup>9)</sup> 2005	Randomized, double-blind, placebo-controlled study	<ul style="list-style-type: none"> <li>• Among 102 females aged 18 or older suffering from DSM-IV BN for at least 12 months were included in the 10-week study, 60 received topiramate (topiramate group: TG, n=30) or a placebo (PG, n=30).</li> <li>• Initial dose was 25 mg/day, titrated to a dose of 250 mg/day in the sixth week and then stayed constant. The duration of study was 10 weeks.</li> </ul>	<p><i>Topiramate is a safe and effective agent for improving the bingeing/purging behavior and the HRQOL in patients with BN</i></p> <ul style="list-style-type: none"> <li>• TG vs. PG in the frequency of bingeing/purging (-3.3 in a week, 95 % confidence interval= -4.3 to -2.1; <math>p &lt; 0.001</math>), body weight (-3.8 kg, 95 % confidence interval= -5.4 to -2.1; <math>p &lt; 0.001</math>), and SF-36 (1.9 to 9.6; all 8 dimension <math>ps &lt; 0.001</math>).</li> </ul>	<ul style="list-style-type: none"> <li>• Study limitations: The sample size was relatively small and only females were included.</li> </ul>

**Table 1. continued**

Investigator, Year of publish	Type of study	Methods	Results	Remarks
Bernardi et al. <sup>15)</sup> 2005	Case report	<ul style="list-style-type: none"> <li>• 27 year old female suffering from BED, without psychiatric or neuroendocrine comorbidity</li> <li>• Symptoms of BED had not improved by fluoxetine 60 mg &amp; quetiapine 400 mg/day.</li> <li>• Topiramate was given 25 mg (tid) for 3 weeks followed by a 25 mg increase every 3 weeks up to 100 mg (tid) without concomitant treatment.</li> </ul>	<p><i>Topiramate was associated with improvement in the treatment of binge eating disorder associated obesity:</i></p> <ul style="list-style-type: none"> <li>• After 3 weeks, improvements in eating habits and obsessive and compulsive behavior.</li> <li>• After 28 weeks of therapy, weight decreased from 75 kg (BMI=26.57) to 63 kg (BMI=22.32).</li> </ul>	
Barbee <sup>16)</sup> 2003	Case series (5 cases)	<p><i>In 3 out of the 5 cases in the series, topiramate almost completely eliminated bingeing and purging behavior in patients with comorbid mood disorders:</i></p> <ul style="list-style-type: none"> <li>• A 36-year-old female with BN and depression using citalopram 120 mg, gabapentin 800 mg, olanzapine 30 mg, lamotrigine 150 mg (all qhs), and dextroamphetamine, 10 mg (tid). Still, bingeing and purging five to six times daily.</li> <li>• Topiramate 30 mg (qhs) was initiated, and titrated upward to 200 mg.</li> </ul>	<ul style="list-style-type: none"> <li>• Bingeing and purging episodes stopped completely within 4 weeks.</li> </ul>	<p>The efficacy of topiramate for BN in the absence of other psychiatric diagnoses should be further researched, as all patients in this case series suffered from at least one other psychiatric illness.</p>

**Abbreviations:** DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, published in 1994); BED (binge eating disorder); BMI (body mass index); BN (bulimia nervosa); HRQOL (health-related quality of life); SF-36 (A multi-purpose, short-form health survey with only 36 questions; <http://www.sf-36.org/>); qhs (at bedtime); tid (three times a day)

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