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### Cover Page Footnote

Erin Spencer is a fourth year student at Wayne State University School of Medicine

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# Clinical approach to a request for phentermine-topiramate in a young woman with a history of high-risk eating behavior

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**ABSTRACT** A clinical decision report appraising Safer DL, Adler S, Dalai SS, et al. A randomized, placebo-controlled crossover trial of phentermine-topiramate ER in patients with binge-eating disorder and bulimia nervosa. *Int J Eat Disord.* 2019;(September):1-12. <https://doi.org/10.1002/eat.23192> to inform the clinical decision of whether or not to prescribe phentermine-topiramate to an overweight 27-year-old woman who endorses risky eating behaviors.

**Keywords:** *Binge eating disorder, phentermine-topiramate*

## Clinical Context

Ashley Jones (pseudonym), a 27-year-old woman who has not seen her doctor in two years, presented to the outpatient clinic with the chief complaint of joint pain and fatigue. After extensive conversation regarding Ms. Jones' chief complaint, she mentioned that she has had extreme difficulty controlling her appetite over the last couple months. She described consistently eating foods that were not appealing and overeating to the point of pain. She cautiously asked if we, as her healthcare providers, would prescribe her phentermine to help suppress her appetite. She communicated that she trusted our opinion regarding a prescription appetite suppressant and would not seek one out if we recommended against its use. When asked about the chronicity of these binge eating episodes, she said that she has struggled with eating since her late teens, especially in times of stress. She reported that after watching her mother struggle with Bulimia Nervosa (BN), she tends to engage in the opposite behaviors to deal with emotional stress. She does not endorse any compensatory or purging behaviors in response to her binges. Although she does not carry a diagnosis of binge eating disorder (BED), her description of these eating behaviors suggest BED may be present and warrants further work up and consideration. Ms. Jones has a BMI of 29, which places her in the overweight category, but she does not suffer from any other weight-related medical conditions. As Ms. Jones had not been to the doctor in two years, she had not previously been counseled on her weight and had never engaged in treatment for her eating behaviors. The patient was a college educated social worker, so she had a deep understanding of the psychosocial elements contributing to her health. Although the patient's other complaints (fatigue, vague aching pain, stress/anxiety) point to the possibility of an underlying psychological condition, her eating behavior at this time does not appear to be impacting her daily life. She supports herself, cares for herself while living independently in an apartment, has successful employment, and maintains strong relationships with her family and friends. However, she did endorse a level of shame and concern surrounding this behavior, which warranted further consideration of her request for pharmacologic treatment.

ERIN SPENCER is a fourth year medical student at Wayne State University School of Medicine.

## Clinical Question

Is it appropriate to prescribe phentermine-topiramate to an overweight patient with high risk eating behavior as first line treatment?

## Research Article

Safer DL, Adler S, Dalai SS, et al. A randomized, placebo-controlled crossover trial of phentermine-topiramate ER in patients with binge-eating disorder and bulimia nervosa. *Int J Eat Disord.* 2019;(September):1-12. <https://doi.org/10.1002/eat.23192>

## Related Literature

The literature review began by searching PubMed for “phentermine treatment in binge eating”, which yielded 8 results. These results included 1 randomized control trial<sup>1</sup>, 1 study protocol for that randomized control trial<sup>2</sup>, 3 open label prospective trials<sup>3-5</sup>, 1 case series<sup>6</sup>, 1 article discussing the biochemical mechanism of action of appetite suppressant medications<sup>7</sup>, and 1 review article<sup>8</sup>. The same search was conducted using Google Scholar and yielded a much broader 1740 results. However, the most relevant studies were those found on PubMed. The case series and review article found on PubMed were assessed to broaden background knowledge on the topic.

Given the limited scope of available research, the randomized control trial and the 3 open label prospective trials were assessed for critical appraisal. The randomized control trial was ultimately chosen. Although the open label trials were not chosen for appraisal, they were very helpful in providing context for the randomized control trial. The first to be published was Alger et al. in 1999. This study compared weight loss, eating behavior, and mood outcomes in binge eaters and non-binge eaters taking phentermine and dl-fenfluramine.<sup>3</sup> Although the results were promising, the lack of placebo and age of the trial ultimately made it a less reliable source in the context of Ms. Jones. The next trial to be published was by Devlin et al. in 2000. This study examined the use of phentermine/fluoxetine as an adjunct to cognitive behavioral therapy (CBT) to treat overweight binge eaters.<sup>4</sup> Again, the results were promising. Although the multi-modal approach to treatment is ideal, CBT was the primary treatment in this study and Ms. Jones was not particularly open to CBT when she requested appetite suppressing medication. The final open label trial published was done by the same group as the case series found in the search. This trial also presented promising results, however, all enrollees had at least one weight related complication. As mentioned in the clinical context, Ms. Jones did not have any health complications related to her weight at the time of her visit. Thus, the randomized placebo-controlled crossover study by Safer et al. was chosen. Pending formal diagnosis of BED, Ms. Jones met most all of the inclusion criteria for this study. That, in combination with the placebo control, made it the most relevant and powerful study to her case.

## Critical Appraisal

The field of study for phentermine combinations in the treatment of BED is limited, so Safer et al. set out to complete a study that would evaluate the effectiveness of phentermine-topiramate compared with a placebo. Safer et al. recruited individuals with BN and BED and randomized them to start with the phentermine-topiramate or the placebo. The individuals spent 12 weeks taking phentermine-topiramate or placebo, followed by a 2-week wash-out period, and 12 more weeks with the crossover intervention. Multiple subjective and objective outcomes (including, but not limited to, objective and subjective binge eating days, depression score, cognitive restraint of eating, disinhibition, hunger, and weight) were assessed throughout this period and for 8 weeks of follow-up.

One strength of this study is the thoughtful and thorough design. They not only chose to complete a controlled trial, but they also chose to make it a crossover set up which allows all participants to serve as their own controls. One critique of crossover studies is that the group receiving treatment initially may still be experiencing effects during the placebo phase. Safer et al. chose to complete a 2-week washout period before switching the groups, which allowed 5 half-lives of phentermine-topiramate to pass before placebo was started. Phentermine-topiramate was chosen as the combination because it has a lower side effect profile than phentermine alone and would minimize the dropout rate. Another impressive component of this study design was the combination of objective and subjective outcomes they measured. When assessing treatment of BED, it is important to measure behavior in addition to the more objective outcomes, such as weight loss and vitals. Measuring behavior is often a challenge due to the subjective nature of

self-reporting. To make outcomes more objective, Safer et al. utilized blinded assessors to complete the Eating Disorders Examination for evaluation of objective binge eating (OBE) days. Safer et al. included self-reported subjective binge eating (SBE) days as well, which acknowledges the importance of patient perception in BED. Overall the design of this study was superior, the most concerning aspect was the small planned sample size. Statistical analysis required 24 participants to produce significant results, so the researchers planned to recruit 30 individuals with the thought that some would drop out.

Although the design of this trial was impressive, even the best designed studies can fall apart in completion, making it critical to evaluate the execution of this trial. The biggest flaw in the study was the sample size. As previously mentioned, 24 participants were needed to produce statistically significant outcomes. Unfortunately, by the end of the study only 22 individuals were participating. This means that although the outcomes can have clinical meaning, we can't be truly confident in the results until a larger study is completed. Although the sample size was small, it appears that the quality of participants was high, as the compliance with medication was estimated to be 90%. This reassures that most patients were actually taking the medication as directed, so the medication actually had the opportunity to impact the outcomes. Another flaw that should be addressed is that 80% of patients correctly guessed when they were on the phentermine-topiramate and 94.7% of patients correctly guessed when they were on the placebo. Even though this cannot be avoided, it does remove some of the benefit of double blinding the study.

As stated above, the wide range of outcome measures was a strength of this trial. Of all the outcomes measured, the most statistically significant data was found in decreased OBE days/episodes, depression score, eating concern score, and hunger score while participants were taking phentermine-topiramate as opposed to placebo. They also found an increase in the percent of days that individuals abstained from any binge eating behavior while on phentermine-topiramate vs placebo. Notably, the difference in cognitive restraint for eating was not statistically significant between treatment and placebo groups. The group also found an average of 6.5 kg were lost while patients were taking the phentermine-topiramate.<sup>4</sup> In total, these results suggest that phentermine-topiramate not only impacts the physical health of the patient (through weight loss), but also helps with some of the psychological components of binge eating disorder. Although participants cognitively still wanted to overeat, the combination of reduced disinhibition and hunger seemed to put them back in control of their eating behavior and reduce their binge eating episodes. One concerning outcome was the weight re-gain after stopping phentermine-topiramate. As phentermine-topiramate is not safe for prolonged use, there needs to be further investigation into safe and effective maintenance treatment. Overall this study provides level 2 evidence, with the inadequate sample size being the only obstacle keeping it from providing level 1 evidence as described by Ebell et al.<sup>9</sup> In total, the results published by Safer et al. are extremely compelling, but warrant larger studies before this treatment is incorporated as a mainstay treatment for BED.

## Clinical Application

As mentioned in the related literature section, Safer et al. was chosen not only because of its superior study design, but also because the patient population was well aligned with Ms. Jones. The average BMI of study participants was 31.1, which was close to that of Ms. Jones' BMI at 29. Most participants were females with college or post-graduate education like our patient. The major difference between study participants and Ms. Jones was that study participants had a formal diagnosis of BED and were refractory to previous trials of psychotherapy and pharmacotherapy with SSRIs. Although the outcomes of this study are very promising and suggest that Ms. Jones appetite and weight could be acutely managed with phentermine-topiramate, at the time of her visit her condition had not been investigated and managed enough to warrant a leap in treatment to phentermine-topiramate as first line intervention.

It is important to note that binge eating and weight loss were not Ms. Jones' chief complaint when she presented to the clinic. However, as her providers, we sensed that her appetite and weight in the context of her overall physical and mental health was a large part of her concern. Due to her description of her eating behaviors and their emotional triggers, we strongly felt that there was an unaddressed mental health component to her complaint. Given this, it would have been irresponsible to prescribe phentermine-topiramate, a medication with multiple possible adverse events and addictive potential, without first addressing the psychological element and instituting first line treatment based on that. We focused on behavioral counseling for weight loss in a healthy manner including portion control, balanced nutrition, and physical activity. We also suggested CBT and gave her resources to engage with a therapist. Although she was resistant to therapy initially, she seemed to open up to the

idea after extensive conversation. In spite of her resistance, Ms. Jones has multiple family members working in clinical psychology and respects the potential of CBT to help her and understood the benefit of starting with a more conservative approach. We made sure not to minimize her concerns when we recommended against phentermine-topiramate, but rather set a follow-up visit in 1-3 months to monitor her progress closely. Although we determined that phentermine-topiramate was not appropriate treatment at this time, it is entirely possible that with more research and trials of other treatment for Ms. Jones, it could become a helpful tool in managing her risky eating behaviors as well as her weight.

## New Knowledge Related to Clinical Decision Science

The fact that the patient stated that she would respect the doctor's recommendation made it easier to recommend against this therapy. If the patient had insisted or insisted persistently, would the doctors have made the same decision? In fact, there is a broad range of attitudes toward the efficacy of this therapy among providers. Some prescribe it and others don't. When discussing the topic among colleagues, there is a flavor of "wanting to do something" for the patient. The lack of evidence for long term weight loss and the temporary nature of the intervention weighed heavily in this clinical decision. Eventually, the clinical question was nested in an array of other clinical questions, such as a thorough evaluation for eating disorder and other potential therapies. This clinical decision report highlights that initially, there are a whole series of clinical questions that need to be considered while still addressing the patient's direct question at the moment.

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