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Lisdexamfetamine is an effective monotherapy for moderate to severe binge eating disorder

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Lisdexamfetamine is an effective monotherapy for moderate to severe binge eating disorder

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ABSTRACT A clinical decision report using

McElroy SL, Hudson J, Ferreira-Cornwell MC, Radewonuk J, Whitaker T, Gasior M. Lisdexamfetamine dimesylate for adults with moderate to severe binge eating disorder: Results of two pivotal phase 3 randomized controlled trials. *Neuropsychopharmacology*. 2016;41(5):1251-1260. <https://doi.org/10.1038/npp.2015.275>¹

for a young woman requesting a novel pharmacological intervention for a Binge Eating Disorder (BED).

Keywords: *binge-eating, Binge Eating Disorder, weight loss, lisdexamfetamine*

Clinical-Social Context

Johanna Toma (pseudonym) is a 26-year-old Chaldean-American woman with a past medical history of obesity and disordered eating. She presented to the internal medicine clinic with an interest in controlling her binge eating behaviors and improving her weight management. At a BMI of 36 (Class II obesity)², she was at her highest weight and expressed shame over her appearance. "I am too embarrassed and fatigued to go to parties or even work out at the gym." Johanna is a physician associate student who trains long hours and cares for her ailing parents. Johanna has adequate transportation and food security, but she believes that her mother undermines her weight loss goals by insisting on the family's traditional high-calorie diet. As she recently aged out of coverage under her parents' health insurance, she is unsure of the quality of her new plan and whether it covers non-generic medications.

Johanna has a strong understanding of healthy eating, and despite her busy schedule tries to prepare her own food. Her breakfasts include egg whites and tomatoes. For lunch she prepares salads, and often grills fish for dinner. "I do fine until 11 PM. At least five nights during the week I will eat thousands of calories in a less than half an hour. Last week I went to the drive-thru and ate two Whoppers, french fries, and a large shake in the parking lot. I felt physically disgusting after that. And then I did it again three times this week."

Johanna was told by her primary care physician that this eating pattern constituted obsessive compulsive disorder. She agreed to a trial of fluoxetine up to 40 mg/day but discontinued six months later after realizing the selective serotonin reuptake inhibitor (SSRI) offered no symptom relief and a ten-pound weight gain.

Through social media, Johanna became aware of binge eating disorder (BED) and identified that her symptoms were consistent with this diagnosis. Prior to her clinic visit, she completed the Binge Eating Scale, a 16-question instrument available online.³ Her score was 28, placing her in the "severe binge eating symptoms" category. As

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most of her recent care had been provided through her student health center, she questioned whether another primary care clinic was the proper venue to explore weight-related concerns. Johanna believed that weight loss was encouraged by clinicians, yet the strategies she had been given were confined to informational tear sheets about portion control or vague recommendations about regular exercise. She subscribed to the motivational calorie-tracking app, Noom®, but soon discovered that manually inputting her dietary intake was cumbersome and anxiety-provoking. Since her past efforts at SSRIs, psychotherapy, and self-help were unfruitful, Johanna inquired whether an available medication could help achieve better control over her binge eating.

Clinical Question

Is there a pharmacological monotherapy that can reduce the frequency of bingeing in patients diagnosed with Binge Eating Disorder?

Research Article

McElroy SL, Hudson J, Ferreira-Cornwell MC, Radewonuk J, Whitaker T, Gasior M. Lisdexamfetamine dimesylate for adults with moderate to severe binge eating disorder: Results of two pivotal phase 3 randomized controlled trials. *Neuropsychopharmacology*. 2016;41(5):1251-1260. <https://doi.org/10.1038/npp.2015.275>¹

Description of Related Literature

A PubMed search was undertaken in April 2022 using the keywords “binge eating disorder medication treatment”, yielding 987 results. Using additional filters for clinical trial, randomized controlled trial, meta-analysis and publication date within the past ten years, the search was refined to 109 abstracts. As Johanna explicitly discounted non-pharmacological modalities, abstracts focusing on psychotherapy, diet control, physical exercise, purely sociological observations, and other eating disorders were scanned and excluded. This reduced the pertinent publications to 23. Of these, early phase trials, retrospective analyses and redundant publications about the same study were discarded, leaving seven articles for deeper appraisal.

The 2015 McElroy et al. study was a randomized, placebo-controlled trial comparing armodafinil (150-250 mg/day) to placebo for patients diagnosed with BED.⁴ 60 participants were randomized in a ten-week, prospective, parallel-group, double-blind, flexible-dose, single-center trial. The primary outcome measure, improvement in binge eating day frequency, was not statistically different between active agent and placebo. However, armodafinil was more effective in decreasing the frequency of binge eating episodes. Furthermore, armodafinil was associated with greater reduction of obsessive-compulsive features of binge eating and overall BMI. Armodafinil was well-tolerated by the patient population. As the primary outcome measure was not realized, interest in this therapeutic waned, and no further studies are reported in the literature. The medication was never submitted for FDA-approval.

In 2020, McElroy et al.⁵ evaluated the efficacy and safety of dasotraline versus placebo in a randomized, flexible-dose, multicenter clinical trial in adults with BED. The subjects (n=315) were assigned to either 4, 6, or 8 mg per day of dasotraline or placebo over a 12-week double-blind study. Compared to placebo, dasotraline was associated with greater reduction in binge eating days by study's end (P <0.0001). Although this study was positive, dasotraline encountered other challenges during clinical development and support for the medicine was withdrawn, thus not making this a realistic option for Johanna.

Brownley's 2013 study examined the dietary supplement chromium-picolinate for BED. 24 overweight adults were enrolled in a six-month, double-blind, placebo-controlled trial.⁶ Subjects received either “high-dose” chromium (1000 mcg), “moderate-dose” chromium (600 mcg), or placebo. In this small single-site trial, the study drug did not demonstrate a statistically significant improvement in binge frequency, weight loss, or symptoms of depression. High-dose groups showed a trend toward improvement in fasting glucose. Although chromium-picolinate is widely available, this study was not chosen for deeper analysis as its preliminary findings did not support a reduction in binge eating frequency.

In 2021, Grilo et al.⁷ evaluated naltrexone and bupropion (NB) for the treatment of BED with obesity. This was a randomized, placebo-controlled, fixed-dose study (naltrexone + bupropion XL 50/300 mg per day) that investigated 22 adult patients over three



months and a six-month post-treatment period. The primary outcome measure was change from baseline of binge eating frequency and overall weight. This study did not reveal significant differences between NB and placebo, although the percentage of subjects on study agent who attained a 3% weight loss was greater than placebo. Johanna's primary concern was reducing the frequency of her binges. This study found that frequency was unaffected by NB. As the trial was not directly on point, and other agents have emerged as more promising treatments for BED, the Grilo study was not selected for critical appraisal.

In 2019, Safer et al.⁸ published a randomized, placebo-controlled, crossover trial of phentermine-topiramate ER in 22 patients with BED and bulimia nervosa. In this study, participants were randomized to either PHEN/TPM-ER (3.75 mg/23mg – 15 mg/92 mg) or placebo over a 12-week study period. The primary outcome measure was number of binge-eating days over four weeks, with binge abstinence as the secondary outcome measure. The study revealed a statistically significant decrease in the primary outcome measure ($P < 0.0001$). Notably, subjects on active treatment experienced more weight loss than the placebo group. The dropout rate was comparable for both placebo and active agent, and the drug was well-tolerated. This research suggests that PHEN/TPM-ER addresses many of Johanna's concerns. The product has been commercially available since 2012 (Qsymia®). This article was not chosen because the findings of this single-site study were limited by the small sample size. The medication can cause fetal harm and is relatively contraindicated in women with childbearing capacity. It has not been widely adopted by clinicians.

The question as to which monotherapy is most appropriate for symptom management is best answered by McElroy's 2016 original investigation.¹ This paper outlines the safety and efficacy of lisdexamfetamine (LDX) for BED in two contemporaneous, double-blind, placebo-controlled, multicenter trials. In both studies, which enrolled a combined total of 773 adult subjects, LDX (50 or 70 mg per day) was superior to placebo in decreasing the number of bingeing days per week. Subjects had 2.51 fewer binge days with placebo but 3.87 fewer binge days with LDX, an effect size calculated at 0.97 ($P < 0.0001$; 95% CI). Treatment emergent adverse events (dry mouth, insomnia, headache) were congruent for both studies and mirrored previously published data on the side effects of LDX. This was the largest study to date for the condition and proved pivotal in the FDA's first approval of a monotherapy for BED.

The use of LDX for BED deserves an B grade Recommendation according to the SORT system because of the single study publication with moderate bias.²

Critical Appraisal

McElroy details two prospectively registered studies performed over a 12-week period with weekly visits.¹⁰ 1342 subjects were assessed for eligibility and 569 were excluded soon thereafter. 383 subjects were randomized into study #1 and 390 subjects into study #2. Across both studies, 82 subjects in the placebo arm discontinued and 82 subjects in the LDX arm discontinued, due to adverse events, protocol violations, study withdrawal, lack of efficacy, and other reasons. No subjects of the active arm ended their participation because of lack of efficacy. Subjects on active treatment completed the study at a higher rate.

Subjects were recruited from investigator databases and national advertising. Eligible participants were men and non-pregnant women (ages 18-55) who met American Psychiatric Association guidelines for moderate to severe BED with functional impairment. Other inclusion criteria were BMI between 18 and 45 and a Clinical Global Impressions-Severity score of 4 or greater. Subjects were excluded if they had a non-BED eating disorder, major depression or had recently began receiving supportive therapies.¹¹ Johanna falls squarely within these recruitment parameters.

The randomization was well-executed. Patients were recruited in a consecutive manner using gold-standard rating scales. Comparisons were completed in a blind fashion and the inclusion/exclusion criteria was consistently applied across the many clinical sites. As the two studies were done contemporaneously and produced similar results, the trial can be viewed as highly reproducible. Both LDX and placebo groups had equivalent representation of Whites, Blacks, Asian-Americans, and Native Americans. Women constituted about 85% of the studied population, a number consistent with the current understanding of those who seek treatment for BED.¹² Nonetheless, active recruitment efforts of men would have been advisable as the condition may be even more stigmatized in this group.

The primary outcome in this 12-week study was change in number of binge-eating days from baseline to study end. It appears that all clinically relevant outcomes were reported. The statistical method employed was a mixed-effects model for repeated measures. In both studies, the least squares mean treatment difference significantly favored LDX. LDX was superior to placebo with a robust



effect size of 0.97. Other psychotropic medications, such as antidepressants, typically have an effect size range between 0.3 and 0.5.¹³ Secondary outcomes related to binge-eating behavior: changes in weight, vital signs, tolerability, and compliance were also achieved.

Potential biases must be considered. This large research initiative was funded by the pharmaceutical company Shire (now Takeda) and was undertaken to achieve commercial approval. As the study enrollment targets were high, sites of variable quality were included and the data from several sites had to be excluded. Variability between trial sites might have compromised the integrity of the clinical findings. Furthermore, subjects recruited from an investigator's local database may feel obligated to participate in a manner that nationally recruited subjects may not. Another limitation is that this study obtained short-term data; most patients with BED require long-term treatment. Gasior's 2017 study reported on the open-label 12-month extension study of the McElroy trials. The researchers found LDX safe and efficacious over the next year, noting a slight but persistent increase in blood pressure from baseline.¹⁴

Although other eating disorders were excluded, the authors did not aggressively exclude the participation of patients with attention deficit and hyperactivity disorder (ADHD). LDX has been approved for ADHD since 2008. BED and ADHD share the common symptom of impulsivity and it is possible that the robust response to LDX was due to the undetected presence of ADHD among study participants. If this is true, the study supports what was already known.

Clinical Application

My interaction with Johanna was limited to a single visit. During our interview she expressed anguish over her frequent binges and high BMI. She had little confidence that behavioral approaches alone would help her gain control over her disordered eating. She desired a pharmacological intervention and was skeptical that the outpatient clinic was the proper venue for her issues.

Johanna tasked me with exploring whether a viable medication option existed. LDX can cause side effects such as dry mouth, insomnia, and dyspepsia. In McElroy's trials, 3.1% discontinued treatment due to unwanted side effects and 1.5% had serious treatment emergent adverse events. The activating properties and well-tolerated side effect profile of LDX would likely be acceptable to her.

New Knowledge Related to Clinical Decision Science

Johanna had a firm idea of what she wanted when she presented to the clinic. After poor results with behavioral interventions, she desired a pharmacological option to treat her disordered eating. Johanna had limited barriers to care, high health literacy, and motivation to try a new medication. These factors improved her likeliness to succeed if her new insurance made a branded medication feasible.

In general, Johanna's medical team did not feel comfortable treating her binge eating and elevated BMI with a schedule II drug. Oftentimes, patients with obesity experience implicit bias that they are "lazy" or unwilling to make personal sacrifices for what is considered a lifestyle problem. Physicians might believe that LDX makes patients' more dependent on external help. It is not hard to imagine how a less-informed patient or one with financial and transportation limitations would experience even greater resistance from their care team.

Given my unique relationship with Johanna and my understanding of her situation and preferences and after carefully reviewing the clinical research, I was able to share my insight in a "medical-education" format with the team members, which potentially would help Johanna or others like her in the future.

There is universal acceptance in primary care that high BMI is a risk factor for many medical conditions and that addressing obesity and disordered eating confers direct benefit. One might speculate that ambulatory clinics are uncomfortable using psychiatric medications, particularly controlled substances. Logistic factors play a role; ongoing management of controlled medications require monthly refills and frequent clinic checkups, clear obstacles in a clinic driven by rotating resident physicians. My colleagues were



intrigued that LDX was an accepted treatment with an enduring track record of safety and efficacy. Further inroads integrating psychiatric and primary care approaches should be a priority if patients like Johanna are to be comprehensively managed.

The patient completed the Binge Eating Scale, a 16-question instrument available online.³ This provides a valuable tool to monitor her response to therapy—an important part of Clinical Decision Science that has been a theme of Clinical Decision Reports published in this journal.

Conflict Of Interest Statement

The author declares no conflicts of interest.

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