

Overcoming Diagnostic and Therapeutic
Challenges in the Individualized Management of

BINGE EATING DISORDER

Supported by an educational grant from Sunovion Pharmaceuticals, Inc.

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Disclosure

- **Dr. Citrome:** Consultant—Acadia, Alkermes, Allergan, Intra-Cellular Therapeutics, Janssen, Lundbeck, Merck, Neurocrine, Noven, Otsuka, Pfizer, Shire, Sunovion, Takeda, Teva, Vanda; Royalties—Springer Healthcare (book), *UpToDate* (reviewer), Wiley (Editor-in-Chief, *International Journal of Clinical Practice*); Shareholder (and spouse)—Bristol-Myers Squibb, Eli Lilly, J & J, Merck, Pfizer; Speaker—Acadia, Alkermes, Allergan, Janssen, Lundbeck, Merck, Neurocrine, Otsuka, Pfizer, Shire, Sunovion, Takeda, Teva, Vanda.
- **Dr. Grilo:** Consultant—Sunovion, Weight Watchers; Research Grants—National Institutes of Health; Royalties—Guilford Press, Taylor and Francis Publishers.

Disclosure

- The faculty have been informed of their responsibility to disclose to the audience if they will be discussing off-label or investigational use(s) of drugs, products, and/or devices (any use not approved by the US Food and Drug Administration).
 - The off-label and investigational use of antidepressants, topiramate, sibutramine, naltrexone, and dasotraline for the treatment of binge eating disorder will be discussed.
- Applicable CME staff have no relationships to disclose relating to the subject matter of this activity.
- This activity has been independently reviewed for balance.

Learning Objectives

- Outline the diagnostic criteria that distinguish binge eating disorder (BED) from other eating disorders and potentially comorbid psychiatric and physical conditions
- Evaluate the latest clinical data surrounding available and emerging BED pharmacotherapies, including their mechanisms of action, available efficacy and safety data, and potential impact on long-term outcomes
- Integrate the latest clinical data and patient-specific considerations, including potential comorbidities and misperceptions, into individualized BED management strategies that incorporate both psychosocial and pharmacologic therapy as appropriate

Part 1:
Academic Overview of BED

What is Binge Eating Disorder (BED)?

- *DSM-5* defines BED as recurrent episodes of binge eating:
 - Eating, in a discrete period of time, an amount of food larger than most people would eat in a similar amount of time under similar circumstances
- AND**
- A sense of ***lack of control*** over eating during the episode
 - Occurring at least once a week for 3 months
 - Associated with marked distress

DSM-5 Associated Features

Binge episodes are also associated with ≥ 3 of the following:

1. Eating more rapidly than usual
2. Eating until feeling uncomfortably full
3. Eating large amounts of food when not feeling physically hungry
4. Eating alone because of feeling embarrassed by how much one is eating
5. Feeling disgusted with oneself, depressed, or guilty afterwards

*Not unusual for **all 5** features to be present*

DSM-5 Severity

- Levels of severity are based on the number of weekly binge eating episodes:



- Severity level can be increased to reflect other symptoms and functional disability
- Validity of *DSM-5* severity indicators uncertain

Binge Eating Disorder Diagnostic Caveats

- Although overvaluation of shape or weight is often seen (40%)...
 - it is not part of the *DSM-5* criteria for BED
- BED vs bulimia nervosa?
 - BED is *not* associated with regular compensatory behaviors such as purging or excessive exercise, or with dietary restriction, although frequent dieting may be reported
- Since often a secretive behavior, and associated with embarrassment or shame...
 - It is not ordinarily revealed unless the clinician makes a direct inquiry regarding eating patterns

Context is Important

- An excessive amount of food for a typical meal might be considered normal during a celebration or holiday meal
- A single episode of binge eating $\neq$ one setting
 - ie, from office to car to home
- The food consumption **must** be accompanied by a sense of lack of control
 - eg, not unusual for an individual to continue binge eating if the phone rings
- Types of foods consumed can also be “healthy”
 - eg, fruits, yogurt

Etiology of Binge Eating Disorder

- Multiple neurobiological explanations, including:
 - Dysregulation in reward center and impulse control circuitry
 - Potentially related disturbances in dopamine signalling (“wanting food”) and endogenous μ -opioid signalling (“liking food”)
- Additionally, there is interplay between genetic influences and environmental stressors
 - Functional polymorphisms of the dopamine D₂ receptor gene and of the μ -opioid gene may influence proneness to BED
 - Antecedents to binge eating include negative affect; interpersonal stressors; dietary restraint; negative feelings related to body weight, body shape, and food; and boredom

Binge Eating Disorder is the Most Common Eating Disorder

- Estimated lifetime prevalence of 0.85% among US adults
 - BED > bulimia nervosa and anorexia nervosa
- Lifetime prevalence for BED:
 - 0.42% for men and 1.25% for women
- Important caveats:
 - Although many people with BED are obese (BMI ≥ 30 kg/m²), roughly half are not (yet)
 - Odds Ratio BED with severe obesity (BMI > 40) is 4.61

BMI = body mass index.

Citrome L. *CNS Spectr.* 2015;20 Suppl 1:44-50. Udo T, et al. *Biol Psychiatry.* 2018;84(5):345-354.

Binge Eating Disorder is the Most Common Eating Disorder (cont'd)

- Roughly comparable across ethnic/racial groups:
 - Non-Latino white (0.94%)
 - Latino (0.75%)
 - African-American (0.62%)
- The onset of BED occurs at a later median age (21 years) than anorexia nervosa (17 years) or bulimia nervosa (16 years), and with a much wider distribution
- The mean persistence of BED is about 16 years

Binge Eating Disorder: The “Invisible Disorder”

- BED is often a *secret* disorder – spouse and children often unaware
- BED is often *shameful* – reluctance to bring it up
- BED is an *unknown* disorder to patients – many have not heard of it
- BED is an *under-recognized* disorder to clinicians
 - Among the 22,397 respondents to an Internet survey:
 - 344 participants (1.5%) met the *DSM-5* criteria for BED in the past 12 months
 - Of these 344 respondents with BED, only 11 (3.2%) had ever been diagnosed with BED by a health care provider



Every clinician has patients with unrecognized BED:
They come for treatment of other disorders!

How to ask? *Make it Routine*

- We already ask about disturbances in appetite and change in weight, both up and down – a barometer for general health
- **How** a person eats is not always a subject for discussion:
 - ASK: “Have you ever eaten more than you intended?”
 - Follow up with: “Did you feel like it wasn’t possible to stop?”



How to ask?

Preferred Words

Preferred Words? ✓

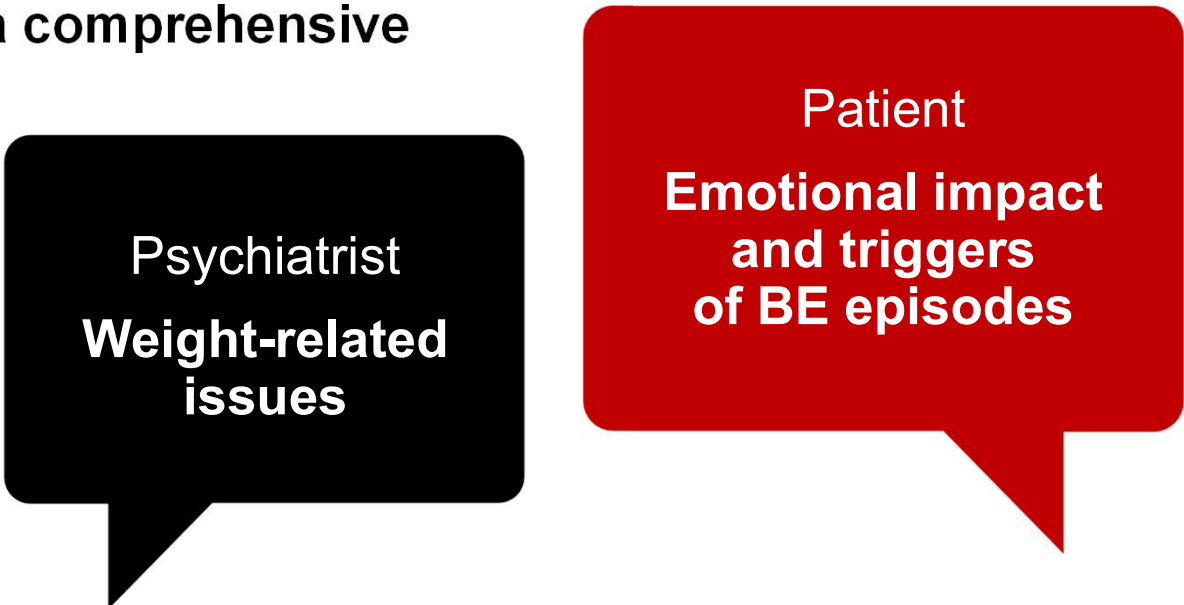
- Preferred obesity-related terms
 - “Weight”
 - “BMI”
- Preferred binge-related descriptions
 - “Kept eating even though not physically hungry and loss of control”

Words to Avoid? ✗

- “Fatness”
- “Excess fat”
- “Large size”
- “Heaviness”
- “Obesity”
- “Willpower”

Miscommunication

Obstacles to a comprehensive evaluation...



**Psychiatrist
Weight-related
issues**

**Patient
Emotional impact
and triggers
of BE episodes**

There is often miscommunication about the severity of binge eating episodes, as well as judgment, bias, and shame surrounding BED.

Share the Binge Eating Disorder Criteria with Your Patient

- The *DSM-5* criteria are a useful educational tool
- If asked, patients will endorse that they have the symptoms
- They will feel validated that these symptoms “are real”
- They will feel validated that this is a “real” disorder
- They will be more open to share their thoughts and feelings about this “shameful secret” they have kept to themselves for years

7-item Binge Eating Disorder Screener (BEDS-7)

- Developed based in part on the *DSM-5* diagnostic criteria
- 100% sensitivity and 39% specificity
- Completed by the patient (easily and quickly)
- Intended for screening use only
- The first question is:
 - “During the last 3 months, did you have any episodes of excessive overeating (ie, eating significantly more than what most people would eat in a similar period of time)?”
 - If “no”, stop screener
 - If “yes”, depending on the answers provided, this should trigger a more thorough clinical evaluation based on the complete *DSM-5* criteria for BED

Comorbidities

- Comorbidities bring the patient in for treatment → associated BED often goes unrecognized
- Typical physical comorbidities (even with normal BMI, include a heightened risk for metabolic syndrome):
 - Sleep disturbances
 - Pain (musculoskeletal, headaches)
 - Gastrointestinal conditions
 - Menstrual irregularities
 - Shortness of breath
 - Diabetes
 - Low health-related quality of life

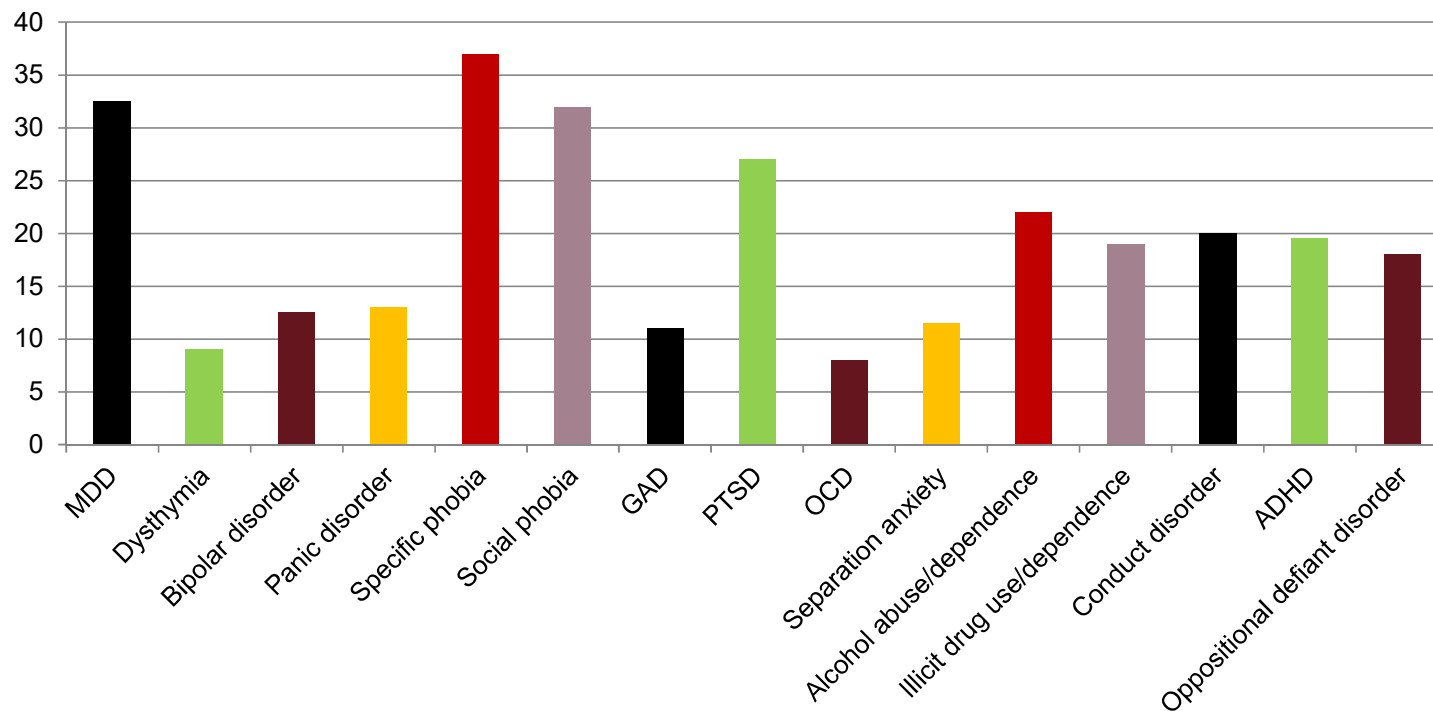
Comorbidities (cont'd)

- Psychiatric comorbidities are ubiquitous...
 - Mood disorders
 - Anxiety disorders
 - Substance use
 - Attention deficit disorder
- 80% of patients with BED will meet criteria for other psychiatric disorders
- Suicide attempt risk is elevated in individuals with BED, even after accounting for the presence of major depressive disorder
 - Psychiatric comorbidity is linked to the severity of binge eating and not to the degree of obesity

Prevalence of Psychiatric Comorbidities

Rate of Comorbidity by Specific Illness

Data from the National Comorbidity Survey Replication (N=9282)



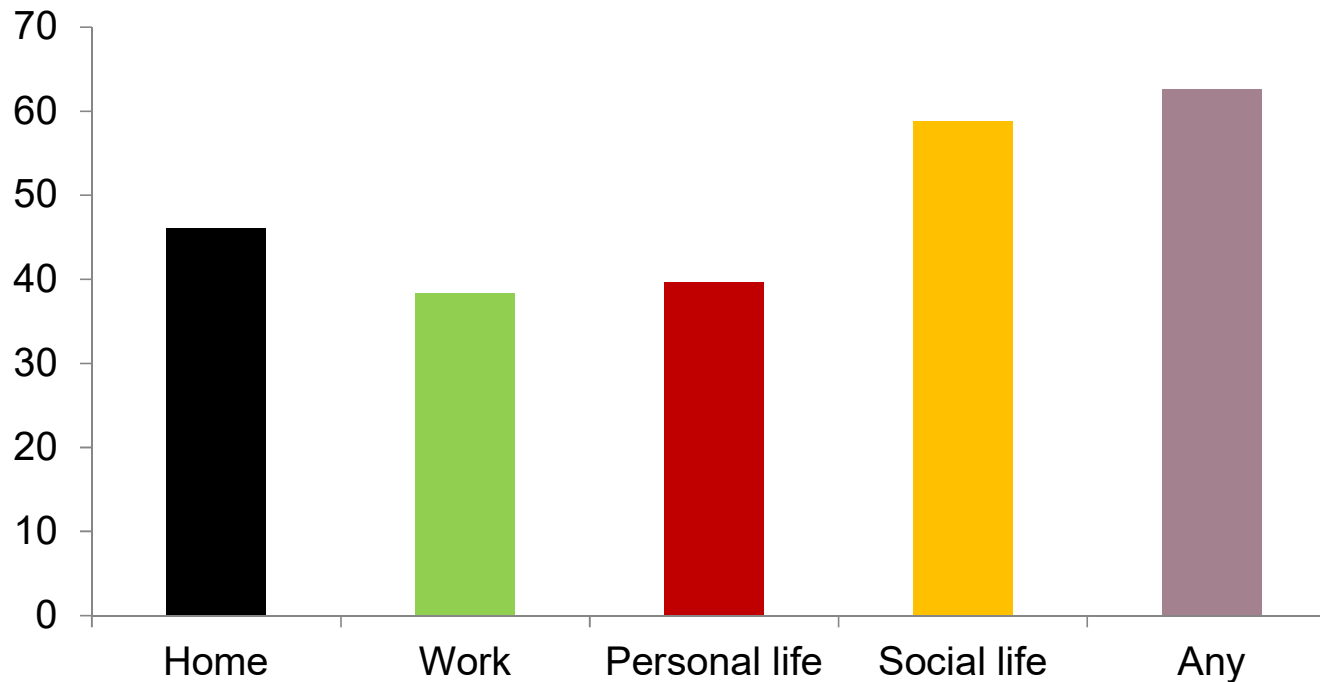
MDD = major depressive disorder; GAD = generalized anxiety disorder; PTSD = posttraumatic stress disorder; OCD = obsessive-compulsive disorder; ADHD = attention-deficit/hyperactivity disorder.

Hudson JI, et al. *Biol Psychiatry*. 2007;61(3):348-358. Figure adapted from: Citrome L. *J Clin Psychiatry*. 2017;78 Suppl 1:9-13.

Burden of Binge Eating Disorder: *Functional Impairment*

Role Impairment Associated with BED

Data from the National Comorbidity Survey Replication (N=9282)



Hudson JI, et al. *Biol Psychiatry*. 2007;61(3):348-358. Figure adapted from: Kornstein SG. *J Clin Psychiatry*. 2017;78 Suppl 1:3-8.

Psychological Treatments for Binge Eating Disorder

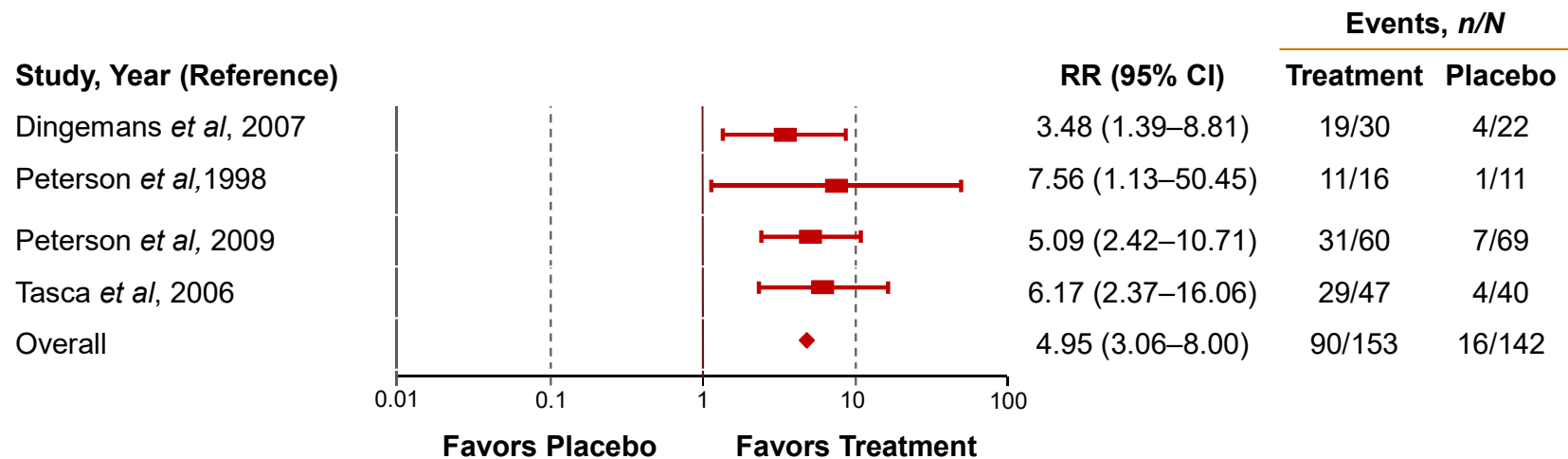
- CBT and IPT can reduce binge eating behavior
 - Access to such treatments may be limited because of local availability and/or cost
- 33% to 50% of patients with BED do not appear to benefit completely or sufficiently from psychological and behavioral treatment
- Generally little to no weight loss, although successfully eliminating binge eating can protect against future weight gain

CBT = cognitive-behavioral therapy; IPT = interpersonal psychotherapy.

Citrome L. *CNS Spectr.* 2015;20 Suppl 1:44-50. Grilo CM. *J Clin Psychiatry.* 2017;78 Suppl 1:20-24.

Psychological Treatments for Binge Eating Disorder (cont'd)

Effect of Therapist-Led CBT on Abstinence from Binge Eating



Pharmacologic Treatments for Binge Eating Disorder

- Antidepressants (SSRIs, SNRIs, NDRI)
 - Can reduce BE frequency
 - Not effective for weight loss
 - May increase appetite
- Anticonvulsants (topiramate)
 - Efficacious in reducing BE and weight
 - Negative impact on cognitive function
- Antiobesity/anorectic agents that target appetite and weight (sibutramine)
- Medications for addictive disorders (naltrexone)
- ADHD medications (lisdexamfetamine)
- Dual-acting dopamine and norepinephrine reuptake inhibitor (dasotraline)

None indicated for BED

Falls short in terms of robustness of effect, tolerability, or both

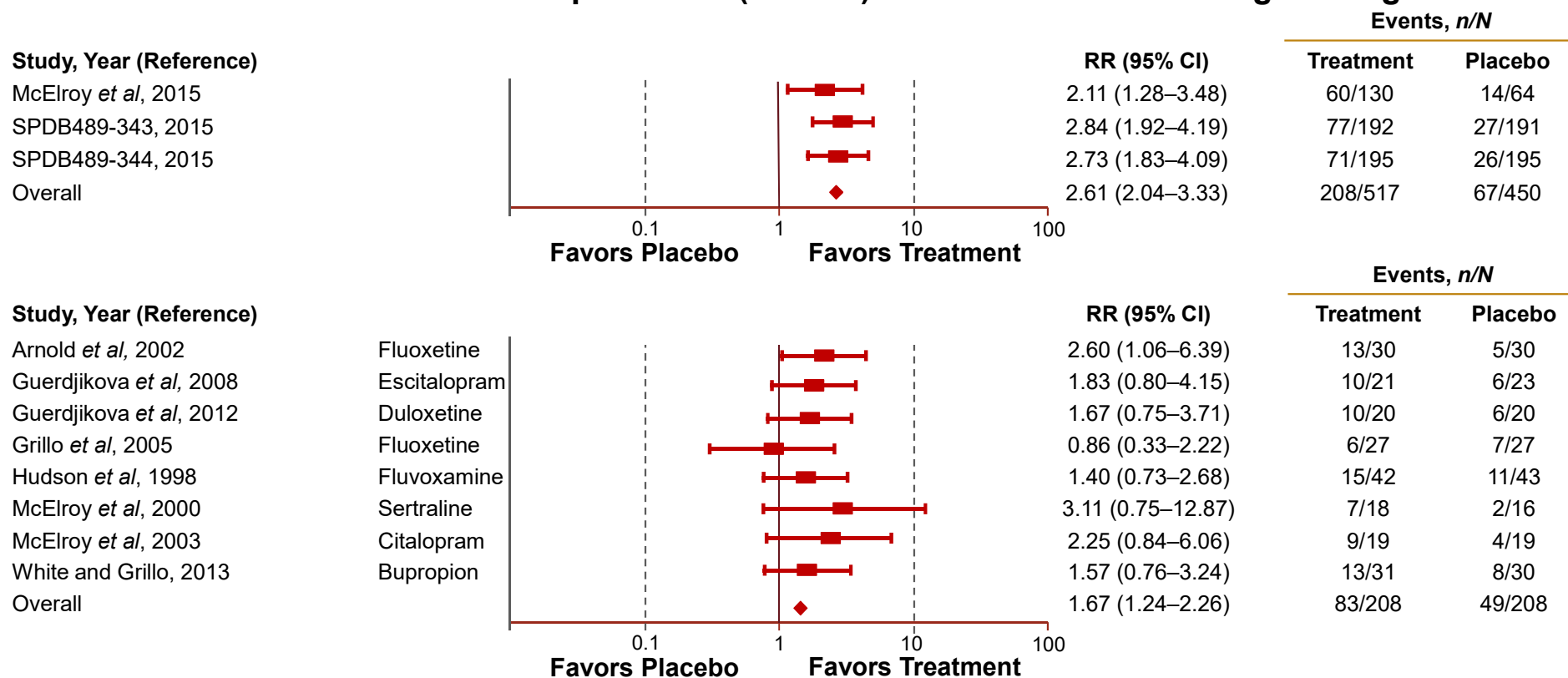
Sole agent approved for BED

Phase 3 for BED

SSRI = selective serotonin reuptake inhibitor; SNRI = serotonin–norepinephrine reuptake inhibitor; NDRI = norepinephrine–dopamine reuptake inhibitor.
Citrome L. *CNS Spectr.* 2015;20 Suppl 1:44-50.

Pharmacologic Treatments for Binge Eating Disorder (cont'd)

Effect of Lisdexamfetamine, 50 mg/day or 70 mg/day (top), and Second-Generation Antidepressants (bottom) on Abstinence from Binge Eating



Brownley KA, et al. *Ann Intern Med*. 2016;165(6):409-420.

More Details about Lisdexamfetamine

- Lisdexamfetamine is indicated for the treatment of moderate-to-severe BED and is not indicated for weight loss
- Cardiac disease and risk of abuse must be assessed when prescribing
- Recommended starting dose 30 mg/day
- Titrated in increments of 20 mg at approximately 1 week intervals to achieve the recommended target dose of 50–70 mg/day
- Lisdexamfetamine is taken once daily in the morning, with or without food
 - Afternoon doses are to be avoided because of the potential for insomnia

Lisdexamfetamine and Specific Adverse Events

Number and percentage of participants with common adverse events and NNH vs placebo and 95% CIs from the Phase 2 or 3 double-blind, 11- to 12-week placebo-controlled trials of lisdexamfetamine in adults with BED

Adverse Event	Lisdexamfetamine (all doses) (N=569)	Placebo (N=435)	NNH (95% CI)
Dry mouth	207 (36.4%)	32 (7.4%)	4 (3–5)
Decreased appetite	70 (12.3%)	13 (3.0%)	11 (8–17)
Insomnia	79 (13.9%)	21 (4.8%)	11 (8–18)
Headache	81 (14.2%)	39 (9.0%)	19 (11–75)
Constipation	35 (6.2%)	6 (1.4%)	21 (15–40)
Feeling jittery	30 (5.3%)	2 (0.5%)	21 (15–35)
Nausea	47 (8.3%)	22 (5.1%)	32 (16–696)
Irritability	36 (6.3%)	23 (5.3%)	97 (ns)
Fatigue	31 (5.4%)	21 (4.8%)	162 (ns)

NNH = number needed to harm; ns = not significant.

Citrome L. *Int J Clin Pract.* 2015;69(4):410-421.

Lisdexamfetamine Maintenance

- A 39-week, long-term maintenance of efficacy study of lisdexamfetamine for BED
- Of 418 enrolled participants, 275 responded to lisdexamfetamine (per protocol) and were randomized at the end of open-label treatment
- During the 26-week, double-blind, randomized-withdrawal phase of the study, lisdexamfetamine demonstrated superiority over placebo on time to relapse
- Observed relapsed rates for lisdexamfetamine vs placebo were 3.7% vs 32.1%, resulting in an NNT of 4

NNT = number needed to treat.

Citrome L. *Int J Clin Pract*. 2015;69(4):410-421. Hudson JI, et al. *JAMA Psychiatry*. 2017;74(9):903-910.

Tips for Rx Lisdexamfetamine for Binge Eating Disorder

- Explain that the goal is to decrease the frequency of binge episodes and that lisdexamfetamine is not being Rx'd for weight loss or for obesity
 - Weight loss will probably occur and you should continue with weighing the patient at every visit
- Warn that dry mouth will probably occur
- Ask that you be told right away if they experience being “revved up” or irritable, or otherwise feeling not themselves
- Be open-minded about dosing
 - The clinical trials compared groups of patients, but we treat individuals

In Phase 3 of Development: Dasotraline

- Dasotraline is a novel compound with DNRI pharmacology
- Slow absorption and a long half-life, resulting in stable plasma concentrations over 24 hours with once-daily dosing and low potential for abuse
- Being studied in ADHD and BED
- While a number of neurotransmitter systems are likely to be involved in BED pathophysiology, disturbances in dopamine and norepinephrine circuitry play a key role in the pathogenesis of BED
- Generally well-tolerated and most common adverse events were insomnia, dry mouth, and decreased appetite

DNRI = dopamine and norepinephrine reuptake inhibitor.

Navia B, et al. Poster P7-084 – Dasotraline for the Treatment of Moderate to Severe Binge Eating Disorder in Adults: Results from a Randomized, Double-blind, Placebo-controlled study. Presented at: 170th Annual Meeting of the American Psychiatric Association; May 20–24, 2017; San Diego, CA. Koblan KS, et al. *Drug Alcohol Depend.* 2016;159:26-34.

In Phase 3 of Development: Dasotraline (cont'd)

- In a randomized, double-blind, placebo-controlled, 12-week trial in adults with moderate to severe BED, flexibly dosed dasotraline 4–8 mg/day demonstrated meaningful improvement in BED symptoms vs placebo
 - Change from baseline in:
 - Number of binge days per week
 - BE-CGI-S score
 - Y-BOCS-BE total score
 - 4-week cessation from binge eating in 47% of the dasotraline group vs 21% of the placebo group

BE-CGI-S = Binge Eating Clinical Global Impression-Severity; Y-BOCS-BE = Yale-Brown Obsessive Compulsive Scale Modified for Binge Eating. Navia B, et al. Poster P7-084 – Dasotraline for the Treatment of Moderate to Severe Binge Eating Disorder in Adults: Results from a Randomized, Double-blind, Placebo-controlled study. Presented at: 170th Annual Meeting of the American Psychiatric Association; May 20–24, 2017; San Diego, CA.

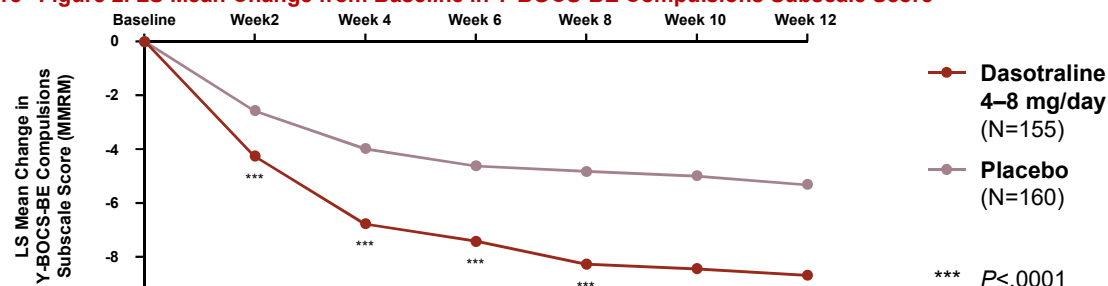
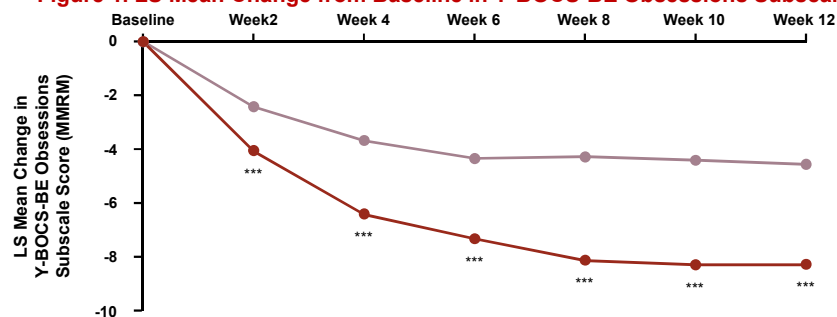
In Phase 3 of Development: Dasotraline (cont'd)

- A second randomized, double-blind, placebo-controlled, 12-week trial in adults, with a fixed dose design was recently reported
 - Statistically significant decrease in number of binge days per week from baseline to Week 12 in the group treated with 6 mg/day vs placebo, but not for the lower dose of 4 mg/day
 - Both dose groups showed statistically significant improvement vs placebo in BE-CGI-S score and Y-BOCS-BE total score
- Discontinuation rates due to adverse events in the 4 mg/day, 6 mg/day, and placebo groups were 8.6%, 14.1%, and 1.2%, respectively; the most common ($\geq 10\%$) adverse events in either dose group were insomnia, dry mouth, headache, decreased appetite, nausea, and anxiety, consistent with previous dasotraline studies
- Option of 12-month, open-label extension study evaluating the long-term safety and tolerability of dasotraline for BED

ClinicalTrials.gov Identifier: NCT03107026. Sunovion. July 25, 2018. <https://news.sunovion.com/press-release/sunovion-announces-positive-top-line-results-pivotal-study-evaluating-dasotraline>. Accessed September 6, 2018.

Dasotraline: Effect on Behavioral Outcomes

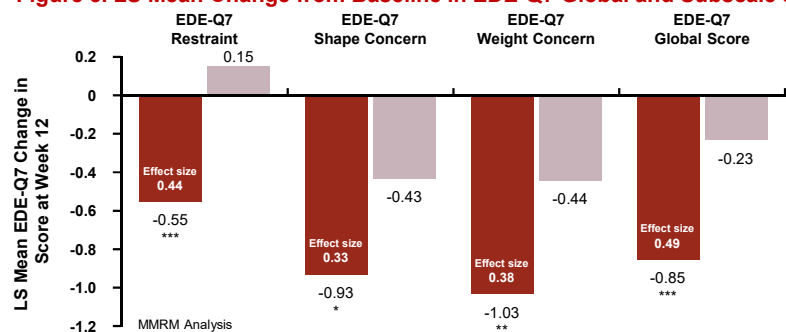
Figure 1. LS Mean Change from Baseline in Y-BOCS-BE Obsessions Subscale Score **Figure 2. LS Mean Change from Baseline in Y-BOCS-BE Compulsions Subscale Score**



*** $P < .0001$

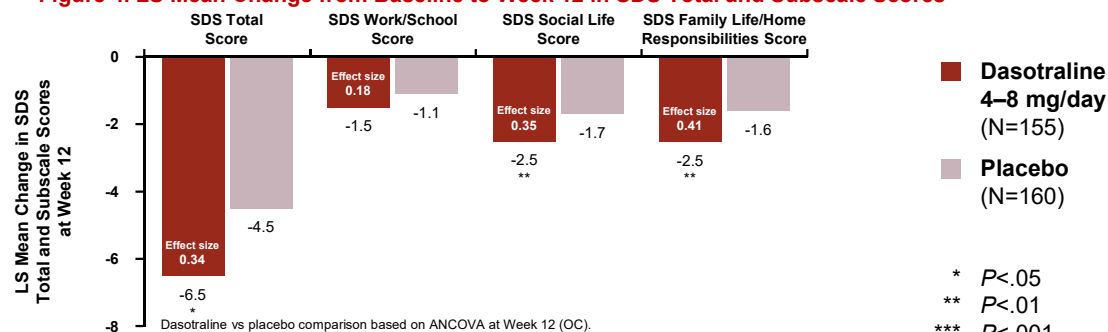
* Dasotraline demonstrated significant efficacy in reducing both obsessional thoughts and compulsive behaviors related to binge eating, with onset of efficacy within the first 2 weeks of treatment. At week 12, effect sizes were comparably large on both Y-BOCS-BE Obsessions and Compulsions subscales (0.95 and 0.87).

Figure 3. LS Mean Change from Baseline in EDE-Q7 Global and Subscale Scores



* Dasotraline demonstrated significant efficacy in reducing the severity of psychological features common to BED as measured by the EDE-Q7 total and subscale scores. At week 12, effect sizes were in the moderate range for EDE-Q7 global and subscale scores.

Figure 4. LS Mean Change from Baseline to Week 12 in SDS Total and Subscale Scores



* $P < .05$

** $P < .01$

*** $P < .001$

Dasotraline vs placebo comparison based on ANCOVA at Week 12 (OC). Analysis of Work/School subscale score (and therefore the SDS-total score) was limited to patients who were working or going to school on dasotraline (n=145) or placebo (n=145).

* Numeric differences favoring dasotraline vs placebo were found on LOCF analysis on the SDS total score (-1.5 vs -1.1), the SDS social life score (-2.3 vs -1.7), or the SDS family life/home responsibilities score (-2.1 vs -1.7).

EDE-Q7 = 7-item version of the Eating Disorder Examination Questionnaire; SDS = Sheehan Disability Scale.

Navia B, et al. #W45 – Dasotraline for Treatment of Adults with Binge-Eating Disorder: Effect on Behavioral Outcomes. Presented at: American Society for Clinical Psychopharmacology; May 29-June 1, 2018, Miami Beach, FL.

Combination Therapy

- Adding pharmacotherapy to CBT failed to enhance binge eating outcomes in 6 of 7 published studies testing a variety of medications
- One study with statistical advantage for a combined approach: topiramate + CBT
 - Produced better outcomes than placebo + CBT for reducing both binge eating and weight
- CBT plus lisdexamfetamine has not been tested

Binge Eating Disorder: Summary

- BED is different from overeating and requires the presence of distinguishing features, notably and specifically **loss of control**, marked distress, and strong feelings of shame and guilt
- Psychiatric and somatic co-occurrences are very common, as are functional impairments
- **BED may go undiagnosed** for many years because patients are not always specifically asked about their eating behaviors
- BED occurs in **both men and women** across racial and ethnic groups, and although BED is frequently associated with obesity, many adults with BED are of healthy weight or overweight
- Effective treatment modalities include certain specific psychotherapy (**CBT, IPT, behavioral weight loss**) and pharmacologic approaches, of which **lisdexamfetamine** has received regulatory approval, and **dasotraline** in Phase 3 of clinical development

Part 2: Case-Based Discussion

Case #1: *The Failed Diet*

- Jane: 50-year-old woman with MDD, treated for the past 25 years with good control of her depressed mood
- Responds to and tolerates only paroxetine
 - Increased appetite and is “always hungry”
- Has gained weight gradually over the years, despite diet and exercise
- Complains: “I am not able to lose weight even though I am on a diet”
- Prescriber (me) assumed it was because of the paroxetine
- When finally asked about eating in secret, she revealed bingeing every evening once her husband went to bed
- She was very surprised to hear this was BED
- Treatment response to MDD and BED do not necessarily “travel together”

Case #2: *Like Mother, Like Son*

- Geno: 25-year-old student in a biology PhD program at an Ivy League University, has been “irritable and moody”
- His girlfriend urges him to go to the college counselling service
 - At his first appointment talks about the stressors of failed experiments and that if he doesn’t get back on track, he will lose the year
 - He is thought to have a major depressive episode and placed on fluoxetine
- Over the course of several weeks Geno remains unhappy and talks about having an insatiable appetite, worsened by his antidepressant therapy, and mentioned, casually, that he has been eating “just like his Mother”
- Geno was never asked about his family history of psychiatric problems and now after his casual remark, his clinician finally makes the inquiry and finds that Geno’s Mother has been treated over the years for bulimia nervosa and for “non-purging bulimia”
- Fluoxetine was discontinued and an eating diary was started
- Binge eating episodes were clearly noted, the clinician educated himself about BED, and lisdexamfetamine was prescribed
- After 2 months on lisdexamfetamine 50 mg/day, Geno’s mood was improved, and his eating behaviors normalized

Case #3: *The Specter of Body Image*

- Mary: 45-year-old African American woman, banking executive, long history of weight fluctuations
- Long history of “failed diets” and being told to “lose weight” by internists
- Highly successful in competitive banking field despite long history of perceived negative biases about her sex, race, and weight
- Saw recruitment flyer for a study at university for “concerns about eating behaviors” and after volunteering she learned she met criteria for BED
- She had moderate acute responses to pharmacotherapy trials but “relapsed”
- When finally asked about her concerns regarding weight and shape, she revealed how they dominated how she felt about herself
- She was referred to a therapist specializing in CBT

Case #4: *Is More Really Better?*

- Jane: 50-year-old woman with history of recurring depression and anxiety, history (non-recurring substance use problems)
- Currently struggling with managing several medical problems, including severe obesity, metabolic syndrome, and pain disorder
- Presence of BED recently recognized by provider in a multidisciplinary practice
- Discussion centered on treatment needs and options given this patient's "complexity"
- The psychologist in the practice suggested starting with "just" CBT

Q&A