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Is the Pharmacological Management of Bulimia Nervosa Plausible?

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Abstract

Bulimia nervosa (BN) is a severe psychiatric disorder of unknown etiology and with a complex bio-psycho-social psychopathology. Specific treatment is primarily based on psychotherapy, and only one medication, fluoxetine, has been approved for BN. This raises the question of whether the use of medication is a possible direction for innovative intervention in BN. This article reviews behaviors and neurobiology that have been associated with BN pathophysiology and identifies and discusses potential pharmacological interventions to target emotional instability, self-regulation, impulse control, and neurotransmitter function in BN. The expert opinion describes a practical approach for the use of medication in the treatment of BN, comorbid conditions, and behavior traits that can interfere with recovery.

1. Introduction

Bulimia nervosa (BN) is a severe psychiatric disorder that is characterized by 1) eating, in a discrete period of time, an amount of food that is definitely larger than most people would eat during similar circumstances and 2) a sense of lack of control over eating during the episode. Those binge eating episodes are typically followed by guilt and shame, which trigger compensatory behaviors to avoid weight gain, such as self-induced vomiting, use of laxatives or diuretics, fasting or exercise *[1]*. BN is associated with increased mortality for all causes of death including

suicide, and often has a chronic course. Lifetime prevalence estimate for BN is 1.0%, and comorbidity is high (80% with an anxiety disorder, 70% with a mood disorder, 60% with an impulse control disorder, 40% with substance use disorder) *[2]*. Cognitive behavioral therapy, interpersonal therapy and the selective serotonin reuptake inhibitor (SSRI) fluoxetine are the treatments of choice, but about 50% have a chronic course or are only partially recovered. Thus, treatment effects are modest, and we lack pharmacological interventions that target BN as standalone treatments or in conjunction with behavioral interventions. The goal of this editorial is to briefly review behaviors and pathophysiology that have been associated with BN and identify and discuss pharmacological treatment targets.

2. Behavioral Traits as Vulnerability Factors

The underlying etiology of BN is not well understood. BN has been associated with inadequate mechanisms to control food intake beyond ones physiological needs, and behavioral traits could contribute *[3]*. One of those traits is altered emotion regulation, the process responsible for monitoring, evaluating, and modifying emotional reactions. Individuals with BN have difficulties modulating strong emotions and controlling rash, impulsive response. Most, but not all studies suggest that negative affect precedes binge-eating episodes, followed by initial relief. Impulsivity, is a trait to react rapidly to stimuli without regard for potential negative consequences. Binge-eating behaviors frequently occur impulsively in response to external or internal triggers, and increased impulsivity has been found in BN. Negative urgency, the tendency to experience strong impulses under the influence of negative emotions, or to act rashly when distressed, has also been associated with BN. Another trait, sensitivity to reward, described in the reinforcement

sensitivity theory, was elevated in BN and it has been hypothesized that an imbalance between reward sensitivity, impulsivity and inhibition are mechanistically involved in driving binge-eating episodes.

3. Neurocircuitry of Emotion Regulation, Impulsiveness and Cognitive Control

A complex interplay exists between emotion regulation and cognitive control. Emotions affect attention, drive cognitive bias and may interrupt proper decision making, while attention to specific goals can control emotions and override strong feelings *[4]*. Control of food cravings is thought to involve prefrontal cortical areas, whereas greater caloric intake has been related to higher activation in gustatory cortex and brain regions for reward computation. Studies in BN found reduced prefrontal cortical activity when viewing food pictures, hypoactivity in brain areas involved in self-regulation and impulse control, such as prefrontal cortex or insula, and positive correlations between negative affect and striatal brain response during food anticipation *[3]*. Altogether, research suggests altered brain function related to emotion regulation in BN, but the literature is small.

4. Neurotransmitters and Hormones

Dopamine, serotonin, acetylcholine and norepinephrine have been associated with cognitive control and impulse control in frontal cortical circuits *[5]*. Studies in BN found that serotonin 1A and dopamine D2/3 receptor binding correlated with anxiety and behavior inhibition *[3]*. Hormones such as ghrelin, leptin, sex hormones and cortisol can also influence food intake behaviors *[6]*. Basic research on the gut-brain axis showed that stress, via cortisol and gut hormone activation leads to

dopamine mediated altered food intake implicating those feedback mechanisms but how they contribute to BN is still elusive *[3]*.

5. Neurobiology of Taste and Reward Processing

Brain reward circuits are key to the motivational aspects of food approach. Individuals with high versus low food addiction scores showed greater prefrontal cortex and caudate activation during food anticipation, but lower orbitofrontal activation in response to food receipt; this suggested that the tendency to overeat is associated with high reward system response to expectation (stimulating food approach), but reduced behavior-inhibition associated cortex response (low food intake inhibition) *[7]*. Brain response in BN after recovery showed deficits when distinguishing gain versus loss in a monetary reward paradigm, suggesting distinct reward circuit alterations depending on stimulus saliency *[3]*. A study in BN that used the dopamine related prediction error reward learning paradigm, found weaker response to unexpected stimulus receipt or omission *[8]*. In another study, negative affect correlated positively with putamen and caudate activation during food anticipation and it was hypothesized that negative affect may increase the reward value of food in BN *[9]*.

6. Targets for Pharmacological Intervention

The above reviewed literature suggests several key areas of underlying disturbances in BN. Those are behavioral traits for emotional instability, alterations in brain regions that process self-regulation and impulse control, and the neurotransmitters dopamine and serotonin as well as gut hormones as potential vulnerabilities to develop and maintain BN behaviors (Figure 1.). The importance of

SSRIs is supported by the effectiveness of fluoxetine at high dose for treatment of BN *[10]*. The mechanism of fluoxetine's action is uncertain, but effects on mood and anxiety likely play a role, since antidepressant/antianxiety medication in general is superior to placebo in improving BN *[11]*. Only one true long term study exists, conducted over 52 weeks, and while fluoxetine was superior, attrition rate was very high with over 80% *[12]*. In that study there was worsening over time on all measures of efficacy, and the authors suggested that fluoxetine alone may not be an adequate treatment after acute response in most patients. This makes the search for other medication approaches ever more important.

Mood instability in BN suggests that mood stabilizers could be of help. Small, uncontrolled studies suggested that the mood stabilizer lamotrigine could be beneficial in controlling BN behaviors *[13]*. A case report suggested that the stimulant methylphenidate was beneficial in a patient with comorbid ADHD, targeting executive function and impulse control circuits *[14]*. Stimulants have been used with success in binge eating disorder and further investigation is warranted *[3]*. Several neurotransmitter specific drugs that target appetite, reward system or hormone regulation, are being considered as potential therapeutic agents, but this search has overall being disappointing *[15]*. Different reasons may be the case. First, BN is a multifactorial problem and one drug may not be sufficient to target the biological, psychological and social factors. Second, we need to understand BN's underlying pathophysiology better first to apply pharmacological treatments more effectively. Third, we will need to identify a range of treatment modules that in concert address the many illness-contributing factors to overcome the illness. Those treatments will include various psychotherapies (for instance interventions for eating disorder specific behavior management, general emotion regulation, etc.)

and psychopharmacological interventions that target mood instability, anxiety, and impulse control, depending on severity and need. Importantly, binge eating and purging modulate brain biology and different treatments may become indicated at different time points during the course of illness. Thus, psychopharmacology in BN clearly has a role, but usually not as the only treatment for BN at this point, and often to address comorbidity and BN-related behaviors such as labile emotions and impulse control.

7. Expert Opinion

The only approved medication for BN is fluoxetine, either started at or up-titrated over several days to 60mg daily *[10]*. This should be considered for someone with severe form of the illness. There are several caveats though. Many patients are hesitant to start medication or agreeing to fast up-titration and gradual medication increase is more tolerable. BN is also associated with high rates of depression and SSRI aggressive dose increase may trigger suicidal behavior. Furthermore, the treatment effect may not be sustained and other treatments may be needed *[12]*. Thus, BN patients should be referred to psychotherapy that uses evidence based strategies such as BN focused cognitive behavior therapy. Comorbid depressive, anxiety, obsessive compulsive and impulse control disorders are common, and a substantial number of patients has a substance use disorder *[2]*. Another comorbid condition that is often not readily disclosed is post-traumatic stress disorder, which can trigger BN behaviors. Although systematic research on this topic is lacking, my clinical experience is that diligently identifying and treating those conditions with approved treatment regimens supports overall clinical outcome including that of BN. In the case of comorbid ADHD, there is the concern that prescription of a

stimulant or other possibly appetite reducing medication may be used to avoid normal food intake and promote the eating disorder drive to lose weight. Thus, careful weight monitoring is important. While I do not hesitate to treat ADHD in BN, it is usually the last comorbidity to address after depression, anxiety and OCD have stabilized, as those may also contribute to inattention and distractibility. Individuals with substance use history may not be good candidates for stimulant treatment but other non-habit forming treatments might be a consideration. If the patient continues to have poor response, then more experiential treatments using medications that have been found overall safe in other conditions could be used. One such treatment that could be tried is lamotrigine with the rationale of mood stabilization and helping with impulse control, to strengthen cognitive control over urges to binge eat, and a low risk of weight gain, which is a frequent reason why patients with eating disorders decline medication interventions.

Article highlights box

- Bulimia nervosa has a complex bio-psycho-social etiology and psychopharmacology has been limited.
- The only approved medication is fluoxetine, but research suggested that fluoxetine alone may not be an adequate treatment in most patients to support long term recovery.
- Research has implicated behavioral traits for emotional instability, alterations in brain regions that process self-regulation and impulse control, and the neurotransmitters dopamine and serotonin as well as gut hormones as potential vulnerabilities to develop and maintain bulimia nervosa behaviors.
- Bulimia nervosa is highly comorbid with depressive, anxiety and obsessive compulsive disorder and comorbid conditions should be treated aggressively.
- If the combination of evidence based psychotherapy and traditional treatments including fluoxetine for bulimia nervosa or other agents to treat comorbidities has not been sufficiently successful, other approaches such as a mood stabilizer could be of benefit.

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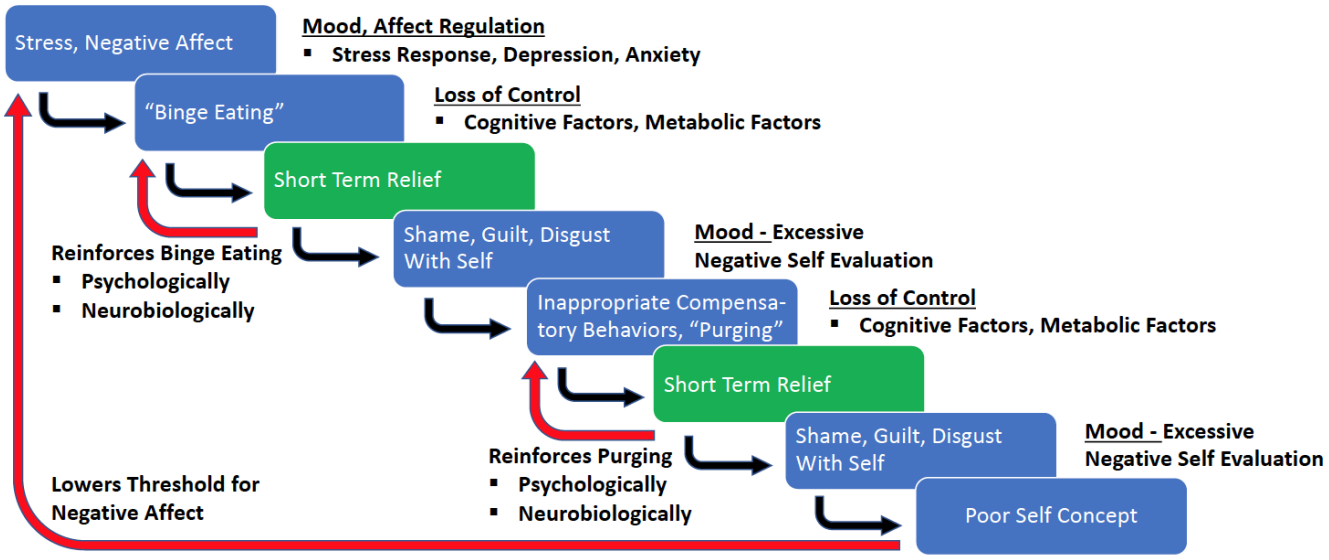
Figure 1.


Stress, Negative Affect
Mood, Affect Regulation
Stress Response, Depression, Anxiety
"Binge Eating"
Loss of Control
Cognitive Factors, Metabolic Factors
Short Term Relief
Reinforces Binge Eating
Psychologically
Neurobiologically
Shame, Guilt, Disgust With Self
Mood - Excessive Negative Self Evaluation
Inappropriate Compensa-tory Behaviors, "Purging"
Loss of Control
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