EXPLORING THE USE OF LISDEXAMFETAMINE DIMESYLATE AS A TREATMENT FOR ADULTS WITH BULIMIA NERVOSA: A QUANTITATIVE AND QUALITATIVE ASSESSMENT

by

Laura M. Dixon

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Dalhousie University is located in Mi'kma'ki,
the ancestral and unceded territory of the Mi'kmaq.
We are all Treaty people.

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Abstract

As part of an open-label eight-week feasibility trial examining the use of lisdexamfetamine dimesylate (LDX) for BN, I conducted a mixed-methods sub-project to investigate whether eating disorder symptoms and measures of eating disorder cognitions, obsessive, compulsive, and impulsive features, and functional impairment change during treatment with LDX and to explore participant experiences with LDX treatment. In the intent-to-treat sample, reductions in the frequency of objective binge episodes and total compensatory behaviours were observed (Cohen's d = 1.81 and 1.85, respectively). Furthermore, scores on measures of eating disorder cognitions, obsessive and compulsive features, and food-related impulsivity decreased (Cohen's d range: .38 - 4.22). In the qualitative analysis, I found four overarching themes regarding participants' experiences with LDX: 1) reprieve from the eating disorder, 2) improvement in function and quality of life, 3) renewed hope for recovery, and 4) ability to normalize eating.

List of Abbreviations Used

ADD	Attention Deficit Disorder
ADHD	Attention Deficit Hyperactivity Disorder
ADR	Adverse Drug Reaction
AE	Adverse Event
BED	Binge Eating Disorder
BIS-11	Barratt Impulsiveness Scale
BMI	Body mass index
BN	Bulimia Nervosa
CBT	Cognitive Behavioural Therapy
CBT-BN	Cognitive Behavioural Therapy for Bulimia Nervosa
CBT-E	Enhanced Cognitive Behavioural Therapy
CIA	Clinical Impairment Assessment
CSSR	Columbia Suicide Severity Scale
DSM-5	Diagnostic and Statistical Manual of Mental Disorders 5th Edition
ECG	Electrocardiogram
ED	Eating Disorder
EDE	Eating Disorder Examination 17.0D
ET	End of treatment
FDA	United States Food and Drug Administration
IPT	Interpersonal Psychotherapy
ITT	Intent-to-treat
Kg	Kilogram
kg/m^2	Kilogram per square meter
LDX	Lisdexamfetamine Dimesylate
LOCF	Last observation carried forward
M	Sample mean
mmHG	Millimetre of mercury
MPH	Methylphenidate
RCTs	Randomized Controlled Trials
SCID-5-RV	Research Version of the Structured Clinical Interview for DSM-5 Disorders
SD	Standard deviation
SSRIs	Selective Serotonin Reuptake Inhibitors
TFEQ	Three-Factor Eating Questionnaire
YBOCS-BP	Yale Brown Obsessive Compulsive Scale modified for binge eating and purging
y/o	Year old

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Chapter 1 – Introduction

1.1. Overview of Bulimia Nervosa

Bulimia nervosa (BN) is a psychiatric disorder characterized by recurrent episodes of binge eating (eating an unusually large amount of food in a discrete period of time while experiencing a loss of control) and use of compensatory behaviours to prevent weight gain such as self-induced vomiting (e.g., purging), laxative, diuretic or other medication misuse, fasting, or excessive exercise (American Psychiatric Association, 2013). As specified in the Diagnostic and Statistical Manual of Mental Disorders (5th ed.; DSM–5; American Psychiatric Association, 2013), to meet criteria for a diagnosis of BN, episodes of binge eating and compensatory behaviours must both occur at least once a week on average over three months, self-evaluation must be unduly influenced by shape and weight, and episodes must not occur exclusively during periods for which criteria are met for anorexia nervosa. The prevalence of BN has been reported as 1-3% (Keski-Rahkonen & Mustelin, 2016; Smink et al., 2012).

Bulimia nervosa is associated with potentially serious medical complications directly related to the method and frequency of compensatory behaviours used, specifically self-induced vomiting and laxative abuse (Mehler, 2011). The medical complications of BN include dental and esophageal erosion, esophageal rupture, electrolyte abnormalities (hypokalemia, hypochloremia, metabolic alkalosis) and cardiac arrhythmias (Mehler, 2011). In addition to medical complications and risks, increased rates of suicide and high comorbidity with other psychiatric disorders (e.g., depression and anxiety disorders), self-harm behaviours, personality disorders, and substance/alcohol use disorders have been reported in people with BN (Keski-Rahkonen

& Mustelin, 2016; Martinussen et al., 2017). Studies have found that BN is associated with increased risk of mortality as well as reduced quality of life (Arcelus et al., 2011; van Hoeken & Hoek, 2020).

1.2. Treatment of Bulimia Nervosa

1.2.1. The Goals of Treatment

Before describing the current evidence for BN treatments (i.e., psychotherapy and pharmacotherapy), it is relevant to first discuss *how* treatment outcome is defined and measured. Researchers commonly assess 'outcome', however, the eating disorder field has "failed miserably" at defining outcomes *consistently* (Bardone-Cone et al., 2018). To this point, the goal of treatment is often 'recovery', yet recovery is not consistently defined. In their 2018 paper, Bardone-Cone et al. attempt to provide a solution for this inconsistency. Specifically, the authors propose that recovery from an eating disorder involves A) physical recovery (e.g., body mass index), B) behavioural recovery (e.g., decreased frequency of binge eating and compensatory behaviours), and psychological recovery (e.g., decrease in eating disorder cognitions such as concerns about weight, shape, eating and dietary restraint). Although Bardone-Cone et al. (2018) provide some parameters for defining recovery, there are still inconsistencies to consider. For example, researchers use varying parameters to quantify an acceptable *degree* of recovery (e.g., complete abstinence vs. a 50% reduction of behavioral outcomes) and the *duration* for which the recovery must occur to be considered a positive outcome (e.g., 1 vs 6 vs 12 months).

Although the definition of recovery remains a topic of debate, evidence suggests that the occurrence of residual symptoms (i.e., physical, behavioral and/or psychological)

after treatment completion is a predictor of relapse and worse longer-term outcomes (Keel et al., 2005). Therefore, the goal of achieving symptom abstinence is ostensibly a desirable outcome of any treatment. As I will illustrate in Sections 1.2.2 and 1.2.3, current psychotherapies and pharmacotherapies for BN often fail to achieve abstinence, and therefore the development of new treatments is warranted.

1.2.2. Psychotherapy Treatments for Bulimia Nervosa

Cognitive behavioural therapy for BN (CBT-BN) is considered the first line treatment for BN (Fairburn, 2008). CBT-BN has been extended to an enhanced form of CBT known as CBT-E which was developed for the transdiagnostic treatment of eating disorders in both a focused and broad form (Fairburn, 2008). As outlined by Hagan and Walsh (2021), CBT-E utilizes techniques such as the development of an individualized formulation, self-monitoring, weekly-weighing during therapy sessions, psychoeducation about weight and weighing, and prescribed regular eating (eating three meals and 2-3 snacks/day) to interrupt and address eating disorder behaviours. The focus of treatment shifts to targeting cognitive elements such as the overvaluation of weight and shape thought to underpin the disorder, identifying triggers, and modifying behaviours that maintain body image concerns such as body checking and body avoidance. The broad form of CBT-E also includes optional modules (perfectionism, mood intolerance, interpersonal difficulties, and low self-esteem) that are utilized depending on clinical presentation. Treatment concludes by reviewing progress and areas to continue working on, and discussing relapse prevention (Hagan & Walsh, 2021).

A second form of therapy, interpersonal psychotherapy (IPT), aims to indirectly reduce eating disorder symptoms by addressing interpersonal problems (Hagan & Walsh,

2021). IPT has been shown to be effective for the treatment of BN particularly over the longer-term (at 1-year follow up) and is considered a relatively efficacious second-line treatment for BN (Agras et al., 2000; Fairburn et al., 1993). There was no significant difference between CBT and IPT at 8 to 12-month follow up; 31% of participants in the CBT group and 19% of participants in the IPT group had no episodes of binge eating or purging over the 28-days prior to assessment (Agras et al., 2000). Dialectical Behavior Therapy for BN and Integrative Cognitive-affective Therapy also have preliminary evidence to support their use in BN populations (Hagan & Walsh, 2021). Svaldi et al. (2019) conducted a meta-analysis on the efficacy of psychotherapies and pharmacotherapies for BN by examining 79 RCTs. The authors noted that psychotherapy treatments were predominantly CBT. With respect to reductions in frequency of binge eating and compensatory behaviour episodes, Svaldi et al. (2019) reported that psychotherapy for BN is associated with large effects (binge eating: $g = 0.98$; CI 0.54-1.41, compensatory behaviours: $g = 0.82$; CI 0.58-1.05).

Despite the existing support for CBT and IPT approaches for the treatment of BN, Linardon and Wade (2018) reported that a large proportion of patients who undergo psychological interventions for BN do not achieve complete abstinence from core eating disorder symptoms (i.e., binge eating and/or compensatory behaviours). The investigators conducted a meta-analysis of 45 randomized controlled trials (RCTs; 78 psychotherapy conditions) and found that following treatment 35% of individuals were abstinent from binge eating and/or purging. When considering all randomized individuals (intent-to-treat; ITT), 30% were abstinent. At follow-up, results were unchanged. These results indicate that 65-70% of individuals with BN continue to experience binge eating and/or

purging behaviours following psychotherapy. Similar results were found by Svaldi et al. (2019); namely, rates of abstinence from binge eating and compensatory behaviours were roughly 40% when considering pre-post treatment analysis within psychotherapy arms. Taken together, these results support the need for novel treatment approaches that improve rates of abstinence from core eating disorder symptoms in patients with BN.

1.2.3. Pharmacotherapy Treatments for Bulimia Nervosa

While psychotherapy is considered the first-line treatment for BN, evidence suggests pharmacotherapies may also offer benefit. McElroy et al. (2019) propose pharmacotherapy may play an important role in the treatment of BN, particularly for individuals who do not respond to, are not interested in, or are not able to access psychotherapy, those with comorbid psychiatric or medical conditions, and those with longstanding BN. With respect to reductions in frequency of binge eating and compensatory behaviour episodes, Svaldi et al. (2019) reported that pharmacotherapy for BN is associated with moderate to large effects (binge eating: $g = 0.61$; CI 0.31-0.91, compensatory behaviours: $g = 0.69$; CI 0.48-0.90).

Presently, fluoxetine remains the only agent approved by Health Canada and The Food and Drug Administration (FDA) for the treatment of BN (McElroy et al., 2019). Doses of 60mg/day have shown to be superior to placebo at reducing binge eating (groups receiving 60mg/day had median reductions of 67% in binge eating episodes per week vs. 33% for the placebo [$p < .001$]) and vomiting behaviours (groups receiving 60mg/day had median reductions of 56% in vomiting episodes per week vs. 5% for the placebo [$p < .001$]), with doses of 20mg/day producing intermediate effects (Fluoxetine Bulimia Nervosa Collaborative Study Group, 1992). Other selective serotonin reuptake

inhibitors (SSRIs), tricyclic antidepressants, monoamine oxidase inhibitors, and agents such as mianserin, trazodone, and bupropion have some supportive evidence (McElroy et al., 2019). Guidelines have also proposed that antidepressants are effective treatments for BN (Aigner et al., 2011; Hay et al., 2014). When considering antidepressant treatment compared to placebo for BN, Bacaltchuk and Hay (2003) found the pooled relative risk for remission of binge episodes was 0.87 (95% CI 0.81-0.93; $p<.001$) favouring active medications. They concluded that antidepressant agents were modestly superior to placebo at stopping binge eating; however, they were associated with higher rates of dropout (Bacaltchuk & Hay, 2003).

The antiepileptic agent topiramate has been investigated for BN as an off-label use in two randomized controlled trials (Hedges et al., 2003; Hoopes et al., 2003) where topiramate was superior to placebo at reducing binge/purge behaviours (mean weekly number of binge and/or purge days decreased 44.8% from baseline with topiramate versus 10.7% with placebo [$p = .004$]). Although binge/purge symptoms were significantly reduced relative to the placebo groups, roughly 50-60% of patients in the treatment group did not achieve a 50% or greater reduction in binge/purge episodes.

Various other agents including zonisamide, carbamazepine, valproate, naltrexone, phentermine-topiramate, ondansetron, and lithium carbonate have been investigated for use in BN in RCTs, open-label trials, or reported in case data (Alger et al., 1991; Faris et al., 2000; Guerdjikova et al., 2013; Herridge & Pope, 1985; Kaplan et al., 1983; Marrazzi et al., 1995; McElroy et al., 1987, 2005; Mitchell et al., 1989; Safer et al., 2020). There are mixed findings with respect to these agents' efficacy, thus the evidence base for these pharmacotherapy options is less extensive than that for fluoxetine and topiramate.

Stimulant medications have emerged as promising agents that have not yet been investigated in prospective studies in BN. While the research on stimulants for BN is limited to case data (described in Section 1.4), large studies have examined the efficacy of stimulants for binge eating disorder (BED) where binge eating is not followed by inappropriate compensatory behaviours. The evidence for the use of stimulants in BED is further described in Section 1.3.3.

Further research is needed to investigate promising agents with limited evidence bases, determine which agents are useful for certain BN presentations, and to assess pharmaceutical agents with novel mechanisms of action (McElroy et al., 2020). As proposed by Frank (2020), it is also necessary that the field achieve a better understanding of the underlying pathophysiology of BN as this would allow pharmacotherapy to be applied more effectively.

1.2.4. Combined Psychotherapy and Pharmacotherapy

Combined pharmacotherapy and psychotherapy for BN has been investigated. Study designs and results are variable; thus, it is difficult to draw firm conclusions regarding the results (McElroy et al., 2020). With respect to reductions in frequency of binge eating and compensatory behaviour episodes, Svaldi et al. (2019) reported that combined psychotherapy and pharmacotherapy for BN is associated with large effects (binge eating: g = 1.37; CI 0.68-2.06, compensatory behaviours: g = 1.28.; CI 0.82-1.74) based on 4 RCTs with a total of 62 participants. Bacaltchuk et al. (2000) found that combined psychotherapy and antidepressant treatment was superior to psychotherapy alone. In one meta-analysis of studies that compared antidepressant treatment alone to combined antidepressant and psychotherapy treatment, remission rates (defined as 100%

reduction in binge-eating episodes from baseline to endpoint) were 42% for combined antidepressant and psychotherapy treatment versus 23% for antidepressants alone (Bacaltchuk et al., 2000). In their second meta-analysis of studies that compared psychotherapy treatment alone to combined psychotherapy and antidepressant treatment, remission rates were 49% for combined treatment and 36% for psychotherapy alone. However, they noted the number of trials available may be insufficient to determine whether combination therapy, or psychotherapy alone was superior to antidepressants alone. Psychotherapy is generally more acceptable to individuals with BN and adding antidepressants to psychotherapy reduces the acceptability (Bacaltchuk et al., 2000).

In one study that did not assess concurrent pharmacotherapy and psychotherapy but rather psychotherapy and successive pharmacotherapy, it was found that treatment with fluoxetine was superior to placebo at reducing episodes of binge eating and purging in individuals with BN who had inadequate response (i.e., continued to binge eat and to induce vomiting on average at least once weekly over 1 month) to treatment with CBT for BN or IPT (Walsh et al., 2000). More research is needed to clearly determine whether combined pharmacotherapy and psychotherapy is ultimately beneficial, and to assess the efficacy of pharmacotherapy following inadequate response to psychotherapy.

1.3. Rationale for Examining Psychostimulants as a Treatment for BN

Since current psychotherapy and pharmacotherapy treatments for BN have limited effectiveness, it is pertinent to study novel interventions. To this point, there are several reasons that examining psychostimulants as a novel treatment for BN is warranted: A) psychostimulants affect the neural circuitry that underlies BN, B) there is a relationship between features of BN and attention deficit hyperactivity disorder (ADHD; a disorder

treated with psychostimulants), and C) there is robust evidence that psychostimulants are an effective treatment for BED (i.e., a disorder that overlaps with BN neurobiologically and symptomatically). Finally, case data suggests that psychostimulants are a plausible treatment for BN (see Section 1.4).

1.3.1. A Neurobiological Rationale for Examining Stimulants as a Treatment for BN

Psychostimulants enhance dopamine transmission in the brain, especially in limbic regions, by inhibiting reuptake, promoting neuronal dopamine release, and inhibiting monoamine oxidase (Dela Peña et al., 2015). The modulation of dopamine may have particular relevance to BN. Striatal dopamine is important in the neurobiological regulation of food intake and alterations in striatal dopamine have been found in animal and clinical models of BN, particularly when considering binge eating and food restriction (Broft et al., 2011). In animal models, binge eating and food restriction result in changes in striatal dopamine release and binding, a similar response to that seen in substance use disorders (Broft et al., 2011). In later stages of BN, low striatal levels of dopamine have been seen in neurochemical studies and concepts such as reward deficiency syndrome posits that insufficient internal dopamine-mediated reward systems drive these patients to seek external rewards (such as binge eating) to boost their dopamine levels (Comings & Blum, 2000). Further, Kessler et al. (2016) propose that the combination of decreased cortical inhibition, decreased reward sensitivity, and an imbalance in signaling between the direct striatonigral pathway (involved in reward response; elevated dopamine D1 signaling) and indirect striatonigral pathways (involved in behaviour flexibility; decreased dopamine D2 receptors) may mediate compulsive binge eating. Given that dysregulation of systems involving dopamine has been found in

BN, it is relevant to consider pharmacotherapy agents which target these systems (e.g., psychostimulants).

1.3.2. Relationship Between BN and ADHD

There is an apparent relationship between BN and ADHD. First, the two disorders commonly co-occur. For example, Biederman et al (2007) found that girls with ADHD were 5.6 times more likely to develop BN. Bleck et al (2015) found those diagnosed with ADHD were more likely to have been diagnosed with an eating disorder and experience current binge eating/purging and restriction. Further, in a sample of 1165 women seeking treatment at a specialized ED (eating disorder) clinic, Svedlund et al. (2017) reported that 31.3% of the sample had scores that suggested possible ADHD diagnosis (scores >13 on Adult ADHD Self-Rating Scale) and the highest prevalence rates were found in those with BN and anorexia nervosa binge eating/purging subtype. When considering a community-based sample of 4719 individuals, lifetime ADHD was significantly associated with lifetime BN, even after adjusting for demographic variables and psychiatric comorbidities, including depression and anxiety (Ziobrowski et al., 2018).

Second, the presence of ADHD symptoms has been found to be associated with more severe eating disorder symptoms. For example, Fernández-Aranda et al. (2013) found that more severe ADHD symptom levels were associated with increased frequency of binge eating episodes among those who binge/purge. The presence of ADHD symptoms has also been linked to worse treatment outcomes in some instances. For example, more severe ADHD symptoms at baseline were found to predict non-recovery at 1-year follow up in individuals with loss of control overeating, binging, or purging (Svedlund et al., 2018).

Finally, some research has proposed a biological link; namely a shared heritability between ADHD and binge eating (a core behaviour in BN). In one twin study, it was found that 91% of the covariance between ADHD and binge eating behavior was explained by genetic factors (Capusan et al., 2017). Psychostimulants are an effective treatment for ADHD and given the apparent relationships between the two disorders (ADHD and BN) it is relevant to consider psychostimulants as a treatment for BN.

1.3.3. Evidence for Psychostimulant Treatment of BED

There is robust evidence to support that one psychostimulant, lisdexamfetamine dimesylate (LDX), is an effective treatment for BED. Specifically, in a Phase II efficacy and safety trial, patients with BED who were assigned 50 and 70mg/day doses of LDX, demonstrated reduced binge eating days per week, greater binge eating cessation rates, and greater rates of clinical global improvement at 11 weeks when compared to the placebo group (McElroy et al., 2015). The safety outcomes were consistent with known safety profiles of LDX in ADHD trials. Two identically designed Phase III trials demonstrated consistent findings for the efficacy of LDX for BED, ultimately leading to FDA approval in 2015 and Health Canada approval in 2016. Given that LDX is a psychostimulant that has been approved by the FDA and Health Canada for the treatment of moderate to severe BED in adults (as well as ADHD) and there is shared symptomatic overlap between BN and BED (i.e., binge eating), LDX is a stimulant that warrants consideration for the treatment of BN.

1.4. Current Evidence for Using Stimulants in Bulimia Nervosa

To date, no clinical trials have specifically examined the use of stimulant medications in BN populations aside from one small trial by Ong et al. (1983). The

investigators administered methylamphetamine or placebo intravenously to eight participants with BN. Participants were randomized to receive either methylamphetamine or placebo on day one and one week later received the alternative substance. Four of the eight participants binged and purged following administration of the placebo and none of the eight participants binged or purged after receiving methylamphetamine.

While randomized trials are limited to the aforementioned study, case reports describing BN patients treated with psychostimulants have been published dating back to 1989. A total of 26 individuals have been described in 9 case reports (see Table 1). Ages ranged from 15 to 42. Only one patient included was male, therefore 96% of patients were female. ADHD/ADD (attention deficit disorder) was the most common comorbid diagnosis whereby 17/26 patients (65%) had a comorbid ADHD or ADD diagnosis. All patients had received previous psychotherapy treatment of varying intensities and durations. Most commonly, patients received outpatient or individual psychotherapy. Several patients had previous admissions to inpatient, residential, and/or intensive eating disorder outpatient or day treatment programs. Most had received previous pharmacotherapy, antidepressants being the most common agents. The type of antidepressant was often not specified, however at least six patients had been treated with fluoxetine. All patients demonstrated significant improvement (reduced frequency of binge eating/purging). Eight patients had complete cessation of binging and purging behaviours which was maintained at follow up (average follow up period was 10.6 months). An additional three patients had complete cessation of binge eating/purging aside from a few instances when a medication dose was forgotten or during a trial of medication discontinuation (average follow up period was 10.3 months). Only one patient

had concerning weight loss and resumed binging and purging after stopping all medications. No instances of medication misuse or concerning adverse drug reactions were reported.

Case reports provide the opportunity to present novel findings and generate hypotheses, however there are limitations of case report evidence including the inability to determine causality, inability to generalize findings to the population, and greater potential for publication bias and/or overinterpretation (Nissen & Wynn, 2014). With these limitations in mind, the available case data suggest stimulants are a treatment option for BN that warrants further investigation.

Table 1

Overview of available case data of bulimia nervosa patients treated with psychostimulants

Citation (authors, year)	Patient (age, sex, diagnoses, past treatment)	Psychostimulant (name, dose)	Treatment outcome
Messner (1989)	27 year old (y/o), female, BN. Past pharmacotherapy (amitriptyline, lithium carbonate), psychotherapy (unspecified "cognitive counselling"), nutrition counselling.	Methylphenidate (MPH), 5mg, 1-3x/day. Later changed to MPH, 20mg sustained release tablet, once daily.	Patient was free of binge/purge behaviour for 10 weeks (had one purge when medication was not taken). Patient discontinued MPH and binge/purge episodes gradually increased to more than once daily over a 4-week period. Resumed MPH (20mg sustained release tablet, once daily) and had 1-2 episodes of binging/purging over 5 weeks.

Citation (authors, year)	Patient (age, sex, diagnoses, past treatment)	Psychostimulant (name, dose)	Treatment outcome
Schweickert et al. (1995)	25 y/o, female, BN, ADHD, alcohol dependence. Previous treatment for BN was nonspecific. Pharmacotherapy for ADHD in childhood (MPH, pemoline) was discontinued at age 12.	MPH, 5mg twice daily (increased to 3x/day after 1 week).	No episodes of binge eating or purging at 16-week follow up.
Sokol et al. (1997)	20 y/o female, BN, cluster B personality disorders (borderline and histrionic), ADHD. Previous psychotherapy (unspecified) and pharmacotherapy (fluoxetine, paroxetine).	MPH titrated to 20mg/day.	One episode of binge eating and two episodes of purging (occurred on days medication was not taken) during 10-month of follow-up.

Citation (authors, year)	Patient (age, sex, diagnoses, past treatment)	Psychostimulant (name, dose)	Treatment outcome
Sokol et al. (1997)	38 y/o female, BN, borderline personality disorder, generalized anxiety disorder, major depressive disorder. Several years of psychotherapy (unspecified) and various antidepressants (fluoxetine, venlafaxine).	MPH 5mg 3x/day	Treated for 1 month. Binge/purge episodes decreased from 20x/week to 3x/week. Continued psychostimulants and fluoxetine for 1 year. Trial of pemoline given due to rebound effect from MPH (returned to baseline binge/purge symptoms). Prescribed long-acting MPH (dose not specified). During the 4-months taking long-acting MPH prior to follow-up binge/purge behaviours further reduced (frequency not specified).

Citation (authors, year)	Patient (age, sex, diagnoses, past treatment)	Psychostimulant (name, dose)	Treatment outcome
Drimmer (2003)	42 y/o female, BN, ADD. Previous pharmacotherapy (for depression, fluoxetine). Treated with MPH when diagnosed with ADD at age 39.	MPH 10mg twice daily, increased to 20mg twice daily.	Within 3 weeks of MPH initiation binging ceased. Continued MPH over a 2-year period (when MPH was stopped binging and purging returned) and experienced 2-3 "brief and mild relapses" over this period.
Drimmer (2003)	31 y/o female, BN, ADD. Previous pharmacotherapy (fluoxetine, sertraline, venlafaxine, risperidone), inpatient eating disorder treatment, several self-help groups.	Adderall, 10mg twice daily.	Within 3 weeks of Adderall initiation, binging and purging was reduced from 3-5x/day to binging once every 9-10 days. Changes were maintained at 10-month follow-up with continued Adderall use.

Citation (authors, year)	Patient (age, sex, diagnoses, past treatment)	Psychostimulant (name, dose)	Treatment outcome
Drimmer (2003)	21 y/o female, BN, major depressive disorder, post-traumatic stress disorder. Previous pharmacotherapy (sertraline), psychotherapy (unspecified).	Dexedrine, 5mg twice daily.	Within 1 week patient was no longer binging/purging. Continued to abstain from binging and purging at 2 months follow-up (was then lost to follow-up).
Dukarm (2005)	19 y/o female, BN, ADHD. Outpatient eating disorder treatment program.	Dextroamphetamine sulfate, 5mg 3x/day. Increased to 15mg 3x/day for ADHD symptoms.	Within 2 weeks no longer binging and purging, abstinence was maintained at 15 months follow-up.
Dukarm (2005)	18 y/o female, BN, ADHD. Outpatient eating disorder treatment program.	Dextroamphetamine sulfate, 5mg 3x/day, decreased to 5mg twice daily (due to ADRs, jittery & insomnia), later increased to 10mg 2x/day without recurrence of ADRs.	Reported immediate cessation of binging and purging which was maintained at 15 months follow-up.

Citation (authors, year)	Patient (age, sex, diagnoses, past treatment)	Psychostimulant (name, dose)	Treatment outcome
Dukarm (2005)	21 y/o female, BN, ADHD Previous family psychotherapy and treatment with SSRI (unspecified).	Dextroamphetamine sulfate, 5mg 3x/day, increased to 10mg 3x/day.	Had 2 episodes of binge eating and purging when medication was not taken. At 2-year follow up patient remained abstinent from binge eating/purging.
Dukarm (2005)	24 y/o female, BN, ADHD. Previous CBT for BN, outpatient eating disorder program. Pharmacotherapy for BN and depression (several SSRIs and antiepileptics, unspecified).	Dextroamphetamine sulfate, 5mg 3x/day, increased to 10mg 3x/day.	In 4 months prior to follow-up, had 2 episodes of binge eating and purging when medication was not taken.
Dukarm (2005)	15 y/o male, BN, ADHD. Previous family psychotherapy, pharmacotherapy for ADHD (previous treatment with MPH, discontinued for unknown reasons).	Dextroamphetamine sulfate, 10mg 3x/day.	After one week on medication had no further episodes of binge eating or restrictive intake. At 6-month follow up eating disorder behaviours remained completely resolved.

Citation (authors, year)	Patient (age, sex, diagnoses, past treatment)	Psychostimulant (name, dose)	Treatment outcome
Dukarm (2005)	17 y/o female, BN, ADHD. Outpatient eating disorder treatment program.	Dextroamphetamine sulfate, 5mg 3x/day, increased to 10mg 3x/day.	The patient experienced rapid improvement and had no further episodes of binge eating or purging (maintained at 17-month follow-up).
Guerdjikova & McElroy (2013)	32 y/o female, BN, ADHD, alcohol dependence, cocaine dependence, bipolar I, panic disorder. Previous treatment included residential, inpatient, outpatient intensive psychotherapy (unspecified). Previous pharmacotherapy (paroxetine, mirtazapine, atomoxetine, quetiapine, lamotrigine, aripiprazole, topiramate, acamprosate, ondansterone).	MPH 18mg/day increased to 72mg/day. Switched to 20mg MPH transdermal patch (later increased to 30mg)	Achieved complete remission of binge/purge symptoms with 72mg/day MPH. Remission continued when switched to transdermal patch. At follow up patient had been in complete remission for over one year.

Citation (authors, year)	Patient (age, sex, diagnoses, past treatment)	Psychostimulant (name, dose)	Treatment outcome
Keshen & Ivanova (2013)	34 y/o female, BN, ADHD. Nine months eating disorder outpatient treatment, one month eating disorder day treatment.	Adderall extended release, titrated to 40mg/day.	Stopped binging and purging with initiation of Adderall (previously 12 episodes per month). Had no further episodes of binge eating/purging until month 3 during a 1-week trial off the medication (began binging/purging 1-3x/day). Resumed Adderall treatment and binging and purging immediately remitted.
Keshen & Ivanova (2013)	20 y/o female, BN, ADD. Two months eating disorder outpatient treatment.	Adderall extended release, titrated to 40mg/day.	Binging and purging decreased from 16 episodes in the month prior to starting Adderall to 2 episodes/month in the 3-4 months after starting Adderall.

Citation (authors, year)	Patient (age, sex, diagnoses, past treatment)	Psychostimulant (name, dose)	Treatment outcome
Keshen & Ivanova (2013)	23 y/o female, BN, ADHD, alcohol use disorder, borderline personality disorder. 2 inpatient admissions (5 months) and 2 admissions to outpatient eating disorder program (total 16 months). Previous pharmacotherapy (antidepressants including fluoxetine, benzodiazepines, quetiapine).	Adderall extended release, titrated to 40mg/day.	Binging and purging decreased from 20 episodes in the month prior to starting Adderall to 1 episode/month in the 3-4 months following initiation of Adderall. The patient experienced significant weight loss and there were concerns of increasingly restrictive eating. The patient relapsed into binging/purging after discontinuing all medications.

Citation (authors, year)	Patient (age, sex, diagnoses, past treatment)	Psychostimulant (name, dose)	Treatment outcome
Keshen & Ivanova (2013)	22 y/o female, BN, ADHD, borderline personality disorder. Previous psychotherapy and pharmacotherapy (multiple antidepressants, lamotrigine, quetiapine).	Adderall extended release, titrated to 20mg/day.	Binging and purging decreased from 20 episodes in the month prior to starting Adderall to 1 episode/month in the 3-4 months following initiation of Adderall. In the 4th month after starting Adderall the patient discontinued the medication for several days and experienced episodes of binging and purging which remitted once Adderall was restarted.

Citation (authors, year)	Patient (age, sex, diagnoses, past treatment)	Psychostimulant (name, dose)	Treatment outcome
Keshen & Ivanova (2013)	32 y/o female, BN, ADHD. Previous eating disorder outpatient treatment and day treatment.	Dexedrine spansules, 20mg/day.	Binging and purging decreased from 22 episodes in the month prior to starting dexedrine to 1 episode/month in the 3-4 following medication initiation. The patient stopped dexedrine due to cost after 3 months and did not relapse into binging and purging behaviours, however she experienced increased urges to binge. MPH was initiated.
Ioannidis et al. (2014)	23 y/o female, BN (history of anorexia nervosa at age 15), ADHD, depression Previous inpatient eating disorder treatment, CBT for BN.	MPH extended release, 18mg/day (was later increased, dose not specified).	Binging and purging 3-4x/day prior to admission and MPH treatment, decreased to 3x/week at 8-months post discharge with continued community treatment (Cognitive Analytical Therapy).

Citation (authors, year)	Patient (age, sex, diagnoses, past treatment)	Psychostimulant (name, dose)	Treatment outcome
Keshen & Helson (2017)	25 y/o female, BN, marijuana use disorder, dependent traits Individual therapy (non-specified) for 4 months, eating disorder support group). No previous pharmacotherapy.	LDX (40mg AM, 20mg noon).	In the month prior to starting LDX, the patient had 17 binge/purge days. This remained consistent during the first month of treatment with LDX (17 binge/purge days). At 4-months follow up, the patient had 3 binge/purge days in the month prior.
Keshen & Helson (2017)	23 y/o female, BN. Previous individual therapy. No previous pharmacotherapy.	LDX (30mg AM, 20mg noon).	In the month prior to starting LDX, the patient had 30 binge/purge days. In the first month of treatment, the patient had 2 binge/purge days. The final follow-up reported was at 13 months. In the month prior to follow up, the patient had 5 binge/purge days.

Citation (authors, year)	Patient (age, sex, diagnoses, past treatment)	Psychostimulant (name, dose)	Treatment outcome
Keshen & Helson (2017)	22 y/o female, BN, avoidant dependent, obsessive-compulsive personality traits. Previous psychotherapy (7 years supportive psychotherapy/medication management), 6-month admission to intensive outpatient eating disorder program. Pharmacotherapy (current venlafaxine, methotrimeprazine, zopiclone).	LDX (50mg AM, 20mg noon).	In the month prior to starting LDX, the patient had 13 binge/purge days. This reduced to 4 binge/purge days during the first month of treatment with LDX. At 5-months follow up, the patient had 1 binge/purge day in the month prior.
Keshen & Helson (2017)	27 y/o female, BN obsessive-compulsive personality traits. Previous individual therapy (non-specific and ED specific). Previous failed trial of fluoxetine.	LDX (30mg AM, 20mg noon).	In the month prior to starting LDX, the patient had 8 binge/purge days. This reduced to 1 binge/purge day during the first month of treatment with LDX.

Citation (Authors, year)	Patient (age, sex, diagnoses, past treatment)	Psychostimulant (name, dose)	Treatment outcome
Keshen & Helson (2017)	23 y/o female, BN. Eight sessions of CBT for BN. No previous pharmacotherapy.	Amphetamine/dextroamphetamine extended release (20mg AM, 20mg noon).	In the month prior to starting Amphetamine/dextroamphetamine extended release, the patient had 30 binge/purge days. This reduced to 0 binge/purge days during the first month of treatment with LDX. At 14-months follow up, the patient had 0 binge/purge days in the month prior.
Keshen & Helson (2017)	36 y/o female, BN, persistent depressive disorder, social anxiety. Previously completed two CBT group programs for EDs. Treated with several antidepressants (unspecified).	LDX (30mg AM, 20mg noon).	In the month prior to starting LDX, the patient had 30 binge/purge days. This reduced to 1 binge/purge day during the first month of treatment with LDX. At 11-months follow up, the patient had 0 binge/purge days in the month prior.

1.5. Why Have Stimulants Not Been Tested in Patients with BN?

Contrary to the preliminary support of clinical and neurobiology research, some experts raise concerns regarding treating BN with stimulants, primarily because of the potential to misuse the drug for appetite suppression and weight loss (Herzog et al., 2006). Compared to BED populations, BN populations demonstrate higher rates of restrained/restrictive eating, which could be exacerbated by stimulants and become problematic if excessive weight loss occurs (Elran-Barak et al., 2015). Despite theoretical and anecdotal validation of this concern, there are no clinical data to support the claim that stimulants should be contraindicated in BN because of the risk of intentional misuse. To the contrary, available published case evidence suggests that problematic weight loss may be the exception rather than the rule, especially under careful monitoring (Dukarm, 2005; Keshen & Helson, 2017). Only one of the 26 cases described in case report/case series literature relapsed and experienced clinically significant weight loss while treated with a stimulant (Keshen & Ivanova, 2013).

There is also potential for increased risk of cardiovascular complications or seizures given that individuals with BN are more susceptible to dehydration/volume depletion and/or electrolyte imbalances secondary to compensatory behaviours (i.e., vomiting, laxative use, and/or diuretic use; Mehler & Rylander, 2015). Volume depletion and electrolyte imbalances (especially potassium) from these behaviours may result in tachycardia, hypotension, orthostasis, and/or cardiac arrhythmia (Mehler & Rylander, 2015). While psychostimulants are generally found to be safe with low risk for adverse cardiac events and seizures (Martinez-Raga et al., 2013; Wiggs et al., 2018), some research suggests their use is associated with increased risk for transient ischemic attack,

sudden death/ventricular arrhythmia, and seizures in adults (Man et al., 2020; Westover & Halm, 2012). Individuals with BN may be more vulnerable due to volume depletion and electrolyte imbalances and thus may be at greater risk for adverse cardiac events and seizures than other populations (i.e., adults with ADHD or BED).

1.6. A Feasibility Study as the Next Logical Step

Since this is a novel medication use in this patient population (i.e., BN) where only case data are available, it is necessary to examine the feasibility of implementing the proposed protocol prior to initiating a larger efficacy trial (Tickle-Degnen, 2013). The ultimate goal is to conduct an adequately powered, randomized, double-blind, parallel-group, dose-optimization, placebo-controlled trial. Prior to conducting a study of this magnitude, preliminary procedural, and effect size/safety data should be collected to inform trial design.

1.7. Study Objectives

The current data were collected as a sub-project from a larger feasibility study (Keshen et al., 2021). The objective of the larger feasibility study was to collect information regarding the practicality of a study assessing LDX for the treatment of adults with BN. For a complete list of the objectives of the larger study see Appendix A.

The objective of the sub-project was to investigate the outcomes of LDX treatment by generating preliminary effect size data, and to explore participants' experiences with LDX treatment through semi-structured qualitative interviews during an open-label study for moderate to extreme BN. Specifically, the sub-project aimed to incorporate both quantitative and qualitative elements to answer the following questions:

1. How does treatment with LDX over an eight-week period change eating disorder symptoms, measures of eating disorder cognitions, functional impairment, and obsessive, compulsive, and impulsive features in participants with moderate to extreme BN?
2. What are participants' experiences with LDX treatment for symptoms of moderate to extreme BN?

The literature suggests that feasibility studies should "descriptively assess the feasibility and validity of the RCT plan and not test the hypotheses of the main RCT" (Tickle-Degnen, 2013). Therefore, it would not be appropriate in this study to generate specific hypotheses regarding intervention effectiveness as these should be tested in future studies that are informed by the feasibility study, and that are adequately powered to conduct null hypothesis significance testing. The effect size data from the present sub-project will be used for power calculations in subsequent RCTs.

Chapter 2 - Method

2.1. Study Design

This feasibility study utilized a single site, open-label, uncontrolled, dose-optimization, mixed-methods design. The study was approved by the local research ethics board and Health Canada and conformed to the International Conference on Harmonization Good Clinical Practice guidelines. The trial was conducted out of the Nova Scotia Health Eating Disorder Clinic, located in Halifax, Nova Scotia. Participants visited the Nova Scotia Health Eating Disorder Clinic for study-related procedures.

2.2. Inclusion and Exclusion Criteria

Criteria for inclusion in the study were as follows:

- 18-55 years of age and signed consent.
- Moderate to extreme BN as per the Research Version of the Structured Clinical Interview for DSM 5 Disorders (SCID-5-RV).
- Body mass index between 21-30kg/m^2.
- Participant is consistently able to swallow a capsule as per self-report.
- Females who are not breastfeeding and are not of child-bearing potential (the latter is defined as last menstruation at least 24 months prior to baseline, undergone tubal ligation, or undergone hysterectomy).
- Females of child-bearing potential who have a negative serum pregnancy test prior to enrollment and agree to use a reliable method of birth control (reliable methods of birth control include abstinence, tubal ligation, vasectomy, intrauterine devices, birth control pills, hormonal implants, injectable contraceptives, and using barrier methods such as condoms, vaginal diaphragm

with spermicide, or sponge) during the study and for one month following last dose of study drug.

Participants who met any of following criteria were excluded from the study:

- Comorbid bipolar disorder, psychotic disorder, moderate-severe depression, and/or ADHD as per the SCID-5-RV.
- Previous history of anorexia nervosa.
- Severely restrictive eating behaviors, defined as routinely (> 2 days a week) eating less than two meals a day.
- Clinically meaningful abnormalities in the laboratory tests or electrocardiography results, as determined by the supervisor. Concerns most relevant to BN participants who are taking LDX would include abnormal levels described in Appendix B: Abnormal Lab/ECG Values (see Table B1).
- Personal or family history of cardiovascular disease that could increase the vulnerability to the sympathomimetic effects of stimulants (e.g., structural cardiac abnormalities, cardiomyopathy, serious heart arrhythmia, advanced arteriosclerosis, or coronary artery disease) or any current symptomatic cardiovascular disease, as determined by the supervisor, and/or in consultation with a cardiologist (as needed).
- Participant has moderate to severe hypertension (>140/90 mmHg).
- Participant is receiving psychotherapy specifically treating BN (e.g., cognitive behavioral therapy for BN).
- Participant is taking or has taken a stimulant within the past 3 months.

- Participant is on another psychotropic medication, and the dose has been changed within 4 weeks of study drug initiation.
- Participant is on an antipsychotic medication.
- History of substance use disorder in the preceding six months (or more distant at supervisor discretion) or a lifetime history of stimulant substance use disorder.
- Participant is taking or has taken an irreversible monoamine oxidase inhibitor within the last 14 days.
- Participant is pregnant, plans to become pregnant, or is nursing.
- Participant uses syrup of ipecac (to self-induce vomiting) due to its association with cardiac complications as a direct toxic result of its active ingredient, emetine, which could be further exacerbated by stimulant usage (Sachs & Mehler, 2016).
- Participant is considered a suicide risk, according to the Columbia-Suicide Severity Rating Scale (Screening Version), and at the discretion of the supervisor.
- Participant has a known allergy to amphetamines, or other non-medical ingredients in LDX, or is sensitive to, is allergic to, or has had a reaction to other stimulant medications.
- Participant has been diagnosed with glaucoma.
- Participant has been diagnosed with hyperthyroidism.
- Participant has insufficient knowledge of English.

2.3. Outcome Measures

2.3.1. Eating Disorder Symptom Frequency

Episodes of binge eating and compensatory behaviours per week were collected from paper food records. Participants completed paper food records (see Appendix C) for

the duration of the study starting the day of the screening visit and continuing until the day before the final follow-up visit. Through food records, information was collected on meal times, types and amounts of food/beverage consumed, episodes of binge eating, self-induced vomiting, and/or laxative/diuretic use. Monthly binge eating and compensatory behaviour frequencies were extracted from the Eating Disorder Examination at baseline and post-treatment.

2.3.2. Eating Disorder Examination

The Eating Disorder Examination 17.0D (EDE; Fairburn et al., 2014) was selected to measure eating disorder psychopathology. The EDE is a semi-structured interview that can be administered by trained interviewers. The EDE is considered the gold standard measure of eating disorder psychopathology in the eating disorder field, assessing psychopathology on four subscales (Restraint, Eating Concern, Shape Concern and Weight Concern) and provides a global score (Fairburn et al., 2014). A systematic review by (Berg et al., 2012) reported internal consistency coefficients of EDE subscales in clinical populations with Anorexia, Bulimia or Eating Disorder Not Otherwise Specified ranged from 0.64 to 0.78 for the Restraint subscale, 0.68 to 0.78 for the Eating Concern subscale, 0.70 to 0.85 for the Shape Concern subscale, and 0.67 to 0.76 for the Weight Concern subscale.

2.3.3. Three Factor Eating Questionnaire

The Three-Factor Eating Questionnaire (TFEQ) is a 51-item self-reported questionnaire (Stunkard & Messick, 1985). This questionnaire was selected to measure three dimensions of eating behaviour: cognitive restraint, disinhibition, and hunger.

Estimates of internal consistency for each factor are as follows, cognitive restraint, α = .93, disinhibition, α = .91, and hunger, α = .85 (Stunkard & Messick, 1985).

2.3.4. Yale-Brown Obsessive-Compulsive Scale Modified for Binge Eating and Purging

The Yale–Brown Obsessive Compulsive Scale modified for binge eating and purging (YBOCS-BP) is a modified version of the Y-BOCS (Goodman et al., 1989). This clinician administered measure was selected to assess obsessiveness of thoughts related to binging and purging and the compulsiveness of binge eating and purging behaviours. The YBOCS-BP is composed of 10 items (five items each for obsessive thoughts and for compulsive behaviours) rated on five-point scales ranging from 0 (no symptoms) to 4 (extreme symptoms). Internal consistency has not been reported for the modified version of the YBOCS being used in this study, however internal consistency of the YBOCS modified for binge eating (used in samples with binge eating disorder) has been reported at 0.81 (Deal et al., 2015).

2.3.5. Clinical Impairment Assessment

The Clinical Impairment Assessment questionnaire (CIA; Bohn & Fairburn, 2008) is a 16-item self-report measure of the severity of psychosocial impairment due to eating disorder features. Items cover impairment in domains of life that are typically affected by eating disorder psychopathology: mood and self-perception, cognitive functioning, interpersonal functioning, and work performance. The CIA has excellent internal consistency, Cronbach's alpha has been reported as 0.97 (Bohn et al., 2008).

2.3.6. Barratt Impulsiveness Scale

The Barratt Impulsiveness Scale (BIS-11; Patton et al., 1995) is a self-report questionnaire that was selected to assess the personality/behavioral construct of

impulsiveness. It is composed of 30 items that describe common impulsive or non-impulsive behaviours and preferences. A global score can be obtained, as well as second order factors related to attentional, motor, and non-planning impulsivity. In populations of general psychiatric patients completing the BIS-11, internal consistency has shown to be 0.83 (Patton et al., 1995).

2.3.7. Medication Adherence

Medication adherence was calculated during study visits at Week 2, Week 3, Week 4, Week 5 (only calculated if maintenance dose/quantity was not dispensed at Week 4 visit), and Week 9. Capsules returned by participants were counted by a study team member. This quantity was subtracted from the total quantity dispensed. It was assumed that capsules not returned were doses taken by participants. Therefore, total adherence was calculated as the total number of capsules *not* returned (i.e., capsules presumably taken by the participant) divided by the total number of days.

2.3.8. Adverse Events and Adverse Drug Reactions

Adverse events (AE; any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment) were assessed at each study visit/phone check-in by my supervisor. A checklist was developed from the common adverse reactions listed in the Product Monograph for LDX. The supervisor reviewed the list with participants at each contact and inquired about any adverse events participants may have experienced that were not listed. Adverse Drug Reactions (ADR) are defined as any Adverse Event that occurs during the study for which the causal relationship between

the study medication and the adverse event is at least a reasonable probability (i.e., the relationship cannot be ruled out).

2.4. Qualitative Interviews

Participants in the study completed three semi-structured interviews during the study. Full interview guides have been included as an Appendix (see Appendix D). I developed the interview guides to explore similar constructs to those being assessed by quantitative scales (e.g., eating disorder cognitions, eating disorder behaviours, ability to function) and participant experiences with study (e.g., study procedures, taking LDX, decreased appetite). I received feedback from my supervisor and other study team members to refine questions and probes. The first interview occurred during the baseline visit. This interview assessed expectations for treatment and asked about prior experiences with eating disorder treatment. The second interview took place at the end of the titration period, midway through the study (i.e., during the Week 5 visit). This interview focused on participants' experiences starting the medication and taking the medication since the beginning of the study. An interview was included half-way through the study based on the observation that following the initiation of LDX, binge/purge symptoms often improve in the first 1-2 weeks of taking the medication (Keshen & Helson, 2017). Conducting an interview after participants have taken LDX for four weeks allowed for inquiry on early symptom change (i.e., how participants perceive their symptoms) while the experience is recent as opposed to waiting until the end of the study when it may be challenging to recall 4-6 weeks prior. The final interview, or exit interview, was conducted at the follow-up visit (Week 10). If a participant was withdrawn from the study or withdrew consent, every effort was made to complete a final

interview at the time of discontinuation. This interview was an opportunity for participants to discuss their experience taking the medication during the study period, how the medication may/may not have improved their symptoms, and to report their experiences with the study. The audio of interviews was recorded.

2.5. Study Procedures

2.5.1. Recruitment and Pre-Screening

Recruitment occurred primarily online through advertisements on social media websites (e.g., Facebook, Instagram, Twitter) and local classifieds (e.g., Kijiji). Paper recruitment handouts were posted at various locations in the Halifax area (e.g., psychology clinics, university health clinics, local coffee shops, public libraries etc.). Both the recruitment poster and online advertisements directed potential participants to a secure online data collection website (SimpleSurvey) which provided study information and collected consent to undergo pre-screening. Individuals who were referred to the Nova Scotia Health Eating Disorder Clinic with moderate to extreme BN were informed of the study and directed to the online pre-screening website if interested. During the online pre-screening, individuals responded to validated screening items selected to assess preliminary eligibility criteria and provided contact information. Potential participants were contacted by email or telephone by myself with follow-up questions to confirm details of eating disorder symptoms and other eligibility criteria. This pre-screening procedure was used to minimize the time requirement for both participants and research staff, and to reduce the burden of data recording for individuals who failed to meet preliminary eligibility. Participants who did not meet the initial eligibility criteria were informed of their ineligibility, provided information about alternative treatment

options, and provided with my supervisor's contact information should they have any follow up questions. Individuals who met preliminary eligibility criteria were invited to attend in-person screening at the Nova Scotia Health Eating Disorder Clinic.

2.5.2. Screening

In-person screening involved collection of written informed consent, confirmation of initial pre-screening criteria responses, and medical and psychological assessments to determine whether inclusion/exclusion criteria were satisfied.

2.5.2.2. Informed Consent Procedure. The informed consent process for the study was twofold. In summary, participants provided consent electronically prior to completing the online pre-screening form. This allowed for collection of pre-screening information online and over the phone. Participants invited to attend in-person screening completed a second informed consent procedure where myself or another research assistant reviewed the consent form with the participant and collected written signatures. Complete details of the consent procedure for the trial are outlined in the Informed Consent Process Standard Operating Procedure (see Appendix E).

2.5.2.3. Medical Assessment. Medical criteria were assessed by the supervisor during in-person screening. The supervisor administered a Medical History Interview which inquired about past and current medical conditions, current and recent medications, allergies (e.g., all drug allergies, allergy to non-medical ingredients in LDX, previous reaction(s) to other stimulant medications), family history of cardiovascular conditions, birth control and pregnancy, and current treatment for bulimia. Blood pressure and heart rate were measured by the supervisor using a calibrated Welch Allyn Spot Vital Signs device. Height and weight were measured by the supervisor using a

calibrated Health o meter professional 597 KL Heavy Duty Eye Level Digital Scale. Participants were weighed wearing only a hospital gown to obtain a consistent measurement during the study.

A baseline electrocardiogram (ECG) was completed by Nova Scotia Health Cardiology Department during the screening visit. Results were reviewed by the supervisor and a cardiologist. Laboratory samples were drawn by Nova Scotia Health blood collection services to measure sodium, potassium, glucose (random), calcium, phosphate, magnesium, chloride, bicarbonate, human chorionic gonadotropin qualitative, and a complete blood count. Samples were analyzed by Nova Scotia Health Central Lab and results were reviewed by the supervisor.

2.5.2.4. Psychiatric Assessment. Assessment of psychiatric criteria were based on the Structured Clinical Interview for DSM 5 Disorders Research Version (SCID-5-RV) administered by myself or another research assistant. Only modules that assessed psychiatric features relevant to eligibility criteria were administered. This included the Non-Patient overview, Mood Episodes without specifiers, Psychotic Screening, Mood Differential, Substance Use Disorders, Obsessive Compulsive and Related Disorders, Feeding and Eating Disorders, and Externalizing Disorders. The Columbia Suicide Severity Scale (Screening Version; CSSR) was administered during the SCID-5-RV. Whenever possible two raters were present during administration of the SCID-5-RV and CSSR. Any discrepancies between ratings were resolved between raters or the supervisor if necessary.

Following completion of in-person screening and receipt of lab and ECG results, participants who met eligibility criteria were invited to return for the baseline (Week 1)

visit where the study medication was provided. A participant was considered enrolled if they took at least one dose of the study medication. Those not interested in participating in the study or who failed to meet the eligibility criteria were informed of alternative options for treatment. As reflected by the inclusion/exclusion criteria (see section 2.2), this study recruited participants who are both a) experiencing moderate to extreme degrees of pathology, and b) at a lower risk of abusing the appetite suppressing effects of LDX (e.g., not severely restrictive, no previous history of anorexia).

2.5.3. Treatment Phase

2.5.3.1. LDX Dosing and Treatment Schedule. The trial began with a 4-week titration period followed by a 4-week maintenance period for a total LDX treatment duration of eight weeks. LDX was started at 30mg/day and increased weekly by 20mg/day increments until the optimal dose was achieved (50mg/day or 70mg/day), as determined by the supervisor. The final week of the titration period was allotted for one gradual dose reduction (from 70mg/day to 50mg/day) in case the participant experienced any intolerance at the maximum dosage. Patients were instructed to take LDX once daily and were advised to take the medication in the morning to minimize the risk of insomnia/difficulty sleeping. This titration protocol was based on the study by (McElroy et al., 2015), which found that 30mg doses of LDX were ineffective for BED, and that participants required variable doses (i.e., 50mg or 70mg) based on tolerability and clinical effect. The rationale for an 8-week treatment duration in the present trial was based on two studies by McElroy et al. (2015, 2016), which examined the use of 50 and 70mg/day doses of LDX in adults with BED. While both studies used an 11-week treatment duration, approximately 90-99% of the total change in binge eating days, binge

eating severity scores, and impulsivity/compulsivity scores were observed in the first 8-weeks of treatment. Case data supports the assumption that reductions in binge/purge behaviours occur within the first 1-2 weeks after initiation of a stimulant (Keshen & Helson, 2017). Therefore, there is a reasonable probability that the main effects of LDX in a BN population would be apparent in an 8-week treatment duration and would be sufficient to estimate the treatment effect size. Furthermore, an 8-week treatment phase would be adequate to assess the other study parameters since most LDX adverse drug reactions occur in the first week of treatment and at lower dosages (Findling et al., 2009). No dose changes were permitted during the maintenance period.

2.5.3.2. Psychoeducation. At the baseline study visit, participants received a 15-minute psychoeducation session from a member of the research team who described the etiology of binge/purge behaviour, and how LDX is thought to reduce behaviors. Education on the reasons that restrictive eating could be treatment interfering and negate the positive effects of LDX was provided.

2.5.3.3. Food Records. Participants recorded any binge/purge episodes and their food intake for each day using paper food records. These were reviewed by the supervisor weekly with the participant (see Appendix F for full participant study schedule by week). During the weeks participants complete telephone check-ins as opposed to in-person visits (Week 6 and 8), binge/purge frequency was collected via verbal self-report of symptoms and confirmed by food records at the next in-person visit.

2.5.3.4. Assessment Administration. The EDE was conducted by myself or another research assistant at Baseline (Week 1) and Post (Week 9). All remaining

outcome measures including, YBOCS-BP, BIS-11, TFEQ and CIA were collected during study visits at Baseline, the end of the titration period (Week 5), and Post. In-person follow-up occurred approximately one week after treatment discontinuation.

2.6. Quantitative Statistical Analysis

Descriptive statistics including means, standard deviations, and frequencies were computed for demographic information at Baseline. Means and standard deviations were computed for safety data (i.e., heart rate, systolic and diastolic blood pressure, and weight), eating disorder symptom frequency data (i.e., average number of objective and subjective binge episodes and total compensatory behaviours in the past 28 days) at Baseline and Post/ET (end of treatment). The percentage of participants who experienced an adverse drug reaction during the study was calculated. Questionnaires/rated interviews were scored according to published scoring instructions for each measure. Means and standard deviations for all outcome measures of interest were calculated at Baseline, Week 5 timepoint (where applicable), and Post/ET. Effect sizes (Cohen's *d*) for the changes from Baseline to Post/ET were calculated for eating disorder symptom frequency data and questionnaire/rated interview data. Results are presented for both the intent-to-treat (ITT) sample (all participants enrolled), and the Completer sample (participants who were on the maintenance dose for at least 28 days and completed a Post-visit, $n = 19$). With respect to missing data, last observation carried forward (LOCF) was used in cases where participants dropped out or were withdrawn prior to completing Week 5 or Post assessments.

2.7. Qualitative Analysis

Thematic analysis using methodology outlined by Braun and Clarke (2006) was utilized. Qualitative interviews were transcribed verbatim into Microsoft Word and checked for accuracy by myself. All transcripts were checked for accuracy again by a second researcher. Any discrepancies between transcripts and audio were noted using track changes in Microsoft Word. I reviewed the track-changes and resolved the discrepancies by reviewing the audio. All transcripts were reviewed on two separate occasions by myself and initial codes were generated through inductive coding. Using these initial concepts and new concepts as they arose, transcripts were coded by myself in *Nvivo* for organization purposes (i.e., data analysis features of *Nvivo* were not utilized). Themes were developed through an iterative review of codes alongside the transcripts. Throughout the coding process and theme development, meetings were held on an ongoing basis with team members familiar with the transcripts and trial. There was continuous reflection and review of transcripts and coding to assess elements of the data that supported these themes and elements that diverged from the themes that I was developing. The focus of the analysis was descriptive in nature and aimed to share participants' experiences using their own narratives.

For the mixed-method component, quotes from transcripts were selected to supplement quantitative findings. Quotes from a variety of participants were selected to represent the findings for the sample as a whole. This process also involved ongoing review of transcripts and codes to ensure that quotes which supported *and* refuted quantitative findings were considered and presented when available.

2.7.1. Reflexivity

I have been fortunate to work and volunteer in the eating disorder field over the last five years. During this time, I have gained experience in both research and clinical settings in an adult eating disorder treatment program that offers inpatient, day treatment, and outpatient care. My interest in the clinical aspect of eating disorders and the experiences I have had in this setting lead me to consider the clinical implications of this trial while interpreting and discussing our results. I have also seen the outcomes of current treatment approaches from both research and clinical lenses allowing me to witness that not all individuals with BN fully respond to existing psychotherapy or pharmaceutical treatments. Because of these experiences, I believe that alternative treatment options, and/or supplements to existing options are important to investigate and disseminate. While interpreting results, I aimed to critically evaluate our findings and to highlight important clinical implications related to the use of stimulants in this population.

From a research perspective, I have observed that there is often focus on statistically significant reductions in symptom frequency, particularly in pharmaceutical RCTs, with less consideration of changes to quality of life or clinical significance. When analyzing the data for this trial, particularly qualitative interviews, it was clear that participants experienced changes that extended beyond reduced eating disorder symptom frequency, yet in the eating disorder literature, participants' experiences with pharmacological treatments are generally not included. Therefore, when analyzing the data and presenting results, I believed it was important to shed light on the experiences participants described and how participating in this trial impacted their lives.

Before beginning my Master of Science in Psychiatry Research, I completed my undergraduate degree in biology and psychology, conducting my honours thesis with Dr. Aaron Keshen. It was during this time that I began helping to develop the grant proposal for a feasibility study examining the use of LDX in adults with BN. I was involved with this trial from the very beginning stages of grant writing, protocol development, ethics and Health Canada applications, developing study documents, procedures, and qualitative interviews. I took on the role of coordinating the trial and was immersed in all aspects of the day-to-day management. I was responsible for duties such as recruitment, pre-screening, conducting in-person screening, study visits, and assessments/interviews, administrative aspects, data entry and transcribing all qualitative interviews, as well as Health Canada and REB correspondence. While I am thankful for the opportunity to coordinate this trial, I find myself most grateful for the opportunity to work closely with the participants in the trial. I am in awe of their openness and willingness to share their experiences. Administering assessments such as the EDE, SCID-5-RV, and qualitative interviews gave me the privilege of learning the most private details of each participant's experiences with an eating disorder, as well as important aspects of their lives outside of the eating disorder. I heard stories about their children and loved ones, their studies, jobs, and saw photos of their pets. I got to hear the excitement in their voices when they returned to our office and reported that aspects of the eating disorder they feared could never change had improved after starting the medication. While I was familiar with the previous case reports that described successful treatment of BN with stimulants, the results of this trial exceeded any expectations I had. The literature has called for trials investigating the use of stimulants for BN since 1989 and our team was able to take an

initial step that will lay the groundwork for future RCTs to fully assess the safety and efficacy of treatment with stimulants in this population. I have been immersed in this process, working closely with each participant and all aspects of the data. Therefore, I am uniquely positioned to tell the story of this trial and to share the experiences of the participants who made it possible. My analysis and interpretation of the data was conducted with these goals in mind and is shaped by the clinical, research, and educational experiences I have described.

Chapter 3 - Results

3.1. Sample Demographics

As shown in Table 2, participants in the study were on average 26.83 years of age. The mean body mass index was 24.53kg/m^2. The sample was exclusively female, and the majority identified as white (95.7%). Most participants were employed and/or students (92.3%), and almost all had completed at least some post-secondary education (95.7%). The average duration of illness was 9.33 years and 65% of participants had previously attempted treatment or received support for their eating disorder. In terms of types of previous support or treatment received, seven had received outpatient treatment, eight had psychotherapy (type of therapy not specified), six reported receiving treatment from their primary care provider, two had received treatment from a psychiatrist, and three had participated in a peer support program or group. Nine individuals were currently taking another psychiatric medication at the time of their participation in the trial. Concomitant psychiatric medications included: fluoxetine (n = 3), duloxetine (n = 1), sertraline (n = 2), bupropion (n = 1), vortioxetine (n = 1), moclobomide (n = 1), phenytoin (n = 1), and aripiprazole (n = 1). The decision was made by the supervisor to include the participant prescribed aripiprazole given that the exclusion criteria specific to antipsychotic medications was based on theoretical concern related to opposing mechanisms of action and this would be especially unlikely at low doses of aripiprazole (Yanofski, 2010).

For participant flow and study CONSORT, see Figure 1. Eighteen individuals completed the study per protocol. Participants (n = 2) who were withdrawn by the supervisor met predefined withdrawal criteria. One participant did not adhere to the protocol (missed study visits, did not complete food diaries, or take the medication

consistently) and the second was withdrawn due to rapid weight loss (defined as a body weight reduction of >5% in a given month). Three participants who dropped out prematurely would have been eligible to continue (i.e., did not meet withdrawal criteria or formally withdraw consent) had they attended subsequent visits. One of the three participants who could not fully complete the study due to personal circumstances unrelated to the trial was available to attend a Post-visit and data were collected 10 days early. At the time of data collection, the participant had been on the maintenance dose for 39 days and was therefore considered a Completer for data analyses. Nineteen individuals were included in the Completer analysis and all 23 enrolled participants were included in the ITT analysis. The average total medication adherence (n = 23) was 99.43% (SD = 5.20). For participants who did not complete (i.e., those who dropped out or were withdrawn) adherence was calculated based on available data prior to withdrawal or dropout.

Table 2

Participant Demographic Characteristics at Baseline (n = 23)

Baseline characteristic	*n*	%	*M*	*SD*
Age, years			26.83	7.96
BMI, kg/m^2			24.53	2.54
Duration of illness, years			9.33	7.73
Gender:				
Female	23	100.0		
Ethnic origin:				
White	22	95.65		
Other	1	4.35		
Employment status:				
Employed, full-time	11	47.83		
Employed, part-time or casual	2	8.70		
Student	5	21.74		
Student & employed, part-time or casual	3	13.04		
Unemployed	2	8.70		
Highest level of education:				
High school graduate, diploma or equivalent	1	4.35		
Some college credit, no degree	2	8.70		
Trade/technical/vocational training	2	8.70		

Baseline characteristic	*n*	%	*M*	*SD*
Highest level of education:				
Some university, no degree	6	26.09		
Bachelor's degree	7	30.43		
Master's degree	1	4.35		
Other	4	17.39		
Marital Status:				
Single	18	78.26		
Married	3	13.04		
Other	2	8.70		
Previous treatment attempt(s) for ED:				
Yes	15	65.22		
No	8	34.78		
Current psychiatric medication:				
Yes	9	39.1		
No	14	60.87		

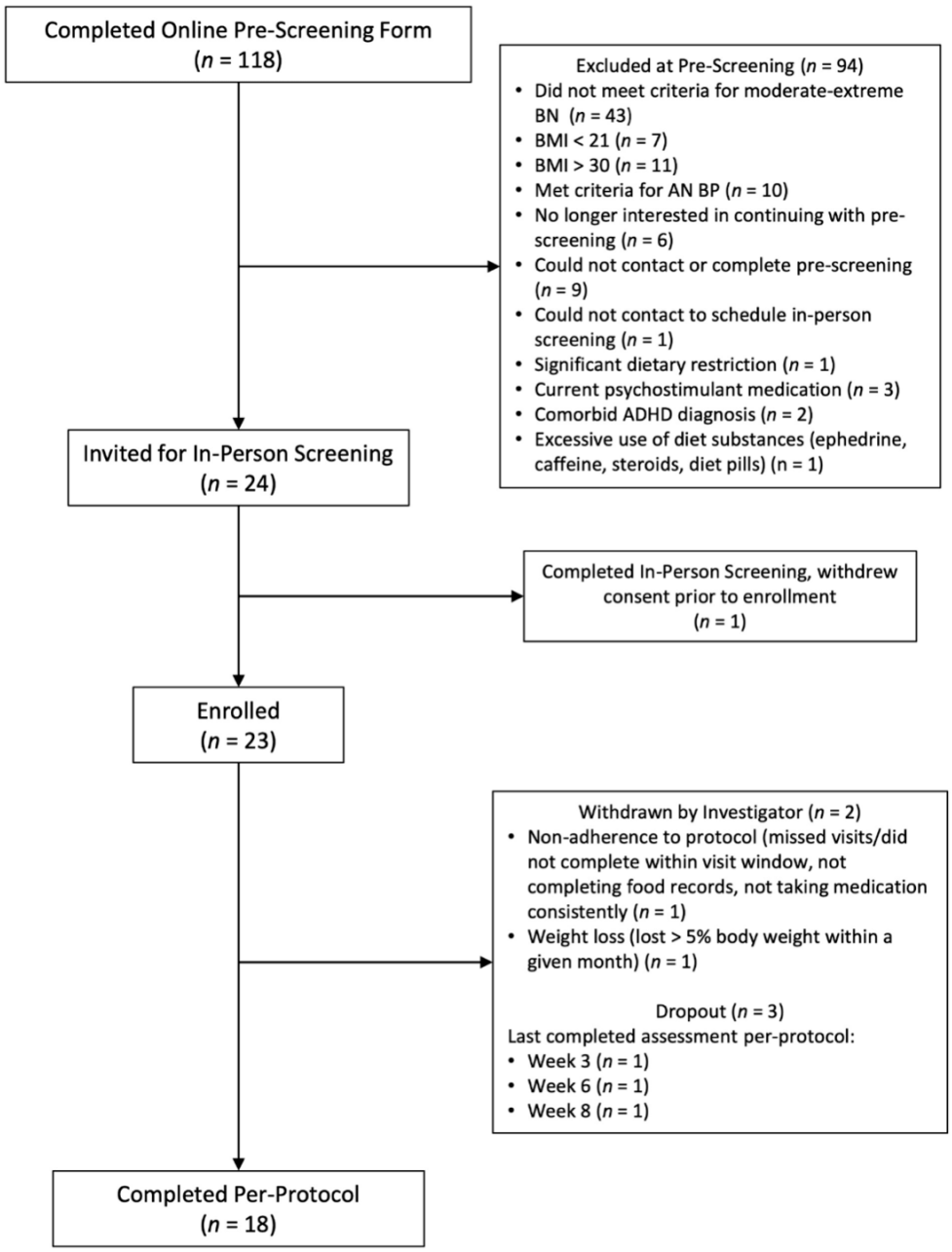

Figure 1. Study CONSORT diagram.

3.2. Results Part A: Description of Mixed-Methods Results

3.2.1. Eating Disorder Symptom Frequency

In the ITT sample, reductions in objective binge eating episodes and episodes of compensatory behaviours that corresponded to large effect sizes were observed over the course of the study. Means, standard deviations, and effect sizes are presented in Table 3.

In the 28-days prior to Baseline, participants experienced an average of 35 objective binge episodes and 39 compensatory behaviour episodes. In the 28-days prior to Post, participants experienced an average of 4 objective binge episodes and 5 compensatory behaviour episodes. Cohen's *d* corresponding to the reduction in objective binge episodes was 1.81. A similar effect size was observed for the reduction in episodes of compensatory behaviours (Cohen's $d = 1.85$). Reductions in subjective binge episodes corresponded to a medium effect size (Cohen's $d = 0.50$). On average participants in the ITT analysis had 4 subjective binge episodes in the 28 days prior to Baseline which reduced to approximately one episode in the 28 days prior to Post.

Similar results were observed in the Completer analysis (see Table 4). Reductions in objective binge episodes and compensatory behaviour episodes corresponded to large effect sizes of 2.07 and 2.18, respectively. At Baseline, participants had on average 37 objective binge episodes in the 28 days prior, which was reduced to 2 episodes on average in the final 28 days of the study. Compensatory behaviours at Baseline were on average 42 episodes in the 28-days prior. This was reduced to 2 episodes on average in the final 28-days of the study. Reductions in subjective binge episodes corresponded to a medium effect size (Cohen's $d = 0.65$). When considering study completers, 10 out of 19 participants (52.63%) were completely abstinent from binge eating and compensatory

behaviours in the 28 days prior to Post treatment. Sixteen out of 19 participants (84.21%) had a subthreshold number of compensatory behaviors (i.e., <4) in the 28 days prior to Post.

Table 3

Change in Eating Disorder Symptoms for the Intent-to-Treat Sample (n = 23) with 8-weeks of Lisdexamfetamine Dimesylate Treatment

Eating Disorder Symptom	Baseline		Post or LOCF		Cohen's *d*
	M	*SD*	*M*	*SD*	
Objective Binge Episodes, past 28 days	34.70	22.22	4.87	7.70	1.81
Subjective Binge Episodes, past 28 days	3.87	7.77	0.83	3.67	0.50
Compensatory Behaviour Episodes[a], past 28 days	38.78	24.57	5.00	7.90	1.85

[a] Compensatory Behaviour Episodes are compiled episodes of self-induced vomiting, laxatives, diuretics, and fasting. No participants engaged in excessive exercise as per the EDE.

Table 4

Change in Eating Disorder Symptoms for Study Completers (n = 19) with 8-weeks of Lisdexamfetamine Dimesylate Treatment

Eating Disorder Symptom	Baseline		Post		Cohen's *d*
	M	*SD*	*M*	*SD*	
Objective Binge Episodes, past 28 days	36.79	23.79	1.68	3.48	2.07
Subjective Binge Episodes, past 28 days	3.63	7.80	0.05	0.23	0.65
Compensatory Behaviour Episodes[a], past 28 days	41.84	25.57	2.05	3.66	2.18

[a] Compensatory Behaviour Episodes are compiled episodes of self-induced vomiting, laxatives, diuretics, and fasting. No participants engaged in excessive exercise as per the EDE.

3.2.2. Eating Disorder Cognitions

Changes in secondary measures of eating disorder cognitions are presented for the ITT and Completer sample in Tables 5 and 6, respectively. In the ITT sample, reductions on all subscales and the Global score of the EDE were observed. Reductions corresponded to large effect sizes ranging from 0.78 to 0.94 with the exception of the Restraint subscale where a medium effect size (Cohen's $d = 0.59$) was found. Further, scores on the Restraint and Hunger subscales of the TFEQ were reduced at post relative to baseline. Reductions in Hunger corresponded to a large effect size (Cohen's $d = 1.14$),

while reductions in Restraint corresponded to a small-medium effect size (Cohen's d = 0.38).

In the Completer sample, the changes in secondary measures of eating disorder psychopathology were in the same directions as those described above (i.e., reductions on all subscales of the EDE and TFEQ) with more pronounced effects. Effect sizes for all changes in these measures over the course of the study were large (> 0.8), with the exception of the Restraint subscale of the TFEQ for which the reduction observed corresponded to a medium effect size (Cohen's d = 0.56).

During qualitative interviews, participants discussed their experiences with changes to the frequency and intensity of eating disorder thoughts (e.g., thoughts about food, eating, urges to binge/purge, shape and weight) that are consistent with changes observed in the quantitative results. Participants often described a reduction or absence of eating disorder thoughts while on the medication. For example, when asked to describe any changes in their eating disorder thoughts, one participant stated:

> *"It's just so weird because they're just not there as much, like hardly at all, when that is literally all I used to think about and now it's just like I can go all day and you don't think about it at all. There are some days I literally did not even, that wasn't even on my mind whatsoever which has never happened in 10 years." [Participant #1]*

Body image concerns and thoughts about shape and weight were common eating disorder thoughts that some participants continued to experience during the trial. However, there were mixed responses in this regard as other participants described thoughts about body image to be less important or prominent while on the medication. For example, one

participant described the medication did not change anything about their body image concerns:

> *"Well, it [the medication] hasn't changed anything about like my pre-existing body image issues, you know that's still a problem that I got to cope with. But I don't, like I said, I don't feel like it's a lost cause anymore. Like I feel like I can control what I eat and like do it in a healthy way as long as I just eat consistently is the moral of the story." [Participant #2]*

A second participant did notice their body image concerns seemed less important while taking the medication:

> *"I notice, especially when the medication has like kicked in, my thoughts about body image issues or like what I look like or food related stuff, don't seem as important, like I don't care as much, it's not like I would fuss about like how my body would look as much when the medication's in. When I wake up in the morning at the very beginning, and the night, sometimes those thoughts would come back in a little bit more when the medication wasn't there." [Participant #3]*

Table 5

Change in Measures of Eating Disorder Cognitions for the Intent-to-Treat Sample (n = 23) During 8-weeks of Lisdexamfetamine Dimesylate Treatment

Measure	Baseline		Week 5		Post or LOCF		Cohen's *d*
	M	*SD*	*M*	*SD*	*M*	*SD*	
EDE							
Restraint	1.76	1.41			0.97	1.27	0.59
Eating Concern	2.23	1.28			1.03	1.26	0.94
Shape Concern	3.48	1.66			2.06	1.67	0.85
Weight Concern	2.79	1.56			1.63	1.40	0.78
Global Score	2.56	1.29			1.42	1.27	0.89
TFEQ							
Restraint	12.52	5.26	11.87	4.34	10.57	4.99	0.38
Hunger	8.22	3.81	4.30	2.72	3.96	3.69	1.14

Abbreviations: EDE, Eating Disorder Examination; TFEQ, Three Factor Eating Questionnaire

Table 6

Change in Measures of Eating Disorder cognitions for Study Completers (n = 19) During 8-Weeks of Lisdexamfetamine Dimesylate Treatment

Measure	Baseline		Week 5		Post		Cohen's *d*
	M	*SD*	*M*	*SD*	*M*	*SD*	
EDE							
Restraint	1.53	1.38			0.58	0.91	0.81
Eating Concern	2.01	1.25			0.57	0.68	1.43
Shape Concern	3.19	1.67			1.47	1.09	1.22
Weight Concern	2.57	1.61			1.16	0.99	1.06
Global Score	2.32	1.26			0.94	0.69	1.36
TFEQ							
Restraint	12.47	5.33	11.26	4.00	9.68	4.57	0.56
Hunger	8.00	3.87	3.84	2.59	3.42	3.72	1.21

Abbreviations: EDE, Eating Disorder Examination; TFEQ, Three Factor Eating Questionnaire

3.2.3. Obsessive-Compulsive and Impulsive Features

Changes in secondary measures of bulimia related obsessive-compulsive and impulsive features are presented for the ITT and Completer samples in Tables 7 and 8, respectively. In both the ITT and Completer samples, very large reductions in total scores and subscale scores on the YBOCS-BP were observed. In the ITT sample total YBOCS scores were reduced from an average of 22.30 at Baseline to 5.83 at Post (Cohen's *d* =

4.22). In the Completer sample total scores were reduced from an average of 22.63 at Baseline to 4.89 at Post (Cohen's *d* = 5.36).

In qualitative interviews, participants reported similar reductions (or complete absence) of bulimia related obsessive and compulsive features. As an example, one participant described a complete absence of compulsive thoughts and urges related to binging and purging after starting the medication:

> *"The biggest difference is now, just the absence of the kind of compulsive thoughts and urges that were directly about either acting on behaviours, or trying not to act on behaviours, it was always like one way the other, and it was always about being in that destructive bubble that binging and purging had me in every day. Like that is not there anymore." [Participant #4]*

A second participant who did continue to experience some urges to binge and purge described how their experience with urges changed throughout the study:

> *"Yeah, I did still have urges, but I found when I did I was able to kind of talk myself through them and they weren't as strong when I did have them. When I first started taking it I didn't have any at all, but then as I got used to it I did still have them but I was able to control them." [Participant #5]*

Scores on the Disinhibition subscale of the TFEQ were reduced at Post relative to Baseline in the ITT sample. Reductions in Disinhibition corresponded to a large effect size (Cohen's *d* = 1.85). In the Completer sample, reductions corresponding to a large effect size were also observed on the Disinhibition subscale (Cohen's *d* = 2.31).

In the ITT sample, total scores and subscale scores on the BIS-11 remained consistent during the trial and effect sizes for the difference from Baseline to Post were

negligible (<0.2). Similar results were observed in the Completer sample; however, effect sizes were small except for the Attention subscale where a negligible effect size was observed.

Although scores on measures of trait impulsivity as assessed by the BIS-11 did not change throughout the study, scores for disinhibition as assessed by the TFEQ were reduced (i.e., a measure eating related impulsivity). In qualitative interviews, participants described a greater degree of control over their binge eating and purging behaviours while on the medication, including increased ability to consider the outcomes of these behaviours instead of acting impulsively on urges to binge/purge. In discussing what the medication had helped them with the most, one participant described the following:

> *"Controlling urges to binge and purge for sure. Especially the whole binge part, I don't know if it was because my appetite was reduced or anything, but I just didn't feel that need or drive, and even when I did it allowed me that space to be like is this a good idea? Should I do this? Like that kind of a thing, where I never had that foresight." [Participant #6]*

Table 7

Change in Obsessive-Compulsive and Impulsive Features for the Intent-to-Treat Sample (n = 23) during 8-weeks of Lisdexamfetamine Dimesylate Treatment

Measure	Baseline		Week 5		Post or LOCF		Cohen's *d*
	M	*SD*	*M*	*SD*	*M*	*SD*	
YBOCS-BP							
Obsessional	10.97	1.62	4.09	2.04	3.52	2.78	3.27
Compulsion	11.39	2.04	3.22	1.76	2.65	2.23	4.09
Total	22.30	3.42	7.30	3.55	5.83	4.33	4.22
TFEQ							
Disinhibition	12.74	2.49	6.74	3.65	6.26	4.27	1.85
BIS-11							
Attention	17.83	4.42	17.17	4.15	17.48	4.61	0.08
Motor	23.04	3.87	22.13	3.90	22.52	4.09	0.13
Non-Planning	24.39	3.86	23.91	4.84	23.87	4.66	0.12
Total	65.26	8.80	63.22	10.83	63.87	11.61	0.13

Abbreviations: YBOCS-BP, Yale Brown Obsessive Compulsive Scale (modified for Binge Eating & Purging)*;* TFEQ, Three Factor Eating Questionnaire; BIS-11, Barratt Impulsiveness Scale

Table 8

Change in Obsessive-Compulsive and Impulsive Features for the Completer Sample (n = 19) during 8-weeks of Lisdexamfetamine Dimesylate Treatment

Measure	Baseline		Week 5		Post		Cohen's *d*
	M	*SD*	*M*	*SD*	*M*	*SD*	
YBOCS-BP							
Obsessional	11.00	1.41	3.79	1.72	2.68	2.06	4.71
Compulsion	11.63	1.86	2.89	1.49	2.21	1.99	4.89
Total	22.63	2.99	6.68	2.89	4.89	3.60	5.36
TFEQ							
Disinhibition	12.47	2.57	5.74	2.96	5.16	3.67	2.31
BIS-11							
Attention	17.58	4.44	16.74	3.75	17.12	4.40	0.10
Motor	23.00	3.51	21.68	3.74	22.16	4.03	0.22
Non-Planning	24.53	3.64	23.63	4.62	23.58	4.39	0.24
Total	65.11	7.89	62.05	10.02	62.84	11.12	0.24

Abbreviations: YBOCS-BP, Yale Brown Obsessive Compulsive Scale (modified for Binge Eating & Purging)*;* TFEQ, Three Factor Eating Questionnaire; BIS-11, Barratt Impulsiveness Scale

3.2.4. Functional Impairment

As shown in Table 9, in the ITT sample, average scores on the CIA were reduced from 32.42 at Baseline to 13.04 at Post, corresponding to a large effect size (Cohen's d = 1.88). In the Completer sample (Table 10), average scores on the CIA were reduced from 31.72 at Baseline to 11.42 at Post corresponding to a large effect size (Cohen's d = 2.86).

During qualitative interviews, participants discussed how eating disorder thoughts and behaviours impaired their ability to function in different domains including work, school, and with friends and family. As an example, in discussing their experience since starting the medication, one participant described improved productivity at work and social functioning:

> *"I remember when I did our first interview, I always said my work wasn't affected but then when you go from that until now and I realize how much more I get done at work, then I realize like holy shit, yes I was definitely affected. Like I'm super, not that I was bad at my job before, but I'm super efficient now. And maybe because I didn't realize how much my mind was preoccupied versus now where I am solely focused on my work and just even being able to do more. I can go out and do anything really, go out with friends or whatever cause I didn't spend my day binging and purging. Like a lot is different." [Participant #1]*

Table 9

Change in Clinical Impairment for the Intent-to-Treat Sample (n = 23) during 8-weeks of Lisdexamfetamine Dimesylate Treatment

Measure	Baseline		Week 5		Post or LOCF		Cohen's *d*
	M	*SD*	*M*	*SD*	*M*	*SD*	
CIA	32.42	8.04	15.04	11.42	13.04	12.17	1.88

Abbreviations: CIA, Clinical Impairment Assessment

Table 10

Change in Clinical Impairment for the Completer Sample (n = 19) during 8-weeks of Lisdexamfetamine Dimesylate Treatment

Measure	Baseline		Week 5		Post		Cohen's *d*
	M	*SD*	*M*	*SD*	*M*	*SD*	*SD*
CIA	31.72	7.76	11.42	8.02	9.00	8.15	2.86

Abbreviations: CIA, Clinical Impairment Assessment

3.2.5. Weight and Vital Signs

Changes in weight, body mass index, blood pressure and heart rate are presented in Table 11. An average weight loss of 2.1 kg was observed from Baseline to Post/ET, corresponding to a 0.76 kg/m^2 BMI reduction. Participants experienced an average increase of 6.87 mmHg in systolic blood pressure and 3.21 mmHg in diastolic blood pressure from Baseline to Post/ET. An average increase in heart rate was also observed. Heart rate increased on average by 12.1 beats/min based on readings from a calibrated

blood pressure machine at Baseline and Post/ET, and 7.45 beats/min based on ECG completed at Screening and Post/ET.

Table 11

Change in Vital Signs and Weight during 8-weeks of Lisdexamfetamine Dimesylate Treatment

Measure	Baseline		Post or End-of-Treatment	
	M	*SD*	*M*	*SD*
Systolic Blood Pressure, mmHg	114.74	11.23	121.61	10.87
Diastolic Blood Pressure, mmHg	73.22	8.70	76.43	6.87
Heart Rate, bpm based on blood pressure machine	63.35	9.44	75.48	16.23
Heart rate, bpm based on ECG[a]	58.78	9.02	66.45	10.55
Weight, kg	65.91	9.21	63.84	8.20
Body Mass Index, kg/m^2	24.54	2.54	23.78	2.35

Abbreviations: bpm, beats per minute;

[a] ECGs were completed at Screening and Post/End-of-Treatment.

3.2.6. Adverse Drug Reactions

Adverse drug reactions (ADR) that occurred in at least 10% of participants are shown in Table 12. The most commonly reported ADR was decreased appetite, which was reported at least once during the study period by all participants. Participant experiences of decreased appetite are described in Section 3.2.6.3. No serious unexpected adverse drug reactions were reported during the trial. One participant was withdrawn for

experiencing clinically significant weight loss which was predefined as experiencing a weight reduction of >5% in a given month. There were no participant-initiated discontinuations due to adverse drug reactions.

3.2.6.1. Pattern and duration of ADRs. During qualitative interviews, participants frequently discussed their experience with ADRs. The discussions often centered around the duration that ADRs lasted, their pattern of occurrence, and the way participants managed ADRs. During the interviews, attention was focused on discussing decreased appetite as a specific ADR that has particular relevance in this population.

It was common for participants to notice ADRs early in the trial, especially while titrating the medication to the maintenance dose. When initially starting LDX, and at each dose increase, participants would often report experiencing a more severe degree of ADRs. These often resolved or returned to baseline levels within a few days of being on a stable dose. As an example of the pattern of ADRs, one participant stated the following:

> *"Well the week that I was on the 30mg, and then there was the first week of being on the 50[mg], those were definitely a lot more side effects, but then the second week of being on the 50s it was definitely a lot better and easier to manage the side effects." [Participant #7]*

3.2.6.2. Factors that mitigated ADRs. On some occasions, ADRs persisted throughout the duration of the study. In these instances, participants learned to manage these on their own or with guidance from the research team. Participants were encouraged to avoid taking the medication at the same time as consuming a caffeinated product, to take the medication in the morning to minimize insomnia, and to take the medication in temporal proximity with food. Dry mouth was a common ADR, which

tended to persist throughout the study. The research team recommended consuming adequate fluids and using readily available over the counter products for dry mouth in these cases. As an example of the discussions around managing ADRs, at the Week 5 interview one participant described the following:

> *"It's been good. There were some negative side effects, especially starting the 50 [mg] um but I think all of that is kind of gone away. There's a little bit of dry mouth but it's really easy to deal with that, like have water, have fluids. So I haven't noticed any significant side effects anymore um, so it's good. I'm able to take it about the same time every day, like it doesn't negatively impact my life." [Participant #8]*

Another participant highlighted the importance of maintaining meal structure and regular eating while on the medication to help prevent or lessen ADRs:

> *"I just like, and you guys would always warn me too and like 'you have to eat or else you're going to get like side effects' like that kind of thing, and make sure you space out your meals well and not too far apart or anything like that, and I was kind of like yeah okay, sure. And then I noticed that that was definitely a thing. But I found near the end I knew how to manage it kind of thing, um and I find even now, I'm just used to always having a granola bar just in case." [Participant #9]*

3.2.6.3. Appetite, hunger and restriction. During qualitative interviews, participants were specifically asked about their experiences with changes in appetite or hunger. All participants in the study reported decreased appetite to some degree during the trial, however the duration and intensity of the decreased appetite was variable. Some participants described only experiencing decreased appetite during the titration phase

while the dose of LDX was being increased. When asked about changes in appetite or hunger common examples of responses included:

> *"Um for the first two days of the medication I had a suppressed appetite, but other than that I haven't noticed that." [Participant #10]*
>
> *"My appetite's been really suppressed to the point where I don't feel hungry but I know I need to eat. Um but that was mostly at the beginning of the 70s like the dosage [increasing the dose to 70mg/day] where I could literally, I felt like I could eat nothing all day and I still wouldn't want to eat food. But um now [Week 5 interview] it's pretty good." [Participant #11]*

However, some participants continued to experience varying degrees of decreased appetite throughout the trial. Participants described different ways of managing decreased appetite including setting reminders to eat at regular times, meal planning ahead of time, and continuing to eat mechanically in the absence of hunger cues. Participants also discussed the importance of the expectation from the research team that weight loss or increased restriction could result in discontinuation of the medication and withdrawal from the trial. For example, one participant discussed the following ways they managed decreased appetite on the medication:

> *"Definitely had loss of appetite, mostly because I just wouldn't really remember unless I kind of set reminders for myself, which was easy enough to do while in school because like I had set breaks and stuff like that, so I would have everything planned out…but like if I hadn't been proactive and tried to make myself, it would have been really easy to not, which is also part of the reason why I tried to keep everything like pretty standard." [Participant #3]*

Participants in the trial reported an understanding of the importance of maintaining meal structure, not only as an expectation of the trial, but also to maintain health, function optimally, and to continue benefiting from the medication. As a second example of an experience with decreased appetite, one participant stated:

> *"It just felt like, I don't want to use cover girl easy breezy…, first 2-3 weeks were really rough as far as no appetite, and initially there was like, I want to say the first like couple of days there was almost this sense of pride, like oh I don't even have to eat. But then it's like, girl you need to eat. Like this, this is it's own issue, you need to eat. Like if you're going to a spin class and burning whatever amount of calories you need to, your body requires food to function. So that was the only kind of downside [of the medication] that required like having to think about food and consuming food, and then after that it was just easy." [Participant #8]*

Some participants, particularly those with a history of more restrictive eating patterns, expressed concern that experiencing decreased appetite on the medication may rekindle previous restrictive behaviours:

> *Yeah, really worrying about becoming more restrictive…, like I really worry about losing control over that. Like is that why it's hard to eat? I'll be hungry and I'll make something, and then I'll just completely lose my appetite…, and trying to take a bite of [the meal] is almost like, it's physically hard to do that and that is not normal. That wasn't something I had an issue with before. I wasn't sure where exactly that was coming from…, I was starting to worry that was something else that was developing, or if it was just anxiety over everything else. I wasn't quite sure how to look at that 'cause when I was a teenager and this first started coming*

up, I had just been restricting for a little while… and when the binging and purging started that wasn't something I planned either, so I guess I'm just also worried about it kind of reverting. [Participant #4]

Table 12

Adverse Drug Reactions[a] Reported at least once during 8-weeks of Lisdexamfetamine Dimesylate Treatment[b]

Adverse Drug Reaction	*n*	%	Adverse Drug Reaction	*n*	%
Decreased Appetite	23	100.0	Excessive sweating	9	39.13
Dry Mouth	19	82.61	DBP Increased	7	30.43
Fatigue	19	82.61	Abdominal Pain Upper	6	26.09
Insomnia	17	73.91	Dizziness postural	6	26.09
Feeling jittery/restlessness	17	73.91	Tremors	6	26.09
Increased Heart Rate	15	65.22	Euphoric Mood	5	21.74
Nausea	14	60.87	Diarrhea	4	17.39
Bruxism	14	60.87	Constipation	4	17.39
Weight Decreased	12	52.17	Dysgeusia	4	17.39
Headache	12	52.17	Nightmares	4	17.39
Palpitations	11	47.83	Dizziness	4	17.39
SBP Increased	10	43.48	Vomiting	3	13.04
Irritability	9	39.13	Dyspnea	3	13.04
Anxiety	9	39.13	Cold Extremities	3	13.04
Depressed Mood	9	39.13			

Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure.

[a] Adverse Drug Reactions are defined as any adverse event that occurs during the study for which the causal relationship between the study medication and the adverse event is at least a reasonable probability (i.e., the relationship cannot be ruled out).

[b] Adverse Drug Reactions that occurred at least once in at least 10% of the participants are shown.

3.2.7. Restarting Lisdexamfetamine Treatment

Of the 18 participants who had the option of restarting the medication after completion of the trial (i.e., those who were not withdrawn/did not drop out), 16 participants elected to restart the medication. During qualitative interviews, participants discussed having either a strong desire to restart the medication, having a moderate desire to restart, or not wanting to restart at that time.

3.2.7.1. Strong desire to restart LDX. Participants who had a strong desire to restart the medication generally cited the remission or reduction of binge episodes, compensatory behaviours, urges, and/or intrusive thoughts they experienced while on the medication as a reason for wanting to resume treatment. Participants felt the improvements to binge eating and compensatory behaviours on the medication improved their ability to function in their daily lives, that they had more control and freedom, and some described feeling as though they no longer had an eating disorder. These participants wanted to resume the medication to prevent losing their progress. As an example of what participants described when discussing their reasons for wanting to restart the medication, one participant stated the following:

> *"I think just, it was just overall like the first time ever that I actually had that much of [a] reduction in symptoms so I don't want to change that I guess and also just the ability to function more normally and when you're not thinking about that all the time and you notice how easy it is to do things." [Participant #12]*

3.2.7.2. Moderate desire to restart LDX. Few participants had a moderate desire to restart the medication. Of those who did, the most common hesitation around restarting the medication was a belief that the medication would not be the "be-all end-all". These participants wanted to resume the medication in addition to some form of psychotherapy for their eating disorder, or support that could provide additional feedback on normalized eating. They wanted another form of support to replace the medication or wanted to discontinue the medication more gradually in the future. One participant reported their hesitation around restarting the medication was specific to the logistics of taking LDX longer-term (e.g., plans to become pregnant in the future, how long they would need to take the medication):

> *"Well I know that the medication isn't just going to be the be-all end-all, but I feel like with the medication and maybe if I did outpatient or something like that, then that could help me. So I definitely don't want to come off the medication until I find something else that can help me 'cause I feel like by myself I'm not going to do a very good job." [Participant #5]*

3.2.7.3. No desire to restart LDX at this time. Only two participants decided not to restart the medication at the end of the trial. Both participants reported a desire to try and maintain their progress first without the medication given the short follow up period in the trial. Both reported that they would be open to taking the medication in the future if they felt it was necessary. As an example, one participant described the following:

> *"I can't say that at this point in time since I haven't been off it long enough to know if I can continue to do healthy stuff in my normal life. If I'm not able to maintain*

this off the medication then I would take it again, but I would hopefully be able to do all of the things that I was doing without it." [Participant #2]

3.3. Results Part B: Thematic Analysis of Participants Experience with Lisdexamfetamine

3.3.1. Theme 1: Reprieve from the Eating Disorder

One overarching theme was the ways in which participants experienced a reprieve from eating disorder behaviours, urges, and cognitions during the study. Participants often discussed experiencing a sense of relief and freedom from the burden of the eating disorder behaviours and urges while on the medication. This was often described as a sudden or unexpected change soon after starting LDX that accompanied the reduction in binge/purge behaviours reported. It was not only the degree of symptom reduction participants experienced, but the quality of that change that appeared unique to this form of treatment. Participants described being surprised by how easy it now felt to abstain from binging and purging, that a weight had been lifted off their shoulders, and the stress of being consumed by the cycle of binge/purge behaviours and the eating disorder was alleviated:

"It's a weird adjustment to make, suddenly to not just have so much of my day consumed by that, that cycle, right? Like every day too…, I was never feeling good, I was just taken over by it and I didn't have like a desire to do anything really or like put myself in situations where I'd have to do things, and to not have that kind of hanging over me anymore was a strange feeling but a good one. It was like suddenly having like this huge weight not there anymore." [Participant #4]

As a second example of the way participants described reduced stress from the burden of the eating disorder one participant stated the following:

> *"Yeah it's been interesting to see how life is without having to worry about binging every day and purging every day and just obsessive thoughts about being hungry all the time and then being upset because you don't want to eat bad food but you want to. So yeah, 'cause I experienced that for like 10 years straight so it's been like a lot of stress lifted from not having those thoughts." [Participant #13]*

3.3.2. Theme 2: Improvement in Function and Quality of Life

A second overarching theme was the improvements to quality of life and ability to function while on the medication. Commonly, participants developed increased awareness and insight into the level of impairment from eating disorder behaviours, thoughts, and urges prior to beginning the trial once they had experienced symptoms/urges reducing/remitting on the medication:

> *"I didn't even, even answering the questions now compared to the beginning… I didn't really know how much it [the eating disorder] influenced my life until it wasn't as prevalent and it wasn't there every single day. Like that drive and that obsessive thought process behind it, I didn't even realize that was a component to it so just realizing that it can be different than it was [has been the best part about participating]." [Participant #14]*

With the reduction of symptoms and urges that occurred during the trial, and increased awareness/insight into the ways the eating disorder previously impaired their life, participants often reflected on their experiences with impairment prior to starting the medication compared to their experiences during the trial. During qualitative interviews,

participants reported improvements in many domains that had been affected by their eating disorder, such as their ability to function at work and school, ability to engage with others socially, increased feelings of connection with their families and loved ones, and improvements to their mood:

> *"Just like a) financially definitely is a big one. While I was on [the medication] at least, being able to go out with my friends, and you could go out to eat or whatever and you wouldn't have any issues, that is a big thing. So like socially too, and with my family things were a lot better too... I think probably because I didn't realize before how you do become agitated when you are always having these thoughts and you're not agitated at the people, you're just agitated in general. So I think I didn't realize how bad that was [before] versus now." [Participant #1]*

As another example of improved function and quality of life, one participant described how their life had changed since being on the medication:

> *"Oh my goodness, so radically really. Like I just, I just feel so much more in control of who I am and I feel like I'm a better mom, I feel like I'm better at my job, I, you know, I just feel, I feel better, I feel you know. I don't know how else to put it but it's, it's really changed." [Participant #15]*

3.3.3. Theme 3: Renewed Hope for Recovery

A third overarching theme was the sense of renewed hope for recovery that participants reported during their time in the trial. While interviews did not probe further about participants' definitions of "recovery", it can be presumed that recovery from an eating disorder involves both cessation of eating disorder behaviours (e.g., binge eating and compensatory behaviours), as well as an absence of impairing disorder specific

cognitions (e.g., preoccupation with weight/shape, rigid rules around food/eating). Participants often reported that prior to the trial, they felt hopeless and had little confidence in their ability to stop binging and purging behaviours and fully recover from their eating disorder. Participants expressed that taking the medication and the subsequent improvements to eating disorder behaviours they experienced during the trial offered them a glimpse of what recovery could be, and a newfound sense that recovery was possible. For example, one participant stated the following:

> *"I felt like I had my life back. Like, and that makes me get super emotional saying that, it sounds so corny, but it's like I haven't been able to do what I've been doing the last two months in years, and I can remember how driven and how ambitious and how hard working I used to be, and that all got taken away with the eating disorder…, and I hadn't realized how much the eating disorder itself had taken away from my life, and like being on this medication just made everything easy. It made my like life function, I could do what I wanted to do, I didn't have to even think about wanting to binge and purge, which I haven't had in years…, I could see the light and the hope of what life could then be like again …, I don't know if I've ever really gotten that since this eating disorder started." [Participant #3]*

An additional example of how participants described a renewed sense of hope for recovery is as follows:

> *"I'm feeling a little bit more hopeful that I can change this, there was a time that I felt, you know, like this will just be how I, how life is, which was a very sad thought to think but I'm starting to get some, see the light at the end of the tunnel and see*

that you know, change is possible and um I can have a life free of this hopefully." [Participant #16]

The renewed sense of hope for recovery was exciting to participants after many years of living with the eating disorder:

"It's given me a lot of hope and that's been a really exciting thing. I felt really lost for a really long time and it's given me, and in some aspects more than others definitely, but it's given me a sense of normalcy that I really enjoy." [Participant #17]

3.3.4. Theme 4: Ability to Normalize Eating

A fourth overarching theme was participants' ability to normalize eating patterns. Participants spoke about their ability to normalize their eating during the trial in different ways. They described the ability to implement more consistent meal structure or to improve on existing meal structure while on the medication. In some cases, this involved eating mechanically in the absence of regular hunger cues. One participant described their experience as follows:

"I feel like the medication was like a nice reset so I can like, I got myself on this whole plan of I'll eat every 3 hours and I'll eat vegetables or whatever and I was just able to like start fresh you know? And now I can hopefully continue that for the rest of my life." [Participant #2]

Participants reported experiencing increased flexibility and freedom around food that allowed them to incorporate variety into meals/snacks and previous "fear/risky foods". As an example, one participant described their ability to incorporate foods they would normally restrict while trying to stop binging and purging in the past:

"Prior to the study, say if I was trying to stop binging and purging I think I was super restrictive on what I would eat when I didn't really realize that back then. There was foods I almost had deemed bad foods and now, slowly over the last couple of weeks I introduce different things that maybe prior to this I wouldn't have eaten if I was trying to not binge and purge." [Participant #1]

In some instances, participants reported feeling that the medication normalized their appetite which they described as "excessive" or "insatiable" prior to the study. Some participants described how taking the medication allowed them to experience regular hunger and fullness cues. For example, one participant described their experience as follows:

"I think [my appetite] probably has gone down a little bit but I've also been able to sort of listen to my hunger cues in ways that I wasn't able to before. Even though I still sort of eat no matter what, but I'm aware of them. Sometimes I would try to listen to my hunger cues before but they were so out of whack I had no idea. I didn't even really know what it felt like to be hungry or full or yeah, so it's definitely sort of helped me get to a stable place where I can start sort of remembering what that feels like." [Participant #18].

Chapter 4 - Discussion

The objective of the sub-project was to investigate various outcomes of LDX treatment by generating preliminary effect size data, and to investigate participants' experiences with LDX treatment through semi-structured qualitative interviews during an open-label study for moderate to extreme BN.

4.1. Eating Disorder Symptom Frequency

Reductions in objective binge eating episodes and total compensatory behaviour episodes corresponding to large effect sizes were observed in both the ITT and Completer samples. These results were expected based on the available case data described in the Introduction, which have all reported improved or fully remitted binge/purge behaviours when patients were treated with stimulants. When considering study completers, 52.63% were completely abstinent from binge eating and compensatory behaviours in the 28 days prior to Post and 84.21% had a subthreshold number of compensatory behaviors (i.e., <4) in the 28 days prior to Post. In the fluoxetine trials for BN, approximately one third of participants receiving the 60mg/day dose achieved abstinence from binge eating and self-induced vomiting at the end of the study (Wood, 1993). Previous research in BED patients treated with LDX by McElroy et al. (2015) found that 42.2% and 50% of the sample treated with 50 or 70mg LDX respectively were abstinent from binge eating in the four weeks prior to their post assessment at Week 11.

Reduced eating disorder symptom frequency was commonly discussed by participants during qualitative interviews and is supported by findings from Theme 1: Reprieve from the Eating Disorder. Theme 1 describes an element of participants' experience with behaviour change, namely the sudden/unexpected sense of relief and

freedom from the burdens of the eating disorder they felt while on the medication. Previous qualitative research that included patients with BN has mainly considered participants' experience with binging and/or compensatory behaviours and the role these behaviours play in regulating emotions, as a means of coping/controlling, influencing shape and weight, providing physiological reinforcement, and achieving release and fullness (Eli, 2015; Jeppson et al., 2003). There has been little research investigating participants' experience with *changing* binging and compensatory behaviours. One study on young women's experiences with recovery from bulimia found that participants described a sense of freedom with recovery, and that the freedom from ED behaviours allowed them to see opportunities in a life no longer controlled by BN (Lindgren et al., 2015). While somewhat different from the finding from Theme 1: Reprieve from the Eating Disorder which involved the sudden/unexpected sense of relief and freedom, the findings from Lindgren et al. (2015) support that a sense of freedom from the disorder, whether sudden or more gradual, is an important part of recovery as described by individuals with BN. Future research might consider participants' experiences of changing binging/purging behaviours, not only the experience of living with these behaviours. This could enhance our understanding of how best to support individuals with BN through behaviour change.

4.2. Eating Disorder Cognitions

4.2.1. Restraint

In both the ITT and Completer analyses, reductions on all subscales and the Global score of the EDE were observed. These quantitative results are supported by participants' descriptions of the reduction in the frequency and intensity of eating

disorder cognitions during qualitative interviews. The reductions observed corresponded to large effect sizes, aside from the Restraint subscale where a medium effect size was observed. The Restraint subscale of the EDE assesses attempts to restrict food intake to influence shape and weight. As a result of inclusion/exclusion criteria, participants in the study had minimally restrictive eating habits prior to enrollment, which may account for the relatively low baseline scores on the Restraint subscale. However, when compared to established norms from a community-based sample of 243 young women (Fairburn et al., 2014), Baseline scores on the Restraint subscale were elevated above community norms in both the ITT and Completer sample. At Post, the scores on the Restraint subscale of the EDE in the ITT sample were virtually identical to community norms (0.94 in the community sample and 0.97 in the sample). The Completer sample had Restraint subscale scores below community norms at Post despite having scores above community norms at baseline.

A reduction corresponding to a small-medium effect size was also observed for the Restraint subscale of the TFEQ in the present study. The Restraint subscale of the TFEQ evaluates dietary restraint and conscious mechanisms for restraining food intake. Scores between 0 and 10 are considered low to average, those between 11 and 13 are considered high, and those between 14 and 21 are considered to be at a level of clinical concern. At Baseline, when considering the ITT sample, participants scored 12.52 on average which corresponds to a high level of restraint, but below the level of clinical concern. At Post, average scores in the ITT sample were reduced to 10.57 which could be considered low-average. Similar to the EDE Restraint subscale, it is possible that because participants started with relatively low levels of restraint at Baseline (by virtue of

inclusion/exclusion criteria) there was minimal room for further decreases. In previous studies that have utilized the TFEQ in samples with BED treated with LDX, the authors proposed that an increase on the Restraint subscale would indicate improvement as individuals with BED exhibit low-average restraint with mean scores of 7-9 (McElroy et al., 2016). During 11-weeks of treatment with LDX, participants with BED had increased average scores on the Restraint subscale of the TFEQ whereby scores increased from the low-average range to the high range (McElroy et al., 2016). In the present study's sample, the inverse change was observed where average scores on the Restraint subscale of the TFEQ decreased during treatment with LDX from the high range to the low-average range. Again, this would be expected since those with BED often are under-restrained in their eating patterns and treatment involves *increasing* restraint; whereas the opposite is true in BN treatment where the goal of treatment is often to *decrease* restraint (Linardon, 2018; Masheb & Grilo, 2000; Wilfley et al., 2000).

It is important that we did not observe an increase in restraint during treatment with LDX as assessed by both the EDE Restraint subscale and TFEQ Restraint subscale. Despite participants' reports of decreased appetite there did not appear to be an increase in dietary restriction or restraint, in fact, it appears levels of restraint decreased during the study. These results suggest that over the course of 8-weeks of LDX treatment, participants with BN in the present study's sample had reduced attempts at restricting their food intake to influence shape and weight. It is possible that in a sample of individuals with BN who are minimally restrictive, and motivated to maintain meal structure and not lose weight, LDX may facilitate reduced restraint over eating. This is consistent with results discussed in Theme 4: Ability to Normalize Eating, where

participants reported having more flexibility and freedom around food, allowing for less restrained eating. Participants often reported feeling more in control of their eating during qualitative interviews along with experiencing reduced urges to binge and reduced binging behaviours. As a result of this, participants may have been less driven to restrict food intake to compensate for loss of control eating.

4.2.2. Eating Concern, Shape and Weight Concern, and Global Eating Disorder Examination Scores

In the ITT sample, Eating Concern, Weight Concern, Shape Concern, and the Global score of the EDE remained elevated above established community norms at Post despite reductions in scores that corresponded to large effect sizes. However, in the Completer sample, average scores for Weight Concern, Shape Concern and the Global score of the EDE were essentially the same or lower than community norms. In the community sample, average scores were as follows: Weight Concern 1.18, Shape Concern 1.34, and the Global score 0.93 (Fairburn et al., 2014). These results suggest that after 8-weeks of treatment with LDX, participants in this sample experienced a reduction in concern about shape and weight relative to baseline. At Post, participants who completed the trial experienced a level of weight and shape concern and global eating disorder psychopathology comparable with that of young women in the community. In qualitative interviews, there were mixed findings related to body image concerns and concerns about weight/shape. While some participants continued to experience the same degree of concern about their weight/shape and body image, others reported these thoughts and concerns had decreased in frequency and importance.

It is somewhat surprising that participants experienced a reduction in measures of eating, weight, and shape concern given no aspects of the trial specifically targeted eating disorder cognitions or concerns about weight/shape/body image. A recent review that examined the efficacy and effectiveness of CBT-E for adults and older adolescents found that CBT-E reduces EDE global scores, dietary restraint, eating, shape, and weight concern subscale scores and that reductions correspond to large effect sizes (Atwood & Friedman, 2020). This is to be expected given CBT-E is directly designed to target the cognitive and behavioural elements of an eating disorder. One possible explanation for the finding of reduced eating, weight, and shape concern in the present study is that participants had less concern about weight gain with reduced binge eating which resulted in less distress about weight/shape. Another explanation comes from one of the foundational components of CBT approaches for eating disorders wherein participants learn to make more accurate connections between their eating and their weight (Waller & Mountford, 2015). While the trial was not intentionally designed to facilitate this learning, participants' weight was measured at each in-person study visit and they were free to see their weight each week if they chose to (all participants did). Measuring body weight during the trial was done to monitor for rapid weight loss. No feedback was given about weight, and no connections between weight and behaviour were discussed by members of the research team. However, participants may have still learned independently through this monitoring that their weight *did not* change rapidly even though meal structure was maintained (or even improved) during the trial. This incidental learning may have resulted in reduced concern about weight, shape and eating as assessed

by the EDE. Another possibility is that reduced weight and shape concern occurred secondary to weight loss as participants lost on average 2.1kg during the trial.

4.2.3. Hunger

With respect to the Hunger subscale of the TFEQ, reductions in average scores corresponding to a large effect size were observed from Baseline to Post. The Hunger subscale of the TFEQ is a measure of the perceived feeling of hunger and its behavioural consequences. Scores between 0 and 7 are low to average, those between 8 and 10 are high, and those between 11 and 14 are of clinical concern. In the ITT and Completer sample, average scores on the Hunger subscale at Baseline were in the high range. Scores decreased to the low to average range by Week 5 and these changes were maintained at Post. Similar results were seen in the study by McElroy at al. (2016) where participants with BED treated with LDX had average Hunger subscale scores corresponding to the high range at Baseline and these were reduced to the low to average range for all treatment groups receiving LDX by Week 3. This is consistent with the findings from Theme 4: Ability to Normalize Eating as some participants described feeling that the medication normalized their appetite which they described as “excessive” or “insatiable” prior to the study. It is also consistent with Theme 1: Reprieve from the Eating Disorder as some participants described experiencing a reprieve from excessive hunger, thoughts about food, and urges to binge while taking the medication.

It is possible that reduced scores on the Hunger subscale of the TFEQ are a result of decreased appetite whereby the medication could be reducing appetite from A) a "normal" level to "low" levels, or B) "high" (dysregulated) levels to "normal" levels (or low levels). It is challenging to say with certainty where baseline levels of appetite fell

(i.e., “normal” or “high”) as this is subjective and distorted from chronically dysregulated eating. It has been suggested that individuals with BN have dysregulated fasting appetite hormones (e.g., ghrelin, leptin, cortisol, etc.) relative to healthy controls (Tortorella et al., 2014) that may explain abnormalities in levels of hunger. Although research has produced inconsistent findings regarding appetite hormones in BN, it has been suggested that abnormalities in appetite hormones may be A) caused by BN behaviours, B) may maintain BN behaviours, and/or C) may be associated with behavioural and cognitive ED symptom severity (Presseller et al., 2021). To my knowledge, research has not examined the relationship between scores on the Hunger subscale of the TFEQ and appetite hormones. Future research is needed to better elucidate differences in perceived hunger and appetite in individuals with BN.

4.3. Obsessive Compulsive and Impulsive Features

4.3.2. Obsessive Compulsive Features

Large effect size reductions on the compulsive subscale, obsessional subscale, and the total score of the YBOCS-BP were observed in both the ITT and Completer samples. Total scores on the YBOCS are classified as subclinical (0-7), mild (8-15), moderate (16-23), severe (24-31), and extreme (32-40). The total score is a summed composition of the obsessional and compulsive subscales and therefore reflects elements of obsessive thoughts and urges associated with binge eating/purging, as well as binge eating/purging behaviours. At Baseline, average total scores on the YBOCS-BP were categorized as moderate for both the ITT and Completer samples. By the Week 5 assessment, scores were in the subclinical range and this reduction was maintained at Post. Similar results were found by McElroy et al. (2016) who reported that individuals with BED treated with

LDX over 11 weeks had reductions in total scores on the YBOCS modified for binge eating. These results suggest that in the present study, treatment with LDX coincides with reduced obsessional and compulsive features associated with binge eating and purging in a similar manner to that observed in participants with BED.

The compulsive subscale of the YBOCS-BP assesses the amount of time spent on, interference caused by, distress associated with, resistance to, and degree of control over binge/purge behaviours. The obsessional subscale specifically assesses time occupied by, interference due to, distress associated with, attempts at resisting, and degree of control over obsessive thoughts, impulses or ideas to binge and purge. Scores on both the compulsive and obsessional subscales decreased as expected, and responses in the qualitative interviews were consistent with the quantitative scores. It is interesting to consider why a reduction in intrusive thoughts and urges were observed. One explanation is that decreased appetite secondary to LDX reduces the hedonic value of the food, thereby diminishing urges and thoughts about engaging in the behaviour. It is also possible that with less binge eating and compensatory behaviours, participants had more consistent nourishment which can result in less preoccupation with food and eating and less hunger-driven urges to binge (Södersten et al., 2017). Further, Kessler et al. (2016) propose that the combination of decreased cortical inhibition, decreased reward sensitivity, and an imbalance in signalling between the direct striatonigral pathway (involved in reward response; elevated dopamine D1 signalling) and indirect striatonigral pathways (involved in behaviour flexibility; decreased dopamine D2 receptors) may mediate compulsive binge eating. Thus, imbalances in dopaminergic signalling between pathways related to both reward and compulsive-habitual behaviour may be important

targets regulated by treatment with LDX. While research has shown LDX produces sustained dopamine increases in striatal regions in rats (Rowley et al., 2012), future studies could investigate this line of research in humans.

4.3.3. Impulsive Features

With respect to the Disinhibition subscale of the TFEQ, reductions in average scores corresponding to large effect sizes were observed from Baseline to Post. The Disinhibition subscale of the TFEQ is food/eating behaviour specific and considers the disinhibition of eating related control. Items assess ability to control eating, tendency to eat in response to environmental, situational, emotional, and food related triggers, and the experience with the consequences of eating in this manner (i.e., fluctuations in weight). For the Disinhibition subscale, scores between 0 and 8 are classified as low to average disinhibition, those between 9 and 11 are high levels of disinhibition, and scores from 12 to 16 are classified as disinhibition levels that are at a level of clinical concern. At baseline, average scores for both the ITT and Completer samples corresponded to levels of disinhibition that are of clinical concern. By Week 5 of treatment, average scores on the Disinhibition subscale were well within the low to average range and these changes were maintained at Post. Similar results were observed by McElroy et al. (2016) in a sample of participants with BED treated with LDX over 11 weeks. At Baseline average scores on the Disinhibition subscale were in the range of clinical concern. By Week 3, Disinhibition subscale scores for treatment groups receiving 50 and 70mg doses of LDX were in the low to average range and these changes were maintained at Week 11.

Total scores and subscale scores on the BIS-11 remained consistent throughout the trial in both the ITT and Completer samples. The changes observed from baseline to

post corresponded to negligible effect sizes. The BIS-11 produces a total score ranging from 30 to 120 and is a measure of trait impulsivity (Stanford et al., 2009). Three of the BIS-11 subscales were investigated: attention impulsivity (inability to focus or concentrate), motor impulsivity (acting without thinking), and non-planning impulsivity (lack of forethought/future orientation). At Baseline, total BIS-11 scores were similar to the average total score of 62.3 observed in healthy adult populations and below the average total score of 72 which classifies high impulsivity (Stanford et al., 2009). In both the ITT and Completer sample, scores at baseline were similar to those observed by McElroy et al. (2016). In their sample with BED treated with LDX over 11 weeks, BIS-11 total scores and scores on the motor impulsivity and non-planning impulsivity subscales (but not attention impulsivity subscale) were significantly reduced for the treatment group administered 70mg of LDX relative to the placebo group. Reductions on the total BIS-11 scores and all subscale scores for the treatment groups receiving 30mg and 50mg doses were not significantly different from the placebo group.

It is of interest to consider why Disinhibition assessed by the TFEQ decreased, but impulsivity as assessed by the BIS-11 was unchanged. One explanation is that because we excluded participants with ADHD from this trial, the resulting sample of individuals with BN did not have an abnormally high degree of general, or trait, impulsivity (i.e., as measured by the BIS-11). In other words, this sample had an average level of trait impulsivity at baseline which was not further reduced by treatment with LDX. This is supported by the observation that baseline total scores on the BIS-11 for this sample were similar to healthy adult populations at baseline. On the other hand, this sample *did* have clinically concerning levels of Disinhibition at baseline (i.e., food/eating

specific impulsivity). The Disinhibition subscale of the TFEQ is food/eating behaviour specific and considers the disinhibition of eating related control. Items assess ability to control eating, tendency to eat in response to environmental, situational, emotional, and food related triggers, and the experience with the consequences of eating in this manner (i.e., fluctuations in weight). In qualitative interviews, participants often described experiencing a greater degree of control over binge/purge behaviours and urges while on the medication, which is consistent with the reduced scores on the Disinhibition subscale of the TFEQ. In summary, while general trait impulsivity did not improve over the course of treatment (possibly due to the exclusion of those with ADHD), *eating specific impulsivity* (or Disinhibition as measured by the TFEQ) did improve in the expected direction.

In those with BN, treatments that modify food related disinhibition are of interest because several theories of BN pathoetiology revolve around impaired food related impulse control; namely, A) binge eating/purging are inherently impulsive behaviours (i.e., trait impulsivity → BN symptoms; Fischer et al., 2008), B) restriction mediates the relationship between impulsivity and binge eating (i.e., restriction → impulsivity → BN symptoms; Michael & Juarascio, 2021), and C) binge eating/purging is an impulsive response to distress/negative affect (i.e., negative emotion → impulsivity → BN symptoms; Fischer et al., 2008). There is no clear consensus on the exact role of impulsivity in BN and it is likely a combination of trait and state impulsivity, personality, comorbidity and disorder specific elements (e.g., restriction) that differ between individuals. Hopefully, the findings from the present study will provide some insights for future research on this important topic.

4.4. Functional Impairment

Reductions corresponding to large effect sizes were observed for average scores on the CIA from Baseline to Post in both the Completer and ITT sample. The CIA is a measure of the severity of psychosocial impairment from features of the eating disorder and scores of 16 are the best cut off point for predicting eating disorder case status (Bohn et al., 2008). At post, average scores in the ITT sample were 13.04 and 9.0 in the Completer sample, both below the cut-off of 16. This finding was also captured in qualitative interviews (e.g., Theme 2: Improvements in Function and Quality of Life); for example, participants often reported improvements to various functional domains (e.g., school, work, socially).

While previous research has not examined the use of the CIA in eating disorder populations treated with LDX, various forms of CBT for eating disorders have been shown to improve quality of life (Linardon & Brennan, 2017). As an example, over the course of a 10-session abbreviated form of CBT-E known as CBT-T, average CIA scores for the ITT sample decreased from 28.13 to 11.12 at Post intervention, corresponding to a large effect size (Pellizzer et al., 2019). In their Completer sample, average CIA scores decreased from 27.12 to 9.45, also corresponding to a large effect size. These results are comparable to those seen in the present study. While CIA scores in the ITT and Completer sample started slightly higher (average scores were approximately 32) in the present study's sample verses that reported by Pellizzer et al. (2019), they were reduced to similar endpoints after 8-weeks of treatment with LDX. This is particularly interesting as CBT-T is a more extensive intervention compared to what was offered in the present study. In CBT-T, patients receive individualized feedback related to improving eating

behaviours and patterns there is an expectation for rapid behaviour change and normalizing eating. Participants set specific goals and conduct behaviour experiments. The therapy addresses body image, shape and weight concerns, and emotional triggers for eating disorder behaviours. In the present study, no psychotherapy and no feedback on eating disorder behaviour change was provided. Feedback provided on meal structure was minimal and aimed to manage participants' experience of adverse drug reactions and reinforce the importance of non-restrictive eating as a requirement for continuing the trial and staying on the medication. Despite the differences in an approach such as CBT-T and participating in this trial, we observed comparable reductions in psychosocial impairment from the eating disorder. Since the CIA focuses on impairment from the eating disorder it is possible that the reprieve from the eating disorder participants experienced (Theme 1) could account for reduced impairment. Having freedom from the consuming nature of eating disorder thoughts, urges, and behaviours may have allowed participants to engage more in aspects of their lives that they value. There is evidence of this from qualitative interviews (see section 3.3.2 for examples) where participants discussed feeling more connected with family/friends/significant others, being more engaged at work, having more time to study and do schoolwork, and having more time to explore other interests.

It is also relevant to consider that some of the improvements that participants described related to their ability to function at work/school and/or their improved mood may be explained exclusively by taking a stimulant (i.e., are unrelated to changes in ED symptoms). This is supported by research that outlines how stimulants may be used for a variety of non-ADHD disorders and medical conditions and that the improvements

reported may be attributed to reductions in fatigue, as well as improved concentration, cognitive function, and mood (Sinita & Coghill, 2014).

4.5. Weight and Vital Signs

Findings from this data set related to changes in weight, BMI, and vital signs have been discussed in a recent publication by Keshen et al. (2021). In summary, an average weight reduction of 2.1 kg was observed during the trial. In the fluoxetine trials that lead to the Health Canada and FDA approval for fluoxetine as a treatment for BN, patients treated with 60mg/day experienced an average weight reduction of 1.6 kg during the 8-week study (Wood, 1993). One participant in the present study was withdrawn for experiencing clinically significant weight loss (>5% body weight reduction in a given month). However, no participants were withdrawn for BMI decreasing below 20 kg/m^2. As described by Keshen et al. (2021), a clinically significant increase in heart rate was observed in this sample. While the increase in heart rate was greater than that observed in stimulant treated adults with ADHD and that observed in the LDX trials for BED, no participants experienced clinically significant ECG abnormalities or concerning cardiac symptoms during the trial. It is not known whether this increase in heart rate is an artifact, or a factor secondary to BN such as orthostasis-induced tachycardia due to relative dehydration, these findings suggest both weight and cardiac symptoms should be closely monitored in future RCTs examining LDX for BN.

4.6. Adverse Drug Reactions

4.6.1. Participants' Experience with Adverse Drug Reactions

Overall, quantitative and qualitative results suggest that the medication was well tolerated. There was no participant-initiated drop out due to ADRs and there were no

serious unexpected adverse drug reactions. The qualitative component in this sub-study allows for comment on participants' experience with ADRs during treatment with LDX in a more comprehensive manner than reporting only ADR frequency. This is particularly useful given the use of LDX in a BN population has not been empirically studied. Participants experienced ADRs that are commonly reported by adults treated with LDX for BED or ADHD (Takeda Canada Inc, 2020). Previous case reports of BN patients treated with stimulants generally did not comment on ADRs, or reported that participants experienced minimal to no ADRs. Decreased appetite was not reported as a common ADR in previous case reports, which is contrary to the finding that decreased appetite was reported in 100% of participants in this study. A possible explanation to account for the differences in ADR frequency in previous case reports compared to this trial is the difference in monitoring of ADRs in clinical trials compared to clinical practice. To assess ADRs in a consistent manner in the present study, participants were asked about ADRs at every encounter using a checklist developed from the LDX product monograph. An ADR was recorded if it was reported at any time during the trial regardless of the intensity or duration. This method may improve monitoring of adverse events by prompting participants to consider specific symptoms instead of relying on participants to recall all potentially relevant experiences.

4.6.2. Pattern and Duration of Adverse Drug Reactions

The qualitative component of this trial allows us to comment on the pattern and duration that participants experienced ADRs. It was found that most ADRs occurred early in the trial (during the titration phase) and tended to increase in intensity with a dose change before ADRs returned to baseline levels within a few days. When ADRs persisted

past the early phase of the trial, participants learned to manage them independently or with guidance from the research team. Participants were encouraged to avoid taking the medication with a caffeinated product, to take it in the morning to avoid insomnia, and to take it in temporal proximity with food. Participants also noted the importance of maintaining adequate meal structure and eating regularly to help prevent or lessen ADRs. Future trials could include these instructions when educating participants about the use of LDX.

4.6.3. Decreased Appetite

Decreased appetite was an ADR that was given particular attention during qualitative interviews due to its relevance to a BN population. As mentioned previously, all participants in the trial reported some degree of decreased appetite but the duration and intensity was variable. For some, decreased appetite was only present during the titration phase and it resolved once a stable maintenance dose was achieved. For others, decreased appetite persisted throughout the trial and participants utilized various strategies to avoid problematic restriction secondary to decreased appetite. These included setting reminders to eat regularly, meal planning in advance, and continuing to eat mechanically in the absence of regular hunger cues. Of note, participants were not provided with specific feedback or instruction from the research team related to improving or modifying their eating habits (aside from the previously mentioned recommendation to take the medication in temporal proximity to food). That being said, there were clear expectations that participants would be withdrawn from the trial if they experienced rapid weight loss (>5% reduction in body weight in a given month), or became increasingly restrictive in their eating habits (e.g., frequently skipping meals).

Participants did express the importance of these expectations as a non-negotiable for continued use of the medication and as a motivator for maintaining adequate intake when experiencing decreased appetite. Given that this trial included these expectations for medication discontinuation/study withdrawal with weight loss and/or increased restriction and only one participant was withdrawn due to problematic weight loss, we propose it is critical these expectations be maintained in future RCTs examining the use of stimulants in BN populations.

A final consideration with respect to decreased appetite relates to participants with histories of more restrictive eating patterns. While we excluded individuals with severely restrictive eating habits (defined as routinely (> 2 days a week) eating less than 2 meals a day) and those with a history of anorexia nervosa, some participants had a history of restrictive eating and weight suppression at an earlier point in their disorder. These participants expressed concern that the decreased appetite they experienced on the medication may rekindle previous restrictive eating patterns. While this did not occur to our knowledge as per examination of food records, responses on the EDE, or self-report from participants, it is important to monitor eating patterns of individuals with BN prescribed stimulants, particularly those with histories of restrictive eating.

4.7. Restarting Lisdexamfetamine Treatment

Of the 18 participants who had the option of restarting the medication after completion of the trial (i.e., those who were not withdrawn/did not drop out), 16 participants elected to restart the medication. Most participants had a strong desire to resume treatment, citing improvements in their eating disorder symptoms and ability to function as reasons for wanting to restart LDX. Some participants had a moderate desire

to resume treatment as they believed the medication would not be the "be-all end-all". As such, they wished to resume treatment in conjunction with additional support or psychotherapy and/or to taper off the medication in a more gradual manner after a longer duration of treatment. There was also a desire to have more information about the logistics of taking LDX longer-term (e.g., pregnancy, length of treatment). Two participants did not want to restart the medication at the end of the trial without first having a longer period off the medication to determine whether they could maintain improvements. These findings speak to the acceptability of LDX to participants and have implications for future avenues of research.

In the present study's sample of participants eligible to resume LDX treatment after completion of the trial, 89% restarted the medication. This suggests that the majority of participants felt the advantages of the medication (e.g., ED symptom improvement, improved function etc.) outweighed the potential disadvantages (e.g., adverse drug reactions). It is also worth noting that 39% of the sample were currently taking another psychiatric medication, which suggests participants were generally open to medication options for psychiatric disorders. There is limited research that has considered participant experience in pharmaceutical trials, especially in the eating disorder field. One study by Antonucci et al. (2010) reported on patient experience and satisfaction with LDX using a large real-world sample of adults with ADHD who were beginning LDX treatment. Outcome measures were collected at the onset of treatment and after six weeks. The authors reported that 82% of patients intended to continue LDX treatment at the 6-week time point. Further, patients in the sample rated LDX as well tolerated and reported being very satisfied with the medication. Given the lack of data related to participant

experiences in clinical trials, future research could continue investigating clinical trial participants' experiences with study medications and desire to resume treatment at the end of a trial. This may support and enhance understanding of efficacy and tolerability of treatments.

Another consideration relates to the experience of participants who described that the medication would not be the "be-all end-all" and who wished to have further support or psychotherapy in addition to the medication. It is relevant to consider whether combining treatment with LDX and an evidence-based psychotherapy approach such as CBT-E or CBT-T may further improve outcomes of both treatments. Psychotherapies such as CBT-E or CBT-T are designed to specifically target features of BN such as the body image concern that we found persisted in some individuals during treatment with LDX. Further, these psychotherapy approaches involve detailed monitoring of eating behaviours similar to that utilized in this trial, but include individualized feedback, goal-setting, and psychoeducation around eating habits that we were unable to offer in a clinical trial setting. This may be protective against the development of increased restrictive eating secondary to decreased appetite on LDX and would serve to fill a gap identified by participants in the trial who wanted more direct feedback and support with behaviour change, emotions, ED cognitions, and further normalization of eating. We also observed that participants experienced a rapid reduction in binge/purge behaviours after starting LDX and rapid behaviour change has consistently been reported as a predictor of positive outcome in CBT approaches (Linardon et al., 2016). Treatment with LDX may aid in facilitating the rapid improvements in ED behaviours that improve outcomes for psychotherapy approaches.

Hope and hopelessness are other factors that have been found to predict outcome in CBT for BN. Namely, a greater degree of hopelessness was found to predict dropout from CBT for BN (Steel et al., 2000). Further, hope for the future has been identified as a key factor in promoting motivation to recover from an eating disorder (Venturo-Conerly et al., 2020) and as a factor that is an integral part of the recovery process (Bardone-Cone et al., 2018). A renewed sense of hope for recovery was one of the key themes identified in the present study (Theme 3). Participants reported their experience with the study was one that fostered a sense of hope that recovery from the eating disorder was possible. As described by Bardone-Cone et al. (2018) qualitative work in eating disorders has highlighted the importance of hope and the ability to envision recovery. It has been proposed that recovery hinges on hope being present (Acharya & Agius, 2017) and thus interventions that result in increased hope should not be discounted. Future research examining the use of LDX in a population with BN should consider combining medication treatment with a form of psychotherapy as this may offer advantages over the use of either intervention alone.

4.9. Strengths and Limitations

There are several strengths and limitations of the present study that warrant consideration. With respect to limitations, this was not a placebo-controlled trial and therefore placebo effects cannot be ruled out and the efficacy of LDX relative to placebo in BN was not assessed. This trial was a feasibility study that aimed to assess the feasibility of the protocol and generate preliminary effect size data that can inform future RCTs. As feasibility trials are not adequately powered to conduct hypothesis testing the results from this trial are limited to effect sizes. Participants were also informed that to

remain enrolled in the trial their eating habits could not become increasingly restrictive, nor could they experience rapid weight loss. These expectations for maintaining regular meal structure may have contributed to the reductions in binging/purging observed. The use of a placebo condition would help to investigate these elements. The sample was exclusively female and predominantly white, which limits ability to generalize these findings to a more diverse population. Additionally, there were stringent inclusion/exclusion criteria meaning the sample represented a narrow subset of individuals with BN. For example, only those with moderate to extreme severity of illness, a BMI between 21 and 30 kg/m^2, no history of anorexia nervosa, minimally restrictive eating patterns, limited comorbidities (e.g., no ADHD, no current major depressive disorder), no personal or family history of concerning cardiovascular conditions. The duration of treatment in the trial was relatively short (eight weeks) and the follow-up period off the medication was very short (one week). While these aspects of the design are suited to the nature and aims of a feasibility trial, the generalizability of these findings is limited to a highly specific subset of individuals with BN.

There are several strengths of this study including the use of established clinical interviews such as the EDE and SCID. These interviews have established validity and reliability and are widely used which is important for research replication. Participants also completed daily food records to monitor their eating and any eating disorder behaviours. This form of daily monitoring is more accurate than retrospective recall alone (Wilson & Vitousek, 1999). A qualitative component was also included to incorporate the participants' experience with the trial, a perspective that is often unaccounted for in pharmaceutical trials. Finally, this study tests a novel medication class (psychostimulants)

for use in this population which is particularly important given the relative paucity of other medication options for BN.

4.10. Directions for Future Research

An appropriate next step in this area of research would be to utilize the results from this feasibility trial to conduct an adequately powered, placebo-controlled RCT to assess the efficacy of LDX in BN. It is also important to continue to monitor safety (particularly weight and vital signs) and tolerability/adverse events (especially decreased appetite) in a population with BN. Future trials could include the outcome measures used in this trial to further build upon our understanding of how treatment with LDX may modify eating disorder cognitions, obsessive/compulsive and impulsive features, and levels of clinical impairment. It would be important to assess the validity of the YBOCS modified for binge eating and purging. It would also be of interest to combine the use of neurocognitive tasks, neuroimaging, and/or computational methods to achieve a more in depth understanding of the complex interplay between variables such as impulsivity and obsessive/compulsive features. If safety and efficacy are established, it would be interesting to investigate the use of LDX combined with and compared to first-line psychological interventions such as CBT-E.

4.11. Conclusion

In conclusion, this study provides a first look at changes in secondary outcome measures that assess eating disorder cognitions, obsessive, compulsive, and impulsive features, and functional impairment in a BN population taking LDX. This study also incorporated qualitative investigation to examine participants' experiences with taking LDX. The results of this study serve to bridge the gap between existing case reports of

psychostimulant use for BN and the initiation of RCTs that can establish the safety and efficacy of this potential treatment option. While the results of this trial are promising, they should be interpreted as preliminary. There is not a sufficient evidence base to recommend clinical use of LDX for BN at this time. These results can guide the development and implementation of adequately powered RCTs and such studies are recommended.

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Appendix A

Objectives of Feasibility Study

The objective of this feasibility study is to collect information regarding the practicality of a study assessing LDX for the treatment of adults with BN. Specifically, this study aims to learn more about a) enrolment rates, b) dropout rates, c) the applicability of our eligibility criteria, d) the potential effects of LDX on neurocomputational mechanisms of decision-making in BN, e) preliminary safety data, and f) estimates of effect size.

Appendix B

Abnormal Laboratory and ECG Values

Table B1. Abnormal laboratory and ECG values for assessments during the trial.

Potassium	<3.4 mmol/L
Sodium	<136 mmol/L
Magnesium	<0.66 mmol/L
Phosphate	<0.74 mmol/L
Glucose	<3.5 mmol/L
Tachycardia	>100 bpm
Hypertension (Stage 1)	>140/90 mmHg
Corrected QT interval	>450 msec (females) >430 msec (males)
ECG	Evidence of structural cardiac abnormalities, cardiomyopathy, serious heart arrhythmia, or coronary artery disease as determined by Supervisor and/or in consultation with cardiologist (as needed).

Appendix C

Food Records

Date: _____

Took medication at (specify time): _____

Time	Food & Amount	Place	Binge	Purge

Did you experience any side effects (specify)?

Did you use any substances/drink alcohol (specify type and amount)?

Did you take any other medications (i.e., Tylenol/Advil/laxatives/diuretics/other prescription medications)?

Comments:

Appendix D

Qualitative Interview Guides

Interview 1 – Baseline Visit (Week 1)

START.

Thank you for meeting with me today. My name is Laura and I'm a research assistant working on this research study. I'm also a MSc student with Dalhousie's Department of Psychiatry. I will be conducting this interview today, as well as two additional interviews that will take place halfway through the study and at the end of the study. The purpose of these meetings is to gather information about your experience with the research study. As this is for research purposes, I will mainly be asking you questions, listening to your answers, and guiding the interview. I won't be able to provide too much feedback during the interview but if anything comes up that you'd like to discuss further with us, we can make a note about that and discuss it afterwards. The purpose of our meeting today is to understand your expectations as a participant in the research study. There will be an opportunity towards the end to ask questions and talk about anything not covered during the question period.

The audio of this conversation will be recorded for research purposes. The recording and the transcript will be transferred to a secure hospital drive where any identifying characteristics or mentions of your name will be deidentified. Only the other members and I of the research team will have access to the recordings and transcripts.

I'm now going to start the recording.

You are free not to answer any questions you're not comfortable answering and you can choose to end the interview at any point.

Do you have any questions before we get started?

1. Can you tell me a little bit about why you want to participate in this study?

Probes:

What are you hoping will change as a result of participating in the study?

Is there anything specific to your eating disorder symptoms that you hope will change?

Is there anything specific to your mood, emotions, or the way you feel that you hope will change?

Is there anything related to your day-to-day life or ability to function that you hope will change?

2. Have you ever received any type of treatment or support for your eating disorder (i.e., therapy, counseling, treatment at the hospital, a support group)? What type(s) of treatment or support have you received?

If treatment has been attended previously:

Probes:

What was your experience like with _____ (treatment received)? Did you find the treatment was helpful/unhelpful? Can you give me some examples of what was helpful/unhelpful?

Do you think the study medication might help you? Do you have a sense of why you think/don't think the medication might help you?

Do you think the medication might help you more than the treatments you've tried in the past? Do you have a sense of why you think/don't think the medication would be more helpful/wouldn't be as helpful?

If treatment has never been attended previously:

Do you think the study medication might help you? Do you have a sense of why you think/don't think the medication might help you?

3. Is there anything else you would like to tell me about how you are feeling about participating in the study?

If there's nothing else you'd like to add, that brings us to the end of the questions for today. Thank you for taking the time to speak with me today, I appreciate your feedback. We'll now proceed to the next section of the study visit.

END.

Stop recording.

Interview 2 – Week 5 Visit

START.

Thank you for meeting with me today. As a reminder, my name is Laura and I'm a research assistant working on this research study. I'm also a MSc student with Dalhousie's Department of Psychiatry. The purpose of this meeting is to gather information about your experience with the research study so far. As this is for research purposes, I will mainly be asking you questions, listening to your answers, and guiding the interview. I won't be able to provide too much feedback during the interview, but if anything comes up that you'd like to discuss further with us, we can make a note about that and discuss it afterwards. There will be an opportunity towards the end to ask questions and talk about anything not covered during the question period.

The audio of this conversation will be recorded for research purposes. The recording and the transcript will be transferred to a secure hospital drive where any

identifying characteristics or mentions of your name will be deidentified. Only the other members and I of the research team will have access to the recordings and transcripts.

I'm now going to start the recording.

You are free not to answer any questions you're not comfortable answering and you can choose to end the interview at any point.

Do you have any questions before we get started?

1. How has your experience been participating in the research study so far?

If study medication not mentioned:

Probe:

How has your experience been taking the study medication?

2. When you think about your day-to-day life before you started taking the medication and your life now, how would you say your life has changed?

Probes:

Have any parts of your life gotten better? Worse?

What do you think the medication has helped you with the most?

What do you wish the medication was helping you with more?

If appetite or hunger is not discussed previously, or to clarify changes:

3. Since the beginning of the study, how would you describe any changes in your eating habits or behaviours?

Probes:

Have you noticed any changes in your appetite or hunger specifically?

Have you noticed any changes in your binge eating and purging specifically?

Have you noticed any changes in your ability to think about the pros and cons of your behaviours before acting?

Overall, would you say the eating disorder symptoms have improved, stayed the same, or gotten worse since starting the medication?

Can you give me an example of what has _____ (improved, stayed the same, or gotten worse) since starting the medication?

If no changes identified: Can you tell me about how your eating habits or behaviours have stayed the same?

Probe:

Is there anything about your eating habits or behaviours that you wish was changing?

4. Since the beginning of the study, how would you describe any changes in your mood, emotions, or the way you feel?

Probe:

Overall, would you say your mood, emotions, or the way you feel has improved, stayed the same, or gotten worse since starting the medication?

Can you give me an example of what has _____ (improved, stayed the same, or gotten worse) since starting the medication?

If no changes identified: Can you tell me about how you think your mood, emotions, or the way you feel has stayed the same?

Probe:

Is there anything related to your mood, emotions, or the way you feel that you wish was changing?

5. Since the beginning of the study, how would you describe any changes in your thoughts or the way you think about things?

If eating disorder thoughts are not mentioned: How would you describe any changes specific to your eating disorder thoughts?

If a participant is unsure or asks for examples of eating disorder thoughts: Some examples would be thoughts about food or eating, thoughts about your weight or body, or urges to binge and purge.

Probe:

Have you noticed any changes in the amount of time you spend thinking about food throughout the day?

If no changes are identified: Can you tell me about how you feel your thoughts or the way you think about things has stayed the same?

Probe:

Is there anything related to your thoughts or the way you think about things that you wish was changing?

6. How are you feeling about continuing with the rest of the study?
7. Is there anything else you would like to tell me about how you have been feeling or doing since the beginning of the study?

If there's nothing else you'd like to add, that brings us to the end of the questions for today. Thank you for taking the time to speak with me today, I appreciate your feedback. We'll now proceed to the next section of the study visit.

END.

Stop recording.

Interview 3 – Follow Up Visit

START.

Thank you for meeting with me today. As a reminder, my name is Laura and I'm a research assistant working on this research study. I'm also a MSc student with Dalhousie's Department of Psychiatry. The purpose of this meeting is to gather information about your experience with the research study. As this is for research purposes, I will mainly be asking you questions, listening to your answers, and guiding the interview. I won't be able to provide too much feedback during the interview but if anything comes up that you'd like to discuss further with us, we can make a note about that and discuss it afterwards. The interview should take approximately XX minutes. There will be an opportunity towards the end to ask questions and talk about anything not covered during the question period.

The audio of this conversation will be recorded for research purposes. The recording and the transcript will be transferred to a secure hospital drive where any identifying characteristics or mentions of your name will be deidentified. Only myself and the other members of the research team will have access to the recordings and transcripts.

I'm now going to start the recording.

You are free not to answer any questions you're not comfortable answering and you can choose to end the interview at any point.

Do you have any questions before we get started?

1. How has your experience been participating in the research study?

Probes:

What would you say has been the best part about participating in the study?

What would you say has been the worst part about participating in the study?

If study medication is not mentioned:

Probe:

How has your experience been taking the study medication?

2. When you think about your day-to-day life before you started taking the study medication and your life now - how would you say your life has changed?

Probes:

Have any parts of your life gotten better? Worse?

What do you think the study medication has helped you with the most?

What do you wish the study medication helped you with more?

If appetite or hunger is not discussed previously, or to clarify changes:

3. Since the beginning of the study how would you describe any changes in your eating habits or behaviours?

Probe:

Have you noticed any changes in your binge eating and purging specifically? Have you noticed any changes in your ability to think about the pros and cons of your behaviour before acting?

Overall, would you say the eating disorder symptoms have improved, stayed the same, or gotten worse since starting the medication?

Can you give me an example of what has _____ (improved, stayed the same, or gotten worse) since starting the medication?

If no changes identified: Can you tell me about how your eating habits or behaviours have stayed the same?

Probe:

Is there anything about your eating habits or behaviours that you wish was changing?

4. Since the beginning of the study, how would you describe any changes in your mood, emotions, or the way you feel?

Probe:

Overall, would you say your mood, emotions, or the way you feel has improved, stayed the same, or gotten worse since starting the medication?

Can you give me an example of what has _____ (improved, stayed the same, or gotten worse) since starting the medication?

If no changes identified: Can you tell me about how you think your mood, emotions or the way you feel has stayed the same?

Probe:

Is there anything related to your mood/emotions or the way you feel that you wish was changing?

5. Since the beginning of the study, how would you describe any changes in your thoughts or the way you think about things?

If participant is unsure or asks for examples of eating disorder thoughts: Some examples would be thoughts about food or eating, thoughts about your weight or body, or urges to binge and purge.

Probe:

Have you noticed any changes in the amount of time you spend thinking about food throughout the day?

If no changes are identified: Can you tell me about the thoughts you are still having or how the way you think about things has stayed the same?

Probe

Is there anything related to the thoughts or the way you think about things that you wish was changing?

6. If you could, would you want to continue taking the medication? Why or why not?
7. Is there anything that would have made participating in the study easier for you?
8. Is there anything else you would like to tell me about how you have been feeling or doing since the beginning of the study?

If there's nothing else you'd like to add, that brings us to the end of the questions for today. Thank you for taking the time to speak with me. I appreciate your feedback. We'll now proceed to the next section of the study visit.

END.

Stop recording.

Appendix E

Informed Consent Standard Operating Procedure

Title	Informed Consent Process
SOP Code	SOP001_03
Effective Date	Nov 19, 2019

1.0 PURPOSE

This Standard Operation Procedure (SOP) describes the procedures for obtaining and documenting initial and ongoing informed consent. This SOP also describes informed consent guidelines. It does not apply to informed consent requirements for emergency situations.

2.0 SCOPE

This SOP is applicable only to protocol LDXBN, and to those research personnel responsible for performing, reviewing, and/or approving the informed consent process associated with this study.

3.0 RESPONSIBILITIES

The QI is responsible for ensuring that the Informed Consent process and the Informed Consent Form (ICF) meet all of the applicable regulatory, International Conference on Harmonization (ICH) Good Clinical Practice (GCP), sponsor, and local requirements.

Any or all parts of this procedure may be delegated to appropriately trained study team members, but remain the ultimate responsibility of the PI.

4.0 DEFINITIONS

Qualified Investigator (QI): Person who is responsible to the sponsor for the conduct of the clinical trial at a clinical trial site, who is entitled to provide health care under the laws of the province where that clinical trial site is located and who is a physician and a member in good standing of a professional medical association.

Standard Operating Procedure (SOP): Detailed, written instructions to achieve uniformity of the performance of a specific function (ICH E6, 1.55).

5.0 PROCEDURE

5.1 Online Consent Procedure for Pre-Screening

5.1.1 Potential subjects who are interested in the study review the full consent form online at:
http://form.simplesurvey.com/f/l/BNprescreen

5.1.2 After reviewing the consent form, potential subjects answer the following True/False questions:

1. *There are <u>no</u> risks associated with participating in this study (consent from section 9).*
2. *This study will involve 9 visits over 2 and a half months (10 weeks) to the Nova Scotia Health Authority Eating Disorder Clinic in Halifax, Nova Scotia (consent form section 6).*
3. *You are <u>not</u> able to quit the study once you agree to participate (consent form section 14).*
4. *You will be compensated for participating in this study (consent form section 16).*

5. *To find out whether you qualify to participate in the research study, you have to undergo screening first (consent form section 7).*

5.1.3 In order to proceed with pre-screening potential subjects must respond correctly to all 5 questions.

5.1.4 Individuals provide electronic consent in response to the question *"Do you agree to participate in this research study?"* by selecting either:

- "Yes, I agree to participate" or
- "No, I do not agree to participate"

Note: This allows potential subjects to proceed with the online pre-screening procedure. If an individual was eligible to attend the in-person screening visit, in-person consent would be obtained prior to beginning any study related procedures as detailed in section 5.2 below.

5.1.5 Individuals who select "no" are given the option of stating why they decided not to proceed further and are unable to continue with the online pre-screening process. They are directed to page with contact information for the QI and treatment options.

5.1.6 Individuals who select "yes" proceed to the next question regarding consent to be contacted via email:

Do you agree to be contacted by a research team member via email, thereby accepting the risks to confidentiality associated with email communication?

(If email correspondence is not agreed to, you will be contacted by a research team member via telephone)

- "Yes, I agree to be contacted via email" or
- "No, I do not agree to be contacted via email"

5.1.7 Individuals who select "yes" may be contacted via email regarding the study, those who select "no" would only be contacted by telephone unless email consent was provided at a later time.

5.1.8 Potential subjects are then able to continue with the remainder of the online pre-screening questionnaire.

5.1.9 Individuals are provided an electronic copy of the consent form/pre-screening questionnaire responses via PDF attachment in an email at the time they are notified of their eligibility, or ineligibility, to attend in-person screening.

5.1.10 Those who do not consent to be contacted via email will be asked for their mailing address at the time they are contacted via telephone to be notified of their eligibility, or ineligibility, to attend in-person screening. A printed copy of their electronic consent form/pre-screening questionnaire responses will be mailed to the address specified.

5.2 Informed Consent Before Study Entry – In-Person Consent Procedure

5.2.1 Ensure that the person obtaining informed consent (as documented on the Delegation Log) is qualified by training to do so, and is knowledgeable in the study procedure.

5.2.2 Review the study details with the subject in a quiet and private location. Do not coerce or unduly influence a subject to participate, or to continue to participate in the study.

5.2.3 Fully inform the subject of all pertinent aspects of the research (i.e., all essential elements as described in the ICF) in language that is easy for the subject to understand.

5.2.4 Provide the subject with a copy of the ICF (ensure that the most recent version of the REB approved ICF is used). Allow the subject ample time to read the ICF and ask questions.

5.2.5 Ask the subject the following questions to assess his/her competence to consent to research and comprehension of the material reviewed:

"Must you take part in this study, or is it OK to say 'no'?

Can you tell me the main things that you would do in this study (e.g., how long you'll be involved, what procedures you'll undergo, how many visits, how much will you be compensated, etc.)?

Can you name some of the risks of participating in this study?

Can you name some of the benefits of participating in this study? Considering both the risks and benefits we have discussed, would you like to take part in this study?"

5.2.6 Document if the subject is deemed not competent to consent or if their comprehension is not at an appropriate level.

5.2.7 Ascertain the subject's willingness to participate. Document the decision of any subject who declines to participate in the Informed Consent Tracking Log and in the progress notes. Document the decision of any subject who agrees to participate with the Consent Form Signature Page (last page of ICF), Documentation of Informed Consent Form, and Informed Consent Tracking Log.

5.2.8 Remind the subject that they may withdraw consent at any time.

5.2.9 Remind the subject that we will notify his/her family physician about participation in the study. Document the family physician's name and number (on Patient Contact Information Sheet), or if the subject does not have a family physician.

5.2.10 Request that the subject sign and date the ICF in the indicated places on the Consent Form Signature Page.

5.2.11 Sign and date the ICF as the person who conducted the informed consent discussion. All required signatures must be obtained prior to enrolling the subject into the research study, or conducting any study related procedures.

5.2.12 Provide the subject with a photocopy of the signed document.

5.2.13 File the original signed ICF with the study related essential documents.

5.2.14 Record that informed consent was completed in the progress notes and on the Study Visit Checklist.

5.3 Ongoing Informed Consent

5.3.1 Ensure that the subject's consent to participate in the study remains valid throughout the study by reaffirming verbal consent at every study visit and recording this in the progress notes and on the Study Visit Checklist.

5.3.2 Communicate any important new information that becomes available and that may be relevant to subject's consent, in a timely manner. This communication should be documented on the Informed Consent Tracking Log.

5.3.3 If changes to the ICF are made, revise the ICF (and any other written material), and submit to the REB for approval.

5.3.4 Re-consent the study subjects affected by the changes, after REB approval is obtained, and record this on the Informed Consent Tracking Log. Re-consent should take place at the participant's next in-person study visit prior to initiating any visit procedures following approval of a new version of the consent form.

5.3.5 Provide subjects copies of the revised ICF.

5.3.6 File the original signed revised ICF with the study-related essential documents.

5.4 Subjects Incompetent to Provide Informed Consent

5.4.1 If a subject lacks the capacity to provide informed consent, the subject will be disqualified from the study and provided alternative treatment options.

5.5 Subjects Unable to Read

5.5.1 If a subject is unable to read, the subject will be disqualified from the study and provided alternative treatment options.

Appendix F

Overview of Participant Schedule

	Titration Phase				Maintenance Phase					Follow-Up Phase
	Baseline	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Post	Follow-Up
Study Visit (in-person)	X	X	X	X	X		X		X	X
ECG*									X	
Blood work*					X				X	
Vitals/Weight*	X	X	X	X	X		X		X	X
ED Symptom Frequency Review	X	X	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X	X
LDX Dispensing	X	X	X	X	X[a]					
LDX Adherence		X	X	X	X[a]				X	
Self-Report Questionnaires	X				X				X	
EDE	X								X	
YBOCS-BP	X				X				X	
Qualitative Interview	X				X					X

Abbreviations: ECG, Electrocardiogram; ED, Eating Disorder; LDX, lisdexamfetamine dimesylate; EDE, Eating Disorder Examination; YBOCS-BP, Yale Brown Obsessive Compulsive Scale (modified for binge eating & purging).

*Item also completed during in-person screening.

[a]Optional dispensing and adherence at Week 5.