Psychiatry Research 273 (2019) 467–474

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

A randomized comparison of long acting methylphenidate and cognitive behavioral therapy in the treatment of binge eating disorder

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ARTICLE INFO

Keywords:
Binge eating disorder
Methylphenidate
CBT
Treatment
Impulsivity

ABSTRACT

Cognitive behavioral therapy (CBT) is a well-established treatment for binge eating disorder (BED); however, this treatment is underutilized, highlighting the need for additional treatment alternatives. Dopamine neurotransmission has been associated with dysregulated eating, and pharmaceutical agents targeting the dopamine system are associated with decreased binge eating and weight. The primary objective of the current investigation was to evaluate the efficacy of psychostimulant medication versus current best practices in the treatment of BED symptoms, in a randomized trial of methylphenidate versus CBT for BED. The secondary objective was to evaluate the ability of impulsivity to predict treatment outcomes. Female outpatients with BED were randomized to receive methylphenidate (n = 22) or CBT (n = 27) for 12 weeks. The primary outcome was objective binge episode frequency; secondary outcomes included subjective binge episode frequency, body mass index (BMI), BED symptoms, and quality of life. Results showed that both treatments had a significant impact on primary and secondary outcomes. Methylphenidate and CBT were associated with decreases in subjective and objective binge episodes; methylphenidate was associated with greater decreases in BMI. Two impulsivity traits predicted clinical outcomes. Results provide preliminary support for the therapeutic benefit of methylphenidate in BED treatment, and prognostic utility of impulsivity in this context.

1. Introduction

Binge eating disorder (BED) is the most prevalent eating disorder, with an estimated rate of 3% in the United States (Hudson et al., 2012; Duncan et al., 2017) and substantial personal and societal cost (Ling et al., 2017). BED commonly co-occurs with a broad range of psychiatric disorders as well as obesity, medical illness, and functional impairment (Becker and Grilo, 2015; Hudson et al., 2007; Ulfvebrand et al., 2015). Numerous promising interventions have been developed for the treatment of BED; yet, even the most long-standing empirically validated treatments such as cognitive behavioral therapy (CBT) have exhibited suboptimal efficacy, with a substantial proportion of patients failing to achieve binge eating remission following treatment (Vocks et al., 2010). Moreover, these specialized interventions are not widely available to, and/or utilized by those with binge eating concerns, prompting the search for novel treatment alternatives. Psychostimulant medications targeting dopaminergic transmission such as methylphenidate may be one such alternative, given previous research implicating the dopamine system in eating behaviors and weight in both animal and human research (Avena and Bocarsly, 2012; McElroy et al., 2012). The current investigation describes a preliminary study of methylphenidate in the treatment of BED, using a randomized trial design to compare the effects of long acting methylphenidate to individual CBT for BED in adult women.

1.1. Cognitive behavioral therapy for BED is effective but infrequently utilized

CBT has accumulated evidence for efficacy in the reduction of binge eating episodes in patients with BED and is generally regarded as a well-established treatment for this condition (Linardon et al., 2017; Peat et al., 2017). Individual, group, and guided self-help adaptations of CBT for BED consistently impact both categorical and dimensional measures of BED symptoms – yet, these interventions are generally associated with little to no change in weight (Vocks et al., 2010). Binge eating episodes are predictive of weight and body mass index (BMI; kg/

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https://doi.org/10.1016/j.psychres.2019.01.066
Received 5 November 2018; Received in revised form 16 January 2019; Accepted 16 January 2019
Available online 17 January 2019
0165-1781/

m^2) in turn, however, providing support for a potential indirect impact of CBT on this important outcome as well (Grilo et al., 2011).

Regrettably, CBT for BED is rarely administered outside of academic or tertiary care settings. Indeed, health care providers in primary care settings, where most patients with mental health concerns present for treatment, rarely have the time or training to provide specialized, empirically validated treatments such as CBT. Evidence suggests that patients presenting with binge eating infrequently receive this form of treatment or a referral to it (Fursland and Watson, 2014; Kazdin et al., 2017; Weissman and Rosselli, 2017). Patients with BED utilize health care services at a level comparable to those with other psychiatric diagnoses overall; however, they make less frequent use of psychotherapy compared to patients with other mental health concerns (Mond and Hay, 2008; Striegel-Moore et al., 2004, 2008). Therefore, pharmacological options for BED that may be feasibly administered across a wide range of clinical settings are critically needed.

1.2. Psychostimulants target the dopamine system and reduce binge eating and weight

Dopamine is strongly implicated in eating behavior and its dysfunction (Mathes et al., 2009). Empirical work has implicated disrupted dopamine neurotransmission in the development and/or maintenance of binge eating in particular (Wang et al., 2011). Pharmacological treatments that target dopamine therefore have the potential to directly impact perceived food reward, craving, and intake in BED (McElroy et al., 2012; Kaplan et al., 2009; Bello and Hajnal, 2010; Epstein et al., 2007). Single-dose administrations of methylphenidate – a dopamine transporter blocker frequently utilized in the treatment of attention deficit hyperactivity disorder (ADHD) – have been associated with decreased food cravings and intake in adults with obesity and BED (Goldfield et al., 2007; Leddy et al., 2004). Psychostimulant medications have resolved symptoms of bulimia nervosa, including binge eating episodes, in clinical reports of patients with ADHD (Dukarm, 2005). Similarly, stimulants administered to obese patients with ADHD have been effective in the reduction of BED symptoms as well as weight loss (Kaplan et al., 2009; Levy et al., 2009). Double-blind drug-placebo studies have demonstrated that a moderate single dose of methylphenidate resulted in decreased appetite, cravings, and food consumption as compared to placebo in adults with obesity or BED, without diagnoses of ADHD (Davis et al., 2016; Goldfield et al., 2007); this effect was more pronounced in women in one study (Leddy et al., 2004).

Recently, psychostimulant medications have received growing empirical attention and placebo-controlled trials have supported their efficacy in the treatment of BED. McElroy and colleagues conducted a series of rigorous clinical trials establishing the efficacy of lisdexamfetamine in the reduction of binge eating, as well as the safety of this medication in patients with BED (McElroy et al., 2015, McElroy et al., 2016a, b). Lisdexamfetamine was associated with decreased binge episode frequency and BED symptoms compared to placebo control, and exhibited an acceptable safety profile. A subsequent systematic review pooled accrued evidence quantitatively, and this medication became the first to receive regulatory approval for the treatment of BED (Citrome, 2015). The extension of this line of research to other psychostimulant medications, particularly those available in generic form and to other control conditions, particularly active controls such as first-line treatments like CBT for BED would meaningfully extend the field.

1.3. The current investigation

The current investigation is a randomized trial of methylphenidate versus CBT for BED in adult women. This medication is presumed to exert its effects by dopamine transporter blockage, and is well tolerated by patients with low levels of treatment attrition (Zhou et al., 2002). The primary objective of the current investigation was to evaluate the therapeutic effect of methylphenidate compared to CBT in patients with BED. We hypothesized that patients randomized to receive methylphenidate would demonstrate a significant decrease in objective binge episode frequency, as well as improvement on secondary outcomes (BED symptom severity, BMI, quality of life). In line with previous research, we hypothesized that patients randomized to receive CBT would demonstrate a significant decrease in these clinical outcomes as well, with the exception of BMI. A secondary objective of the current investigation was to evaluate the predictive utility of impulsivity in the prediction of treatment response. BED, ADHD, and obesity are frequently co-morbid and are characterized by elevated impulsivity (Cortese et al., 2007; Davis, 2010; Fischer et al., 2008; Kaplan et al., 2009). This individual difference is likely to impact treatment engagement and clinical outcomes (Grilo et al., 2012). We hypothesized that reckless action during distress ("negative urgency;" see below) would be associated with negative clinical outcomes, whereas the capacity to initiate and sustain goal-directed behavior ("perseverance;" see below) will demonstrate an inverse pattern, i.e., be associated with positive clinical outcomes.

2. Method

2.1. Participants

The sample consisted of 49 adult women meeting DSM-5 criteria for BED. Participants ranged in age from 19 to 51 (M = 32.78, SD = 8.62). Using Statistics Canada racial groupings, the majority of participants identified as Caucasian (77.6%; n = 38); the remaining participants identified as South Asian (2.0%; n = 1), Black (4.1%; n = 2), or other (e.g., multiple visible minorities; 16.3%; n = 8). Current Axis I diagnoses were assessed with the *Structured Clinical Interview for DSM-IV, Axis I Disorders, Patient Form* (SCID-I/P; First et al., 1995) and found in 33% (n = 16) of the sample in total, primarily including mood disorders (n = 12) and anxiety disorders (n = 17).

All participants met the following inclusion criteria: (1) exhibited DSM-5 criteria for BED based on the SCID-I/P; First et al., 1995) applying DSM-5 criteria for BED (APA, 2013); (2) BMI ≥ 25; and (3) (a) 18–50 years of age, (b) fluency in reading English and (c) capacity to give informed consent. Exclusion criteria included: (1) current pregnancy or lactation; (2) psychotherapy or behavioral treatment for eating or weight initiated during the past month; (3) psychotropic or investigational medication changes during past three months; (4) current psychostimulant use, or use of psychostimulants during the past six months to manage eating or weight; (5) current mental disorders that require alternate treatment or that preclude ability to complete research protocol including mania, psychosis, substance dependence, or dementia; (6) current severe suicidality or homicidality; (7) current uncontrolled medical conditions that affect weight or BED symptoms or that are contraindicated for methylphenidate; (8) other serious medical illnesses or events such as acute myocardial infarction or stroke during the past six months; (9) history of seizures or tics in past year, diagnosis or family history of Tourette's syndrome; (10) uncontrolled or clinically relevant hypertension (>140/90), tachycardia (heart rate > 110), arrhythmias or conduction abnormalities as indicated by electrocardiogram (ECG), abnormal laboratory results including hypokalemia; (11) current medications that affect weight or that are contraindicated for methylphenidate.

2.2. Measures

The primary outcome measure was frequency of objective binge episodes per week, as assessed by a daily binge diary similar to seminal BED treatment studies (e.g., Grilo et al., 2006). Subjective binge episodes comprised eating episodes (meals or snacks) characterized by a lack of control over eating (e.g., feeling unable to stop or control

eating), as indicated by the participant. Objective binge episodes comprised eating episodes characterized by a lack of control as well as the consumption of an excessive amount of food (i.e., an amount of food clearly greater than most would eat in a similar amount of time and under similar circumstances). A blinded assessor reviewed transcripts of daily binge diaries to identify which subjective binge episodes also met criteria for an objective binge episode, according to these (DSM-5) criteria. Other secondary outcome measures included BMI and dimensional measures of BED symptoms and associated features, and quality of life. Dimensional measures included the Eating Disorder Examination-Interview (EDE-I; Fairburn and Cooper, 1993), Binge Eating Scale (BES; Gormally et al., 1982), and Quality of Life Inventory (QOLI; Frisch, 1994). The EDE-I and BES provided interviewer-rated and self-reported measures of eating disorder psychopathology. The EDE-I is a 22-item standardized interview assessing concerns associated with shape, weight, and eating behaviors, whereas the BES is a 16-item questionnaire assessing thoughts, emotions, and behaviors associated with binge eating. The QOLI is a 32-item questionnaire assessing the importance and satisfaction associated with 16 life domains (e.g., work, money, home, community); satisfaction is weighted by the importance of each domain to the individual. Impulsivity was assessed by the *UPPS-P Impulsive Behavior Scale* (Cyders et al., 2007; Whiteside and Lynam, 2001), which is named for the components of impulsivity it assesses: Negative and Positive Urgency, engaging in reckless behaviours during the experience of mood states despite potential long-term destructive consequences; (lack of) Premeditation, difficulty considering the outcomes of an action prior to its initiation; (lack of) Perseverance, difficulty maintaining focus during tedious or challenging tasks; and Sensation Seeking, seeking out and taking pleasure in stimulating activities, as well as being open towards novel activities that may hold some degree of risk. These different components of impulsivity have been differentially associated with obesity and eating disorders (Fischer et al., 2008). Notably, two of the subscales are labeled as the absence of either reflection or focus (i.e., lack of Premeditation and Perseverance, respectively); we interpret and discuss these results with reference to their target (Premeditation and Perseverance) where relevant for clarity (e.g., we refer to “high Premeditation/Perseverance” to avoid confusion or double negatives, such as “low lack of Premeditation/Perseverance”).

2.3. Procedure

Participants were recruited using a multi-faceted approach including local physician referral as well as self-referral in response to online and print advertisements in local transit and media. Interested potential participants completed a telephone interview to assess basic demographic characteristics, binge eating, medical and medication history. Those appearing to meet eligibility criteria then completed an in-person assessment, including the SCID-I/P, medical, psychiatric, and medication history, blood pressure, heart rate, height, weight, blood collection (including CBC, electrolytes, liver function tests, creatinine, BUN, fasting blood glucose, fasting lipids and cholesterol, pregnancy test), ECG, and urinalysis. Randomization of eligible participants was stratified by both moderate depressive symptom severity (assessed by the interviewer-rated Hamilton Rating Scale for Depression, Ham-D_{17} $\geq$ 14; Hamilton, 1960) and ADHD symptom severity (assessed with the Conner's Adult ADHD Rating Scale ADHD Index > 65*T*; Conners et al., 1999). Of the 922 individuals who contacted the laboratory, 384 expressed interest and completed a brief telephone screen. Of these, 116 were invited for an in-person assessment. Of these, 49 were enrolled in the study and initiated treatment. Twenty-two patients were randomized to the study medication, and 27 to CBT. See Fig. 1 for additional details regarding participant flow. Participant attrition was most commonly due to scheduling conflicts or inability to contact; there was no difference across treatment condition in participant attrition ($\chi^2 = 0.04$, $p = 0.84$). The research protocol (NCT01921582) was reviewed and approved by the Centre for Addiction and Mental Health (CAMH) institutional review board, and all participants provided oral and written informed consent. No compensation was provided in return for study participation, which is typical practice for pragmatic treatment trials at this institution and increases the generalizability of results.

2.3.1. CBT treatment

Participants randomly assigned to receive individual CBT attended 12 50-min appointments over the course of 12 weeks with doctoral level research clinicians. CBT was provided according to the widely used manual by Fairburn et al. (1993) and included three phases. Phase 1 undertakes to eliminate binge episodes and introduce a ‘regular’ pattern of eating; Phase 2 aims to reduce food intake and restructure eating-related cognitions; and Phase 3 focuses upon relapse prevention. Notably, although many CBT protocols are 16 to 20 sessions in duration, even low dosage protocols have exhibited efficacy (e.g., ten sessions of guided self-help CBT protocols; Wilson et al., 2010) and longer CBT protocols show that most improvements occur over the first six to eight weeks (Grilo et al., 2006).

2.3.2. Psychostimulant treatment

Participants randomly assigned to receive long acting methylphenidate attended weekly appointments with study psychiatrists for the first four weeks, and then biweekly appointments for the last eight weeks. Psychiatric appointments will include monitoring (medication dose, side effects, and general medical status) as well as supporting ongoing medication compliance using compliance enhancement techniques (adapted from Fawcett et al., 1987). Initial dosage of methylphenidate was 18 mg/day, increased to 36 mg/day at Week 2, 54 mg/day at Week 3, and 72 mg/day at Week 4, as tolerated. Study medication was administered as a single daily dose in the morning. The minimum and maximum dosages throughout the study therefore were 18 mg and 72 mg; this dosage range has demonstrated efficacy in the treatment of adult ADHD, alongside decreased appetite and weight (Medori et al., 2008). Dosage levels were maintained or decreased to manage medication side effects. After 12 weeks, participants were discharged to the care of their family physician.

2.4. Statistical analyses

2.4.1. Effect of treatment condition on study outcomes

Analyses were conducted using an intent-to-treat approach in which all randomized participants were included. The primary outcome variable was frequency of objective binge episodes; secondary outcome variables included frequency of subjective binge episodes and BMI (assessed weekly or biweekly) as well as EDE-I, BES, and QOLI (assessed at Weeks 0, 6, and 12). Objective and subjective binge episodes were log-transformed prior to analyses. To evaluate the effect of treatment type on outcomes assessed weekly or biweekly (objective binge episode frequency, subjective binge episode frequency, and BMI), mixed models were conducted with SPSS Version 24. All models included a random intercept and random slope for time and fixed effects to control for participant age and baseline scores on the dependent variable of interest (covariates were grand-mean centered). Models also included fixed effects for treatment condition, time, and the condition × time interaction. To evaluate the effect of treatment type on outcomes assessed at Weeks 0, 6, and 12, linear regressions were conducted with MPlus. Mplus permits the modeling of missing data using maximum likelihood estimation under the assumption that observations were missing at random (MAR). Participant age and baseline scores on the outcome of interest were added as covariates in each regression. Paired t-tests and analyses of covariance were used to examine the durability of effects at follow-up (Week 24).

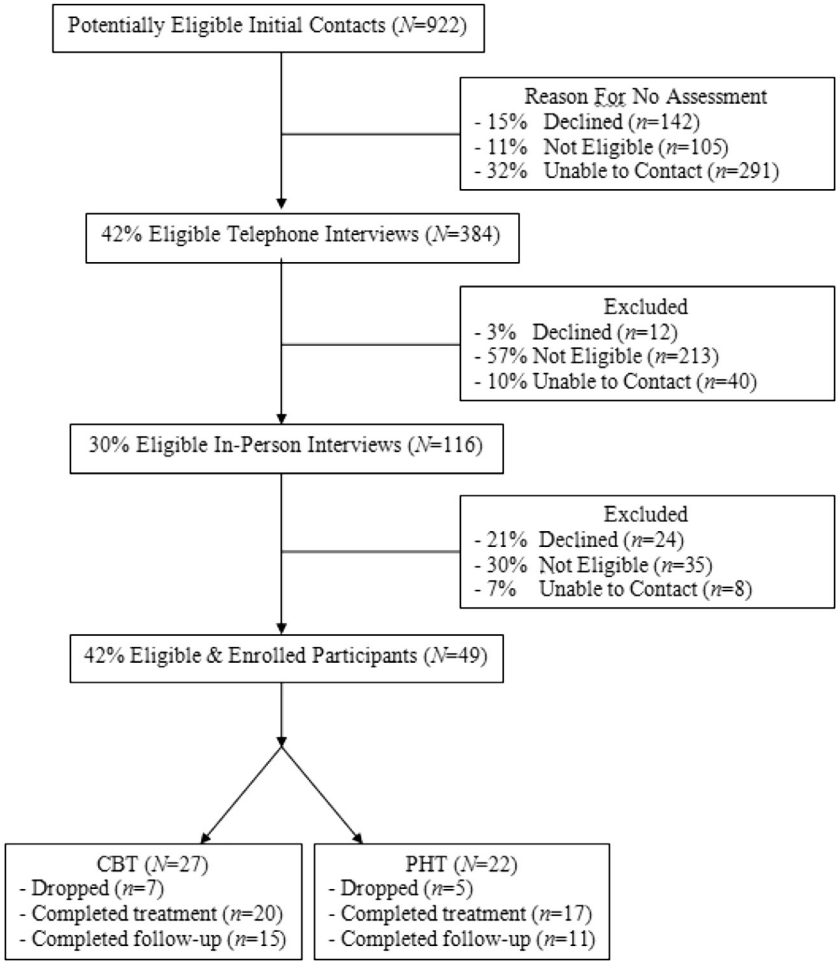

Fig. 1. Participant flow chart.

Table 1
Outcomes variables across treatment groups at baseline and post-treatment.

	Baseline					Post-treatment				
	CBT		MPH			CBT		MPH		
	M	*SD*	*M*	*SD*	*t* (*p*)	*M*	*SD*	*M*	*SD*	*t* (*p*)
OBE	2.26	1.89	2.19	1.47	0.14 (0.89)	0.11	0.32	0.69	1.49	1.53 (0.14)
SBE	5.59	5.92	4.62	4.65	0.62 (0.54)	0.26	0.45	1.38	3.18	1.51 (0.14)
BMI	39.26	8.80	36.53	6.55	1.20 (0.23)	40.16	9.45	34.38	6.22	2.16 (0.04)
EDE-I	3.42	1.11	3.53	0.71	0.44 (0.66)	2.32	1.06	2.39	1.06	0.23 (0.82)
BES	30.70	5.84	30.05	6.28	0.38 (0.71)	16.30	7.95	18.41	9.80	0.72 (0.47)
QOLI	0.48	1.95	0.70	1.63	0.42 (0.67)	1.78	1.29	1.21	1.31	1.30 (0.20)

Note: OBE = Objective binge episode frequency; SBE = Subjective binge episode frequency; BMI = Body mass index; EDE-I = Eating Disorder Inventory – Interview; BES = Binge Eating Scale; QOLI = Quality of Life Inventory; CBT = Cognitive behavioral therapy; MPH = Methylphenidate.

2.4.2. Effect of impulsivity on study outcomes

Analyses were again conducted using an intent-to-treat approach in which all randomized participants were included. Similarly, mixed models were conducted within SPSS to examine the effect of impulsivity on the outcome variables assessed weekly or biweekly (objective binge episode frequency, subjective binge episode frequency, and BMI). Models collapsed across treatment condition, and included fixed effects for each trait subscale, time, and the interaction between time and each trait subscale. UPPS-P subscale scores were first standardized and then entered as simultaneous predictors throughout all analyses in order to control for shared variance between the various subscales. Models were also conducted entering each trait independently, and results are reported on whenever independent prediction yielded an incongruent finding from simultaneous prediction. Also, linear regressions were conducted within MPlus to examine the effect of impulsivity on outcomes assessed at Weeks 0, 6, and 12. Figures present significant findings, with outcomes at mean levels of trait impulsivity, as well as ± 1 SD above/below the mean.

Notably, given the association between race/ethnicity with BMI, all analyses were conducted with participant race/ethnicity as a covariate as well (dummy coded as “Caucasian” [0] or “Other” [1], due to the limited number of participants endorsing other groupings). Very similar parameter estimates were found, including the same pattern of statistical significance. Given our limited sample size, we present results associated with the more parsimonious analyses here.

3. Results

3.1. Effect of treatment condition on study outcomes

Descriptive statistics for primary and secondary outcome variables at pre- and post-treatment are presented in Table 1. There were no differences in primary or secondary outcomes across treatment condition at baseline. A mixed model examining the frequency of objective binge episodes across the two treatment conditions revealed a significant main effect of time $F(12, 317) = 11.94$, $p < 0.001$. Follow-up tests indicated that participants in both groups experienced fewer objective binge episodes at post-treatment than at baseline, $t(158) = 7.53$, $p < 0.001$. The main effect of treatment condition was not significant, nor was the time × treatment condition interaction. The model examining the frequency of subjective binge episodes across treatment types also revealed a significant main effect of time $F(12, 323) = 11.37$, $p < 0.001$. Follow-up tests indicated that participants experienced fewer subjective binge episodes at post-treatment than at baseline, $t(79) = 7.12$, $p < 0.001$. The main effect of treatment condition was not significant, nor was the interaction between time and treatment group. Notably, the number of participants who were binge-free for the last four weeks of treatment did not differ across treatment condition (objective binge episode remission: 47% for medication and 60% for CBT, $\chi^2 = 0.62$, $p = 0.43$; subjective binge episode remission: 41% for medication and 35% for CBT, $\chi^2 = 0.15$, $p = 0.70$).

A mixed model examining BMI over the course of treatment revealed main effects of both time and condition, as well as a significant interaction between treatment condition and time $F(8, 189) = 4.40$, $p < 0.001$. Follow-up analyses indicated that there was a significant difference in BMI at Week 12 compared to Week 0 for the methylphenidate group, $t(49) = 5.18$, $p < 0.001$, but not for the CBT group $t(50) = 1.54$, $p = 0.13$. Total BMI was also significantly higher in the CBT group compared to the methylphenidate group at Week 12, $t(47) = 2.73$, $p = 0.01$. Fig. 2 depicts the average participant BMI in the two treatment conditions across each assessment point. Percent weight loss was 4.4% in the methylphenidate compared to 0.0% in the CBT group ($t(47) = 4.14$, $p < 0.01$).

Linear regressions examining the effect of treatment condition on the three secondary outcome variables assessed at Weeks 0, 6, and 12 are presented in Table 2. Treatment condition was not a significant predictor of post-treatment scores on the EDE-I, BES, or QOLI. All secondary outcomes did change from Week 0 to Week 12 in both medication (all *ts* > 2.66, all *ps* < 0.02) and CBT (all *ts* > 3.33, all *ps* < 0.01).

Primary and secondary outcomes did not change from Week 12 to Week 24 (all *ts* < 1.95, all *ps ns*). There were no differences across treatment group at Week 24 (all *Fs* < 1.00, all *ps ns*).

3.2. Effect of impulsivity on study outcomes

A mixed model examining the effect of the five UPPS impulsivity facets on the frequency of objective binge episodes revealed a significant main effect of time $F(12, 327) = 11.65$, $p < 0.001$ and a significant time × perseverance interaction $F(12, 328) = 2.10$, $p < 0.02$. Notably, this effect was not moderated by treatment group (time × perseverance × treatment group interaction, $F = 0.98$, $p = 0.46$). Fig. 3 depicts the effect of perseverance on frequency of objective binge episodes across the various study assessment points. Plotting the interaction revealed that individuals who were high on baseline perseverance (defined at one standard deviation from the mean) exhibited a more rapid and persistent decline in frequency of objective binge episodes over the course of the study than individuals low on perseverance.

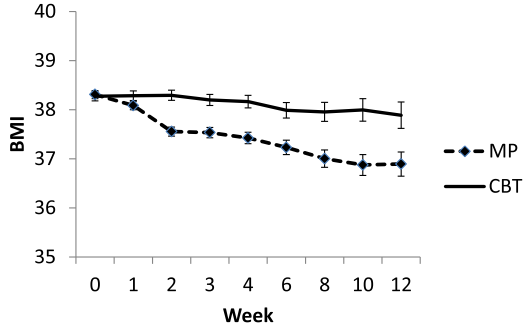

Fig. 2. Time × Treatment condition interaction: BMI.

In the model examining the effect of the five UPPS facets on the frequency of subjective binge episodes, there was once again a main effect of time $F(12, 325) = 12.75$, $p < 0.001$, but no significant interactions between time and any of the five UPPS facets. However, evaluating each of the UPPS facets as independent predictors in separate models revealed a significant interaction between time and negative urgency $F(12, 325) = 1.79$, $p = 0.049$. Again, this effect was not moderated by treatment group (time × negative urgency × treatment group interaction, $F = 1.44$, $p = 0.15$). Fig. 4 depicts the effect of negative urgency on the frequency of subjective binge episodes across the various study assessment points. Plotting the time × negative urgency interaction revealed that individuals who were high on baseline negative urgency reported lower rates of subjective binge episodes by the end of treatment than individuals who scored low on baseline negative urgency.

A mixed model examining the effect of the five UPPS facets on participant BMI over the course of treatment similarly yielded an effect of time $F(8, 181) = 8.80$, $p < 0.001$, but no significant interactions between time and the five UPPS facets. Results from a series of linear regressions examining the effect of the five UPPS facets on the remaining secondary outcomes are presented in Table 2. None of the five UPPS facets significantly predicted post-treatment scores on the EDE-I, BES, or QOLI.

4. Discussion

Results supported the therapeutic benefits of both long acting methylphenidate and CBT for adult women with BED. Consistent with hypotheses, both treatment types were associated with significant improvements on primary and secondary outcomes. Notably, methylphenidate was associated with greater decreases in BMI compared to CBT, which is consistent with the impact of this medication on appetite and weight. Improvements on subjective and objective binge episodes were observed in both treatment groups, as were eating disorder symptoms (in general, as assessed by the EDE and specific to BED, as assessed by the BES) and quality of life. Improvements were maintained at three-month follow-up, although it is important to note that the sample size was small at this time point and that treatment was not controlled during the follow-up period (e.g., participants were not precluded from continuing versus discontinuing mediation, or receiving aftercare, peer support, etc.), precluding strong statements regarding treatment group differences or durability of effects.

This preliminary investigation therefore provides initial support for the therapeutic benefit of methylphenidate in the treatment of BED. Although this investigation was not sufficiently powered to permit conclusions regarding noninferiority (i.e., that methylphenidate exhibits comparable efficacy to CBT), our modest sample size was nevertheless sufficient to detect change over time in each treatment condition, as well as differential change across treatment condition (i.e., BMI). It is possible, however, that we were underpowered to detect smaller effect sizes. Further, although the CBT provided in this trial followed a well-established manual and most benefits are observed within the first six to eight weeks of treatment, the duration of treatment was shorter than many other psychotherapy trials of BED.

Table 2
Linear regressions predicting outcomes from treatment condition and trait subscale scores.

Variable	BES β	*SE*	*p*	EDE-I β	*SE*	*p*	QOLI β	*SE*	*p*
1. Age	−0.03	0.18	0.87	−0.22	0.16	0.17	0.05	0.12	0.71
2. Outcome at Baseline	0.15	0.17	0.38	**0.42**	**0.14**	**<0.01**	**0.72**	**0.08**	**< 0.01**
3. Condition	−0.14	0.17	0.43	0.11	0.16	0.50	0.17	0.12	0.16
Variable									
1. Age	0.04	0.18	0.83	−0.17	0.16	0.29	0.12	0.13	0.36
2. Baseline Outcome	0.05	0.18	0.79	**0.46**	**0.15**	**< 0.01**	**0.73**	**0.09**	**< 0.01**
3. (lack) Premeditation	−0.20	0.21	0.34	0.16	0.20	0.43	0.17	0.15	0.26
4. (lack) Perseverance	0.37	0.19	0.06	0.00	0.18	0.98	−0.01	0.14	0.96
5. Sensation Seeking	−0.07	0.23	0.77	0.28	0.19	0.15	−0.07	0.15	0.65
6. Positive Urgency	0.20	0.23	0.38	−0.29	0.22	0.17	−0.03	0.18	0.86
7. Negative Urgency	−0.02	0.21	0.91	−0.09	0.22	0.67	0.02	0.17	0.93

Note: OBE = Objective binge episode frequency; SBE = Subjective binge episode frequency; BMI = Body mass index; EDE-I = Eating Disorder Inventory – Interview; BES = Binge Eating Scale; QOLI = Quality of Life Inventory; CBT = Cognitive behavioral therapy; MPH = Methylphenidate. Condition coded 0 = MP, 1 = CBT. Significant effects in boldface.

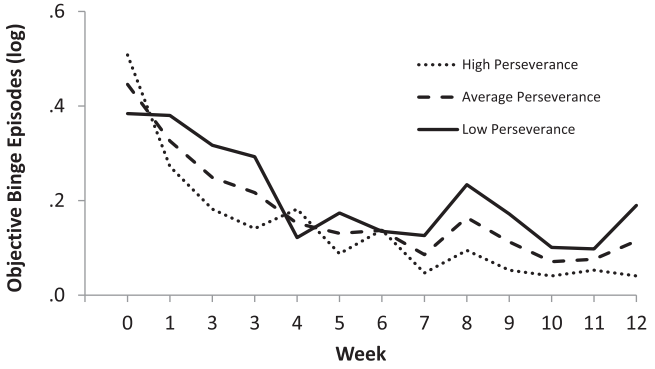

Fig. 3. Time × Perseverance interaction: objective binge episode frequency.

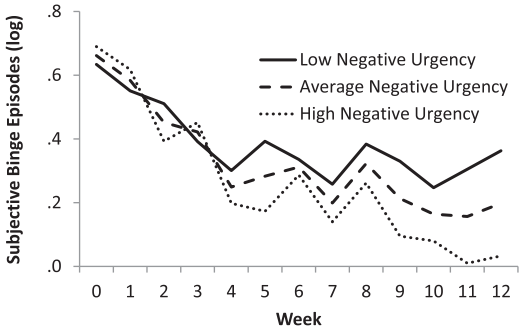

Fig. 4. Time × Negative urgency: subjective binge episode frequency.

Participants receiving medication in this trial also attended weekly and then biweekly appointments with a psychiatrist, and monitored their daily food intake and subjective binge episodes, both of which were likely to have therapeutic value. These treatment features may have combined to reduce the number of differences between groups. Other limitations included the limited reliability of self-reported subjective binge episodes, which are common to this field of research but nevertheless impact results specific to that outcome.

Results further supported the prognostic utility of impulsivity in BED; however, one of these results was in an opposite direction than hypothesized. More specifically, both perseverance and negative urgency were associated with positive treatment outcomes. The former was anticipated, as the capacity to initiate and sustain goal-directed activity is highly likely to be linked to treatment engagement and compliance and in turn, clinical outcomes. The latter was not anticipated, and may have arisen for numerous reasons. It may be that both study treatments are well-suited to building cognitive control and regulatory capacity. It may further be that those high in urgency are under more distress and perhaps more motivated to adhere to treatment or likely to see treatment gains. It is notable that the current sample exhibited relatively low rates of comorbidity (e.g., only six participants were above the Ham-D_{17} cutoff and ten were above the CAARS cutoff); whether this result would replicate in a more emotionally distressed sample is uncertain. Nevertheless, it is clear that although BED has been characterized by elevated impulsivity, the prospective association between impulsive traits and clinical outcomes in BED requires greater attention in the empirical literature (Lammers et al., 2015). Future research with larger sample sizes will permit the further investigation of impulsivity as a moderator in addition to a predictor of treatment response in BED. Given the efficacy of methylphenidate in the treatment of ADHD, for example, impulsivity may predict negative clinical outcomes in CBT more so than methylphenidate. We were unable to evaluate this differential relation in the current investigation, but this remains a fruitful area for future research.

The current research highlights several other areas for future investigation. The comparison of psychostimulant medication versus CBT permits the determination of whether this medication is as good or better than the current evidence-based treatment for BED. Yet, this design precluded conclusions regarding the efficacy of this psychostimulant medication compared to placebo or another form of inactive control condition. We chose not to compare psychostimulant medication to placebo in the treatment of BED as lisdexamfetamine dimesylate has now demonstrated efficacy in the reduction of binge eating in BED in industry-sponsored trials, providing support for the efficacy of psychostimulant medications in the treatment of BED. A meaningful extension of this line of research would be to incorporate combination treatment approaches, for example comparing psychostimulant medication to placebo as an adjunct treatment to CBT. Such an investigation would permit the evaluation of what this medication adds over and above this evidence-based psychological treatment of BED. Moreover, a combination approach may yield a more holistic impact on eating-related cognitions and behaviors as well as weight, metabolic health, and associated comorbidity than monotherapy approaches. Cost-effectiveness studies would be useful to support when this more intensive combination approach is warranted.

Concurrent depression and ADHD were permitted within this investigation, although randomization was stratified by symptom severity to ensure patients were similar across groups in these clinical features. As noted above, patients in the current investigation exhibited lower ADHD and depression symptom severity than anticipated, and lower psychiatric comorbidity overall than epidemiological studies would suggest. This may limit the generalizability of these results, as it is possible that such comorbid psychiatric symptoms would impact treatment process and response differentially across these two

treatment modalities. ADHD symptoms appear likely to negatively impact treatment engagement, compliance, and response more so in CBT (in which outcome is tied to conscientious completion of cognitive and behavioral "homework") than in a pharmacological intervention without such between-session activities. In contrast, the majority of treatment trials have demonstrated that depressive symptoms decrease concomitantly with BED symptoms during CBT for BED (Ricca et al., 2010). Resolution of depression symptoms may be an indirect effect of decreases in binge episodes and weight, and/or the result of decreased self-criticism, which is an active therapeutic target for CBT for BED. Thus, patient depression may be a negative prognostic indicator more so in methylphenidate compared to CBT. The investigation of the moderating influence of co-occurring depression and ADHD symptoms would be another promising line of future research, and contribute to the development of empirically-based and patient-centered treatment delivery guidelines.

The current investigation was restricted to women due to the impact of female sex hormones on neurotransmitter systems underlying response to stimulant medications (Zhou et al., 2002). BED also occurs more frequently in women than men, further supporting the focus upon women in this investigation (Hudson et al., 2012). Future investigations incorporating both men and women will be important to replicate and extend these results: although men with BED exhibit comparable clinical impairment to women, recent evidence suggests that women may be more responsive to psychostimulant medication than men (Davis et al., 2016).

5. Conclusion

The clinical features of BED are associated with dysregulated dopamine functioning – a neural target of psychostimulant medications, which are frequently associated with concomitant weight loss. Such medications may alter the rewarding nature of food and increase the capacity of patients with BED to gain control over their eating behaviors. Despite the efficacy of lisdexamfetamine, psychostimulant medications as a group have not been rigorously evaluated in patients with BED, and have not been compared to the most well-established evidence-based treatment for BED, namely, CBT. Long acting methylphenidate is a promising medication, especially because of its documented history of low adverse effects and attrition, and reduced risk of misuse in its extended release form. The current study provides an initial evaluation of the therapeutic benefit of the impact of this psychostimulant medication on the symptoms of BED in a highly controlled investigation.

Funding

This study was supported by a Type A operating grant awarded by the Ontario Mental Health Foundation to LCQ, CD, and ASK. OMHF did not have any role in study design, data collection, analysis, or interpretation, or article writing or submission.

Conflicts of interest

None.

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