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The Effect of Methylphenidate (MPH) on Appetite, Energy Intake, and Body Composition in Individuals Living with Obesity: A Randomized, Double-Blind, Placebo-Controlled Pilot Study

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Abstract

Objectives: This pilot study examined how Methylphenidate (MPH0.5mg/kg) affects appetite sensations, food reinforcement, energy intake (EI), macronutrient consumption, and weight-loss in youth and adults living with obesity, without ADHD.

Methods: This study employed a randomized, double-blind, placebo-controlled design. Eleven participants aged 28±6.9 yrs. (4 M, 7 F) were randomized to receive either MPH (n=5) or placebo group (n=6) for 60 days. Participants' appetite sensations (Visual Analogue Scale), relative-reinforcing value of food (computer task), EI and macronutrient consumption (*ad libitum* buffet), and anthropometric measurements (DEXA) were measured at baseline and 60 days.

Results: Repeated measures ANOVA revealed group x time interactions for appetite sensations [desire to eat (p=0.01), hunger (p=0.002), and prospective food consumption (p=0.006)]; with greater reductions in MPH group compared to placebo. For the sense of fullness, there was an interaction between group and time (p=0.01), with a greater increase for MPH compared to placebo. Body weight significantly decreased in both groups (p=0.01), with a moderate to large effect size favouring the MPH group (-2.66 kg vs. – 1.16 kg, Cohen's d =0.76). Changes between MPH and placebo did not differ significantly on EI, macronutrient consumption, or food reinforcement.

Conclusions: Our data indicate for the first time that MPH suppresses appetite in individuals with obesity resulting in a moderate–sized effect on weight loss in the short-term. These findings warrant a larger trial to more definitively examine the effect that MPH has on weight loss and maintenance of weight loss, thereby evaluating its potential as a novel pharmacological agent in the management of obesity.

Keywords: Methylphenidate, dopamine, obesity, weight-loss, suppression of appetite, energy intake

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List of Abbreviations

ADHD	Attention Deficit Hyperactivity Disorder
BED	Binge Eating Disorder
BMI	Body Mass Index
DA	Dopamine
DEXA	Dual X-ray Absorptiometry
ECG	Electrocardiogram
EDDS:	Eating Disorder Diagnostic Survey
EI	Energy Intake
FV	Final Visit
MAO:	Monoamine oxidase
MPH	Methylphenidate
NAc	Nucleus Accumbens
NICE	National Institutes for Health and Care Excellence
PFC	Prospective Food Consumption
REE	American Anthropology Association
RRV	Relative Reinforcing Value
TEF	Thermal Effect of Food
TEI	Total Energy Intake
TFEQ	Three-Factor Eating Questionnaire
VAS	Visual Analog Scale

1.0 Rationale

Food is very reinforcing, especially for those who are struggling with obesity (Saelens & Epstein, 1996; Epstein & Saelens, 2000; Johnson, Parry, & Drabman, 1978; Bonato & Boland, 1983). Individuals struggling with obesity have shown a higher desire for energy-dense foods with high-fat and high-carbohydrate content compared to individuals without obesity (Drewnowski & Holden, 1992; Drewnowski, Kurth, Holden, & Saari, 1992; Drewnowski, Krahn, Demitrack, Nairn, & Gosnell, 1992). Dietary restrictions attempt to attain a negative energy balance required for weight-loss by limiting the amount of calorie intake (Franz et al., 2007). However, they often increase the reinforcing value of food and the motivation to consume food, especially palatable snacks high in fat, sugar and salt contents (Fisher & Birch, 1999; Epstein, Truesdale, Wojcik, Paluch, & Raynor, 2003), undermining dietary adherence and weight loss. In addition, these prolonged caloric restrictions also increase the rating of food "liking", which also contributes to increased energy intake (EI) and potentially weight regain (Cameron, Goldfield, Cyr, & Doucet, 2008). The increased palatability and drive for food resulting from dietary restriction, combined with metabolic adaptations resulting from diet-induced weight-loss, have been shown to be strong predictors of weight regain. More than one-third of the weight tends to be regained within the first year, with the majority of the weight regained within 3 to 5 years. (MacLean, Bergouignan, Cornier, & Jackman, 2011). In fact, a 2016 review found that weight regain starts as early as 6 months (Headland, Clifton, Carter, & Keogh, 2016). Physical activity, another method by which a negative energy balance can be achieved, has also been shown to have minimal long-term outcomes in adults with obesity when used in isolation or combined with diet (Franz et al., 2007). These findings indicating poor long-

term efficacy of behavioral weight-loss interventions, (Franz et al., 2007) and the recent inclusion of obesity as a disease by the American Medical Association (Pollack, 2013) suggests that pharmacological interventions that reduce the reinforcing value of food and appetite may improve dietary adherence and weight-loss management in individuals with obesity.

There are limited numbers of approved weight-loss medications available in Canada. Contrave, one the most effective weight-loss medications in Canada has been shown to have serious side effects including nausea, headaches, addiction and even suicide (Sheridan, Lin, Horowitz, 2018; Mordes et al., 2015). Saxenda, another weight-loss medication approved in Canada, is self-administered through injection, which is unappealing to many individuals (Mehta, Marso, & Neeland, 2017). Xenical has a different mechanism of action than suppressing appetite and instead, it works by excretion of fat after ingestion (Yanovski & Yanovski, 2014). Given the discussed literature on long-term weight-loss management, Xenical's mechanism of action is not an effective method. Therefore, a highly tolerable and effective weight-loss medication capable of achieving weight-loss by suppressing appetite and reducing the reinforcing value of food would hold important implications for obesity management.

Dopamine (DA), a neurotransmitter that mediates the brain's reward and pleasure centers, located within the forebrain structures along the limbic path and responsible for controlling the food reward and reinforcing value of food (Berridge, 1996), is considered as an important player in food reward and food intake (Berridge, 1996; Berridge & Robinson, 1998). Increased (reward surfeit) or decreased (reward deficiency) DA levels along with other hormones (such as ghrelin and leptin, insulin) can alter the wanting and liking components of food reward by modulating the mesolimbic dopaminergic pathway, which stems from the midbrain ventral

tegmentum and extending to several limbic structures, including the nucleus accumbens (NAc), the amygdala, and the hippocampus (Berthoud, 2007). Given the fact that under energy balance, food reinforcement predicts food intake in youth and adults (Epstein et al., 2004), individual differences in the reinforcing value of food (i.e. their preferences for food: high fat/high carbs) may play a role in the development of positive energy balance leading to obesity (Epstein et al., 2004; Hanlon, Baldon, Sadeghian, & Kelley, 2004; Martel & Fantino, 1996).

The reward deficiency syndrome (Blum, Cull, Braverman, & Comings, 1996) postulates that reduced levels of brain dopamine are associated with greater risk of overeating, higher food reinforcement (Epstein, Leddy, Temple, & Faith 2007), compulsive (addictive) behavior (Blum et al., 2000) and obesity (Blum, Wood, Braverman, Chen, & Sheridan, 1995), and these behaviors can be considered means of "self-medicating' to compensate for a sluggish or blunted dopaminergic system (Blum et al., 2000).

Methylphenidate (MPH) is an agent that increases the availability of brain dopamine by inhibiting reuptake within the mesolimbic dopaminergic pathway of the brain (Kuczenski & Segal, 2001). Since lower levels of brain dopamine are associated with symptoms of ADHD, MPH is commonly used for the treatment of ADHD. MPH has also been shown to suppress appetite (Davis et al., 2012), decrease the reinforcing value of the food (Goldfield, Lorello, Doucet, 2007), and reduce energy intake in adults with obesity (Leddy et al., 2004) and normal-weight adults in the laboratory studies (Goldfield et al., 2007). These observed effects, together with the literature on reward-driven obesity, makes MPH a good candidate to be evaluated as a pharmaceutical weight-loss therapy.

The purpose of this study was to investigate the effect of MPH on appetite sensations, food reinforcement, laboratory energy intake, macronutrient consumption, and weight-loss in youth and adults living with obesity without ADHD.

2.0 Introduction and Review of Literature

In 2010, obesity was estimated to cause 3.4 million deaths (Ng et al., 2014). Worldwide, the proportion of adults with overweight or obesity (BMI > 25 kg/m^2) has increased from 28.8% to 36.9% in men and from 29.8% to 38% in women in the past 35 years (Ng et al., 2014). According to the Public Health Agency of Canada, as of 2017, 64% of adults over the age of 18 are overweight or obese (Public Health Agency of Canada, 2017). The rising rate of obesity across the world and the inclusion of obesity as a disease by the American Medical Association (Pollack, 2013) has motivated many in the scientific community to find possible solutions to mitigate obesity and its associated adverse health effects, which include increased risk of cardiovascular disease, diabetes, cancer (Public Health Agency of Canada, 2017), and all-cause mortality (Flegal, Kit, Orpana, & Graubard, 2013).

Dietary restrictions and physical activities are the most commonly used methods for obesity management. Although diet and exercise are moderately effective, the weight-loss cannot be maintained in most cases (Franz et al., 2007). Weight-loss appears to plateau within the first 6 months, followed by weight regain (Headland, Clifton, Carter, & Keogh, 2016). More than one-third of the weight lost through diet and exercise tends to be regained within the first year, with the majority of the weight regained within 3 to 5 years. (MacLean, Bergouignan, Cornier, & Jackman, 2011). This is partly because while dietary restrictions attempt to combat against obesity by reducing the energy intake required to produce a negative energy balance, they often increase the reinforcing value of food (Fisher & Birch, 1999; Epstein, Truesdale, Wojcik, Paluch, & Raynor, 2003), and rating of food "liking" (Cameron, Goldfield, Cyr, & Doucet, 2008). This increase in the reinforcing value of food often increases motivation to consume more food,

especially food with high-fat contents (Fisher & Birch, 1999; Epstein et al., 2003), undermines dietary adherence and weight loss and leads to weight regain. These findings, combined with the poor long-term efficacy of behavioral weight-loss interventions (Franz et al., 2007), has encouraged many to develop other approaches to reduce the reinforcing value of food and the rating of food liking in individuals with obesity.

Current literature suggests that dopamine (DA) mediates the rewarding value of appetitive behaviors such as eating, sex, and substance abuse. Therefore, it is not surprising that DA plays an important role in food reinforcement and the development of obesity. (Salamone, 1994; Saelens & Epstein, 1996; Volkow et al., 2002; Cameron, Chaput, Sjödin, & Goldfield, 2017). The role of DA signaling in obesity research is discussed in the next sections.

2.1 Dopamine, Food Reward, and Obesity

Food reward experience is very different across individuals' feeding behaviours. Cameron et al. (2017) model feeding behavior into the following two-tier system: 1) bottom-up signaling and 2) top-down signaling (Cameron & Doucet, 2007). Bottom-up signaling consists of genetic factors (e.g. Taq1A[1], DRD4[2], DAT[3], COMT[3]), as well as long-term (Leptin and insulin)

[1] It is a genotype that is involved in treatment of obesity by altering the availability of DA within the NAc of the brain.

[2] Dopamine receptor: its function is linked to availability of DA within the NAc of the brain (Ilgin, Sensol, Gucuyener, Gokcora, Sener, 2001).

and short-term (ghrelin, glucose, etc.) signals (Havel, 2001), whereas top-down signaling consists of internal and external stimuli such as cognitive factors, rewarding factors and environmental factors (Cameron & Doucet, 2007).

The top-down and bottom-up signaling models suggest that multiple factors mentioned above contribute to energy intake. Therefore, predicting individuals' feeding behaviors and the relation to food reward is complex and does not only depend on brain DA regulation (Cameron et al., 2017; Cameron & Doucet, 2007). With respect to feeding and food reward, two models of brain DA have dominated the research: 1) hypodopaminergic (reward deficiency) (Blum et al., 2000) and hyperdopaminergic (reward surfeit) (Yokum, Gearhardt, Harris, Brownell, Stice 2014; Stice, Burger, & Yokum, 2015; Demos, Heatherton, Kelley, 2012). In other words, both lower than normal levels of brain DA availability and higher than normal levels of brain DA have shown to influence energy intake, food reinforcement, and obesity (Stice et al., 2015), indicating the complex role of DA in regulating eating behavior.

A study conducted by Blum et al. (2000) showed that reduced levels of brain dopamine (reward deficiency syndrome) are associated with greater risk of overeating, food reinforcement, and obesity. Another large prospective study by Stice et al. (2015) looked at the relationship between DA availability and obesity and found that the effect of brain DA on obesity also

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[3] Dopamine transporter: DA reward marker linked to functional changes in brain DA transmission (Nokolova, Ferrel, Manuck, Hariri, 2011).

depends on the frequency of different genotypes in adolescent subjects. An example of the genotypes that play a role in the effect of DA on obesity is *Taq1A* allele. There are three *Taq1A* genotypes: A1/A1, A1/A2, and A2/A2. A1/A1 and A1/A2 are often combined and referred to as $Taq1A^{+}$ while A2/A2 is noted as $Taq1A^{-}$ (Stice et al., 2015). The study of Stice et al. (2015) found that for the adolescents with $Taq1A^{-}$ allele, elevated reward response predicted fat gain (reward surfeit) whereas for the adolescents with $Taq1A^{+}$ allele, a lower reward response predicted fat gain (reward deficiency), providing evidence that both reward deficit and reward surfeit pathways can lead to obesity (Stice et al., 2015; Stice, Spoor, Bohon, & Small, 2008).

The literature reviewed in this section emphasizes the important and complex role of dopamine on reward-driven eating and obesity. Given the quest for identifying pharmaceutical methods to reduce the reinforcing value of food and to control reward-driven overeating, it stands to reason that examining agents that target and regulate the dopaminergic system may be beneficial to weight management.

Methylphenidate (MPH) is an agent that increases the availability of brain dopamine by inhibiting its reuptake (Kuczenski & Segal, 2001; Berridge, 1996). MPH is primarily used in the treatment of attention deficit hyperactivity disorder (ADHD). Although described in more details in the following sections, MPH is also shown to suppress appetite (Davis et al., 2012), reduce the reinforcing value of food (Goldfield et al., 2007), and reducing the energy intake in normal-weight adults (Goldfield et al., 2007) and adults with obesity (Leddy et al., 2004) in laboratory studies. These findings suggest that MPH can be a good candidate to be evaluated as a pharmaceutical solution to reward-driven overeating and weight-loss. Before delving into the role of MPH in obesity research, the literature on MPH and its current use are briefly reviewed.

2.2 MPH, A Dopamine Reuptake Inhibitor

Methylphenidate, with the most common trade name of Ritalin, is a psychostimulant that increases brain dopamine availability by inhibiting dopamine reuptake within the mesolimbic dopaminergic pathway of the brain, including the nucleus accumbens (NAc), the amygdala, and the hippocampus (Kuczenski & Segal, 2001; Berridge, 1996). MPH was approved by FDA in 1955 for the treatment of ADHD in children (Schachter, Pham, King, Langford, and Moher, 2001) and adults (Wilens, Biederman, Spencer, and Prince, 1995). Originally, Ritalin was approved as tablets for oral administration in two forms: Ritalin (instant release) and Ritalin-SR (sustained release) (U.S. Food and Drug Administration Ritalin Medication Guide, 2017). Moreover, in 2002, Ritalin-LA (extended release) was approved by FDA and is now available for oral administration (U.S. Food and Drug Administration Ritalin-LA Medication Guide, 2010). According to FDA's medication guide, Ritalin (instant-release) has time to peak rate of 1.9 hours (0.3-4.4 hours), while Ritalin-SR has time to peak rate of 4.7 hours (1.3-8.2 hours). In contrast, Ritalin-LA produces two distinct peaks, with the first peak being similar to Ritalin (1-3 hours) and the second peak being 4 hours after the first peak. Another brand name for sustained-release MPH that is commonly used in U.S and Canada is Concerta, with a maximum plasma concentration (C_{max}) of 6 – 10 hours (U.S. Food and Drug Administration Concerta Medication Guide, 2007).

The dosage varies across children and adolescent, with an average daily dose of 20 – 30 mg for adults (Morton and Stock, 2000). Most texts suggest a maximum daily dose of 60 mg/day unless otherwise required, but it seems to be arbitrary and not based on clinical research (Morton and Stock, 2000). Instead, studies on adults with ADHD suggests a therapeutic dose of up to 1.0

mg/kg/day (Wilens et al., 1995; Spencer et al., 1995). Dosing and titration of MPH vary as a function of symptoms reduction, side effects, and tolerability. In general, meta-analyses of 144 double-blind randomized controlled trials on 11018 children and adolescents and 5362 adults (Cortese et al., 2018), as well as other studies on both short-acting and sustained release MPH, indicate that MPH is very well tolerated in the vast majority of children and adults (Efron, Jarman, & Baker, 1997; Didoni, Sequi, Panei, Bonati, 2011; Barkley, DuPaul, and McMurray, 1991; Ahmann et al., 1993)

Given the fact that suppression of appetite is one of the well-observed side effects of MPH consumption (Efron et al., 1997; Didoni et al., 2011; Barkley et al., 1991; Ahmann et al., 1993) with other side effects being mild and only impacting a small population, the role of MPH on the suppression of appetite in obesity research is reviewed in the next sections.

2.3 Reward Deficiency Syndrome and the Role of MPH

As mentioned in the previous section, the role that brain DA plays in obesity is very complex with reward deficiency being one of the models that have guided much of the obesity research.

A review paper by Liu et al. (2008) supports the hypothesis that lower levels of brain dopamine can induce appetitive drive, leading to obesity in humans. More specifically, an insufficient release of DA in the brain's striatum is associated with increased food craving, food intake, and subsequent development of obesity in humans (Liu et al., 2008). Similar lower levels of DA have been observed in normal-weight and overweight healthy adults in a controlled laboratory study conducted by Davis et al. (2012). In that study, the prescription of MPH (0.5 mg/kg) reduced appetite, food cravings, and snack food consumptions during a laboratory snack

buffet (Davis et al., 2012). The findings were consistent with the aforementioned reward deficiency model of obesity and that MPH can be a powerful agent in reversing reward-driven overeating.

2.4 MPH and Suppression of Appetite

Several studies have demonstrated the effect of MPH on appetite and energy intake (summarized in Appendix H). A lab study conducted by Davis (2012) and her colleagues on 132 (35 males and 97 females) healthy normal-weight adults and adults with obesity (BMI > 30) found a potential trend in MPH use and the suppression of appetite in women. More specifically, by using a double-blind, crossover design, they found that while men with obesity did not have a diminished food intake response during a snack buffet meal when using a short-acting MPH dose of 0.5 mg/kg, women did show a reduced food intake (Davis et al., 2012). Unlike the study conducted by Davis in 2012, a study by Goldfield et al. (2011) on 12 (normal-weight or higher) adults (6 males and 6 females) found that one hour after the administration of a short-acting MPH (0.5 mg/Kg), energy intake, dietary fat intake, and carbohydrate intake reduced significantly in men when compared to women during a standardized mixed meal buffet-style eating methodology (Goldfield et al., 2011). Another double-blind study conducted by Leddy et al. (2004) on 9 adult males with obesity found that the energy intake measured during a pizza buffet meal reduced by 23%, 1 hour after the administration of a moderate dose of short-acting MPH (0.5 mg/kg).

Another lab study conducted by Gurbuz et al. (2016) on 89 male subjects (48 ADHD patients and 41 healthy subjects) between the ages of 7-14 during 3 months of MPH (0.5 mg/kg) treatment confirmed that the weight-loss caused by the suppression of appetite can also be

influenced by altering leptin and ghrelin hormone levels. Leptin, a single chain peptide hormone released by the three receptors of adipocyte tissue, as well as the placenta, ovaries, stomach, skeletal muscle, breast epithelial cells, bone marrow, pituitary gland, and liver (Baratta, 2002), suppresses appetite by regulating and increasing the body's energy consumption (Wauters, Considine, & Van Gaal, 2000). Conversely, ghrelin, a lipopeptide released by endocrine functioned cells in the stomach fundus and an endogenous ligand of the growth hormone releasing receptor (GHS-R), acts as an opposed element to leptin's function by decreasing the effect of leptin in reducing body's energy consumption and in assisting with weight-loss. Ghrelin does this by altering the release of peptides from the hypothalamus (Nakazato et al., 2001). Therefore, leptin levels appear to increase in subjects taking MPH while ghrelin levels appear to decrease, resulting in reduced energy intake and weight-loss.

2.5 MPH and Macronutrient Consumption

Besides the effect of MPH on appetite and energy intake, few studies have examined the effects of MPH on macronutrient consumption. A single-blind placebo-controlled study on teenagers with obesity (15 females and 7 males) found that a single dose of instant-release MPH (0.3 mg/kg) administration after a 10 hour fast reduced energy intake from fat by 18% (167 vs 203 kcal) and energy intake from carbohydrate by 21% (311 vs 389 kcal) when compared to placebo. The participants were given either a placebo or an oral MPH pill 1 hour prior to an ad libitum breakfast buffet meal (Danilovich, Mastrandrea, Cataldi, & Quattrin, 2014).

Another randomized, double-blind, placebo-controlled crossover study by Goldfield et al. (2007) on 14 adults (7 males and 7 females) with BMI > 20 also found a selective 17% reduction in high fat foods and 11% reduction in the total energy intake 1 hour after the ingestion of a 0.5

mg/kg of short-acting MPH over the course of an ad libitum buffet lunch. These studies indicate that MPH administration not only reduces dietary caloric intake but also alters the macronutrient preference, which can be helpful in the treatment of obesity.

2.6 MPH and Body Composition

A clinical study conducted by Poulton et al. (2012) on 34 children (29 males and 5 females) found that there was an average weight loss of 1 kg in patients with ADHD in the first 6 months of treatment with immediate-release MPH. The dose was titrated to give the maximum therapeutic benefit at the lowest possible dose of medication in line with recommended practice parameters, but dosing was intended for managing MPH symptoms and not weight loss. Dual-energy X-ray Absorptiometry (DXA) measurements demonstrated that the subjects lost an average of 1.4 ± 0.96 kg of body fat while their lean tissue mass increased by 0.04 ± 0.03 kg (Poulton et al., 2012). Another randomized, double-blind, placebo-control, crossover study by Lorello, Goldfield, & Doucet (2008) on 14 healthy adults (7 females and 7 males) showed that fast-release MPH administration of 0.5 mg/kg increased the resting energy expenditure (REE) significantly when compared to placebo (Lorello, Goldfield, & Doucet, 2008). More specifically, the study found that MPH causes resting energy expenditure to increase by 7% over placebo, obtained using calorimetry. Increased resting energy expenditure is important to target given research shows that it can lead to greater weight-loss and that it is critically important for maintenance of weight loss (Nakazato et al., 2001; Wren et al., 2001 & Schwartz, and Doucet, 2010).

In the light of the effect of MPH on the suppression of appetite, macronutrient consumption, body composition, and in the context of a reward deficiency model of obesity, there are compelling reasons to believe MPH may be a viable weight-loss medication.

2.7 Weight Loss Medications

In this section, some of the most common pharmacological medications used as weight-loss treatment and how they compare to MPH are reviewed. Table 1 summarizes the most commonly used weight-loss medications in North America that are approved for long-term use.

Table 1: Commonly Used Weight-Loss Drugs in North America

Generic Name	Trade Name(s)	Common Dose(s)	FDA/Health Canada Approved	Common Side Effects
Orlistat	Xenical, Alli	60 mg 120 mg	√	Diarrhea, Gas, Leakage of oily stools, Stomach pain
Lorcaserin	Belviq	10 mg	Only FDA Approved	Constipation, Cough, Dizziness, Dry mouth, Feeling tired, Headaches nausea
Phentermine/ Topiramate	Qsymia	3.75/23 mg 7.5/46 mg 15/92 mg	Only FDA Approved	Constipation, dizziness, dry mouth, taste changes, tingling of your hands and feet, trouble sleeping
Bupropion/ Naltrexone	Contrave	360/32 mg	√	Constipation, diarrhea, dizziness, dry mouth, headache, increased blood pressure, increased heart rate, insomnia, liver damage, nausea, vomiting
Liraglutide	Saxenda	3 mg	√	Nausea, diarrhea, constipation, abdominal pain, headache, raise pulse

Note: Data for Orlistat, Lorcaserin, Phentermine/Topiramate, Bupropion/Naltrexone, Liraglutide from Yanovski & Yanovski (2014) & Mordes, Liu, & Xu (2015), for drugs approved by Health Canada from Wharton, Lee, Christensen (2017) and Government of Canada (2018)

Orlistat is a gastrointestinal lipase inhibitor for the treatment of obesity (Yanovski & Yanovski, 2014) which leads to excretion of approximately 30% of the ingested fat (Yanovski & Yanovski, 2014). The FDA approved dosage in adults and adolescents is 120 mg/day (Mordes et al., 2015). Meta-analysis of randomized controlled trials shows a small but significant weight loss of around 3% more than diet-alone in overweight adults and adults with obesity (Drew,

Dixon, & Dixon, 2007). More specifically, a meta-analysis of eleven randomized controlled trials using 120 mg Orlistat (3 times daily) found 2.7 kg greater weight loss in the Orlistat group compared to placebo (Drew et al., 2007). More patients treated with Orlistat lost 5% or more of their initial weight in the 1st year compared to placebo and the orlistat group also sustained more of this weight loss in the 2nd year of treatment (Hauptman et al., 2000). Most of the trials included energy reduction, lifestyle intervention, and exercise programs (Yanovski & Yanovski, 2014). A 2003 meta-analysis found high attrition rates ranging from 14% to 52% with an average of 33% during the weight-loss phase of Orlistat use. Other studies indicate even higher attrition rates of 64% to 77% due to the high cost and side effects of Orlistat use (Drew et al., 2007). Gastrointestinal events are the most common side effects, including fatty/oily stool leakage, stomach pain, and diarrhea (Rössner et al., 2000).

Lorcaserin is a weight-loss drug that acts on the serotonin receptors, thereby impacting the physiological and psychological mechanisms of hunger and fullness implicated in excessive food consumption and obesity (Yanovski & Yanovski, 2014). The FDA approved dosage for adults is 10 mg taken twice daily on the basis of two large randomized, placebo-controlled trial studies called BLOSSOM (N=4004) (Fidler et al., 2011) and BLOOM (N=3182) (Smith et al., 2010). On average these studies found a modest loss of 3.2 kg of body weight more than placebo (Smith et al., 2010). It is important to note that the participants were given a 600 daily caloric reduction, along with behavioral modifications including exercise program and counseling (Fidler et al., 2011; Smith et al., 2010). A meta-analysis of the efficacy of Lorcaserin in adults with obesity found a modest 1.6 kg of weight-loss during 8 – 12 weeks of Lorcaserin use (Chan et al., 2013). Lorcaserin did show adverse effects such as headaches, dizziness, fatigue, nausea,

and dry mouth for nondiabetic patients. Additionally, Lorcaserin consumption caused back pain, cough, and hypoglycemia in some patients with type 2 diabetes (Yanovski & Yanovski, 2014). The rate of withdrawal from the study due to adverse side effects ranged from 7.1% to 8.6% (Fidler et al., 2011; Smith et al., 2010). This medication has not been approved for weight loss in Canada.

The combination of Phentermine and Topiramate as a two-component fixed ratio medication for appetite suppression was approved by FDA in 2012 with multiple dosages ranging from 3.75/23 mg/day to 15/92 mg/day (Mordes et al., 2015). A meta-analysis of 28 randomized clinical trials on various obesity medications found a significant excess weight loss of 8.8 kg more than placebo after 1 year of Phentermine-Topiramate use (Khera et al., 2016). However, the drug was not well tolerated with the discontinuation rate of 40%, among the highest attrition rates in comparison to other weight-loss drugs, in trial studies and showed adverse side effects such as constipation, paresthesia, insomnia, and impaired attention and memory (Mordes et al., 2015). As such, it has not been approved for weight-loss in Canada.

Naltrexone/Bupropion (Contrave) is the newest approved weight-loss drug in Canada that has a synergism action in midbrain dopamine areas and reduces food intake as a result (Sinnayah, Wallingford, Evans, Cowley, 2012), suggesting that the mechanism of action of this combination might be modulation of mesolimbic reward pathways (similar to MPH) (Greenway et al., 2010). The FDA approved dosage for Naltrexone/Bupropion in adults is 32/360 mg/day (Yanovski & Yanovski, 2014). A randomized, double-blind, placebo-controlled study on 1742 men and women with obesity (BMI = 30-45 kg/m^2 or 27-45 kg/m^2 with complications) aged 18-65 years showed an average body weight decrease of 4.9 ± 0.3 kg ($5.0 \pm 0.3\%$) and 6.1 ± 0.3 kg

(6.1 ± 0.3%) for 16/360 mg/day and 32/360 mg/day doses respectively compared to placebo who lost 1.4 ± 0.3 kg (1.3 ± 0.3%) during 56 weeks of Contrave treatment (Greenway et al., 2010). This trial implemented an aggressive diet (600 kcal/day) and exercise program (Greenway et al., 2010). Another randomized, double-blind, placebo-controlled study on 1496 overweight adults (BMI=27-45 kg/m^2) or adults with obesity (BMI=30-45 kg/m^2) aged 18-65 years showed an average body weight decrease of9 ± 0.2 kg (6.5 ± 0.2 %) at week 28 of Contrave treatment compared to placebo (2.0 ± 0.3 kg (1.9 ± 0.3%)) and an average weight loss of 6.2 ± 0.2 kg (6.4 ± 0.3%) at week 56 of Contrave treatment compared to placebo (1.3 ± 0.3 kg (1.2 ± 0.3%)) (Apovian et al., 2013). These individual trials are consistent with a meta-analysis of 28 randomized clinical trials with 29,018 patients, in which they found an average of 5.0 kg more than placebo after 1 year of treatment with naltrexone-bupropion (Khera et al., 2016). In the Contrave Obesity Research I (Greenway et al., 2010), the attrition rate was 50% with 29.8% of participants experiencing nausea (Greenway et al., 2010). The attrition rate in another study by Greenway et al. (2009) was reported to be 40% with other attrition rates ranging from 30% to 45% (Greenway et al., 2009). This is a very large attrition rate compared to other approved weight-loss drugs and a limiting reason for its wide adoption. Moreover, Khera et al. (2016) meta-analysis found naltrexone-bupropion to have the highest probability of being discontinued due to adverse events compared to other weight-loss obesity drugs (Khera et al., 2016). Beside nausea affecting approximately 30% of those being treated with naltrexone-bupropion, some other adverse side effects were observed when it was taken with high-fat meals and/or alcohol. Also, Bupropion is known to increase the risk of suicidal thinking, especially in children,

adolescents and young adults (Sheridan, Lin, Horowitz, 2018). Other common side effects include nausea, constipation, headache and insomnia (Mordes et al., 2015).

Liraglutide, a glucagon-like peptide-1 receptor agonist, is a gut hormone that suppresses appetite via peripheral and central pathways (Mordes et al., 2015). The FDA approved dosage for Liraglutide in adults is 3 mg/day (Yanovski & Yanovski, 2014). Meta-analysis of 5 randomized placebo-controlled trials found that in addition to diet and physical activity, the use of Liraglutide results in 4 to 6 kg of weight-loss over the period of 1 year (Mehta, Marso, & Neeland, 2017). The average attrition rate among the analyzed studies was 24.5% with some adverse side effects such as nausea (32.7% - 48.4%), constipation, (11.9% - 26.9%), diarrhea (16.5% - 25.6%), vomiting (7.4% - 16.5%) and abdominal pain (5.4% - 6.2%) (Mehta et al., 2017; Mordes et al., 2015). Beside adverse side effects, one of the major limitations cited for this medication is that it is self-administrated by injection only, which is unappealing to many individuals (Mehta et al., 2017) given the prevalence of needle phobia in adolescents (20-50%) and adults (20-30%) (McLenon & Rogers, 2018).

It is worth mentioning Lisdexamfetamine (Vyvanse) (dose=30, 50, 70 mg/day), a dopamine reuptake inhibitor that is pharmacologically similar to MPH. Lisdexamfetamine, used for the treatment of ADHD and more recently indicated for binge eating disorder (BED), has also been shown to help with weight-loss and the treatment of obesity in ADHD patients (Adler et al., 2008). Several double-blind, placebo-controlled studies have shown that Vyvanse is very well tolerated for the treatment of BED and ADHD in adults (Adler et al., 2008 & Weisler et al., 2009 & McElroy et al., 2015). In a study examining the efficacy and safety of Lisdexamfetamine, McElroy et al. (2015) found in a sample of adults with BED, an average weight loss of 3.0 kg –

4.2 kg (depending on the dose) above placebo after 11 weeks of Lisdexamfetamine administration. In a 7-week phase III study of Lisdexamfetamine on adolescent and children with ADHD, a weight-loss of 2.1 kg was observed in the Lisdexamfetamine group, compared to a weight gain of 0.7 kg (Coghill, Caballero, Sorooshian, & Civil, 2014). However, Lisdexamfetamine is not indicated for weight-loss treatment (Adler et al., 2008).

Another drug, Metformin (dosage=500 to 2550 mg/day), used for the treatment of type 2 diabetes has also shown to help with weight loss in adults with type 2 diabetes (Pérez-Hernández et al., 2016) and non-diabetic individuals with obesity (Seifarth, Schehler, & Schneider, 2013). However, similar to Lisdexamfetamine, it is not indicated for weight-loss treatment. (Pérez-Hernández et al., 2016; Seifarth et al., 2013).

Comparing the side effects of the aforementioned medications to the side effects of MPH discussed in section 2.2 suggests that MPH may be better tolerated when compared to some of the aforementioned approved weight-loss drugs. For example, while Contrave is known to increase suicidal thinking in some cases due to its Bupropion component (and is included in Contrave's product monograph), a population-based (self-controlled case series design) study of 25,629 individuals aged 6 to 25 treated with MPH between 2001 and 2015 did not support a causal association between MPH treatment and suicide attempts, and in fact showed that MPH is well tolerated. (Man et al., 2017). As another example, Qsymia was not well tolerated in the trial studies with the discontinuation rate of about 40% (Mordes et al., 2015) and is not yet approved in Canada. These findings suggest that MPH may be well tolerated as a weight-loss medication when compared to currently approved weight-loss drugs.

2.8 Research Gap

The reviewed literature has established a strong connection between MPH and the suppression of appetite, reduced energy intake, and weight loss in adults with and without obesity in laboratory studies, as well as in clinical research in youth and adults with ADHD. These findings, along with similar or better tolerability of MPH when compared to currently approved weight-loss drugs, make MPH a good candidate to be investigated as a weight-loss therapy. While several different studies reviewed above have shown the efficacy and generalizability of using MPH in youth and adults with ADHD have been well established (Liu et al., 2008; Davis et al., 2012; Poulton, 2012), little to no data exist on the effect of MPH on individuals with obesity without ADHD beyond the laboratory in the natural environment. Therefore, the overarching goal of the proposed study is to examine the effect of MPH on energy intake, food reinforcement, macronutrient preference, and body composition in individuals with obesity without ADHD, and to determining whether MPH might be a good candidate as a weight-loss medication to be tested in larger trials.

2.9 Study Objectives

In this pilot study, using a randomized, double-blind, placebo-controlled design, my thesis attempts to address the following questions:

In individuals with obesity aged 16-40 years:

1. Compared to placebo, does MPH (0.5mg/kg, up to 100 mg/day) lead to greater reductions in appetite sensations and food intake during a laboratory *ad libitum* buffet meal at Baseline and 60-days?

2. Compared to placebo, does MPH (0.5 mg/kg, up to 100 mg/day) have an impact on macronutrient consumption during a laboratory *ad libitum* buffet meal at Baseline and 60-days?
3. Does MPH reduce the reinforcing value of food compared to placebo, and are these changes associated with reductions in energy intake and macronutrient consumption during the laboratory *ad libitum* meal at baseline and 60-days?

2.10 Study Hypotheses

1) It is predicted that MPH consumption will lead to greater reductions in the appetite sensations compared to placebo.

2) It is predicted that MPH will lead to greater reductions in energy intake, high-carbohydrate, and high-fat foods when compared to placebo in the laboratory ad-libitum buffet condition. It is also predicted that MPH will not produce greater changes in protein intake compared to placebo.

3) It is predicted that MPH will lead to greater reductions in the reinforcing value of palatable snack foods compared to placebo, and these changes will be associated with reduced energy intake and intake of high-fat, high-carbohydrate foods in the laboratory ad-libitum meal condition.

3.0 Methods and Study design

3.1 Study Population and Inclusion/Exclusion Criteria

Study population. Study recruitment and conduct were consistent with the CONSORT guidelines (See Figure 2). As illustrated, a total of 12 participants with obesity between the age

of 16 and 40 years completed the study at the University of Ottawa, Lees Campus. Most of the participants were recruited by:

- Posting fliers in the community (hospitals, gymnasia, universities, buses etc.).
- Social media (e.g., Facebook, Instagram, Kijiji) advertisements.

Inclusion criteria. The inclusion criteria consisted of males and females who:

- were between the age of 16[4] and 40 years with a BMI in the obese category (above 29.9 kg/m^2) or above the 95th BMI percentile for age and sex in the case of youth ages 16-17 years [5]
- were willing to comply with the procedures
- signed an informed consent form
- were able to swallow a placebo pill that is used in the study (same size as the study drug).
- passed all the screening tests, including an Electrocardiogram (ECG) after a test dose of MPH (0.5 mg/kg)

Exclusion criteria. Exclusion criteria consisted of individuals who:

- were smokers[6]

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[4] For youth we diagnose obesity as above the 95th BMI percentile on growth charts from the CDC: https://www.cdc.gov/obesity/childhood/defining.html

[5] Growth chart for boys: https://www.cdc.gov/growthcharts/data/set1clinical/cj41l023.pdf; Growth chart for girls: https://www.cdc.gov/growthcharts/data/set1clinical/cj41l024.pdf

[6] Smoking is known to impact appetite

- had serious food allergies (including lactose)
- had a previous history of MPH use or allergy to MPH (Appendix A)
- had a history of ADHD as measured by a self-report called Wender-Utah Rating Scale (See Appendix D) (McCann, Scheel, Ward, & Roy-Byrne, 2000; Rossini & O'Connor, 1995; Stein et al., 1995)
- Had a history of clinical depression [7] measured by the Beck Depression Inventory (scores $\geq$ 30) (See Appendix E) (Heffner, 2016)
- had a history or current eating disorder, including binge eating disorder (BED) measured by the Eating Disorder Diagnostic Survey (EDDS) (Stice, Telch, Rizvi.,2000)
- used antidepressants such as Zyban/bupropion (No agents that target DA, Except SSRI's), thyroid medication, or medications that affect appetite
- had high blood pressure, pre-existing cardiovascular disorders[8], or diabetes
- had a history of alcoholism, or current addictions to alcohol, opiates, cocaine or stimulants as measured by the Drug Abuse Screening Test (See Appendix C)
- were not a restrained eater based on cut-score of 15 or higher on the Three-Factor Eating Questionnaire (TFEQ) (See Appendix F) (Stunkard & Messick, 1985)

[7] Including depression, panic disorder, schizophrenia

[8] Including uncontrolled hypertension, angina pectoris, arterial occlusive disease, heart failure, cardiomyopathies, myocardial infarction, and cardiac arrhythmia

- had a personal or family history of seizure disorder
- were currently taking MAO inhibitors, pressor agents, coumarin, anticonvulsants, phenylbutazone, tricyclic antidepressants or Wellbutrin or other dopamine agents
- had a history of thyroid disease
- had a personal or family history of motor tics or Tourettes's Syndrome,
- were pregnant[9]

3.2 Design of Study and Trial Procedure

In this pilot study, the data was collected using a randomized, double-blind, placebo-controlled 2-arm parallel design. The study consisted of two study groups: the placebo group and the intervention (MPH) group. The two groups were administered either placebo or short-acting MPH two-times daily, before lunch and dinner, for a period of 2 months (60 consecutive days). Participants were randomized in small blocks and stratified by sex to ensure equal numbers of men and women in each group. Prior to being assigned to one of the study groups at random, participants were invited to the laboratory for the screening visit if they meet the inclusion criteria based on a phone screen (see Appendix A). Once the participants were invited to the laboratory, they were examined again to determine whether they meet the eligibility criteria, and

[6] As determined by commercially available pregnancy test taken by female participants prior to test dose of MPH, and lastly after the test dose of MPH

if so, to sign an informed consent form, and to take a test dose of MPH in the presence of a nurse so that any potential side effects were closely monitored prior to starting the trial.

The trial assessments were divided into six visits to the laboratory. There was an initial clinical screening visit of 4 hours, three repeated measurement days of 6 hours each (baseline visit, 7 days, and 60 days), a mid-point (30 day) visit of one-hour long for the assessment of body composition and to renew the prescription of MPH, and a Lunch Box visit (10 minutes to obtain out of laboratory food). Figure 1 summarizes the six laboratory visits.

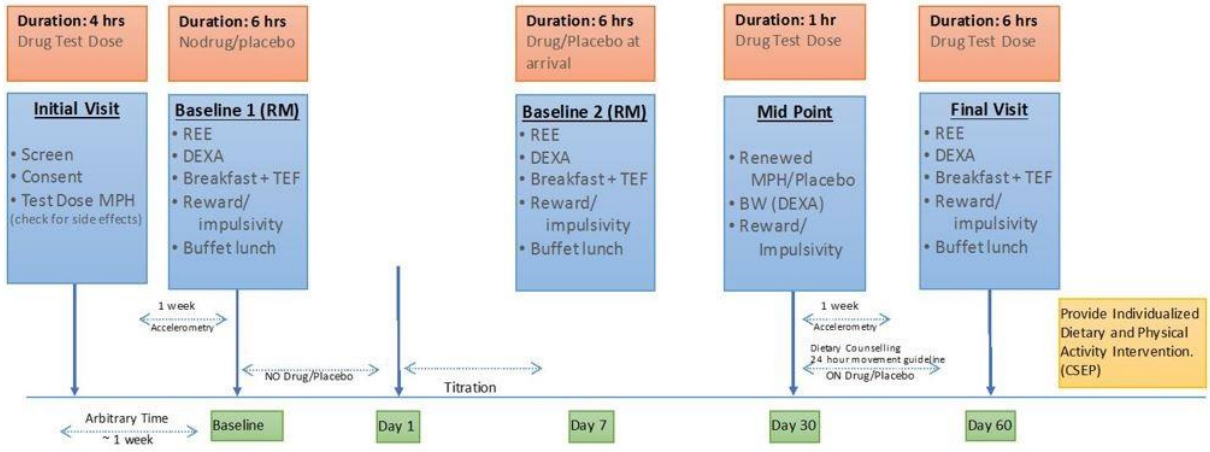

Figure 1: Study Map

REE: Resting Energy Expenditure; DEXA: Dual X-ray Absorptiometry; TEF: Thermal Effect of Food;

Once the initial clinical screening visit was completed, at the end of Baseline visit, participants were randomly assigned to one of the two treatment groups for a 2-month intervention period. Participants were instructed to wear accelerometers for 1 week between the in-lab screening visit and the Baseline visit, and then again for 1 week (while under MPH or placebo) at the mid-point visit and the final measurement day. At the end of the Baseline test

day, participants received a 3-day supply of food from which they exclusively ate until they returned to the lab 4 days later for the Baseline 2 repeated measures test day (i.e. under drug or placebo). This out lab feeding was previously validated to be a much better measure of food intake than self-reported food logs (McNeil et al., 2012). Similarly, 4 days prior to the Final repeated measures test day, participants again had to visit the laboratory for their "Lunch Box" visit to obtain their 3-day supply of food from which they ate exclusively. Participants returned to the laboratory to complete the study at the Final (day 60) repeated measures test day after 3 days of eating from the "Lunch Boxes". One month after the 2 repeated measurement test day (30-day Midpoint), participants returned to the lab to report for an examination of the perceived side effects of MPH/placebo, body weight, and food reinforcement. On the final measurement day (Day 60), participants underwent the full repeated measures as described for baseline and 7-days (see study map in Figure 1). On the same day, participants' sleep and screen time patterns were assessed and they were provided with individualized dietary and physical activity intervention by our expert research staff. Specifically, participants were advised to follow Health Canada's Food Guide for healthy eating practices. They were also advised to return to lab as much as they wanted for the next 30 days after the study to have a dietician's help with healthy eating practices according to Health Canada's Food Guide, and to have a trainer help them with physical activity (resistance and aerobics training) according to the Canadian Society for Exercise Physiology (CSEP) guidelines.

It is important to note that Resting Energy Expenditure (REE), Thermal Effect of Food (TEF), free-living feeding, and free-living physical activity (by accelerometer) were also

measured using indirect calorimetry, but are not focus of this thesis. Also, the data related to out of lab lunch boxes were the focus of another student and as such, it is not reported in this thesis.

3.3 Repeated Measures Test Days

Upon participants meeting the conditions of inclusion and after agreeing to participate in this study, the participant reported to the laboratory for a second time to begin one of 'the three experimental sessions. All participants arrived at the laboratory early in the morning (~7:30) after a 12-hour overnight fast and after having refrained from any vigorous physical activities for at least 48 hours. Participants were then subjected to the following measurements:

7:30: Arrived at the laboratory after an overnight fast. The 150 mm Visual Analog Scale (VAS) measurements to measure appetite was given. Participants were asked questions about their level of physical activity during the last two days to ensure that they did not perform strenuous exercise in the past 48 hours. Those who did not adhere to this condition were rescheduled.

7:40: The vital signs and an assessment of the body composition were measured (blood pressure, heart rate, waist circumference, height, weight, fat mass, fat-free mass, and percent body fat) using the Dual X-ray Absorptiometry (DEXA). Participants were asked to rate their appetite on a 150mm VAS with the assistance of our research staff. They continued to rate their appetite sensations throughout the morning at 60-minute intervals (from 8 am until 1 pm.).

8:00 to 8:30: Participants rested in a bed in silence.

8:30 to 9:00: Resting energy expenditure using indirect calorimetry was measured.

9:05 to 9:20: A standardized breakfast was served (white bread, peanut butter, strawberry jam, and orange juice; 400 Kcals).

9:30 to 12:30: The thermic effect of food (TEF) was measured using indirect calorimetry for 3 hours. In between these measures the participant performed two 10-minute computer tasks, one measuring impulsivity and the other food reinforcement. Only the latter measure was used for this thesis.

12:30 to 13:00 The participant was provided with an ad libitum lunch buffet chosen from the reliable and validated food menu (Appendix G), in which appetite, palatability, and likeliness of food was assessed with VAS before and after lunch (McNeil et al., 2012; Chaput et al., 2016).

End of the experimental session: The above procedures were repeated for the three experimental sessions (baseline, 7-days, 60-days), with the following exceptions: For the Baseline repeated measures session the participants did not have any placebo or MPH prior to eating the standardized breakfast nor the ad libitum lunch, whereas, for the 7-days and for the 60-days final repeated measures the participants took either placebo or their normal dose of MPH. Also, at 60-days repeated measures test day participants were provided with lifestyle counseling for diet and physical activity based on Health Canada's Food Guide and on guidelines by the Canadian Society for Exercise Physiology. At the 7-days and 60-days, repeated measures test days participants returned to the lab with the lunch boxes from which they ate exclusively for the previous 3 days. All foods were weighed to the nearest 0.5g. Finally, on the last day appetite (with VAS), body weight, waist circumference, and body composition (with DEXA) were measured.

3.4 Dose and Screening of MPH Administration

At the initial clinical screening visit, after filling the side effects checklist (Leddy et al., 2004) (see Appendix B), participants were instructed to take the test dose under the supervision

of a registered nurse (supervised for three hours after the administration of the drug) for a dosage of 0.5mg/kg. This screening involved an ECG to monitor cardiovascular responses, with any abnormalities evaluated by the study cardiologists (Dr. Ron Vexler for adults, Dr. Jane Lougheed for children). All, but one participant, showed no abnormalities from this test dose. One participant had a prolonged ST interval in their ECG for which we followed up with another test dose and ECG under the supervision of Dr. Vexler, and the participant did not show any abnormalities. All participants were then titrated to the best-tolerated dose of MPH for 7 days. The dose ranged from 0.25 mg/kg up to a maximum of 100 mg/day for participants. Participants were instructed to rate their side effects nightly for the first two days and inform the study coordinator of any side effects rated as greater than moderate severity. No severe side effects were reported by any of the participants.

3.5 Intervention: MPH, Diet and Exercise Counselling

The double-blind conditions of the MPH/placebo were managed by the CHEO pharmacy team, who have extensive experience conducting blinded studies. The block randomization was conducted by a statistician at the Clinical Research Unit at CHEO, who then informed the CHEO pharmacy. The dose of the administered MPH was changing primarily during the first 7-day of titration based on a well-established titration protocol by the study psychiatrist, and Principal Qualified Investigator, Dr. Philippe Robaey. If required, dosing could have been adjusted during later phases of the study based on the side effects, but this did not occur for any of the participants in this study. Dr. Robaey has over 30 years of conducting randomized, double-and triple-blind studies using MPH, as director of the CHEO ADHD clinic. The coordinator delivered either MPH/placebo to participants in a 30-day supply using a prescriptive label and a

calendar style blister card dispensary system making it clear when and how many tablets should be taken. We chose to administer the medications 1-hour before lunch and dinner. Theoretically, MPH should reduce appetite and food consumption during lunch and dinner, and for approximately four hours after (maximum plasma concentration (C_{max}) of MPH and consequently its maximum effect is reached 1.5 – 2.0 hour after dosing) (Volkow, Wang, & Fowler, 1998). Medication adherence was assessed by CHEO pharmacy by counting the number of pills returned at the laboratory visits and by questionnaires.

Participants in both groups received brief exercise and diet advice at the end of the study. This involved the research staff to meet with clients and inform them of a healthy lifestyle prescription based on Health Canada's Food Guide and guidelines by the Canadian Society for Exercise Physiology.

3.6 Measurements

In this study participants' age and socioeconomic status (SES), as well as anthropometric measurements, food intake, appetite sensations, the relative reinforcing value of food and macronutrient preference were measured as follows:

Demographics: Age was self-reported through the pre-screening questionnaire (See Appendix A). Biological sex was self-reported. Socioeconomic status (SES) was self-reported

Anthropometric Measurements: In each phase of the study, body weight was measured using a SECA scale in the laboratory (Seca GmBH & C. Hamburg Germany). Height was measured by Stadiometer. BMI (kg/m^2) was calculated and BMI percentiles used to determine obesity status ($\geq$95 BMI percentile for age and sex) in youth was determined based on WHO growth curves (www.who.int/growthref). Body composition (percentage of body fat, fat mass,

fat-free mass) was measured using the DEXA method. This measure was taken while the participants wore a hospital gown on an examination table while a low-intensity x-ray scanned the participant's body. The total duration of this test was 10 minutes. The radiation associated with this measure was less than 0.02-0.05 millirem, equivalent to a day of sun exposure.

Energy intake: In each phase of the study food intake was measured during an in lab-ad libitum buffet provided to the participants at lunchtime. The reproducibility of this measurement has been established (McNeil et al., 2012). Briefly, this meal consisted of a variety of foods of differing macro-nutrient compositions such as different bread types and other grain products, fruits, vegetables, cheese, palatable snack foods, juices, and a protein source food (Appendix G). These foods were offered in large amounts, and the participants were instructed to eat as much or as little as they wanted. Participants were informed that they could ask for more of any of the items. If participants asked for more food, it was provided to them in the event of consuming all of the previously provided foods. Participants were given 30 minutes to eat this meal. All foods were weighed to the nearest 0.5 g before and after ingestion. Participants were blinded to this procedure. For the analysis of out lab feeding (free-living food intake), participants selected different food items from a food menu that was packed away into coolers called "lunch boxes" to take home. The food was provided more than needed for the measurement of 3 days of feeding starting once they departed at Baseline visit and ending at the arrival of the 7-days (Baseline 2) test day. Similarly, participants ate exclusively from the Lunch Boxes for the 3 days leading into the Final repeated measures test day. All items and packages were weighed before and after to determine the amount of consumed food during the two 3-day periods using the Food Processor SQL from ESHA Research, Inc., Salem, Oregon. Energy and macronutrient content (in kcals;

carbs, fats, and protein) were assessed with the use of Food Processor SQL from ESHA Research Inc. Energy intake was assessed for this project at baseline and 60-days.

Appetite Sensations: Appetite ratings, hunger, satiety and the projection of food consumptions were self-reported by using 150mm visual analogue scales (VAS) which was validated by Flint et al. (2000). VAS was conducted before and after every meal and every 2 hours during the period in which participants were measured for energy metabolism. Appetite sensations were assessed for this project at baseline and 60-days.

The reinforcing value of food: The relative reinforcing value (RRV) of food is measured as how hard the participant is willing to work to receive snacks high in fat and carbohydrate content compared to fruits and vegetable. This task was carried out using a computer to determine how much work an individual is willing to do in order to obtain foods high in fat and carbohydrate contents compared to fruits and vegetables. Participants were asked to press a button on a keyboard in order to choose between earning points for a preferred palatable snack food (cookies, chocolate, and potato chips) and a preferred healthy alternative (fruit, vegetable). This procedure is well validated as a behavioural choice measure of food reinforcement in children and adults with obesity (Epstein, Lin, Carr, & Fletcher, 2012; Cameron, 2013; Goldfield, Eptein, Davidson, & Saad, 2005). The reinforcing value of food was assessed for this project at baseline and 60-days.

Treatment completion questionnaire: Participants were asked to identify the substance which they received at each measurement session (MPH or placebo). They rated how much they liked (or disliked) its effects by using the CHEO REDCap[10] program. Also, the side effects of taking MPH were measured using a checklist (Appendix B).

3.7 Data Analysis

Baseline characteristics (age, sex, anthropometrics, food reinforcement, and appetite) of each group were summarized and examined by descriptive statistics and independent t-tests. To test the main objectives of whether MPH leads to greater reductions than placebo in energy intake (objective 1), macronutrient consumption (objective 2) and the reinforcing value of food (Objective 3), two-way mixed Analysis of variance (ANOVA) were conducted whereby group (MPH vs placebo) represented the between-subjects' independent variable, and time (baseline and 60-days) represented the within-subjects independent factor. If groups differed at baseline on demographic, anthropometric, eating-related or other potentially confounding variables, they would have been statistically controlled using analysis of Covariance (ANCOVA). All ANOVA analyses are reported with effect sizes based on eta^2 to aid interpretation of findings given the small sample size. The effect size interpretation is demonstrated in Table 2.

Table 2: Effect Size

Effect Size	Small	Medium	Large
Eta^2	0.01	0.06	0.14

[10] CHEO REDCap: Participants used this program to report any side effects to the study coordinator.

Pearson correlations on change scores in food reinforcement and energy intake were conducted within each group to provide insight on whether the effects of MPH on energy intake were associated with reductions in food reinforcement. Ideally, this would have been examined with a mediation analysis but given the small sample size of the current pilot study, this procedure would have lacked the statistical power to yield meaningful results.

The distribution of each outcome variable was examined to ensure they met the assumptions required for ANOVA analyses. Examination of descriptive statistics, skewness, and kurtosis and frequency distributions, along with box plots revealed that there were no outliers in the data. The data were normally distributed as assessed by Shapiro-Wilk's test of normality ($p > 0.05$). There was a homogeneity of variances as assessed by Leven's test of homogeneity of variances ($p > 0.05$) for all outcomes. There was a homogeneity of covariance ($p > 0.05$) as assessed by Box's M test. Mauchly's test of sphericity indicated that the assumption of sphericity was violated for the repeated measure ANOVA ($p=0$; P, 0.05) for weight, in-lab energy intake, food reinforcement, and appetite. Therefore, Greenhouse-Geiser test was considered to be more appropriate given these violations in distributions for weight, in-lab energy intake, food reinforcement, and appetite variables.

3.8 Safety Protocol

It is noteworthy to mention that the administration of MPH may cause several adverse effects such as anorexia, insomnia, and headaches (McGough et al., 2006); however, most of them can be treated by titrating the dosage and the time of MPH administration (Greenhill et al., 2002) since the individual's responses to MPH administration is variable (Shader et al., 1999). These risks of side effects were mitigated by following a standard titration protocol that

administer at low dosage at the beginning (10-15 mg/day) and gradually increase the dosage up to 0.5mg/kg or the closest tolerated dose up to a maximum of 100 mg/day as per the National Institutes for Health and Care Excellence (NICE) guidelines (https://www.nice.org.uk/guidance/CG72). Side effects were monitored daily for the first two weeks using REDCap whereby the research Coordinator reviewed each participant's side effects profile.

4.0 Results

4.1 Participants Characteristics at Baseline

Baseline characteristics of the subjects are reported in Table 3. Groups did not differ significantly on sociodemographic or anthropometric variables as shown in Table 3. Figure 2 displays the recruitment and flow of participants through the trial, consistent with CONSORT guidelines.

Table 3: Participants' Age, Height (cm), Sex, and Education Level

Variables	MPH (n= 5)	Placebo (n=6)	p-value
Age in years (SD)	28.6 (6.7)	28.8 (7.8)	0.959
Age Range < 18 18 – 19 20 – 40 > 40	 0 0 5 0	 0 1 5 0	N/A
Height in cm (SD)	168.7 (11.6)	168.91 (10.3)	0.975
Weight in kg (SD)	102.4 (25.5)	104.6 (23.9)	0.884
Sex Males (%) Females (%)	 2 (40) 3 (60)	 2 (33.33) 4 (66.67)	0.819
Education High School or Less (%) College/University (%) Unknown (%)	 1 (20) 4 (80) 0 (0)	 1 (16.67) 4 (66.66) 1 (16.67)	1.00

CONSORT
TRANSPARENT REPORTING of TRIALS

CONSORT 2010 Flow Diagram

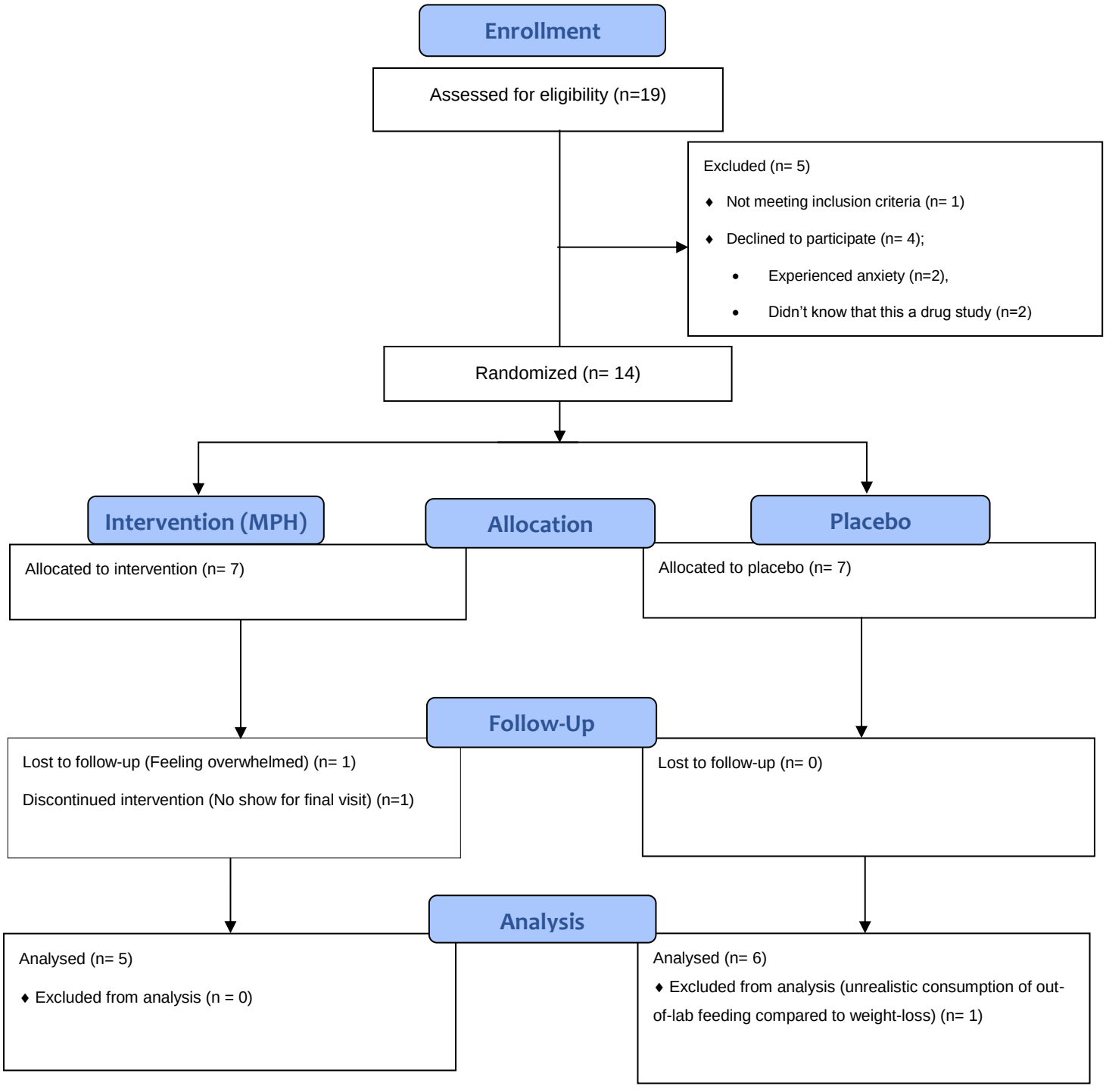

Figure 2: Consort Flow Diagram for Study Population

4.2 Feasibility Indicators: Tolerability, Side Effects, Adherence and Attrition

Upon examining REDCAP online system data regarding MPH side effects and potential titration and/or discontinuation, no side effects requiring titration were observed by the study physician. Table 4 represents the number of participants who displayed the specific side effect for at least one day. The highest degree of severity is considered for each side effect. For example, if a subject displayed mild nausea for Day 2 and moderate nausea for Day 3, the moderate side effect is reported. All participants returned their blister packs empty, suggesting that subjects were 100% compliant with taking their medications. The rates of loss to follow-up for MPH and placebo did not differ significantly (MPH = 2/7, Placebo = 1/7), with chi-square = 0.42, $p = 0.51$, $p < 0.51$.

Table 4: Side Effects Reported by Participants

	MPH None | Mild | Moderate | Severe	**Placebo** None | Mild | Moderate | Severe	Percent of MPH with moderate side effects
Insomnia/Disordered Sleeping	2 | 2 | 1 | 0	4 | 2 | 0 | 0	20%
Nausea	2 | 2 | 1 | 0	5 | 1 | 0 | 0	20%
Headache	4 | 1 | 0 | 0	3 | 3 | 0 | 0	0%
Anxiety	5 | 0 | 0 | 0	5 | 1 | 0 | 0	0%
Palpitations	2 | 3 | 0 | 0	6 | 0 | 0 | 0	0%
Drowsiness/Sedation	5 | 0 | 0 | 0	5 | 1 | 0 | 0	0%
Abdominal Pain/ Cramps	4 | 1 | 0 | 0	5 | 1 | 0 | 0	0%
Irritability	5 | 0 | 0 | 0	4 | 2 | 0 | 0	0%
Confusion/Disorientation	4 | 1 | 0 | 0	5 | 1 | 0 | 0	0%
Sweating	3 | 2 | 0 | 0	6 | 0 | 0 | 0	0%
Flushing	5 | 0 | 0 | 0	6 | 0 | 0 | 0	0%
Dryness of Mouth	3 | 1 | 1 | 0	4 | 2 | 0 | 0	20%
Blurred Vision	5 | 0 | 0 | 0	6 | 0 | 0 | 0	0%
Motor Tics	5 | 0 | 0 | 0	6 | 0 | 0 | 0	0%
Nervousness	4 | 1 | 0 | 0	5 | 1 | 0 | 0	0%
Restlessness	3 | 2 | 0 | 0	3 | 3 | 0 | 0	0%
Skin Rash	5 | 0 | 0 | 0	5 | 1 | 0 | 0	0%
Excessive Sweating	5 | 0 | 0 | 0	4 | 2 | 0 | 0	0%
Depression/Moodiness	5 | 0 | 0 | 0	4 | 2 | 0 | 0	0%
Sore Throat/Runny Nose	5 | 0 | 0 | 0	4 | 2 | 0 | 0	0%
Other	5 | 0 | 0 | 0	6 | 0 | 0 | 0	0%

As it can be observed, the reported side effects did not differ significantly between placebo and the MPH groups. Only 20% of the participants in the MPH group reported moderate insomnia, nausea, and dryness of mouth, and none reported severe side effects.

In the following section, the ANOVA analysis for various measurements is demonstrated in details.

4.3 Chronic Effect (60 days) of MPH on Participants Characteristics

Table 5 demonstrates participant's body weight (kg), BMI (kg/m^2), body fat percentage (%), fat mass (kg), and fat-free mass (kg), at baseline.

Table 5: Participants Anthropometric Characteristics at Baseline

Variables	MPH (n= 5) Mean (SD)	Placebo (n=6) Mean (SD)	P- value
Weight (Kg)	102.4 (25.5)	104.6 (23.91)	0.884
BMI (Kg/m^2)	35.62 (5.75)	36.21 (4.13)	0.846
Body Fat (%)	46.28 (2.78)	48.16 (3.46)	0.353
Fat Mass (Kg)	45.48 (10.17)	48.49 (13.51)	0.692
Fat-Free Mass (Kg)	53.43 (15.85)	51.57 (11.24)	0.825

As shown, groups did not differ significantly on these variables at baseline. Table 6 demonstrates participants' anthropometric characteristics at 60-days.

Table 6: Participants Anthropometric Characteristics at 60-days

Variables	MPH (n= 5) Mean (SD)	Placebo (n= 6) Mean (SD)	P- value
Weight (Kg)	99.7 (26.86)	103.43 (22.98)	0.809
BMI (Kg/m^2)	34.67 (6.28)	35.85 (3.91)	0.712
Body Fat (%)	45.26 (2.90)	48.51 (4.96)	0.230
Fat Mass (Kg)	43.25 (11.02)	48.79 (15.20)	0.515
Fat-Free Mass (Kg)	52.89 (16.58)	50.61 (8.24)	0.773

Table 7 demonstrates the chronic effect of MPH and placebo on changes in participants' anthropometric measurements.

Table 7: Change in Participants Anthropometric Characteristics from Baseline to 60-days

Variables	MPH (n= 5) Mean (SD)	Placebo (n= 6) Mean (SD)	p-value	Eta^2	Effect size
Weight (Kg)	- 2.66 (1.99)	- 1.16(1.94)	0.241	0.149	Large
BMI (Kg/m^2)	- 0.946 (0.709)	- 0.365 (0.69)	0.203	0.173	Large
Body Fat (%)	- 1.02 (1.81)	0.35 (2.07)	0.278	0.129	Moderate
Fat Mass (Kg)	- 2.23 (2.36)	0.30 (2.25)	0.103	0.268	Large
Fat-Free Mass (Kg)	- 0.5420 (0.99)	- 0.96 (3.20)	0.785	0.009	Insignificant

There was a reduction of 2.66 ± 1.99 kg in body weight, a reduction of 2.23 ± 2.36 kg in body fat, and a reduction of 1.02 ±1.81 % in the body fat percentage observed for the MPH group, while there was only a reduction of 1.61 ± 1.94 kg in body weight, an increase of 0.30 ± 2.25 kg of fat mass, and an increase of 0.35 ± 2.07 % in body fat percentage of the placebo group. As per the effect size of the eta^2 (Table 2), a large effect on various measures of body composition was observed in the hypothesized direction. Also, no significant effect was observed for changes in fat-free mass of the MPH group when compared to placebo.

ANOVA revealed no statically significant interaction between MPH group and time on body weight F (1, 9) = 1.57, p = 0.24, partial η2 = 0.15, but a trend favouring greater reduction from MPH. The main effect of time showed a statistically significant difference in body weight F (1, 9) = 10.33, p = 0.01, partial η2 = 0.53, indicating both groups lost weight. The main effect of group showed no statistically significant difference in body weight F (1, 9) = 0.04 p = 0.85, partial η2 = 0.00. Figure 3 illustrates the drop in weight of MPH group compared to placebo.

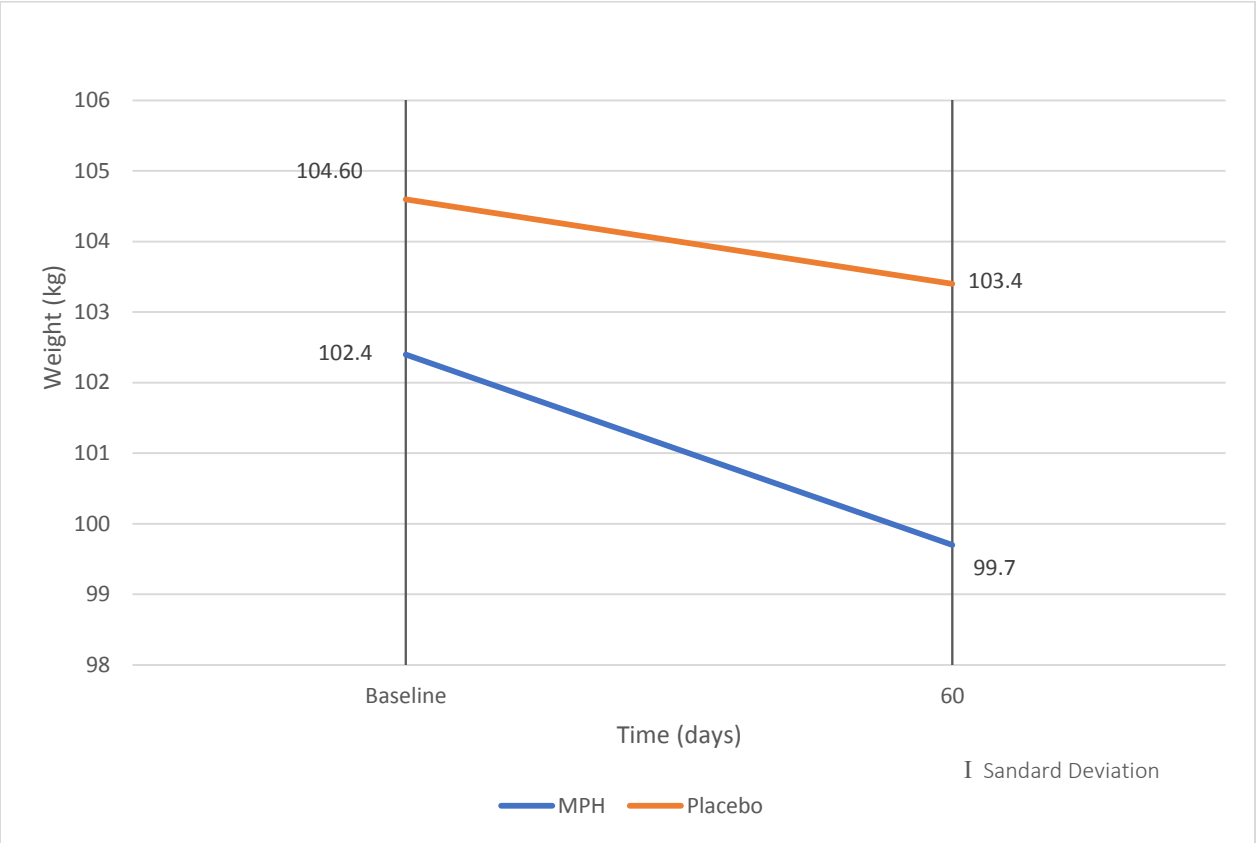

Figure 3: Effect of MPH on body weight from Baseline to 60 days

It was predicted that MPH consumption would lead to greater reductions in the appetite sensations compared to placebo. In the next section, the obtained result on appetite sensations is presented

4.4 Chronic Effect (60 days) of MPH on Appetite

Appetite: Desire to Eat. Fig Figure 4 illustrates the mean change in desire to eat from baseline to 60 days.

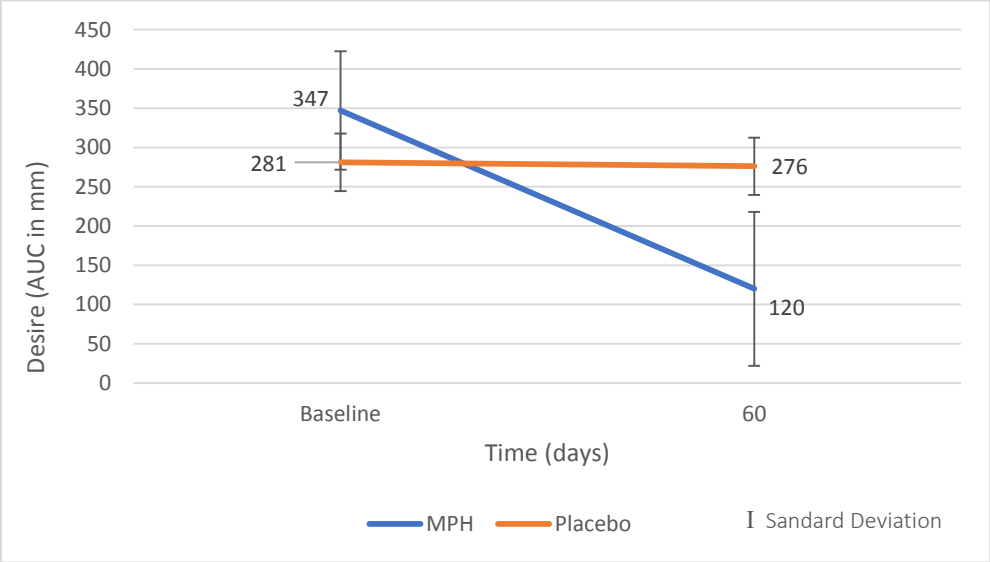

Figure 4: Effect of MPH on desire to eat between baseline and 60 days

ANOVA analysis revealed a statically significant interaction between the MPH group and time on desire (appetite), F(1, 9) = 22.65, p = 0.01, partial $\eta 2$ = 0.716. The reduction of desire to eat was statistically significantly greater in the MPH group (M=-227, SD= 103, p= 0.0001) compared to placebo (M=-5, SD= 47, p= 0.890). The main effect of time showed a statistically significant difference in desire to eat F(1, 9) = 24.51 p = 0.00, partial η2 = 0.73, driven primarily by the MPH group as no changes were observed for placebo. The main effect of group showed no statistically significant difference in desire to eat F(1, 9) = 2.11 p = 0.18, partial $\eta 2$ = 0.19.

Appetite: Hunger. Figure 5 illustrates the mean change in hunger from baseline to 60 days.

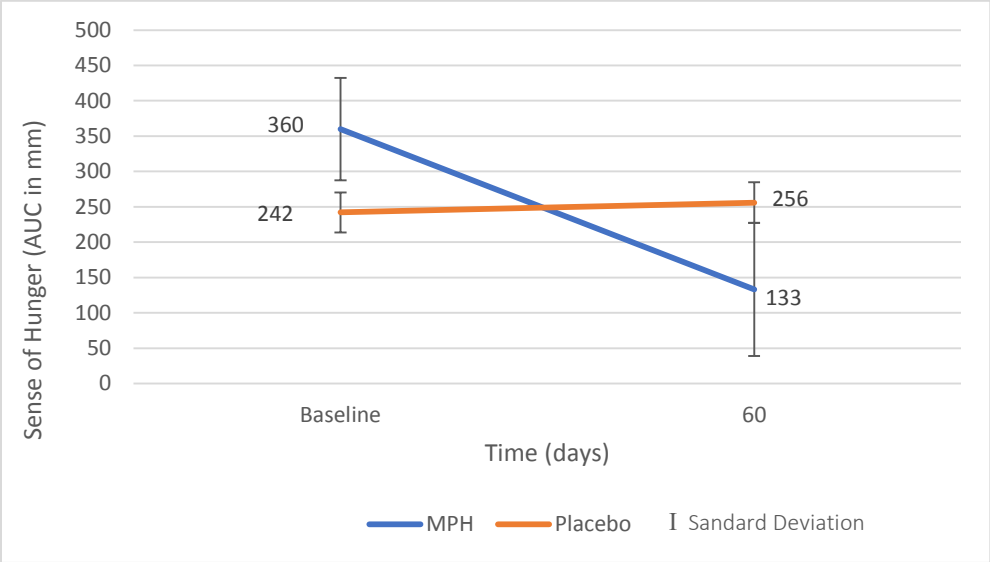

Figure 5: Result of MPH on Hunger between baseline and 60 days

ANOVA analysis revealed a statically significant interaction between the MPH group and time on hunger of appetite $F(1, 9) = 17.27$, $p < 0.002$, partial $\eta 2 = 0.657$. The reduction of hunger sensations was statistically significantly greater in the MPH group (M=-227, SD= 129, p= 0.000) compared to placebo (M=16, SD= 54, p= 0.747). The main effect of time showed a statistically significant difference in hunger $F(1, 9) = 13.73$ $p = 0.01$, partial $\eta 2 = 0.60$, primarily driven by the reduction in the MPH group. The main effect of group showed no statistically significant difference in hunger $F(1, 9) = 0.01$ $p = 0.91$, partial $\eta 2 = 0.00$.

Appetite: Fullness. Figure 6 illustrates the mean change in fullness from baseline to 60 days.

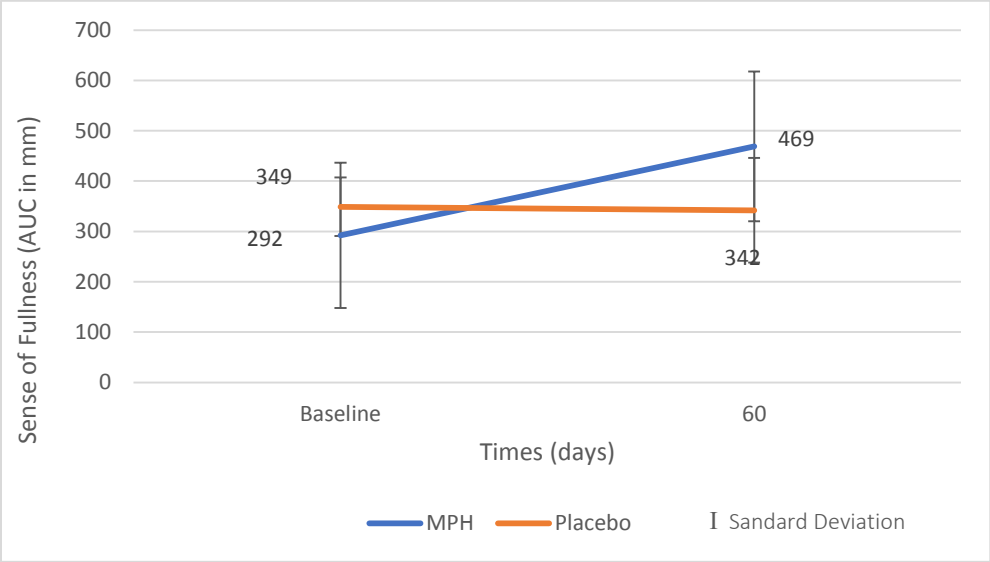

Figure 6: Effect of MPH on sense of fullness between baseline and 60 days

There was a statically significant interaction between the MPH group and time on the sense of fullness F (1, 9) = 10.48, p = 0.01, partial $\eta 2$ = 0.538. The increase was significantly greater in the MPH group (M=177, SD= 117, p= 0.002) compared to placebo (M=-7, SD= 69, p= 0.868). The main effect of time showed a statistically significant difference in the sense of fullness F(1, 9) = 9.04 p = 0.01, partial η2 = 0.50, primarily driven by the increase in from the MPH group. The main effect of group showed no statistically significant difference in the sense of fullness F(1, 9) = 2.75 p = 0.61, partial $\eta 2$ = 0.03.

Appetite: Prospective amount of food consumed (PFC). Figure 7 illustrates the mean change in PFC from baseline to 60 days.

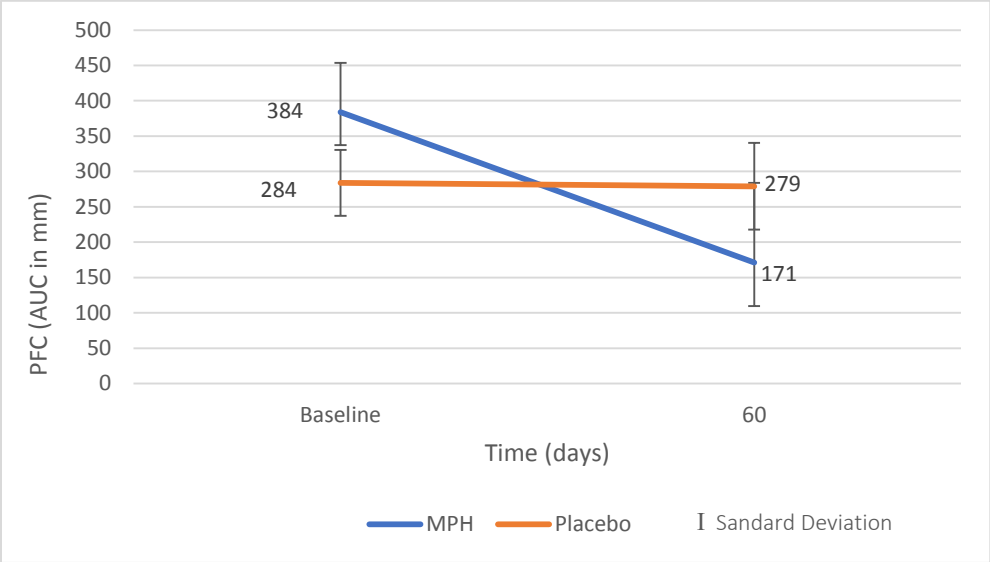

Figure 7: Effect of MPH on PFC between baseline and 60 days

There was a statically significant interaction between the MPH group and time on the prospective food consumed. F(1, 9) = 12.75, p = 0.006, partial $\eta 2$ = 0.586. The reduction was statistically significantly greater in the MPH group (M=-213, SD= 142, p= 0.001) compared to placebo (M=-5, SD= 25, p= 0.905). Figure 7 illustrates the reduction in the prospective food consumed (PFC) between Placebo and the MPH groups from Baseline to 60-days. The main effect of time showed a statistically significant difference in the prospective food consumed (PFC) F(1, 9) = 13.95 p = 0.01, partial η2 = 0.61, primarily driven by the reduction in MPH. The main effect of group showed no statistically significant difference in the prospective food consumed (PFC) F(1, 9) = 0.01 p = 0.91, partial $\eta 2$ = 0.00.

It was predicted that MPH would lead to greater reductions in energy intake, high-carbohydrate, and high-fat foods when compared to placebo in the laboratory ad-libitum buffet

condition. It was also predicted that MPH would not produce greater changes in protein intake compared to placebo. The data on energy intake and macronutrient consumption is presented in the next section.

4.5 Chronic Effect of MPH on Energy Intake and Macronutrient Consumption

Table 8 demonstrates total energy intake (TEI), energy from carbohydrates, protein, and fat, as well as grams of sugar consumed measured by in-lab feeding at baseline.

Table 8: Total Energy Intake (TEI), Energy from Carbohydrates, Protein, and Fat, and Amount of Sugar Consumed as Measured by In-lab Feeding at Baseline

Variable	MPH (n= 5) Mean (SD)	Placebo (n=6) Mean (SD)	P-value
TEI (kcal)	1588 (546)	1558 (562)	0.931
Energy from Carbohydrates (kcal)	896 (218)	918 (365)	0.920
Energy from Protein (kcal)	228 (119)	194 (85)	0.612
Energy from Fat (kcal)	485 (235)	503 (176)	0.899
Sugar (g)	102(25)	120 (49)	0.473

Table 9 demonstrate total energy intake (TEI), energy from carbohydrates, protein, and fat, as well as grams of sugar consumed measured by in-lab feeding at 60 days.

Table 9: Total Energy Intake (TEI), Energy from Carbohydrates, Protein, and Fat, and Amount of Sugar Consumed as Measured by In-lab Feeding at 60-days

Variable	MPH (n= 5) Mean (SD)	Placebo (n=6) Mean (SD)	P-value
TEI (kcal)	1347 (456)	1424 (400)	0.772
Energy from Carbohydrates (kcal)	777 (204)	834 (171)	0.625
Energy from Protein (kcal)	150 (47)	191 (50)	0.202
Energy from Fat (kcal)	454 (245)	468 (197)	0.921
Sugar (g)	92 (20)	114 (32)	0.215

Table 10 demonstrates the chronic effect of MPH on TEI, calories from carbohydrates, protein calories, fat calories, and sugar as measured by in-lab feeding.

Table 10: The Chronic (Baseline to 60 days) Effect of MPH on Total Energy Intake (TEI), Energy from Carbohydrates, Protein, and Fat, and Amount of Sugar Consumed as Measured by In-lab Feeding

Variable	MPH (n= 5) Mean Change	Placebo (n=6) Mean change	MPH % Drop	Placebo % Drop	P-value	Eta^2	Effect size
TEI (kcal)	- 241 (254)	-134 (259)	-15.1	- 8.6	0.510	0.05	Moderate
Energy from Carbohydrates (kcal)	-119 (57)	-84 (229)	-13.6	-9.1	0.723	0.015	Small
Energy from Protein (kcal)	-78 (82)	-3 (60)	-34.2	-1.9	0.117	0.250	Large
Energy from Fat (kcal)	-31 (179)	- 35 (31)	-6.5	-6.8	0.973	0.000	Insignificant
Sugar (g)	-10 (24)	-6 (289)	-10.0	-5.4	0.826	0.006	Insignificant

For the in-lab feeding data, there was a 15.1 % decrease in total energy intake from Baseline to 60-days in MPH group compared to 8.6 % decrease in total energy intake from placebo. There was a decrease in total calories from carbohydrates of MPH group (13.6 %) and placebo group (9.1 %) from baseline to final visit. There was a decrease in the total protein calories of MPH group (34.2%) and a small decrease in the placebo group (1.9 %) from Baseline to 60-days. There was a non-significant decrease in the total fat calories of MPH group (6.5%) and the placebo group (6.8 %) from Baseline to 60-days. There was a small decrease in the total amount of sugar consumed in MPH group (10.1 %) and the placebo group (5.4 %) from Baseline to 60-days.

ANOVA revealed no statically significant interaction between MPH group and time on total energy intake measured by in-lab feeding $F(1, 9) = 0.471$, $p = 0.51$, partial $\eta 2 = 0.05$. The main effect of time showed a statistically significant difference in total energy intake measured by in-lab feeding $F(1, 9) = 5.80$, $p = 0.04$, partial $\eta 2 = 0.39$, indicating both groups reduced intake.

ANOVA revealed no statically significant interaction between MPH group and time on carbs consumption measured by in-lab feeding $F(1, 9) = 0.134$, $p = 0.723$, partial $\eta 2 = 0.02$. The main

effect of time showed no statistically significant difference in carbs consumption measured by in-lab feeding F(1, 9) = 3.79, p = 0.08, partial η2 = 0.29. The main effect of group showed no statistically significant difference in carbs consumption measured by in-lab feeling F(1, 9) = 0.07 p = 0.80, partial η2 = 0.00.

ANOVA revealed no statically significant interaction between MPH group and time on fat consumption measured by in-lab feeding F(1, 9) = 0.001, p = 0.973, partial η2 = 0.00. The main effect of time showed no statistically significant difference in fat consumption measured by in-lab feeding F(1, 9) = 0.66, p = 0.44, partial η2 = 0.08. The main effect of group showed no statistically significant difference in fat consumption measured by in-lab feeling F(1, 9) = 0.01 p = 0.91, partial η2 = 0.00.

ANOVA revealed no statically significant interaction between MPH group and time on protein consumption measured by in-lab feeding F(1, 9) = 3.00, p = 0.12, partial η2 = 0.250. The main effect of time showed no statistically significant difference in protein consumption measured by in-lab feeding F(1, 9) = 3.62, p = 0.09, partial η2 = 0.29. The main effect of group showed no statistically significant difference in protein consumption measured by in-lab feeling F(1, 9) = 0.01 p = 0.94, partial η2 = 0.00.

It was predicted that MPH consumption would lead to greater reductions in the reinforcing value of palatable snack foods compared to placebo. The data on the relative reinforcing value of food is presented in the next section.

4.6 Chronic Effect (60 days) of MPH on food reinforcement

Table 10 demonstrates the snack points earned at baseline, 60 days, and the change from baseline to 60 days.

Table 11: The Mean Snack Points at Baseline, 60-days, and the Change in Snack Points from Baseline to 60-days

Variable	MPH (n= 5) Mean (SD)	Placebo (n=6) Mean (SD)	P-value	Eta^2	Effect size
Snack Point (Baseline) (g)	18 (6)	21 (6)	0.462		
Snack Point (60 days) (g)	13 (13)	15 (12)	0.852		
Change in Snack Point (g) %	- 5 (10) -27	- 6 (8) - 30	0.800	0.007	Insignificant

ANOVA revealed no statically significant interaction between MPH group and time on food reinforcement (snack points) Wilks' Lambda = 0.993, F (1, 9) = 0.07, p = 0.800, partial η2 = 0.00. The main effect of time showed a non-significant trend for a reduction in both groups of food reinforcement (snack points) F(1, 9) = 3.97, p = 0.08, partial η2 = 0.31. The main effect of group showed no statistically significant difference in food reinforcement (snack points) F(1, 9) = 0.17 p = 0.69, partial η2 = 0.02

Table 11 demonstrates the snack responses at baseline, 60 days and the change from baseline to 60 days.

Table 12: The Mean Snack Responses at Baseline, 60-days, and the Change in Snack Responses from Baseline to 60-days

Variable	MPH (n= 5) Mean (SD)	Placebo (n=6) Mean (SD)	P-value	Eta^2	Effect size
Snack Response (Baseline)	939 (553)	1145 (330)	0.51		
Snack Response (60 days)	519 (595)	641 (593)	0.74		
Change in Snack Response (g)	-420 (366)	-504 (423)	0.18	0.24	Large

ANOVA revealed a non-significant interaction between MPH group and time on snack response F (1, 7) = 2.19, p= 0.18, partial η2 = 0.24. The main effect of time indicated there was a significant reduction in in snack responses collapsed across groups F(1, 7) = 13.32, p = 0.01,

partial η2 = 0.66. The main effect of group showed no statistically significant difference in snack response F(1, 7) = 0.00 p = 0.98, partial η2 = 0.00.

4.7 Pearson Correlation on Participants' Anthropometric Characteristics

Correlation between body weight and body fat percentage. There was a strong significant positive correlation between loss in body weight and loss in fat mass (r = 0.93, p = 0.02) in MPH group whereas there was no significant correlation between loss in body weight and loss in BF % (r = 0.30, p = 0.56) for the placebo group, meaning that in the MPH group the weight-loss was from body fat.

4.8 Pearson Correlation on Relative Food Reinforcement

Correlation between relative food reinforcement and energy intake. There was a moderate but not statistically significant negative correlation between relative reinforcing value of food (snack food points) and in-lab energy intake (r = -0.58, p = 0.31) in MPH group compared to no relationship observed for placebo (r = -0.00, p = 0.99).

Correlation between relative food reinforcement and carbohydrate intake. There were small, and insignificant correlations, between in-lab dietary carbohydrate intake and the relative reinforcing value of food of snack foods in MPH group (r = 0.10, p = 0.87) compared to placebo (r = -0.12, p = 0.82).

Correlation between relative food reinforcement and fat intake. There was no significant correlation between snack food points and in-lab dietary fat intake in MPH group (r = -0.62, p = 0.26) or placebo (r = 0.64, p = 0.24).

Correlation between relative food reinforcement and protein intake. There was a moderate sized, but not significant, correlation between snack food points and the total in-lab

dietary protein intake in MPH group (r = 0.49, p = 0.41) and a weaker relationship observed for placebo (r = -0.16, p = 0.98).

Correlation between relative food reinforcement and body fat. There was moderate sized, but not significant, correlation between change in snack food points and body fat percentage in MPH group (r = 0.59, p = 0.29) compared to a small-correlation for placebo (r = 0.29, p = 0.56). There were moderate sized, but not significant, correlations between change in snack food points and change in fat mass in MPH group (r = 0.51, p= 0.39) compared to small correlations observed for placebo (r= 0.20, p=0.70)

4.9 Acute Effect of MPH

The acute effect of MPH on weight-loss, total *ad libitum* EI, macronutrient consumption, food reinforcement and appetite from baseline to 7 days is analyzed and reported in Appendix I. The aforementioned results are not part of the objectives of this thesis, but may be of interest to the reader.

5.0 Discussion

The purpose of this pilot study was to preliminarily examine the effect of MPH on energy intake, food reinforcement, macronutrient consumption, and body composition in individuals with obesity without ADHD. More specifically, the following questions were asked: 1. Compared to the placebo, does MPH lead to greater reductions in appetite sensations and food intake during a laboratory *ad libitum* buffet meal from baseline to 60-days? 2) Compared to placebo, does MPH have an impact on macronutrient consumption during a laboratory *ad libitum* buffet meal from baseline to 60-days? 3) Does MPH reduce the reinforcing value of food compared to placebo during the laboratory *ad libitum* meal from baseline to 60-days, and are these changes associated with reductions in energy intake and macronutrient consumption?

To our knowledge, our data are the first to show that administration of short-acting MPH leads to greater reductions in appetite sensations in adults with obesity without ADHD in the short term. More specifically, all four measures of appetite, namely the desire to eat, hunger, fullness, and prospective food consumption (PFC), showed significantly more favourable changes from MPH administration than placebo. In comparison, Leddy et al. (2004) reported similar findings when investigating the effect of a single dose of MPH (short-acting dose of 0.5 mg/kg) on 9 adult males with obesity 1 hour after a pizza buffet meal. Leddy et al. (2004) also found no significant difference between 0.5 mg/kg and 1.0 mg/kg dose of short-acting MPH on appetite suppression, indicating that higher doses do not necessarily lead to greater appetite suppression. In a lab study, Gurbuz et al. (2016) found a similar trend in the suppression of appetite in 48 ADHD male subjects and 41 healthy subjects between the ages of 7-14. In a controlled laboratory study, Davis et al. (2012) reported similar findings for the suppression of

appetite as the result of short-acting MPH administration in normal-weight females and females with obesity (BMI > 30), but not males. Goldfield et al. (2011) found similar findings in males but not females. Our findings were able to show a similar effect of MPH on the suppression of appetite over a longer period of time (60-days compared to a single dose) and across both genders with a population of young adults living with obesity. But the current study lacked sufficient power to evaluate gender differences. Our findings that MPH induced a suppression of subjectively-rated appetite sensations has clinical relevance in that many studies have shown relations between appetite with food intake. More specifically, in a report investigating the relationship between appetite and energy intake using 23 randomized controlled studies involving 549 subjects, Sadoul et al. (2014) concluded that changes in VAS scores of above 15 mm are associated with consistent and significant changes in energy intake, essential for any weight-loss program. Moreover, the suppression of appetite enhances weight-loss maintenance and adherence to weight-loss programs (Sadoul et al., 2014; Franz et al., 2007).

Our findings show an average weight loss of 2.66 kg in the MPH group compared to placebo (1.16 kg) from baseline to 60-days. This represents a weight loss of 1.5 kg above placebo within 60-days. Although not statistically significant, these findings reflect a large effect size measured by Eta^2 favouring the MPH group.

Because MPH increases brain's dopamine availability by inhibiting its reuptake within the mesolimbic pathway of the brain (Kuczenski & Segal, 2001; Berridge, 1996) and dopamine mediates appetitive behavior such as eating (Berridge, 1996; Berridge & Robinson, 1998), we hypothesised that MPH would lead to greater reductions in energy intake, high-carbohydrate, and high-fat foods when compared to placebo in a laboratory ad-libitum buffet condition. Our

findings showed trends toward a greater reduction in the in-lab energy intake in MPH group with an average reduction of 240.49 kcal (15.2% from baseline) when compared to the placebo group with an average reduction of 133.81 kcal (8.6% from baseline). Although not statistically significant, the effect size using Eta^2 indicate a moderate-size effect in the reduction of the energy intake as the result of taking MPH. While these findings were in the direction of the hypothesis, a larger effect of MPH on energy intake was reported after a single dose of MPH consumption in other studies. For example, Leddy et al. (2004) showed a 23% energy intake reduction during a buffet pizza meal in 9 males with obesity as a result of taking a single dose of short-acting MPH (0.5 mg/kg). However, more in line with our study, Danilovich et al. (2014) found a 17% reduction in the energy intake of 23 teenagers with obesity after a single MPH dose (0.3 mg/kg) during an ad libitum breakfast buffet meal. Interestingly, Goldfield et al. (2007) found a significant 11% reduction in the energy intake over the course of an ad libitum buffet lunch in 14 normal-weight adults (BMI > 20) in MPH group using short-acting MPH dose of 0.5 mg/kg, which is a weaker effect on EI than the current study's findings. It must be noted that compared to these studies, our study considered the effect of MPH over a longer period of time (60 days) rather than a single visit to the laboratory. Taken together, findings suggest that the effect of short-acting MPH on energy intake reduction appear to be clinically meaningful and may represent a primary mechanism in which MPH may promote weight loss. However, effects may vary over time, and this issue needs to be addressed experimentally given the heterogeneity of sample characteristics and methodology across existing studies.

Additionally, our findings did not show any significant effect of MPH on macronutrient consumption in the direction of the hypothesis. More specifically, the reduction in dietary fat and

carbohydrate intake for both MPH and placebo groups from Baseline to 60-days were similar. While we observed a significant 13.6% drop in the carbohydrate intake and a moderate 6.5% drop in the fat intake in the MPH group, we also observed a comparable 9.1% drop in the carbohydrate intake and a 6.8% drop in the dietary fat intake of the placebo group in our study. The significant change observed in the placebo group offsets any significant observation in the effect of MPH. It is not exactly clear why the placebo group had such a significant drop in their total calorie intake (including carbohydrate and dietary fat intake), but one possible speculation could suggest that some participants in the placebo group started a diet, putting them in negative energy balance by consciously ingesting lower calorie foods in light of participating in a weight management study. Given the small sample size, this can produce a significant effect on the data. Moreover, the MPH group showed a significantly larger reduction in the protein intake compared to the placebo group. This is contrary to the effect of a single dose of short-acting MPH observed by Danilovich et al. (2014). In that single-blind placebo-control study, they found that a single dose of short-acting MPH (0.3 mg/kg) reduced the energy intake from dietary fat by 18% and from carbohydrate by 21% when compared to placebo during an ad libitum breakfast buffet meal in 15 females and 7 males with obesity. Another randomized double-blind placebo-control crossover study by Goldfield et al. (2007) found that administration of a single dose of short-acting MPH (0.5 mg/kg) led to a selective reduction of high-fat foods by 17% during an ad

libitum buffet lunch (however with different buffet items[11] compared to our study). However, these studies measured the effect of a single dose of MPH while our study looked at the effect of short-acting MPH during 60-days. The contrast between our findings and the reviewed studies could suggest that the effect of MPH on macronutrient consumption may diminish with time, but this requires further investigation using well controlled trials.

Because MPH increases brain's dopamine availability (Kuczenski & Segal, 2001; Berridge, 1996), dopamine mediates the reinforcing value of appetitive behavior (Berridge, 1996; Berridge & Robinson, 1998), and because studies showed stronger rewarding value for snack foods with high-fat and high-carbohydrates content (Rada, Avena, and Hoebel, 2005), we hypothesized that MPH would lead to greater reductions in the relative reinforcing value of palatable snack foods compared to placebo. This hypothesis was not supported as we found a comparable reduction (27.47% for MPH group and 30.00% for the placebo group) between groups in the relative value of food with high fat and high carbohydrate content relative to fruits and vegetables. We also did not find any correlations between the reinforcing value of food and macronutrient consumption, or between the reinforcing value of food and the energy intake. This null finding could again be partially due to a very large and unexpected reduction in the reinforcing value of food in the placebo group, which was not typical of past research (Goldfield

[11] In the study of Goldfiet et al. (2007) the ad libitum buffet meal items were standardized by Arvantini, Richard, and Tremblay (2000).

et al. 2007). One explanation is that participants in the placebo group enrolled in the study because they wanted to lose weight, thus were consciously trying to reduce access and motivation to eat palatable foods in order to promote weight loss. This desire to lose weight would likely results in working less for access to palatable food and a greater desire to work for access for fruits/vegetables, regardless of being assigned to placebo. It is also possible that given the context of a weight loss study, participants engaged in social desirability responding. In contrast, the study by Goldfield et al. (2007) showed a trend, however not statistically significant, indicating that a single dose of short-acting MPH (0.5 mg/kg) reduced the relative reinforcing value of food with high fat and high carbohydrate content by 29% in normal-weight adults, with a concomitant reduction in energy intake. No other studies have examined the acute or chronic effects of MPH on food reinforcement, an area that needs further inquiry as a possible mechanism in which MPH may promote reduced energy intake and weight loss.

MPH and Other Weight-loss Medications

Our findings showed that in-line with previous studies, MPH is very well tolerated. None of the participants in the MPH group reported any adverse side effects. Only 20% of the participants reported moderate dryness of mouth and nausea. The rates of loss to follow-up for MPH and placebo did not differ significantly. While the attrition rate in the MPH group was 28% (compared to 14% in the placebo group), none of the participants discontinuing the study were attributed to adverse side effects. These results are consistent with the current literature in those with ADHD suggesting that MPH is well tolerated with low discontinuation rates due to adverse side effects. More specifically, a meta-analysis of various types of MPH showed attrition rates of 8% or less during 2 years of MPH treatment in children (Clavenna & Bonati, 2014). The

tolerability and attrition rates are even better within adults based on meta-analyses of 144 double-blind randomized controlled trials on 11,018 children and adolescents and 5362 adults (Cortese et al., 2018).

To show the significance of our data, the effect of MPH on weight-loss is compared to other commonly used FDA and Health-Canada approved weight loss drugs. Contrave (Bupropion/Naltrexone), an FDA and Health Canada approved weight-loss medication, has a similar mechanism of action as MPH in midbrain dopamine, an area that has been shown to modulate the mesolimbic reward pathway (Greenway et al., 2010) to suppress appetite. The meta-analysis of the effect of Contrave on weight-loss suggests an average weight loss of 5.0 kg (above placebo) during 1 year of Contrave administration, representing an average weight loss rate of 0.42 kg/month (Khera et al., 2016). In comparison, our data show an average weight loss of 1.5 kg (above placebo) during a 60-day (0.5 mg/Kg) MPH intervention, representing an average weight loss rate of 0.75 kg/month. More importantly, all four studies (COR-I, COR-II, COR-BMOD, COR-Diabetes) leading to FDA approval of Contrave involved low-intensity lifestyle modifications such as diet (> 500 kcal reduction), exercise, and behavioral interventions (Sherman, Ungureanu, & Rey, 2016). While recognizing that rate of weight-loss may diminish with time and simply taking a monthly average may not be an accurate representation of the trajectory of weight loss, the effects of MPH on weight loss appear to be clinically meaningful given the fact that we did not incorporate exercise, diet, or behavioral intervention. Moreover, there was no report of adverse side effects as the result of MPH administration while 30% of participants reported severe nausea, along with other adverse side effects while being treated with Contrave (Khera et al., 2016; Sherman et al., 2016), with the attrition rates ranging from

30% to 50% (Greenway et al., 2010; Greenway et al., 2009). Moreover, current literature and Contrave's product monograph list suicidal thinking as a potential side effect of Contrave's use especially in children, adolescents and young adults (Sheridan et al., 2018) when compared to MPH which does not show these side effects (Man et al., 2017).

Belviq (Lorcaserin) is another FDA-approved (not approved by Health Canada) that results in weight-loss by acting on the serotonin receptors to suppress appetite. A meta-analysis of the efficacy of Lorcaserin in adults with obesity found a modest 1.6 kg of weight-loss during 8 – 12 weeks of use while also receiving dietary, exercise, and behavioral consultation (Chan et al., 2013). Our data accomplished similar effects without diet, exercise and behavioral modifications, suggesting that MPH may be a more potent medication in the treatment of obesity. Moreover, Lorcaserin has many adverse effects such as headaches, dizziness, fatigue, nausea, and dry mouth (Yanovski & Yanovski, 2014) with the rate of withdrawal from the study due to adverse side effects ranging from 7.1% to 8.6% (Fidler et al., 2011; Smith et al., 2010). Although these side effects do not appear to be prohibitive, this medication has not been approved for weight loss in Canada.

Saxenda (Liraglutide), a gut hormone that suppresses appetite via peripheral and central pathways is another weight-loss medication that has shown significant weight-loss effects (Mordes et al., 2015). Meta-analysis of 5 randomized placebo-controlled trials found that in addition to diet and physical activity, the use of Liraglutide results in 4 to 6 kg of weight-loss over the period of 1 year (Mehta et al., 2017), indicating a weight-loss rate of 0.5 kg/month. Our findings suggest that MPH can produce similar or better effects when compared to Saxenda. Similar to other weight-loss drugs, the average attrition rate among the analysed studies is high

(an average of 24.5%) with some adverse side effects such as nausea (32.7% - 48.4%), constipation, (11.9% - 26.9%), diarrhea (16.5% - 25.6%), vomiting (7.4% - 16.5%) and abdominal pain (5.4% - 6.2%) (Mehta et al., 2017; Mordes et al., 2015). Beside adverse side effects, one of the major limitations cited for this medication is that it is self-administrated by injection only, which is unappealing to many individuals (Mehta et al., 2017).

Xenical and Alli (Orlistat) are gastrointestinal lipase inhibitor used for the treatment of obesity. Orlistat has shown weaker weight-loss results compared to the aforementioned drugs with literature suggesting an average weight loss of 2.7 kg (above placebo) during one year of Orlistat administration when combined with exercise, diet, and behavioral modifications. Our data produced slightly weaker effects of 1.5 kg loss, but our time frame was only 60-days of MPH administration, and we did not incorporate diet, exercise or behavioral modifications. This is equivalent to an average weight loss rate of 0.23 kg/month for Orlistat and 0.75 kg/month for MPH. While acknowledging that weight-loss is not a linear process in real life, our findings were significantly stronger compared to Orlistat. Moreover, Orlistat studies suggest high attrition rates (14% to 52%) due to adverse side effects such as fatty/oily stool leakage, stomach pain and diarrhea (Rössner et al., 2000).

It is noteworthy to mention Vyvanse (Lisdexamfetamine), a stimulant medication administered for the treatment of ADHD, which has recently been approved for the treatment of patients with binge eating disorder (BED) (Adler et al., 2008). Vyvanse is a sustained-release medication that is pharmacologically similar to MPH. Several double-blind, placebo-controlled studies have shown that Vyvanse is well tolerated (Adler et al., 2008; Weisler et al., 2009; McElroy et al., 2015). During an 11-week study, McElroy et al. (2015) found that Vyvanse

administration results in an average weight loss of between 3.0 kg – 4.2 kg (depending on the dose) in a sample of adults with BED (who were not all obese) (McElroy et al., 2015). Based on these findings, Vyvanse has a similar tolerability and efficacy profile as MPH. However, it is not currently indicated for weight-loss.

To summarize the comparisons between MPH and other weight-loss medications, our data suggest that MPH has similar or better weight-loss efficacy when attempting to standardize duration of intervention, with associated ratings of high tolerability and comparable attrition rates. These findings are especially encouraging considering the fact that our study did not include diet, exercise, or behavioral intervention.

Strengths and Limitations

The strength of this pilot study was its rigorous design; a randomized, double-blind, placebo-controlled parallel groups design, which yields the highest quality of data (except for meta-analytic reviews). In addition, this study, to our knowledge, is the first of its kind and therefore contributes novel pilot data that warrants further investigation of MPH as a potential medication for obesity management. Moreover, gold-standard measures of body composition (DEXA), appetite sensations (VAS), food reinforcement (computer task), and laboratory-based energy intake (ad libitum buffet meal) were employed.

The primary limitation of the study was the small sample size (N=11) which limits the generalizability of findings. The small sample size also likely led to higher variability and poor statistical power to detect significant differences between MPH and placebo. Although effect sizes were provided to aid interpretation of clinical relevance and inform sample sizes of future trials, these are based on statistics and do not necessarily reflect clinically significant changes

between groups on weight loss and other variables of interest. Moreover, our data showed a very large placebo effect across multiple factors such as food reinforcement, in lab energy intake and macronutrient consumption, which highlights the importance of incorporating placebo into designs when piloting drug trials. Nevertheless, the influence of social desirability responding cannot be discounted. Although influenced somewhat by the small sample size, results showed high intra-subject variability in both groups, and these differences in response to MPH may reflect biological factors such as individual differences in dopamine-genotypes or hormone levels (Stice et al., 2015; Havel, 2001; Gurbuz, 2016), or sociodemographic, psychological or anthropometric variability. Another limitation of the study was that we did not monitor in-lab food choices to see if the food choices within each macronutrient grouping changed following MPH administration compared to placebo. We also did not have access to participants' weight history to see if that or other patient characteristics influenced their response to MPH. Larger sample sizes, longer study duration, monitoring participants' food choices, collecting a more detailed weight and clinical history, measuring and controlling phenotypic characteristics of the study population, and a crossover study design could address some of these limitations.

Future Research Directions

We examined the effect of MPH over a 60-day period. While this was the longest study examining the effect of MPH on appetite suppression and weight-loss, it is relatively short when compared to studies on currently approved weight-loss medications. To examine the effectiveness of MPH as a weight-loss drug, future studies must use periods of up to 56 weeks (4 weeks of titration followed by one year of treatment), to make results comparable to other weight-loss drug studies. Future studies should also consider the evaluation of maintenance of

weight-loss after the treatment period with MPH to see if MPH is an effective long-term solution for obesity management.

We used a dose of 0.5 mg/kg up to a maximum daily dose of 100 mg. A lab study by Leddy and colleagues (2004) had determined that a dose of 0.5 mg/kg of MPH is as effective as 1.0 mg/kg. However, most of the studies on the dosage of MPH are based on managing ADHD symptoms. Therefore, other studies need to examine the efficacy and side effects of other doses of MPH to identify the least effective dose to induce appetite suppression and weight-loss.

Regarding the type of MPH, we used a short-acting MPH, with the maximum plasma concentration (C_{max}) of 1.5 to 2 hours (Volkow et al., 1998). This means that the effect of MPH on appetite may diminish as the day progresses. Using a sustained release or extended release MPH may help in suppressing the appetite in adults with obesity throughout the entire day and may produce a larger weight-loss effect. Additionally, sustained-release MPH could theoretically reduce the risk of abuse and cross-addictions (Ling et al., 2014; Spencer et al., 2007), although future research is needed to test this theory. Therefore, future studies should evaluate the compliance, effectiveness, tolerability, and attrition rate of sustained release and extended release MPH as a weight-loss drug.

Given the literature on how individual differences affect the role of brain dopamine on appetitive behavior, future research should consider the intra-subject variability when examining the correlation between MPH consumption and the suppression of appetite, the reinforcing value of food, and weight-loss. For example, Stice et al. (2015) found that the frequency of certain genotypes can influence the effect of dopamine on obesity. Stice et al. (2015) found that for the adolescents with *Taq1A*$^{-}$ allele, elevated reward response predicted fat gain (reward surfeit)

whereas for the adolescents with *Taq1A*$^{+}$allele, a lower reward response predicted fat gain (reward deficiency). Other studies such as Gurbuz et al. (2016) and Havel (2001) found that different hormone levels such as ghrelin, leptin, and insulin can also affect weight-loss. As such other, factors such as presence of different genotypes (Stice et al., 2015), different hormone levels (such as ghrelin and leptin, insulin) (Havel, 2001; Gurbuz, 2016), and external stimuli (cognitive factors, demographics, etc.) (Cameron & Ducet, 2007) can influence patient's response to MPH. While some of these factors, such as gender and demographic measures were accounted for, other factors such as genetic and hormonal factors were not controlled in our study. Therefore, future research should attempt to develop measures to characterize potential responders and non-responders when examining MPH as a weight-loss medication.

6.0 Summary and Conclusions

To our knowledge, our pilot data are the first to show that compared to placebo, short-acting MPH administration was feasible, well tolerated and produced significant reductions in appetite during a short intervention period (60-days) in adults with obesity without ADHD, with a concomitant large effect-size on weight-loss and moderate-size effect on energy intake. Our data did not produce any statistically significant or clinically meaningful effect of short-acting MPH on macronutrient consumption or on the relative reinforcing value of food with high fat and high carbohydrate content. This may have been due to an unexpectedly large reduction in placebo (both groups reduced about 30%). However, these findings need to be interpreted with caution because of the small sample size. It is also important to note that similar to many medications, our data indicate that individuals do not respond to MPH equally, evidenced by the large degree of inter-subject variability in our study, potentially due to differences in genetics,

physiological, psychological or environment factors. Future studies should consider sustained-release forms of MPH as it may produce greater medication compliance, although it was believed to be strong in this short-term intervention study. Data generated from this pilot study have important clinical relevance in that they can inform and support the conduct of future studies with larger sample sizes, longer study times, and that can identify phenotypes to help categorize responders and non-responders to provide a more definitive evaluation of the safety and efficacy of MPH for weight loss, and more importantly, the maintenance of weight loss in individuals with obesity.

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Appendices

Appendix A: Pre-Screening Questionnaire

Pre-Screening Questionnaire

THE EFFECTS OF METHYLPHENIDATE ON THE REDUCTION OF FOOD ENERGY INTAKE AND ON THE AUGMENTATION OF ENERGY EXPENDITURE

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1) **What is your age?** _____

2) **Do you smoke?** **Yes □ No□**

3) **Have you maintained a stable body weight (± 2kg) over the last 6 months?** **Yes □ No□**

4) **Do you take medications?** **Yes □ No□**
   a. **If so, which ones** _____

5) **Do you, or have you ever been diagnosed with having ADHD** **Yes □ No□**

6) **Have you ever taken Methylphenidate?** **Yes □ No□**

7) **Do you have known allergies to Methylphenidate?** **Yes □ No□**

8) **Any personal or family of motor tics or Tourette's syndrome?** **Yes □ No□**

9) **Do you have any other known food allergies?** **Yes □ No□**

10) **Do you have diabetes?** **Yes □ No□**

11) **Do you have any hearts problems?** **Yes □ No□**

12) **Do you have high or low blood pressure?** **Yes □ No□**

13) **Do you have asthma or any other respiratory problems?** **Yes □ No□**

14) **Has your doctor ever diagnosed you with thyroid gland abnormalities?** **Yes □ No□**

15) **How many alcoholic beverages do you normally consume in a week** **_____**

16) **Have you ever been diagnosed with glaucoma?** **Yes □ No□**

17) **Do you have any other health problems that were not mentioned in this questionnaire?** **Yes □ No□**
    a. **If yes, please specify** **_____**
    _____

Appendix B: Side Effect Checklist

Side Effect	None	Mild	Moderate	Severe
1. Insomnia/Disordered				
2. Nausea				
3. Headache				
4. Anxiety				
5. Palpitations				
6. Drowsiness/Sedation				
7. Abnominal Pain/ Cramps				
8. Irritability				
9. Confusion/Disorientation				
10. Sweating				
11. Flushing				
12. Dryness of Mouth				
13. Blurred Vision				
14. Motor Tics				
15. Nervousness				
16. Restlessness				
17. Skin Rash				
18. Excessive Sweating				
19. Depression/Moodiness				
20. Sore Throat/Runny Nose				
21. Other				

Appendix C: Drug Abuse Screening Test (DAST)

The purpose of the DAST is 1) to provide a brief, simple, practical, but valid method for identifying individuals who are abusing psychoactive drugs; and 2) to yield a quantitative index score of the degree of problems related to drug use and misuse. DAST scores are highly diagnostic with respect to a DSM diagnosis of psychoactive drug dependence and takes approximately 5 minutes to complete.

Adult Version

These questions refer to the past 12 months.	**Circle Your Response**	
1. Have you used drugs other than those required for medical reasons?	Yes	No
2. Have you abused prescription drugs?	Yes	No
3. Do you abuse more than one drug at a time?	Yes	No
4. Can you get through the week without using drugs?	Yes	No
5. Are you always able to stop using drugs when you want to?	Yes	No
6. Have you had "blackouts" or "flashbacks" as a result or drug use?	Yes	No
7. Do you every feel bad or guilty about your drug use?	Yes	No
8. Does your spouse (or parents) ever complain about your involvement with drugs?	Yes	No
9. Has drug abuse created problems between you and your spouse or your parents?	Yes	No
10. Have you lost friends because of your use of drugs?	Yes	No
11. Have you neglected your family because of your use of drugs?	Yes	No
12. Have you been in trouble at work (or school) because of drug abuse?	Yes	No
13. Have you lost your job because of drug abuse?	Yes	No
14. Have you gotten into fights when under the influence of drugs?	Yes	No
15. Have you engaged in illegal activities in order to obtain drugs?	Yes	No
16. Have you been arrested for possession of illegal drugs?	Yes	No
17. Have you ever experienced withdrawal symptoms (felt sick) when you stopped taking drugs?	Yes	No
18. Have you had medical problems as a result of your drug use (e.g. memory loss, hepatitis, convulsions, bleeding, etc.)?	Yes	No
19. Have you gone to anyone for help for drug problem?	Yes	No
20. Have you been involved in a treatment program specifically related to drug use?	Yes	No

Appendix D: Wender-Utah Rating Scale (WURS) for the ADHD

It is a 61-item questionnaire that will be used to determine if the participant demonstrates symptoms of attention deficit and hyperactivity symptoms. It is reliable and it has also been validated (McCann et al., 2000; Rossini & O'Connor, 1995; Stein et al., 1995). A score > 46 is an indicator of ADHD symptoms; therefore, participants with the mentioned score will be excluded from the study.

Wender Utah Rating Scale:

- 61 questions answered by the adult patient recalling his or her childhood behavior
- 5 possible responses scored from 0 to 4 points

	As a child I was (or had):	not at all or very slightly	mildly	moderately	quite a bit	very much
1	active restless always on the go	0	1	2	3	4
2	afraid of things	0	1	2	3	4
3	concentration problems easily distracted	0	1	2	3	4
4	anxious worrying	0	1	2	3	4
5	nervous fidgety	0	1	2	3	4
6	inattentive daydreaming	0	1	2	3	4
7	hot- or short-tempered low boiling point	0	1	2	3	4
8	shy sensitive	0	1	2	3	4
9	temper outbursts tantrums	0	1	2	3	4
10	trouble with stick-to-it-tiveness not following through. failing to finish things started	0	1	2	3	4
11	stubborn strong-willed	0	1	2	3	4
12	sad or blue depressed unhappy	0	1	2	3	4
13	incautious. dare-devilish involved in pranks	0	1	2	3	4
14	not getting a kick out of things dissatisfied with life	0	1	2	3	4
		not at all or very slightly	mildly	moderately	quite a bit	very much
15	disobedient with parents rebellious sassy	0	1	2	3	4
16	low opinion of myself	0	1	2	3	4
17	irritable	0	1	2	3	4
18	outgoing friendly enjoyed company of people	0	1	2	3	4

19	sloppy disorganized	0	1	2	3	4
20	moody ups and downs	0	1	2	3	4
21	angry	0	1	2	3	4
22	friends popular	0	1	2	3	4
23	well-organized tidy neat	0	1	2	3	4
24	acting without thinking impulsive	0	1	2	3	4
25	tendency to be immature	0	1	2	3	4
26	guilty feelings regretful	0	1	2	3	4
27	losing control of myself	0	1	2	3	4
28	tendency to be or act irrational	0	1	2	3	4
29	unpopular with other children didn't keep friends for long didn't get along with other children	0	1	2	3	4
30	poorly coordinated did not participate in sports	0	1	2	3	4
31	afraid of losing control of self	0	1	2	3	4
32	well-coordinated picked first in games	0	1	2	3	4
33	tomboyish (for women only)	0	1	2	3	4
34	running away from home	0	1	2	3	4
35	getting into fights	0	1	2	3	4
36	teasing other children	0	1	2	3	4
37	leader bossy	0	1	2	3	4
38	difficulty getting awake	0	1	2	3	4
39	follower led around too much	0	1	2	3	4
40	trouble seeing things from someone else's point of view	0	1	2	3	4
41	trouble with authorities trouble with school visits to principal's office	0	1	2	3	4
42	trouble with police booked convicted	0	1	2	3	4

	Medical problems as a child	not at all or very slightly	mildly	moder-ately	quite a bit	very much
43	headaches	0	1	2	3	4
44	stomachaches	0	1	2	3	4
45	constipation	0	1	2	3	4
46	diarrhea	0	1	2	3	4
47	food allergies	0	1	2	3	4
48	other allergies	0	1	2	3	4
49	bedwetting	0	1	2	3	4
	As a child in school I was (or had)	not at all or very slightly	mildly	moderately	quite a bit	very much
50	overall a good student fast	0	1	2	3	4
51	overall a poor student slow learner	0	1	2	3	4
52	slow in learning to read	0	1	2	3	4
53	slow reader	0	1	2	3	4
54	trouble reversing letters	0	1	2	3	4
55	problems with spelling	0	1	2	3	4
56	trouble with mathematics or numbers	0	1	2	3	4
57	bad handwriting	0	1	2	3	4
58	able to read pretty well but never really enjoyed reading	0	1	2	3	4
59	not achieving up to potential	0	1	2	3	4
60	repeating grades	0	1	2	3	4
61	suspended or expelled	0	1	2	3	4

Questions Associated with ADHD

- 25 of the questions were associated with ADHD as follows:

	As a child I was (or had):
3	concentration problems easily distracted
4	anxious worrying
5	nervous fidgety
6	inattentive daydreaming
7	hot- or short-tempered low boiling point
9	temper outbursts tantrums
10	trouble with stick-to-it-tiveness not following through. failing to finish things started
11	stubborn strong-willed
12	sad or blue depressed unhappy
15	disobedient with parents rebellious sassy
16	low opinion of myself
17	irritable
20	moody ups and downs
21	angry
24	acting without thinking impulsive
25	tendency to be immature
26	guilty feelings regretful
27	losing control of myself
28	tendency to be or act irrational
29	unpopular with other children didn't keep friends for long didn't get along with other children
40	trouble seeing things from someone else's point of view
41	trouble with authorities trouble with school visits to principal's office
	As a child in school I was (or had)
51	overall a poor student slow learner
56	trouble with mathematics or numbers
59	not achieving up to potential

Wender Utah rating scale sub score = _____ (sum of 25 questions associated with ADHD)

Interpretation:

- minimum score for the 25 questions is 0

- maximum score 100
- if a cutoff score of 46 was used 86 of patients with ADHD 99 of normal persons and 81% of depressed subjects were correctly classified

References: Wender, P. H., Ward, F., & Reimherr, F. W. (1993). Scale: An Aid in the Retrospective Attention. *Am J Psychiatry*, *150*(June), 885–890. Retrieved from http://ajp.psychiatryonline.org.proxy.bib.uottawa.ca/doi/pdf/10.1176/ajp.150.6.885

Appendix E: Beck Depression Inventory

The Beck Depression Inventory-II (BDI-II) is the most widely used instrument for detecting depression. It is a brief, criteria-referenced assessment for measuring depression severity and is in line with the depression criteria of the *Diagnostic and Statistical Manual of Mental Disorders—Fourth Edition* (DSM–IV). Administration: 5 minutes; self-administered.

Beck's Depression Inventory

This depression inventory can be self-scored. The scoring scale is at the end of the questionnaire.

1.
- 0 I do not feel sad.
- 1 I feel sad
- 2 I am sad all the time and I can't snap out of it.
- 3 I am so sad and unhappy that I can't stand it.

2.
- 0 I am not particularly discouraged about the future.
- 1 I feel discouraged about the future.
- 2 I feel I have nothing to look forward to.
- 3 I feel the future is hopeless and that things cannot improve.

3.
- 0 I do not feel like a failure.
- 1 I feel I have failed more than the average person.
- 2 As I look back on my life, all I can see is a lot of failures.
- 3 I feel I am a complete failure as a person.

4.
- 0 I get as much satisfaction out of things as I used to.
- 1 I don't enjoy things the way I used to.
- 2 I don't get real satisfaction out of anything anymore.
- 3 I am dissatisfied or bored with everything.

5.
- 0 I don't feel particularly guilty
- 1 I feel guilty a good part of the time.
- 2 I feel quite guilty most of the time.
- 3 I feel guilty all of the time.

6.
- 0 I don't feel I am being punished.
- 1 I feel I may be punished.
- 2 I expect to be punished.
- 3 I feel I am being punished.

7.
- 0 I don't feel disappointed in myself.
- 1 I am disappointed in myself.
- 2 I am disgusted with myself.
- 3 I hate myself.

8.
- 0 I don't feel I am any worse than anybody else.
- 1 I am critical of myself for my weaknesses or mistakes.
- 2 I blame myself all the time for my faults.
- 3 I blame myself for everything bad that happens.

9.
- 0 I don't have any thoughts of killing myself.
- 1 I have thoughts of killing myself, but I would not carry them out.
- 2 I would like to kill myself.
- 3 I would kill myself if I had the chance.

10.
- 0 I don't cry any more than usual.
- 1 I cry more now than I used to.
- 2 I cry all the time now.
- 3 I used to be able to cry, but now I can't cry even though I want to.

11.
0 I am no more irritated by things than I ever was.
1 I am slightly more irritated now than usual.
2 I am quite annoyed or irritated a good deal of the time.
3 I feel irritated all the time.

12.
0 I have not lost interest in other people.
1 I am less interested in other people than I used to be.
2 I have lost most of my interest in other people.
3 I have lost all of my interest in other people.

13.
0 I make decisions about as well as I ever could.
1 I put off making decisions more than I used to.
2 I have greater difficulty in making decisions more than I used to.
3 I can't make decisions at all anymore.

14.
0 I don't feel that I look any worse than I used to.
1 I am worried that I am looking old or unattractive.
2 I feel there are permanent changes in my appearance that make me look unattractive
3 I believe that I look ugly.

15.
0 I can work about as well as before.
1 It takes an extra effort to get started at doing something.
2 I have to push myself very hard to do anything.
3 I can't do any work at all.

16.
0 I can sleep as well as usual.
1 I don't sleep as well as I used to.
2 I wake up 1-2 hours earlier than usual and find it hard to get back to sleep.
3 I wake up several hours earlier than I used to and cannot get back to sleep.

17.
0 I don't get more tired than usual.
1 I get tired more easily than I used to.
2 I get tired from doing almost anything.
3 I am too tired to do anything.

18.
0 My appetite is no worse than usual.
1 My appetite is not as good as it used to be.
2 My appetite is much worse now.
3 I have no appetite at all anymore.

19.
0 I haven't lost much weight, if any, lately.
1 I have lost more than five pounds.
2 I have lost more than ten pounds.
3 I have lost more than fifteen pounds.

20.

0 I am no more worried about my health than usual.
1 I am worried about physical problems like aches, pains, upset stomach, or constipation.
2 I am very worried about physical problems and it's hard to think of much else.
3 I am so worried about my physical problems that I cannot think of anything else.

21.

0 I have not noticed any recent change in my interest in sex.
1 I am less interested in sex than I used to be.
2 I have almost no interest in sex.
3 I have lost interest in sex completely.

INTERPRETING THE BECK DEPRESSION INVENTORY

Now that you have completed the questionnaire, add up the score for each of the twenty-one questions by counting the number to the right of each question you marked. The highest possible total for the whole test would be sixty-three. This would mean you circled number three on all twenty-one questions. Since the lowest possible score for each question is zero, the lowest possible score for the test would be zero. This would mean you circles zero on each question. You can evaluate your depression according to the Table below.

Total Score	Levels of Depression
1-10	These ups and downs are considered normal
11-16	Mild mood disturbance
17-20	Borderline clinical depression
21-30	Moderate depression
31-40	Severe depression
over 40	Extreme depression

Appendix F: The Three Factor Eating Questionnaire (TFEQ)

FOOD HABITS QUESTIONNAIRE

(Stunkard et Messick, 1984)

This questionnaire contains a certain number of propositions.

If you agree with the statement or if you feel like it can be applied to you, check the case TRUE who correspond to the statement.

If you disagree with the statement or if you feel like it does not applied to you, check the FALSE case who correspond to the statement.

You have the choice to answer (or not) certain questions.

		TRUE	FALSE
1.	When I smell a sizzling steak or see a juicy piece of meat, I find it difficult to keep from eating, even if I have just finished a meal.	o	o
2.	I usually eat too much at social occasions, like parties and picnics.	o	o
3.	I am actually so hungry that I eat more than 3 times per day.	o	o
4.	When I have eaten my quota of calories, I am usually good about not eating any more.	o	o
5.	Dieting is so hard for me because I just get too hungry.	o	o
6.	I deliberately take small helpings as a means of controlling my weight.	o	o
7.	Sometimes things just taste so good that I keep on eating even when I am no longer hungry.	o	o
8.	Since I am often hungry, I sometimes wish that while I am eating, an expert would tell me that I had enough or that I can have something more to eat.	o	o

9.	When I feel anxious, I find myself eating.	o	o
10.	Life is too short to worry about dieting.	o	o
11.	Since my weight goes up and down, I have gone on reducing diets more than once.	o	o
12.	I often feel so hungry that I just have to eat something.	o	o
13.	When I am with someone who is overeating, I usually overeat too.	o	o
14.	I have a pretty good idea of the number of calories in common food.	o	o
15.	Sometimes when I start eating, I just can't seem to stop.	o	o
16.	It is not difficult for me to leave something on my plate.	o	o
17.	At certain times of the day, I get hungry because I have gotten used to eating them.	o	o
18.	While on a diet, if I eat food that is not allowed, I consciously eat less for a period of time to make up for it.	o	o
19.	Being with someone who is eating often makes me hungry enough to eat also.	o	o
20.	When I feel "blue", I often overeat.	o	o
21.	I enjoy eating too much to spoil it by counting calories or watching my weight.	o	o
22.	When I see a real delicacy, I often get so hungry that I have to eat right away.	o	o
23.	I often stop eating when I am not really full as a conscious means of limiting the amount that I eat.	o	o
24.	I get so hungry that my stomach often seems like a bottomless pit.	o	o
25.	My weight has hardly changed at all in the last 10 years.	o	o
26.	I am always hungry so it is hard for me to stop eating before I finish the food on my plate.	o	o
27.	When I feel lonely, I console myself by eating.	o	o

28.	I consciously hold back at meals in order not to gain weight.	o	o
29.	I sometimes get very hungry late in the evening or at night	o	o
30.	I eat anything I want, anytime I want.	o	o
31.	Without even thinking about it, I take a long time to eat.	o	o
32.	I count calories as a conscious means of controlling weight.	o	o
33.	I do not eat some foods because they make me fat.	o	o
34.	I am always hungry enough to eat at any time.	o	o
35.	I pay a great deal of attention to changes in my figure.	o	o
36.	While on a diet, if I eat a food that is not allowed, I often then splurge and eat other high calorie foods.	o	o

PART 2

Please answer the following questions by circling the number that best corresponds to you.

37. How often are you dieting in a conscious effort to control your weight?

Rarely	**Sometimes**	**Usually**	**Always**
1	**2**	**3**	**4**

38. Would a weight fluctuation of 5lbs (2 kgs) affect the way you live your life?

Not at all	**Slightly**	**Moderately**	**Very much**
1	**2**	**3**	**4**

39. How often do you feel hungry?

Only At mealtimes	**Sometimes between meals**	**Often between meals**	**Almost always**
1	**2**	**3**	**4**

40. Do your feelings of guilt about overeating help you control your food intake?

Never	**Rarely**	**Often**	**Always**
1	**2**	**3**	**4**

41. How difficult would it be for you to stop eating halfway through dinner and not eat for the next 4 hours?

Easy	**Slightly Difficult**	**Moderately Difficult**	**Very Difficult**
1	**2**	**3**	**4**

42. How conscious are you of what you are eating?

Not at all	**Slightly**	**Moderately**	**Extremely**
1	**2**	**3**	**4**

43. How frequently do you avoid « stocking up » on tempting foods?

Almost Never	**Seldom**	**Usually**	**Almost always**
1	**2**	**3**	**4**

44. How likely are you to shop for low calorie foods?

Unlikely	**Slightly Unlikely**	**Moderately likely**	**Very likely**
1	**2**	**3**	**4**

45. Do you eat sensibly in front of others and splurge alone?

Never	**Rarely**	**Often**	**Always**
1	**2**	**3**	**4**

46. How likely are you to consciously eat slowly in order to cut down on how much you eat?

Unlikely	**Slightly Unlikely**	**Moderately likely**	**Very likely**
1	**2**	**3**	**4**

47. How frequently do you skip dessert because you are no longer hungry?

Almost Never	**Seldom**	**At least once per week**	**Almost every day**
1	**2**	**3**	**4**

48. How likely are you to consciously eat less than you want?

Unlikely	**Slightly Unlikely**	**Moderately likely**	**Very likely**
1	**2**	**3**	**4**

49. Do you go on eating binges though you are not hungry?

Never	**Rarely**	**Sometimes**	**At least Once per week**
1	**2**	**3**	**4**

50. On a scale of 1 to 5, where :
- 0 (zero) means no restraint in eating (eating whatever you want, whenever you want it) and,
- 5 means total restraint (constantly limiting food intake and never "giving in"),
What number would you give yourself?

Eat whatever you want, whenever you want it
0
Usually eat whatever you want, whenever you want it
1
Often eat whatever you want, whenever you want it
2
Often limit food intake, but often "give in"
3
Usually limit food intake, rarely "give in"
4
Constantly limiting food intake, never "giving in"
5

51. To what extent does this statement describe your eating behavior?
"I start dieting in the morning, but because of many different things that happen during the day, by evening I have given up and eat what I want, promising myself to start dieting again tomorrow"

Not like Me	**Little like me**	**Pretty good description of me**	**Describes me perfectly**
1	**2**	**3**	**4**

Appendix G: Food Menu

☐ Croissant

☐ Nature Bagel

☐ Whole wheat bagel with sesame seed

☐ White bread

☐ Whole wheat bread

☐ Orange

☐ Apple

☐ Banana

☐ Green grapes

☐ Honey nut

☐ All bran cereal

☐ Corn Flakes

☐ Harvest crunch cereal

☐ Honey nuts cheerios

☐ Valley nature sweet and salty granola bar (grilled mixed nuts)

☐ Chocolate chips dipps Quaker

☐ Nutri-grain blueberry bar

☐ Tropicana apple juice

☐ Tropicana orange juice

☐ Pepsi

☐ 7up

☐ Skittle

☐ Kit Kat

☐ Caramilk

☐ Hershey chocolate with almonds

☐ 70% Black chocolate

☐ Chocolate chip cookies

☐ Lays nature chips

☐ Lays BBQ chips

☐ Water

☐ 1% milk

☐ 3.25% milk

☐ Chocolate milk

☐ Butter

☐ Silhouette 0% yogurt

☐ Yogurt Danone

☐ Red pepper

☐ Baby carrots

☐ Cucumber

☐ Dip for vegetables

☐ Cheddar cheese

☐ Brie cheese

☐ Breton original crackers

☐ 3 cheese pizza

☐ Meat lasagna

☐ Marinara grilled chicken

☐ Sweet sesame chicken

☐ Chicken pot pie

☐ Beef pot roast

☐ Vegetable soup

☐ Chicken noodle soup

☐ Beef and vegetables soup

☐ Creamy peanut butter

☐ Cream cheese

☐ Strawberry jam

☐ Salt

☐ Pepper

☐ Mustard

☐ Mayonnaise

☐ Ketchup

Appendix H: Summary Table for the Effect of MPH on Appetite and EI

Study Name	Population	Study Duration	Year	Suppression of Appetite	Weight-loss Effect	Reduction in EI of Medicated Participants (% if applicable)	% of reduction in dietary fat-intake	% of reduction in dietary carbs-intake
Leddy et al.	9 males with obesity	Not Clear	2004	√	√	23		
Goldfield et al.	14 adults BMI>20	3 weeks	2007	√	√	11	17	N/S
Davis et al	ADHD overweight	Not Clear	2009	√	√	√		
Davis et al	35 males & 97 females (BMI,25 &BMI>30)	2 weeks	2012	√	√	√		
Goldfield	Overweight adults and adults with Obesity	1 day	2011	√	√	√	√	√
Danilovich et al	15 female and 7 male teenagers with obesity	1 day	2014	√		19	18	21
Gurbuz	89 ADHD and healthy male (aged 7-14)	3 months	2016	√	√	√		
Poulton	34 ADHD children	1 year	2012		√			

N/S : Not Signifiant

Appendix I: Acute Effect of MPH

Table 13: The Mean of the Body Weight, Total In-lab EI, Macronutrients Consumptions, Snack Points, and Appetite Variables (Desire, Hunger, Fullness, Prospective Food Consumed (PFC)) at 7 days

Variable	MPH (n= 5) Mean (SD)	Placebo (n=6) Mean (SD)	P-value
Body weight (7 days) (kg)	101.16 (25.56)	104.65 (24.43)	0.82
Total in-lab EI (7 days) (kcal)	1386.66 (419.03)	1474.01 (499.55)	0.76
Total in-lab Carbs intake (7days) (kcal)*	829.94 (192.15)	919.86 (348.32)	0.62
Total in-lab fat intake (7 days) (kcal)	388.64 (178.02)	425.11 (150.65)	0.74
Total in-lab protein intake (7 days) (kcal)	179.92 (88.74)	186.89 (47.85)	0.87
Total in-lab sugar intake (7 days) (g)	94.70 (21.14)	128.16 (42.77)	0.15
Snack Points (7 days) (g)	10.4 (11.33)	12.6 (11.87)	0.77
Desire (AUC*)	167.4 (112.96)	275.41 (67.63)	0.08
Hunger (AUC)	169.55 (123.72)	250.41 (49.78)	0.17
Sense of fullness (AUC)	476.8 (101.96)	353.4 (58.85)	0.03
PFC (AUC)	198.5 (129.46)	286.8 (59.22)	0.17

AUC: Area under the curve
EI: Energy intake
PFC: Prospective Food Consumed

Table 14: The Change in Body Weight, Total In-lab EI, Macronutrients Consumptions, Snack Points, and Appetite Variables (Desire, Hunger, Fullness, Prospective Food Consumed (PFC)) from baseline to 7 days

Variable	MPH (n= 5) Mean (SD)	Placebo (n=6) Mean (SD)	P-value	Eta^2	Effect size
Change in body weight (kg)	-1.2 (0.37)	0.05 (1.24)	0.06	0.34	Large
Change in total in-lab EI (kcal)	-201.21 (260.57)	-84.15 (190.96)	0.41	0.08	Small
Change in total in-lab carbs intake (kcal)	-69.66 (121.52)	1.9 (130.52)	0.38	0.09	Small
Change in total in-lab fat intake (kcal)	-96.86 (79.13)	-77.59 (65.03)	0.68	0.02	Small
Change in Total in-lab protein intake (kcal)	-48.14 (68.22)	-7.40 (78.66)	0.39	0.08	Small
Change in total in-lab sugar intake (g)	-7.07 (26.09)	8.11 (23.63)	0.38	0.1	Small
Change in snack points (g)	-7.8 (6.14)	-8.8 (8.87)	0.84	0.00	N/S
Change in Desire (AUC diff)	-180.1 (131.41)	-5.75 (83.29)	0.02	0.44*	Large
Change in Hunger (AUC diff)	-190.65 (166.93)	7.83 (40.07)	0.02	0.47*	Large
Change in sense of fullness (AUC diff)	116.6 (68.08)	110.81 (79.59)	0.04	0.38	Medium
Change in PFC (AUC diff)	-185.9 (172.68)	2.75 (71.64)	0.04	0.40*	Medium

AUC: Area under the curve
EI: Energy intake
PFC: Prospective Food Consumed