2017

Hedonic Mechanisms of Weight Changes in Medication Assisted Treatment for Opioid Addiction

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HEDONIC MECHANISMS FOR WEIGHT CHANGES IN MEDICATION
ASSISTED TREATMENT FOR OPIOID ADDICTION

A Thesis Presented

by

Elizabeth McDonald

to

The Faculty of the Graduate College

of

The University of Vermont

In Partial Fulfillment of the Requirements
For the Degree of Master of Science
Specializing in Nursing

January, 2017

Defense Date: November 10, 2016
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Abstract

Opioid abuse and addiction affects more than 2.4 million people in the United States. Medication assisted treatment (MAT), in combination with counseling, is recognized as the most effective treatment for patients with opioid dependence and abuse. Although MAT is considered the most effective treatment, previous research has found clinically significant weight gain with methadone. The purpose of this study was to determine if hedonic eating behaviors, sugar cravings, and addictive like eating was related to weight gain in opioid addicted patients receiving methadone and buprenorphine/naloxone (Suboxone™). Hedonic eating behaviors were measured using three validated surveys. Following survey collection, a chart review was completed to determine weight changes over time. One hundred twenty surveys were completed and 113 were analyzed. No differences were found between the medication groups in terms of mean age, weight at entry, BMI at entry, race, sex, and Hepatitis C status. A subset of 39 participants was analyzed for weight changes during treatment. There were no differences in food addiction scores, hedonic eating behaviors, and food cravings between the medication groups. We found significant weight gain in patients receiving methadone and no weight changes for those receiving Suboxone™. Weight gain in methadone maintenance does not appear to be related to addictive like eating, food craving, or hedonic eating. This research suggests that weight gain seen in methadone maintenance for opioid addiction treatment is related to something other than hedonic eating behaviors. Clinically significant weight gain should be considered when prescribing methadone for opioid addiction.

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Introduction

Opioid abuse and addiction affect over 2.4 million people in the United States. In 2014, 1.9 million people abused prescription pain medication and 586,000 people were addicted to heroin (Substance Abuse and Mental Health Services Administration, 2015). In Vermont alone, nearly 4,000 people are currently in treatment for opioid addiction (Vermont Department of Health, 2014). Medication assisted treatment (MAT), in combination with counseling, is recognized as the most effective treatment for patients with opioid dependence and abuse (Stotts, Dodrill, & Kosten, 2009). However, Fenn, Laurent, and Sigmon (2014) found a mean increase of 17.8 pounds for patients following entry into methadone treatment within, on average, the first 18 months of treatment. Although research supports the use of MAT for opioid addiction, the implications for weight gain are significant. Obesity is associated with higher risk for many serious diseases and health conditions including hypertension, type II diabetes, stroke, anxiety, depression, heart disease, and overall mortality (CDC, 2014).

Methadone is a mu-opioid agonist (Yaksh &Wallace, 2011). In a systematic review, Mysels and Sullivan (2010) found that mu-opioid receptor activation is associated with increased preference for sweets, hyperglycemia, and potential insulin resistance. There is a growing body of research demonstrating that particular foods and food additives act on similar neural pathways as addictive drugs (Gearhardt et al., 2011). The literature also suggests that food addiction or addictive like eating is a contributing factor to obesity (Blumenthal & Gold, 2010). Methadone is associated with significant weight gain, however, the mechanisms of this weight gain are not fully understood.

Volkow et al. (2002) describe neural pathways in individuals with food addiction consistent with neural pathways found in individuals with opioid addiction. It is plausible that some of the weight gain seen in methadone treatment for opioid addiction might be attributable to hedonic preferences toward highly sweetened foods.

Additionally, substitute addiction, the process of replacing one addictive or compulsive behavior with another (McFadden, 2010), might be a plausible mechanism for increased food consumption and weight gain in methadone treatment. The literature on substitute addiction posits that for a substitute addiction to occur, the new compulsive behavior must replace at least one key function, such as pleasure or escape, previously achieved by a former addiction (Sussman & Black, 2008). This study may provide additional evidence into the potential contribution of substitute addiction and addictive like eating in medication assisted treatment for opioid addiction.

It is unclear if buprenorphine, a partial mu-opioid agonist used in the treatment of opioid addiction, has similar effects as methadone on weight gain. Buprenorphine is increasingly used in addiction treatment in the primary care setting. Because buprenorphine and methadone affect the mu-opioid receptor differently, understanding weight changes in buprenorphine treatment compared to methadone may provide insight into overall hedonic mechanisms of weight gain in MAT. If differences between the two drugs in weight gain are determined, the weight gain may be more attributable to the drug side effects than to eating behavior. If, however, similar weight trends are observed between the two drugs, it is plausible that eating behavior is implicated in weight gain in MAT regardless of the medication used in treatment.

Purpose of the study

The aim of this study is to determine the relationship between hedonic eating behaviors, sugar cravings, and weight gain in opioid addicted patients receiving medication assisted treatment. A secondary aim is to determine if there is a difference between weight gain and hedonic eating behaviors for individuals undergoing methadone compared to buprenorphine treatment. Our hypothesis is that hedonic eating behaviors and addictive like eating will be associated with weight gain in medication assisted treatment for opioid addiction for both methadone and buprenorphine. Despite the hedonic mechanisms, we expect greater weight gain in those receiving methadone than those receiving buprenorphine based on the pharmacodynamics of the drugs.

Theoretical framework

Robinson and Berridge's *Incentive-Sensitization Theory* will be utilized to inform study design and procedures. The theory suggests that in certain individuals with repeated exposure to a stimulus, a hypersensitivity response occurs in the brain and transforms the perception of that stimulus into pathological wanting. This pathological wanting is known as incentive salience. In certain individuals, repeated exposure to addictive drugs can alter the neural systems responsible for incentive salience to make an individual hypersensitive or sensitized to that drug and associated stimuli. This results in pathologic attachment to the drug and associated stimuli. Drug 'wanting' is then transformed into excessive drug craving. This can occur independently of the neural systems that mediate the pleasurable ('liking') and withdrawal effects of drugs, meaning that drug seeking may occur in absence of withdrawal or pleasure. As a result, addictive behaviors such of compulsive drug seeking and taking occur despite strong desires to quit and

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consequences of continued use. Neural adaption recurs and is responsible for drug wanting, which may last for years even after discontinued use (Robinson & Berridge, 1993, Robinson & Berridge, 2008). Recent literature suggests that certain foods and food additives may trigger addictive process in the brain similar to those seen in drug addiction (Gearhardt, Corbin, & Brownell, 2008), suggesting similar pathological wanting.

Significance

With the potential obesity related health problems patients recovering from drug addiction may face, understanding the mechanism behind weight gain is essential in order to provide optimal care, minimize risks, and impart the most appropriate education for patients. A clearer understanding of the mechanisms of weight gain in MAT can alter treatment paradigms for nurse practitioners and other clinicians. The information gleaned from our study has the potential to create recommendations for a multidisciplinary treatment approach that includes nutrition support, mental health services, social service resources, and food and addiction counseling. This research will provide further understanding of the relationships among these phenomena and, in particular, of the hedonic mechanisms of weight gain in medication assisted treatment for opioid addiction, and may contribute to future research aimed at gathering empirical evidence on substitute addiction.

APRN Competencies

Several nurse practitioner core competencies as outlined by the National Organization of Nurse Practitioner Faculties are addressed within this study including scientific foundation, leadership, practice inquiry, policy, and ethics (NONPF, 2012). The information discovered from this study has the potential to enhance the scientific

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foundation from which advanced practice registered nurses (APRNs) practice in primary care by furthering the understanding of the implications and side effects of MAT. Advanced practice registered nurses provide direct care to individuals receiving MAT and may, in the future, be prescribers of MAT. Advanced practice registered nurses are in a key position to be leaders in addressing the ongoing opioid and obesity epidemics. It is expected that the study findings will be applicable to a broad inter-professional audience that provides full spectrum care to this underserved, high-risk population, furthering the policy, ethical, and leadership impacts.

Comprehensive Literature Review

This chapter outlines the current literature related to weight gain in patients receiving methadone for opioid addiction, sugar cravings in medication assisted treatment (MAT), and food addiction. It concludes by proposing a hypothesis for substitute addiction as a plausible mechanism for weight gain seen in MAT. At the time this literature review was prepared, the weight effects of buprenorphine were absent from the literature.

Weight changes in medication assisted treatment

A 2005 study evaluated body mass index (BMI) and adiposity of opioid addicted patients (n=30) before treatment and after four years of treatment with methadone. The study compared BMI and mid arm muscle circumference (MAMC) in patients in treatment for opioid addiction. At the four-year follow-up, female patients (n=7) had a decrease in BMI with the percentage of fatty tissue in general body mass significantly below recommended values. In male patients (n=23), BMI increased with a concurrent increase in MAMC. This suggested that weight changes in methadone treatment may differ by gender. The study may not be generalizable to a US population and was significantly limited by its small sample size. Little statistical generalizability can be gleaned from the female population based on the sample size (Kolarzyk et al., 2005). Despite these limitations, this study provided early insight to potential differential effects of weight gain in men receiving methadone treatment.

In a retrospective chart review, Fenn, Laurent, and Sigmon (2014) examined changes in body mass index (BMI) among patients participating in methadone treatment for opioid addiction. Health records of 96 non-pregnant, opioid-dependent adults enrolled

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in an outpatient methadone treatment program for at least 6 months between 2002-2011 were analyzed. Significant increases in BMI were found following entry into methadone treatment. The mean BMI increased from 27.2 to 30.1 kg/m^2, representing a mean weight gain of 17.8 lbs. A significant difference between female and male weight gain was observed with female patients gaining on average of 28 pounds compared to men who had an average increase of 12 pounds. Collectively, this represented clinically significant weight gain (Donnelly et al., 2009). This study provided evidence that methadone may contribute to weight gain, but the mechanisms behind the weight gain were not addressed. These findings were in contrast to Kolarzyk et al. (2005) who reported a decrease in adiposity in females. The sample size was small (n=7) which may explain this descrepency. Confounding medication use was not isolated.

Mysels et al. (2011) conducted a retrospective chart review to compare weight changes in patients on naltrexone compared to methadone. Health records of 36 opioid-dependent patients within the first six months of treatment were reviewed. Both groups showed significant weight gain compared to baseline weight. At six months, the methadone maintained group had a mean increase in weight of 3.67% and the naltrexone group had a 4.63% increase compared to baseline. There was no statistically significant difference between the groups in weight gain at xix months. Strengths of this study include that it compared both treatments. The sample size was small, which limited the power of the study. The study was also limited in that it compared different clinics each with different treatment protocols. Although the data was limited, these results suggest that medication side effects alone may not account for weight gain found in medication assisted treatment. If so, one would expect to see differing weight gain between the

methadone and naltrexone. Similarly, if weight gain on methadone maintenance was attributable to an increase in sugar cravings alone, one would not expect to see an increase in weight with administration of an opioid antagonist such as naltrexone. This may suggest hedonic mechanisms as a potential etiology of weight gain in MAT regardless of drug.

Okruhlica and Slexakova (2012) explored the question of whether weight gain with methadone maintenance treatment was stable over time or transitory. The authors also examined the possible contributions of pharmacological and sociologic factors on body weight changes in methadone maintenance treatment. This longitudinal, observational study included 42 patients participating in a methadone maintenance program in Slovakia. Significant increases in mean BMI change were seen after one year and a less significant increase between one and two years. Further, no statistically significant weight changes were found between one and four years after entry into treatment. These findings suggest weight gain is more significant in the first year of treatment and plateaus after year two. No association was found between amount of weight gain and dose of medication. This lack of association adds evidence suggesting eating behavior and sociologic factors might play more of a role in the weight gain than the pharmacological factors, particularly early in treatment.

Parvaresh, Sabahi, Mazhari, and Gilani (2015) investigated the effects of methadone treatment on sexual function, sleep, and weight after six months of MAT. The cross-sectional study used a convenience sample of patients (n=199) from a methadone clinic in Iran. Patients were weighed at the beginning and end of treatment. Additionally, all patients completed demographic questionnaires, sleep and sexual experience

evaluations. Patients weight significantly increased compared to baseline over the course of the 6-months in methadone maintenance treatment (MMT). The incidence of sexual dysfunction and sleep disorders also significantly increased with MMT. This study examined a larger sample size than many previous studies. The results are comparable with other studies suggesting an increase in weight for both male and female patients receiving methadone maintenance. The study also highlights other important side effects of methadone to consider while providing patient counseling.

In summary, patients receiving methadone for opioid addiction demonstrate significant weight gain. However, the exact mechanisms of this remain unclear. Lack of comparison studies using buprenorphine make it difficult to determine if weight gain is related to recovery, medication, or other mechanisms. Mysels et al. (2011) found similar weight gain for naltrexone and methadone. Although Kolarzyk et al. (2005) found a decrease in BMI in female patients, it should be noted that the sample size was very small (n=7). More recently published studies with larger sample sizes have shown increase in BMI for both female and male patients, one showing a significantly higher increase in BMI in females than in males (Fenn et al., 2014). Weight gain among methadone patients was clinically significant.

Sugar cravings in opioid use

Cirello et al. (1987) conducted an early case control study examining plasma glucose and insulin responses to oral and intravenous glucose administration in users of heroin and methadone compared to healthy controls. Both heroin and methadone users had altered response to the oral and IV glucose load compared to the case controls with lower fasting plasma glucose and significantly higher basal insulin than controls. The

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acute insulin response in the methadone and heroin users was significantly less than the controls. Both groups of opioid users also had increased fasting insulin levels. This provided early evidence that heroin and methadone addiction may alter glucose metabolism in a pattern similar to what is observed in individuals with non-insulin dependent diabetes. Altered glucose metabolism may contribute to weight gain seen in opioid addiction. Limitations included that the study was relatively small and lack of matched comparison group.

Nolan and Scagnelli (2007) conducted a pilot study to examine food preferences and eating habits in patients receiving methadone treatment. Food preference and eating habit questionnaires were distributed to participants receiving outpatient methadone maintenance treatment (n=28) and controls (n=14). Patients on methadone reported higher consumption of sweets, higher eagerness to consume sweet foods, and a wish to consume larger quantities than healthy controls. In addition to reporting higher consumption of sweet foods, methadone patients had higher BMIs overall than controls, suggesting a link between methadone, an increased cravings and consumption of sweet calorically dense foods, and weight gain. There were several limitations of this study including its small sample size with unmatched controls, the food craving instruments used were not validated, and height and weight were self reported. Despite these limitations, this study provides important preliminary information about potential mechanisms of weight gain in methadone treatment including preferences for sweets and increased consumption of such foods.

Mysels and Sullivan (2010) conducted a literature review to explore the relationship between opioid use and development of preference for sweet tastes and

associated dental pathology, weight gain, and loss of glycemic control. The review included studies with patients using heroin and patients receiving methadone treatment. No studies were included that examined patients who exclusively abused prescription opioids. They found activation of the mu-opioid receptor by methadone or heroin was associated with increased palatable (sweet) taste preference, weight gain, and tooth decay. Opioid use was also associated with increased hyperglycemia induced by direct action on pancreatic islet cells, which has been shown to increase dietary preference for sugary foods and associated increased insulin resistance (Reed & Ghodse, 1973; Willenbring et al., 1989). Opioid antagonists were not associated with weight gain or glycemic dysregulation. Methadone maintained patients were found to be especially susceptible to weight gain, poor dentition, and diabetes. Studies that examined buprenorphine effects on weight were not included due to a lack of research in this area. This study provides important evidence to the association of sweet taste preference, weigh gain, and methadone maintenance. This further supports that hedonic mechanisms may be implicated in weight gain in methadone maintenance treatment for opioid addiction.

Food addiction and hedonic eating

Through the advancement of imaging technologies, much more is understood about the brain activity in addiction. Recent literature suggests that certain foods and food additives may trigger addictive processes in the brain similar to those seen in individuals with drug addiction. Drugs and food both trigger reinforcing pathways mediated by dopamine in the meso-limbic system (Gearhardt, Corbin, & Brownell, 2008).

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Volkow et al. (2002) examined the role of dopamine in "nonhedonic" food motivation. Participants (n=10) were shown pictures of food after being food deprived for 16-20 hours. The response was monitored through positron emission tomography (PET) and raclopride, a dopamine receptor radioligand that binds to the dopamine receptor and competes with endogenous dopamine. Subjects were pretreated with methylphenidate in order to block the dopamine transporter and amplify any dopamine changes. Food cues, in combination with methylphenidate, were associated with an increase in extracellular dopamine in the dorsal striatum. The dorsal striatum mediates decision-making, especially action selection and initiation (Balleine, Delgado, & Hikosaka, 2007). Food cues and increase in extracellular dopamine were associated with increased self-reports of hunger and desire for food. This suggests that dopamine in the dorsal striatum is involved in food motivation. No change was seen in the ventral striatum, including the nucleus accumbens (NA). This suggests that dopamine in the dorsal striatum is involved in food motivation distinct from dopamine's role in food motivation related to the NA and reward system. Food was not consumed in this study suggesting that without food consumption, the reward system associated with those stimuli were not activated.

A 2011 study examined the neural correlates of addictive-like eating using functional magnetic resonance imaging (fMRI) in healthy adults. Forty-eight healthy women were recruited with BMIs ranging from normal to obese. Participants with eating disorders were excluded. Food addiction scores were compared to fMRI brain activation in response to receipt and anticipation of palatable food. Females meeting the threshold for food addiction showed similar brain activation on fMRI as was seen in individuals with drug addiction – including activation of reward circuitry (dorsolateral prefrontal

cortex and caudate, anterior cingulate cortex, medial orbitofrontal cortex, and amygdala) and reduced activation of inhibitory regions (lateral orbitofrontal cortex) in response to anticipation of food. There was no significant correlation found between food addiction scores and BMI. Although the sample size was small, this was the first study to look at the relation between food addiction and neural reward activation. Activation of the neural rewards system suggests a similar process in the brain in response to food as is found in drug addiction (Gearhardt, et al., 2011). It is plausible that individuals who have greater susceptibility to drug addiction might also be more susceptible to food addiction due to the similar neural pathways and processes.

Stojek, Fisher, and MacKillop (2015) utilized drug addiction paradigms to understand eating behaviors and motivations for high sugar, high fat food consumption. This study utilized an experimental design and well documented addiction paradigm. Subjective cravings, relative reinforcing value of foods (RRV_{foods}), negative and positive affect, amount of food consumed, and latency to first bite were measured following exposure to food cues. Adults (n=133) who endorsed liking high fat, high sugar snacks and denied eating pathology were recruited. Participants were randomly assigned to one of two mood conditions – stress or neutral and to one of two cue exposure conditions – food cues or neutral cues (office supplies). Participants in the stress condition reported no change in craving or in $RRV_{foods,}$. Food cues increased participants cravings and RRV_{foods}. No interaction was found between stress and food cues. Calories consumed were not different in subjects in either the stress or food cues conditions, but those in the food cues condition had shorter latency to first bite. The addiction literature suggests guided imagery does not elicit cravings in social drinkers only in those with alcohol use

disorder. Only adults without eating pathology were included, therefore the results may not be generalizable to a population with eating pathology. No biomarkers such as cortisol were collected. This study underlines the role that food cues play in food motivation, suggesting that increased food cues created a higher risk for overeating.

Gearhardt, Corbin, & Brownell (2009) examined the food addiction literature in the context of each diagnostic criterion for dependence in the Diagnostic and Statistical Manual of Mental Disorders (4th ed., text rev.; DSM-IV-TR; American Psychiatric Association, 2000). The diagnostic criteria for substance dependence in the DSM-IV consisted of: tolerance; withdrawal; taking the substance in larger amounts or over a longer period than was intended; persistent desire or unsuccessful effort to cut down or control substance use; spending a great deal of time in activities necessary to obtain or use the substance or to recover from its effects; giving up social, occupational, or recreational activities because of substance use; and continuing the substance use with the knowledge that it is causing or exacerbating a persistent or recurrent physical or psychological problem. The review found increasing evidence to support that a subset of people lose control over eating, are unable to abstain from certain types of foods in spite of negative consequences, and fail at attempts to reduce intake. The other categories of dependence (i.e. tolerance, withdrawal, spending a great deal of time in activities necessary to obtain or use the substance or to recover from its effects, and giving up social, occupational, or recreational activities because of substance use) have less clear evidence from which to draw conclusions. Collectively, it appears the evidence suggests that addictive-like eating may affect a subset of individuals.

Jasinska et al. (2012) explored the role of impulsivity and inefficient inhibitory control in individuals with unhealthy eating behaviors. Structural equation modeling was utilized to explore in-depth relationships among impulsivity, inhibitory control, eating behavior, and body mass index. Undergraduates (n=210) with BMIs ranging from underweight to obese were recruited. Impulsivity and inhibitory control deficits were associated with overeating in response to food cues, negative emotional states, and making food choices based on health preferences - not health value. Participants with lower inhibition were more likely to eat more unhealthy foods and had lower intake of healthy foods. Unhealthy eating behaviors and choices were associated with an increased BMI. This suggests there similar biological mechanisms involve in food and drug addiction. Impulsivity and inhibitory control deficits may put individuals at higher risk for both drug and food addiction.

How prevalent is substitute addiction?

Substitute addiction, also known as addiction transfer or cross-addiction, is a phenomenon that occurs when a person replaces one compulsive behavior that causes impairment with another (McFadden, 2010). Sussman and Black (2008) describe substitute addition as "any addictive behavior that serves at least one key function previously achieved by another addictive behavior (e.g., relaxation, escape, excitement, pleasure, reduction of negative affect, social lubrication)." Although there have been anecdotal discussions of substitute addiction in the recovery community, there is little empirical research on the topic. In a 2007 literature review, 27 webpages on a Google Scholar search and 2 articles in a search of OvidMEDLINE and PsycINFO were found on the topic (Sussman & Black, 2008). As early as 1966, the concept of substitute addiction

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was being discussed in the literature. One of the earliest studies on the topic by Valiant (1966) included food, in addition to marijuana, chloriazepoxide, religion, and participation in alcoholics anonymous, as common substitute addictions in narcotic abusers. A 2012 literature review found an increase in the prevalence of eating disorders in particular bulimia nervosa in patients with concomitant drug use disorder compared to the general population (Nøkleby, 2012).

In a retrospective chart review, Kleiner et al. (2004) examined the relationship between obesity and alcohol consumption. An inverse relationship was found between BMI and alcohol consumption in women (n=298) who were in active weight management. Obese patients had lower rates of alcohol use than the general population. The authors hypothesize that overeating may compete with alcohol in the reward system in the brain, suggesting that one substance may be able to replace another in the reward circuit of the brain.

Although the empirical evidence on substitute addiction is limited, there is significant anecdotal support of this phenomenon in the recovery literature. Utilizing this framework, it is plausible that food addiction may serve as a substitute addiction for those in recovery for opioid addiction and food may fill one or more key functions (relaxation, pleasure, escape, etc) that opioid addiction had previously served for patients. These key functions might be related to the reward pathway in the meso-limbic dopamine reward circuit. It is also plausible that those who are more susceptible to drug addiction may be more susceptible to food addiction both in terms of brain chemistry as well as impulsivity and inhibitory control. The research suggests a relationship between methadone use and weight gain; opioid intake appears to correlate with increased sugar intake; and food

addiction follows similar pathways in the brain to opioid addiction. The proposed research will provide further understanding of the relationships among these phenomena and, in particular, of the hedonic mechanisms of weight gain in medication assisted treatment for opioid addiction. In addition, it may contribute to future research aimed at gathering empirical evidence on substitute addiction.

Hedonic Mechanisms of Weight Changes in Medication Assisted Treatment for

Opioid Addiction

Abstract

Background and purpose: Opioid abuse and addiction affects more than 2.4 million people in the United States. Medication assisted therapy (MAT) with methadone or buprenorphine, along with behavioral counseling, is considered the most effective treatment for opioid use disorders. Previous research has found clinically significant weight gain with methadone treatment for opioid addiction, but the mechanisms behind weight gain remain unclear. The purpose of this study was to determine if hedonic eating behaviors, sugar cravings, and addictive like eating was related to weight gain in opioid addicted patients receiving buprenorphine/naloxone (Suboxone™) and methadone. **Methods:** Patients undergoing MAT (n=113) completed three questionnaires to measure hedonic eating and sugar craving. A chart review was completed to determine baseline weight and weight changes over time. **Results:** No differences were found between the medication groups in terms of mean age, weight at entry, BMI at entry, race, sex, and smoking and Hepatitis C status. A subset of 38 participants was analyzed for weight changes over time. Weight gain in patients receiving methadone was evident with no weight changes for those receiving Suboxone™. There were no differences in food addiction scores, hedonic eating behaviors, and food cravings between the medication groups. Both medication groups demonstrated higher levels of cravings and "giving in" to those cravings for sweets than for fats. **Conclusions:** Our findings demonstrate that individuals receiving methadone for MAT have greater weight gain than individuals receiving Suboxone™. The groups had similar eating behaviors suggesting that weight gain associated with methadone may not be attributable to hedonic eating.

1. Introduction

Opioid abuse and addiction affect over 2.4 million people in the United States. In 2014, 1.9 million people abused prescription pain medication and 586,000 people were addicted to heroin (Substance Abuse and Mental Health Services Administration, 2015). Medication assisted therapy (MAT), in combination with counseling, is recognized as the most effective treatment for patients with opioid use disorders (Stotts, Dodrill, & Kosten, 2009). Both buprenorphine and methadone maintenance have been shown to reduce rates of illicit drug use, deaths from overdose, risky behavior linked to HIV and Hepatitis C transmission, crime, and overall mortality (Thomas et al., 2014). Although research supports the use of MAT for opioid addiction, it is not without adverse effects. Several studies document clinically significant weight gain (i.e. >5% of baseline) as a side effect associated with methadone maintenance posing additional risks unrelated to substance addition (Mysels et al., 2011; Fenn et al., 2014). Obesity is associated with higher risk for many serious diseases and health conditions including hypertension, type II diabetes, stroke, anxiety, depression, several types of cancers, heart disease, and overall mortality (Centers for Disease Control, 2014). Further, a 5% increase in weight from baseline increases risk of hypertension, hyperlipidemia, diabetes, and heart disease (Donnelly et al, 2009).

The exact mechanisms associated with weight gain for individuals receiving methadone maintenance remain unclear. Weight changes associated with buprenorphine/naloxone (Suboxone™) have not been documented. Methadone's strong affinity for the mu-opioid receptor makes it highly effective in MAT. However, preclinical trials from animal studies suggest that agonism of the mu-opioid receptor in

certain areas of the brain, specifically in the nucleus accumbens, hypothalamus, and paraventricular nucleus, may increase the craving for and consumption of sugar rich foods and certain carbohydrates (Mysels et al., 2010). Further, clinical studies have shown methadone maintained patients report increased consumption of highly-sweetened foods (Kolarzy et al., 2005). Similar findings regarding sugar craving, sugar consumption, and weight gain associated with Suboxone™ are not well documented.

There is a growing body of research demonstrating that particular foods and food additives, including sweets, act on similar neural pathways as addictive drugs (Gearhardt et al., 2011; Volkow et al., 2002). Gearhardt et al. (2011) examined neural pathways of addictive like eating in women using functional magnetic resonance imaging (fMRI). Participants meeting the threshold for food addiction showed similar brain activation on fMRI that is seen in individuals with drug addiction – including activation of reward circuitry (dorsolateral prefrontal cortex and caudate, anterior cingulate cortex, medial orbitofrontal cortex, and amygdala) and reduced activation of inhibitory regions (lateral orbitofrontal cortex) in response to anticipation of food. It is plausible that some of the weight gain seen in methadone maintenance might be attributable to hedonic preferences toward highly sweetened foods. Agonism of the mu-receptor in these key neural reward pathways may potentiate the hedonic response for sweet foods and beverages. Differences between the binding properties of buprenorphine and methadone might explain the anecdotal reports of sugar cravings in methadone but not in buprenorphine/naloxone.

The purpose of this study was to determine if hedonic eating behaviors, sugar cravings, and addictive like eating were related to weight gain in opioid addicted patients

receiving medication assisted therapy. A secondary aim was to determine differences between weight gain and eating behaviors for individuals receiving methadone compared to individuals receiving Suboxone™ for MAT. Our hypothesis was that hedonic eating behaviors and increased food addiction symptom scores would be associated with weight gain in medication assisted treatment for opioid addiction for both methadone and Suboxone™. Despite the hedonic mechanisms, we expected greater cravings for sweets and carbohydrates and higher associated weight gain in individuals receiving methadone compared to those receiving Suboxone™.

2. Methods

Patients enrolled in medication assisted treatment for opioid addiction in an outpatient treatment facility in the northeastern United States were recruited for this study. Inclusion criteria consisted of: English speaking individuals 18 years of age and older receiving either methadone or buprenorphine/naloxone (Suboxone™) daily, receiving treatment for at least six months, and who were at a stable medication dose. Exclusion criteria included women who were pregnant and breastfeeding women while receiving MAT.

Following informed consent, participants completed three validated eating behavior surveys. A chart review was conducted. Demographic data (i.e age, gender, ethnicity), height and weight upon entry into treatment, most recent weight, weight time interval, MAT medication (methadone or Suboxone™), medication dose, other concurrent medications, smoking status, and duration in program were collected. This study was approved by the University's Institutional Review Board prior to the onset of the study.

2.1 Measures

The Food Craving Inventory (FCI) (White et al., 2002) is a validated 28-item self-administered instrument used to determine specific food cravings. It was developed using two subscales: subjective cravings and consumption of particular foods. Subjective cravings were found to correlate with consumption. Frequency of cravings is rated on a 5-point Likert scale ranging from 1 ("not at all") to 5 ("nearly every day"). The inventory contains four scales that measure high fats, sweets, carbohydrates/starches, and fast-food fats.

The Yale Food Addiction Scale (YFAS) (version 2.0, Gearhardt, Corbin, & Brownell, 2009) is a validated 25-item self-report questionnaire. It is used to identify symptoms of addictive-like eating and food addiction. Food addiction is present when three or more symptoms of addictive like eating are endorsed and at least one of two of clinical significance items (i.e impairment or distress) are endorsed (Gearhardt, Corbin, & Brownell, 2009).

The Power of Food Scale (PFS) (Lowe et al., 2009) is a validated 15-question self-administered questionnaire used to evaluate the impact food-abundant environments by evaluating appetite for palatable foods. It assesses the psychological impact independent of homeostatic hunger. Higher scores suggest greater appetitive responsiveness (Laurent & Sibold, 2016; Lowe et al., 2009).

2.2 Analysis

T-tests were computed to compare means of continuous variables between medication groups for age, weight at entry, body mass index (BMI) at entry, addictive like eating, appetitive responsiveness, and food craving. Chi-sqaure tests were used to compare

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differences in race, sex, smoking status, Hepatitis C status, and the presence or absence of food addiction between the two medication groups. T-test was used to compare mean BMI change and mean weight change between medication groups. Analysis of covariance was computed to determine if BMI and weight change were associated with length of time in treatment, food craving, appetitive responsiveness, and food addiction scores, and if those associations were different between medication groups. Significance was set at $\alpha=.05$, two sided. Data was analyzed using SPSS v. 23 (IBM Corp, 2015).

3. Results

One hundred twenty surveys were completed. One hundred thirteen (methadone=63, Suboxone™= 50) met inclusion criteria and were analyzed. Those that were omitted were excluded based on the following: two participants received only buprenorphine (Subutex™), two were excluded for duplicate data, and three were excluded for treatment duration less than six months. Baseline and follow up BMI data was available for 38 participants (methadone=29, Suboxone™=9) and was analyzed for weight and BMI changes over time. One participant from the Suboxone™ group was excluded from sub-group analysis for a reported weight loss of 50 pounds in two months.

Patient characteristics are presented in Table 1. Medication groups were not statistically different for mean age, weight at entry, and BMI at entry. There were no between group differences for sex, race, smoking status, and Hepatitis C status. Patients receiving methadone had significant increase in BMI and weight. Sub-group analysis using Levene's test assuming unequal variances ($p < 0.01$) demonstrated a mean BMI increase of 1.37 kg/m^{2,} ($p<0.05$) translating to a mean increase of 10.48 pounds ($p<0.01$) in the methadone group over the course of an average of 16 months. Patients receiving

Suboxone™ did not have significant change in BMI (p>0.9) over time.

No significant differences were found between the MAT groups for YFAS symptoms count, food addiction, food craving/give in sub scores and aggregate scores, and appetitive responsiveness. Participants in both medication groups had significantly higher cravings and gave into these cravings (p<0.01) more frequently for sugars than for fats.

4. Discussion

Our findings indicate that individuals receiving methadone for MAT have significant weight gain during treatment. Conversely, receiving Suboxone™ maintenance was weight neutral. The average weight gain in the methadone group was 6%, which is clinically significant and associated with an increased risk of hypertension, hyperlipidemia, diabetes, and heart disease (Donnelly et al, 2009). The range of weight change was from -20 to 48 pounds. Our findings are consistent with previous studies showing gain in methadone maintenance. For example, Mysels et al. (2011) reported a 10-pound weight gain in the first six months of methadone MAT. Fenn et al. (2014) found a 17.8-pound weight gain within approximately the first two years of treatment. Okruhlica and Slexakova (2012) found that weight gain attributed to MAT plateaued at approximately 2 years following the initiation of methadone MAT. Although our data showed similar weight gain overall, the weight changes observed in our sample we did not find a significant relationship between time in treatment and methadone MAT reported in previous studies. This may be attributed to our small sample size between groups and the variability of time between such measurements (1.25-71 months).

Previous research suggested that patients enter opioid treatment underweight and malnourished (Gronbladh & Ohlund, 2011; Okruhlica & Slezakova, 2008) and have attributed in-treatment weight gain associated with methadone treatment to an overall improvement in nutritional status. The mean BMI at entry into treatment was 27.0 kg/m^2 for the methadone group and 25.2 kg/m^2 for the Suboxone™ group, meaning that individuals were overweight upon initiating MAT. This is consistent with more recent research by Fenn et al. (2014) who found patients initiating treatment, on average, are overweight rather than underweight. Thus, clinical consideration should be given when prescribing methadone to an already overweight population. Given the more current research and the ongoing obesity epidemic using methadone MAT may be creating additional obesity related health risks to a population that is already high risk of co-morbidities associated with substance dependence and addiction.

We were unable to isolate predictors of weight gain. Thirty eight percent of individuals receiving methadone had clinically significant weight gain. Those with clinically significant weight change gained, on average, greater than 28 pounds. This suggests that a subset of individuals may be more susceptible to weight gain and the weight gain for these individuals may be greater than suggested by mean weight change of the entire sample. Further research is indicated to determine predictors of weight gain during treatment. Proposed mechanisms include genetics, physical activity, and individualized response to drug pharmacodynamics.

Interestingly, we did not find any relationship between hedonic eating, appetitive responsiveness, and addictive like eating in either the methadone or Suboxone™ groups. Our original hypothesis that hedonic eating was a contributing factor to weight gain more

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specifically in the methadone MAT was not supported. Previous research and anecdotal reports from individuals receiving methadone MAT suggests that such individuals have an increased preference for sweet foods. Mysels et al. (2010) reported that individuals using both methadone and heroin showed increased preference for sweet tastes and associated dental pathology compared to healthy controls. Both groups had mean scores demonstrating higher sweet cravings (i.e. sometimes to often) when compared to fat cravings (i.e. rarely to sometimes). Participants mean scores for giving in to sweet cravings were high (i.e. sometimes to often) for both groups compared to scores for giving in to fat cravings (i.e. rarely to sometimes). This suggests that methadone and Suboxone™ may both be associated with an increase in sweet preferences over other types of palatable foods high in fat. Increased craving and giving in to such cravings of highly sweetened foods does not appear to contribute to weight gain as previously proposed. We, however, did not evaluate the dietary intake of our participants. Further studies should examine craving as well as total dietary intake.

4.1 Limitations

Limitations exist. The study was limited by a small sample size. In particular, only a small subset of participants had recorded weight information over time thus limiting generalization of our findings. Our sample was primarily White in a rural setting enrolled in MAT. Further, we did not evaluate other potential contributing factors such as psychotropic medications and co-morbid conditions other than Hepatitis C that may affect weight gain and weight status. Physical activity levels were not examined. It is plausible that physical activity levels differ among treatment groups related to potential drug side effects such as drowsiness and fatigue that are generally associated with

methadone (Truven Health Analytics, 2011).

Additionally, we did not assess diet pre-treatment, and a complete food inventory, including sugar-sweetened beverages, was not obtained. It is plausible that the food-craving inventory utilized in this study is appropriate for a population who is comparing craving related to opioids to that of various types of food, including sugar. The Food Craving Inventory uses the term "cravings" to illicit an individual's desire to consume certain foods. The concept of craving for food, including sugar, may not be an appropriate measure for individuals with a history of opioid cravings. Future research should include psychometric testing in substance abusing populations. Similarly, the Food Addiction Scale uses scoring similar to what is used to score other forms of substance abuse. This scale may be interpreted differently by individuals with a history of substance abuse compared to a population without a history of substance addiction.

5. Conclusions

Our findings demonstrate that individuals receiving methadone for MAT have clinically significant weight gain whereas individuals receiving Suboxone™ do not exhibit similar weight changes. Weight gain does not appear to be related to addictive like eating, food craving, and appetitive responsiveness. Both groups had high mean scores for sweet cravings when compared to other types of foods. As our sample was overweight upon entry into MAT, individuals recovering from drug addiction who are treated with methadone maintenance may be at greater risk for obesity and its associated co-morbidities – thus adding one more significant health problem. As a result, potential weight gain associated with methadone treatment should be an important clinical consideration prior to initiating MAT. Further, patients should be informed of the

benefits and risks of treatment, including weight gain for individuals receiving methadone MAT. Increased attention should be directed to providing appropriate patient education and weight-related counseling throughout MAT.

Only approximately one third of our participants had recorded weight data over time. In order to better understand weight change in methadone and buprenorphine/naloxone MAT, more attention should be focused on weight monitoring in outpatient treatment. Further, longitudinal research that examines hedonic eating behaviors during MAT would provide more insight into the mechanisms of weight change.

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Table 1. Characteristics of Sample (N=113)*

	Medication	Count	
Mean Age	Methadone	63	35.67
	Suboxone™	50	34.94
Mean Weight at Entry	Methadone	59	173.66
	Suboxone™	42	161.07
BMI at Entry	Methadone	59	27.02
	Suboxone™	42	26.62
% Male	Methadone	28	44.4%
	Suboxone™	15	30%
% Smoker	Methadone	47	78.3%
	Suboxone™	41	85.4%
% Hepatitis C Positive	Methadone	16	26.2%
	Suboxone	18	37.5%

* not significant at p<0.05, 2 sided

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