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Acute responses to opioidergic blockade as a biomarker of hedonic eating among obese women enrolled in a mindfulness-based weight loss intervention trial

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Abstract

There are currently no commonly used or easily accessible ‘biomarkers’ of hedonic eating. Physiologic responses to acute opioidergic blockade, indexed by cortisol changes and nausea, may represent indirect functional measures of opioid-mediated hedonic eating drive and predict weight loss following a mindfulness-based intervention for stress eating. In the current study, we tested whether cortisol and nausea responses induced by oral ingestion of an opioidergic antagonist (naltrexone) correlated with weight and self-report measures of hedonic eating and predicted changes in these measures following a mindfulness-based weight loss intervention. Obese women (*N*=88; age=46.7±13.2 years; BMI=35.8±3.8) elected to complete an optional sub-study prior to a 5.5-month weight loss intervention with or without mindfulness training. On two separate days, participants ingested naltrexone and placebo pills, collected saliva samples, and reported nausea levels. Supporting previous findings, naltrexone-induced cortisol increases were associated with greater hedonic eating (greater food addiction symptoms and reward-driven eating) and less mindful eating. Among participants with larger cortisol increases (+1 SD above mean), mindfulness participants (relative to control participants) reported greater reductions in food addiction symptoms, *b*=−0.95, SE(*b*=0.40, 95% CI [−1.74, −0.15], *p*=.021. Naltrexone-induced nausea was marginally associated with reward-based eating. Among participants who endorsed naltrexone-induced nausea (*n*=38), mindfulness participants (relative to control participants) reported greater reductions in food addiction symptoms, *b*=−1.00, 95% CI [−1.85, −0.77], *p*=.024, and trended toward reduced reward-based eating, binge eating, and weight, post-intervention. Single assessments of naltrexone-induced cortisol increases and nausea responses may be useful

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time- and cost-effective biological markers to identify obese individuals with greater opioid-mediated hedonic eating drive who may benefit from weight loss interventions with adjuvant mindfulness training that targets hedonic eating.

Keywords

Hedonic Eating; Mindfulness Intervention; Naltrexone; Cortisol; Nausea

The modern food environment is replete with highly processed, hyperpalatable foods that arguably share properties of addictive drugs (Gearhardt, Davis, Kuschner, & Brownell, 2011). Indeed, neurobiological evidence for the construct of food addiction has grown in the past several years (Davis et al., 2011; Gearhardt, Yokum, et al., 2011; Smith & Robbins, 2013; Volkow, Wang, Fowler, Tomasi, & Baler, 2012; Volkow, Wang, Tomasi, & Baler, 2013). Data suggest that obese individuals have alterations in brain regions associated with reward sensitivity, incentive motivation, memory, learning, impulse control, and stress reactivity, similar to those seen in drug addiction (Volkow et al., 2012). Specifically, obese individuals evidence decreased dopaminergic (D_2R) signaling (Wang et al., 2001) and have been found to have lower gray matter density in frontal regions involved in behavioral control and reward processes (Pannacciulli et al., 2006).

Additionally, investigations of blood-oxygen-level dependent (BOLD) responses have demonstrated greater activation in the gustatory cortex and decreased activation in the caudate nucleus among obese individuals in response to drinking a milkshake versus a tasteless solution (Stice, Spoor, Bohon, Veldhuizen, & Small, 2008). These findings are consistent with the prediction that relative to non-obese individuals, obese individuals are more likely to engage in hedonic eating, which we define as the affective, cognitive, and behavioral drive to eat for the pleasurable, rewarding, or relieving aspects of eating (in contrast with homeostatic eating, which refers to eating driven by caloric needs). Assessing the hedonic drive to eat, or in the extreme, food addiction, may help to explain variability in obesity and identify appropriate treatments for individuals who endorse high levels of hedonically driven eating. Weight loss interventions that target awareness and regulation of hedonic eating may be more effective for obese individuals who have altered neurobiological experiences of food-related reward than weight loss programs that mainly emphasize nutritional content and caloric restriction (Daubenmier et al., 2011, 2014).

Accordingly, it is important to assess biological indicators of hedonic eating. The central opioidergic system may be an important target to assess, as human and animal studies indicate involvement of the opioid system in hedonic eating. Acute consumption of highly palatable food stimulates the release of endogenous opioids (Colantuoni et al., 2002; Peciña & Smith, 2010), and opioidergic antagonists decrease both palatability (Barbano & Cador, 2007) and hedonic eating, as evidenced by reductions in rodents' consumption of palatable food following naloxone administration (Boggiano et al., 2005; Pijlman, Wolterink, & Van Ree, 2003). Similarly, human studies show that short-term administration of opioid antagonists to people with prior opioid addiction histories (Langleben, Busch, O'Brien, &

Elman, 2012) or to obese men (Langleben et al., 2012; Spiegel et al., 1987) can result in reduced hedonic responses to, and consumption of, highly palatable food.

Aside from positron-emission tomography (PET) scanning there are no functional markers of central opioidergic activity in humans (Kling et al., 2000; Weerts et al., 2011). Developing accessible, low-cost methodologies to assess endogenous opioidergic action may allow for better assessment and understanding of obesity phenotypes and food and other addiction processes in humans. Indeed, most research examining associations between eating behavior and endogenous opioidergic activity has been limited by measurement challenges (Yeomans & Gray, 2002); however, researchers have begun to assess downstream effects of opioidergic antagonism (e.g., cortisol and/or nausea responses) to assess how opioidergic blockade is related to substance use (e.g., nicotine, alcohol; e.g., Roche, Childs, Epstein, & King, 2010) and more recently hedonic eating (Daubenmier et al., 2014).

Opioidergic antagonists, such as naltrexone and naloxone, cause acute cortisol release by the hypothalamic-pituitary-adrenocortical (HPA) axis (Lovallo et al., 2012; Pechnick, 1993). Specifically, endogenous opioids inhibit the HPA axis via at least two pathways. First, neurons in the arcuate nucleus that contain β-endorphin and enkephalin activate μ-opioid receptors in the hypothalamus and inhibit corticotropin releasing-hormone (CRH) in the paraventricular nucleus (Johnson, Kamilaris, Chrousos, & Gold, 1992). Second, removing opioidergic inhibitory inputs to neurons that release corticotropin-releasing factor (CRF) in the hypothalamus using opioidergic antagonists increases plasma adrenocorticotropin (ACTH) and cortisol release (Pechnick, 1993). Larger cortisol increases following ingestion of an opioidergic antagonist may therefore indicate weaker endogenous opioidergic activity due to (1) fewer endogenous opioids available to occupy receptor sites or (2) reduced opioid receptor density (Wand et al., 2011). Either case could lead to a more complete blockade of inhibitory inputs to the hypothalamus. Hence, assessing cortisol response to opioidergic antagonism may index individual differences in central opioidergic activity. Indeed, researchers have used opioidergic antagonism to study central opioidergic activity in the context of alcohol and nicotine use (Al'Absi, Wittmers, Hatsukami, & Westra, 2008; Roche et al., 2010).

Nausea often follows naltrexone ingestion (e.g., Katsiki, Hatzitolios, & Mikhailidis, 2011; Yeomans & Gray, 2002) and may index opioidergic blockade. For example, Daubenmier and colleagues (2014) recently demonstrated positive associations between nausea (and cortisol increases) and self-reported eating behavior (including emotional, restrained, and binge eating) following oral ingestion of naltrexone in a pilot study of 33 overweight and obese women. In this sample, greater naltrexone-induced nausea at baseline predicted greater weight loss following a mindfulness-based intervention for stress eating compared to a randomized waitlist group. These findings suggest that mindfulness training may be of particular benefit for overweight or obese women with high levels of opioid-mediated hedonic eating.

In the present analyses we sought to replicate and extend findings from Daubenmier and colleagues (2014) in a larger sample of obese women who participated in a randomized

controlled trial comparing a diet and exercise weight loss intervention with or without mindfulness training. We examined associations between naltrexone-induced cortisol and nausea responses and self-report measures of eating behavior. We extended these analyses by including validated self-report measures of hedonic eating, including food addiction symptoms (Gearhardt, Corbin, & Brownell, 2009) and reward-based eating drive (Epel et al., 2014). We also examined whether naltrexone-induced nausea and cortisol responses predicted treatment response to weight loss intervention with or without mindfulness training by examining 6-month change in weight and self-report measures of eating behavior.

Method

Participants

We invited female participants enrolled in a randomized trial of a 5.5-month diet and exercise weight-loss program with or without mindfulness-based eating and stress reduction components to participate in this sub-study. Eligibility criteria for the parent trial included body mass index (BMI) of 30-45.9, abdominal obesity (female waist circumference > 88 cm), and age 18 or older. Exclusion criteria for the parent study included Type 1 or Type 2 Diabetes (or fasting blood glucose≥126); pregnancy; currently breastfeeding or fewer than 6 months post-partum; corticosteroid, immune-suppressing, immune-modulating, or weight-loss prescription medications; untreated hypothyroidism; and history of or active bulimia (see Daubenmier et al., Under Review, for complete trial information). We enrolled participants in 6 cohorts that completed the intervention between July 2009 and February 2012.

We excluded women from the sub-study if they reported contraindications to naltrexone use such as kidney or liver disease, current illicit drug use, or anticipated need for opioid analgesics (Center for Substance Abuse, 2009). Participants were able to decline participation in this sub-study and to continue their participation in the parent study. The most common reason for declining participation was lack of interest. Participants provided a urine sample to rule out pregnancy, opioid medication use, or illicit drugs. Of the 155 women in the parent trial who were eligible and met inclusion criteria for the sub-study, 88 (56.8%) elected to participate, and 74 (84.1% of the sub-study sample) completed self-report and weight assessments at the 6-month follow-up.

Procedure

The University of California, San Francisco (UCSF) Institutional Review Board approved all study procedures and all participants provided informed consent. We invited participants from the parent trial to participate in this sub-study for additional compensation ($50). Participants completed self-report measures at baseline prior to randomization and at 6 months. Prior to randomization, all participants ingested the placebo pill on Day 1, and the 50 mg naltrexone pill on Day 2; however, they were told that the ordering of pills was randomly assigned. We did not counterbalance order so as to collect baseline values free of drug effects, which can last more than 24 hours. Both participants and study coordinators were masked to pill administration order. We provided participants with two identical pills

that differed only in the color of the bottle in which they were provided to ensure that participants were unaware of pill identity. We instructed participants to ingest these pills at 1 PM on two consecutive days, and to refrain from using alcohol or exercising on these two days. Participants collected saliva samples at 1, 3, and 4 PM and stored them in their home freezer. We provided participants pencil-and-paper logbooks in which to record exact times of pill ingestion, saliva sampling, and nausea severity. Participants returned paper logbooks and frozen saliva samples in an insulated bag with cold packs in person.

Intervention

We summarize the interventions below, and direct the reader to further details published elsewhere (Daubenmier et al., Under Review).

Diet and exercise guidelines—Diet and exercise recommendations were the same in both treatment arms. The diet component focused on modest calorie reduction (reducing food intake by 500 Kcal per day) by decreasing calorically dense, nutrient-poor foods such as refined carbohydrates, and increasing fresh fruit and vegetable consumption, as well as healthy oils and proteins. The exercise component focused on increasing activity throughout the day as well as completing structured aerobic and anaerobic exercise, such as bicycling, swimming, strength training, and walking.

Both intervention arms included sixteen 2-2.5 hour sessions (12 weekly, 3 biweekly, and 1 monthly) and one all-day session over the course 5.5 months. We offered all participants three individual consultations with instructors.

Mindfulness intervention arm—Mindfulness training promotes adaptive self-regulation, which is important for maintaining long-term changes in eating habits (Brown, Ryan, & Creswell, 2007; Kristeller & Wolever, 2010). We administered a novel mindfulness intervention that included mindfulness-based training for stress management, eating, and exercise. We drew intervention components from Mindfulness-Based Stress Reduction (MBSR; Kabat-Zinn & Hanh, 2009) and Mindfulness-Based Eating Awareness Training (MB-EAT; Kristeller & Hallett, 1999; Kristeller, Wolever, & Sheets, 2013). Mindful eating practices targeted awareness and regulation of physical sensations of hunger, stomach fullness, taste satisfaction, food cravings, and emotional and other eating triggers. We addressed hedonic eating patterns by encouraging participants to (1) explore mindful awareness of food cravings by allowing cravings to pass, (2) eat their favorite palatable foods mindfully within the context of their calorie goals, and (3) identify alternative responses to triggers to eat when not physically hungry. We also encouraged participants to spend up to 30 minutes per day, 6 days per week, in formal meditation practice, to eat mindfully, and to engage in mini-meditations throughout the day. We provided participants with materials (e.g., CDs with guided mindfulness practices) for home use.

Active control intervention arm—The active control intervention arm received a moderate dose of training in cognitive-behavioral techniques and progressive muscle relaxation for stress management. To account for attention, social support, expectation of benefit, and home practice time of the mindfulness intervention, we provided active control

participants with additional information about nutrition and physical activity, socio-political issues that impact food choice, and how to make well-informed decisions about diet products. We provided participants with materials (e.g., CDs with progressive muscle relaxation) for home practice.

Materials & Measures

Study drug—We instructed participants to orally ingest 50 mg of naltrexone hydrochloride (ReVia; Teva, North Wales, PA), the FDA-approved dose for treatment of alcohol and opioid dependence, or an identical-looking placebo pill. Participants recorded the time they ingested each pill on each study day in their paper logbook.

Cortisol responses—Participants completed home saliva sampling kits to assess cortisol levels on both placebo and naltrexone days. Participants ingested the placebo (Day 1) and naltrexone (Day 2) pills at 1 PM. Participants collected saliva samples at 1 PM, 3 PM, and 4 PM on each day. Timing of cortisol assessments was based on studies demonstrating peak levels of naltrexone and cortisol concentrations 1 to 3 hours after oral ingestion of naltrexone (e.g., King et al., 2002). Participants collected each sample by drooling into a straw in 2 mL tubes. We determined cortisol levels (Hellhammer Laboratory, University of Trier, Germany) using a competitive solid phase time-resolved fluorescence immunoassay with fluorometric end point detection (DELFIA; Dressendörfer, Kirschbaum, Rohde, Stahl, & Strasburger, 1992). We analyzed two assays from each cortisol sample and averaged them to increase accuracy. No cortisol values fell outside of this method's assay range or of physiological plausibility, which was from 0.17 to 100 nmol/L.

Nausea responses—Nausea symptoms can follow naltrexone ingestion (King et al., 2002; O'Malley, Krishnan-Sarin, Farren, & O'Connor, 2000; Roche et al., 2010). Participants self-reported their experience of nausea using a 4-point scale ranging from 0 (*none*) to 3 (*severe*) at 1 PM, 3 PM, and 4 PM on each day. We coded nausea as absent if participants endorsed no nausea at all timepoints and present if participants endorsed nausea at any timepoint.

Hedonic eating measures—We used three self-report measures to specifically assess hedonic eating

Binge eating: Participants completed the 16-item Binge Eating Scale (BES; (Gormally, Black, Daston, & Rardin, 1982), which assesses the extent and severity of compulsive overeating patterns including behaviors (e.g., eating a large quantity of food) and negative feelings related to these behaviors and body image. Participants respond to items on a scale from 1 (least tendency toward eating pathology) to 4 (greatest tendency toward eating pathology). Scale reliability was high (baseline α=.85; 6 months α=.86).

Food addiction: Participants completed the 25-item Yale Food Addiction Scale (YFAS; Gearhardt et al., 2009), which assesses pathological levels of food addiction symptoms based on the 7 symptoms of substance dependence articulated in the DSM-IV-TR (e.g., withdrawal, tolerance, continued use despite problems; American Psychological

Association, 2000). Participants respond according to different scoring schemes, which include dichotomous and frequency scoring (e.g., ranging from *Never* to *Four or more times daily*). Scores range from 0 (*0 symptoms of food addiction*) to 7 (*7 symptoms of food addiction*). Twenty-one (23.9%) of participants met criteria for food addiction (per DSM-IV-TR substance dependence criteria). Scale reliability was high (baseline α=.88; 6 months α=.86).

Reward-based eating: Participants completed 9 items that comprise the recently validated Reward-based Eating Drive (RED) scale (Epel et al., 2014). Of these, 2 items were taken from the Binge Eating Scale (BES; Gormally et al., 1982), 4 items from the Three Factor Eating Questionnaire (TFEQ; Stunkard & Messick, 1985), and 3 items were developed for this scale. While the RED and BES overlap (2 items), we independently examined the RED scale as it assesses three dimensions of the hedonic drive to eat: loss of control, lack of satiety, and preoccupation with food. Sample items include, *"When I start eating, I just can't seem to stop"* (lack of control), *"I don't get full easily"* (lack of satiety), and *"Food is always on my mind"* (preoccupation with food). In this study, participants answered on original scales (e.g., 1 to 4 for BES), and answered original RED items on a scale from 1 (*strongly disagree*) to 5 (*strongly agree*). We computed z-scores before averaging all items. Higher scores reflect higher reward-based eating drive. Scale reliability was high (baseline α=.80; 6 months α=.81).

Secondary eating measures—We also assessed measures of mindful eating and emotional eating that are relevant to hedonic eating. Mindful eating should be inversely associated with hedonic eating, whereas emotional eating should be positively associated with hedonic eating (Adam & Epel, 2007; Epel, Tomiyama, & Dallman, 2012).

Mindful eating: Participants completed the 28-item Mindful Eating Questionnaire (MEQ; Framson et al., 2009), which assesses mindful eating. The MEQ comprises five subscales (awareness, distraction, disinhibition, emotional, and external subscales), the mean of which represents a mindful eating summary score. Likert scale response options range from 1 (*never/rarely*) to 4 (*usually/always*), with higher scores reflecting greater mindful eating. Subscales are computed as the average item response, and total scale scores are computed scores as averages across the five subscales. Scale reliability was good (baseline α=.76; 6 months α=.80).

Emotional eating: The 13-item Emotional Eating subscale of the Dutch Eating Behavior Questionnaire (DEBQ; van Strien, Frijters, Bergers, & Defares, 1986) assesses eating triggered by specific and diffuse emotions such as anger, boredom, anxiety, or fear. Participants respond to items on a scale from 1 (*never*) to 5 (*very often*). Scale reliability was high (baseline α=.96; 6 months α=.95).

Analytic strategy

First, we used repeated measures ANOVA with Greenhouse-Geisser adjustments to examine a time (1 PM, 3 PM, and 4 PM) by day (placebo vs. naltrexone) interaction predicting cortisol levels. Due to a non-normal and skewed distribution of cortisol responses, we

analyzed simple effects using Wilcoxon sum rank tests. Second, recent evidence suggests that naltrexone-induced cortisol responses can vary across menstrual cycle phase (e.g., luteal and follicular phases) and hormone use (e.g., oral contraceptives; Roche & King, 2015; Roche, King, Cohoon, & Lovallo, 2013). Therefore, we first used repeated measures ANOVA to determine whether time (1 PM, 3 PM, and 4 PM) and day (placebo vs. naltrexone) interacted with self-reported menstrual phase (follicular vs. luteal), menopausal status (pre-menopausal vs. menopausal), and hormone use (i.e., oral contraceptives) to predict cortisol levels. Third, we compared nausea presence on the naltrexone day versus the placebo day using a McNemar exact test. Fourth, we examined associations of self-report measures of eating behavior with nausea and change in cortisol from 1 PM to 4 PM (based on prior work showing peak cortisol responses during this time period, e.g., Daubenmier et al, 2014). Due to a non-normal and skewed distribution of cortisol responses, we conducted Spearman rank-order correlations (as in Daubenmier et al., 2014) to assess associations between cortisol responses and other measures. Fifth, we used independent samples *t* tests to examine differences in eating measures and weight between participants who did and did not report naltrexone-induced nausea. Last, we sought to replicate and extend Daubenmier and colleagues' (2014) prospective analyses by using multiple linear regression to examine how naltrexone-induced nausea (present versus absent) and cortisol changes (4 PM – 1 PM) interacted with treatment arm (mindfulness versus active control) to predict 6-month change in (1) weight, and (2) self-report measures that assess aspects of hedonic eating, including binge eating symptoms, reward-driven eating, and food addiction symptoms. We computed 6-month change (Month 6 – Baseline) and included baseline scores as predictor variables in all regression analyses. We deconstructed interactions using MODPROBE for SPSS (Hayes & Matthes, 2009; Preacher, Curran, & Bauer, 2006). We conducted all analyses in SPSS 22.0 (*IBM SPSS Statistics for Windows*, 2013).

Results

Participants

Women who elected to participate in the sub-study (n=88) endorsed statistically significantly more emotional eating (p=.01) at baseline relative to those who did not participate (n=67). Participants and non-participants were otherwise similar. Participants in the present study did not statistically significantly differ from those in Daubenmier and colleagues' (2014) study in terms of emotional eating, t=0.00, 95% CI [−0.34, 0.34], p=1.00, or binge eating t=0.30, 95% CI [−3.37, 2.49], p=.77.

Pill Ingestion and Cortisol Sampling Times

On average, participants reported ingesting placebo on Day 1 at 1:09 PM (SD=14 min) and naltrexone on Day 2 at 1:08 PM (SD=12 min). Participants reported collecting cortisol saliva samples on Day 1 at 1:06 PM (SD=13 min), 3:07 PM (SD=13 min), and 4:06 PM (SD=14 min). On average, participants reported collecting cortisol saliva samples on Day 2 at 1:04 PM (SD=11 min), 3:05 PM (SD=13 min), and 4:06 PM (SD=10 min). Ninety-five percent and 96% of participants reported ingesting the placebo and naltrexone pills within 15 minutes of 1 PM, respectively.

Cortisol Responses

Repeated measures ANOVA revealed a statistically significant Time x Day effect, $F(2, 164)=15.42$, $p<.001$. Wilcoxon sum rank tests indicated that cortisol levels at 1 PM on the placebo day (Median=4.35) and naltrexone day (Median=3.70) were not statistically significantly different, $Z=-1.29$, $p=.20$. Cortisol levels at 3 PM on the naltrexone day (Median=3.87) were higher than those on the placebo day (Median=2.19), $Z=4.25$, $p<.001$. Similarly, cortisol levels at 4 PM on the naltrexone day (Median=4.63) were higher than those on the placebo day (Median=1.95), $Z=5.70$, $p<.001$ (Figure 1).

Effects of menstrual cycle and hormone use—Study day (naltrexone vs. placebo) and Time (1 PM, 3 PM, 4 PM) did not statistically significantly interact with menstrual cycle status $F(1.91, 63.39)=.21$, $p=.812$, menopausal status $F(1.91, 164.06)=.16$, $p=.842$, or oral contraceptive use $F(1.89, 86.71)=.39$, $p=.668$, to predict cortisol values. Because only two post-menopausal women endorsed using hormone replacement therapy (HRT), we did not conduct statistical analysis comparing women using and not using HRT. We therefore combined women for all analyses. The Time x Day effect remained statistically significant after accounting for each type of menstrual cycle and hormone use variable.

Correlations between measures of hedonic eating and cortisol response—Naltrexone-induced cortisol responses at baseline were statistically significantly positively correlated with reward-based eating drive ($\rho=.21$, $p=.048$) and food addiction ($\rho=.21$, $p=.045$), and were negatively correlated with mindful eating ($\rho=-.22$, $p=.040$). Cortisol responses were not statistically significantly associated with binge eating symptoms ($\rho=.04$, $p=.708$), emotional eating ($\rho=.05$, $p=.658$), weight ($\rho=-.003$, $p=.976$), or BMI ($\rho=-.02$, $p=.875$).

Intervention by cortisol effects—The interaction of naltrexone-induced cortisol responses with treatment arm in predicting 6-month change in food addiction symptoms approached statistical significance[1]. See Table 3 and Figure 2.

Deconstructing this interaction revealed that, among participants with naltrexone-induced cortisol increases (+1 SD above the mean), mindfulness participants reported significantly greater reductions in food addiction symptoms from baseline to 6 months relative to active control participants, $b=-0.95$, SE(b)=0.40, 95% CI [−1.74, −0.15], $p=.021$. We did not observe this difference among participants with naltrexone-induced cortisol decreases (−1 SD below the mean), $b=0.17$, SE(b)=0.39, 95% CI [−0.61, 0.96], $p=.663$. Second, among active control participants, larger naltrexone-induced cortisol increases predicted significantly *smaller* reductions in food addiction symptoms from baseline to 6 months, $b=0.08$, SE(b)=0.02, 95% CI [0.006, 0.14], $p=.034$. We did not observe this association among mindfulness participants, $b=-0.01$, SE(b)=0.02, 95% CI [−0.06, 0.04], $p=.794$.

Naltrexone-induced cortisol responses did not interact with treatment arm to statistically significantly predict 6-month change in weight, consistent with Daubenmier and colleagues

[1]Removing the two women using HRT does not substantially change this result, though it lowers the p value ($p=.054$).

(2014; see Table 3). Similarly, this interaction did not statistically significantly predict 6-month change in binge eating symptoms or reward-driven eating (see Table 3). These analyses for mindful or emotional eating were also not statistically significant (not shown).

Nausea Responses

Statistically significantly more women reported experiencing nausea on the naltrexone day (n=38; 43.2%) than on the placebo day (n=15, 17.0%; $p<.001$ by a McNemar exact test). As shown in Table 2, women who endorsed nausea after naltrexone ingestion trended toward reporting more reward-based eating and evidencing greater cortisol rises from 1 PM to 4 PM. Results for binge eating and food addiction symptoms were in the same direction, though not statistically significant (Table 2).

Intervention by nausea effects—We next examined whether naltrexone-induced nausea predicted 6-month changes in eating behavior and weight and whether treatment arm moderated these associations (Figure 3). Models predicting change in food addiction and binge eating symptoms approached statistical significance (Table 4). Deconstructing the interaction predicting change in food addiction symptoms revealed that among participants endorsing naltrexone-induced nausea, mindfulness participants reported statistically significantly greater reductions in food addiction symptoms than control participants, $b=-1.00$, SE(b)=0.43, 95% CI [−1.85, −0.77], $p=.024$. Deconstructing the interaction term predicting binge eating symptoms also revealed that among participants endorsing naltrexone-induced nausea, mindfulness participants trended evidenced a statistical trend toward reporting greater reductions in binge eating symptoms than control participants, $b=-2.93$, SE(b)=1.76, 95% CI [−6.44, 0.57], $p=.100$ (Figure 3). We observed a similar pattern (though not statistically significant) for interaction deconstructions of weight and reward-based eating, but did not observe this pattern for mindful eating, or emotional eating (not shown).

Discussion

Results from this study provide further evidence for the use of physiological responses to acute opioidergic blockade as an index of opioid-mediated hedonic eating. Similar to earlier pilot results (Daubenmier et al., 2014), we found that ingestion of oral naltrexone led to greater cortisol increases among individuals who reported more hedonic eating, as indexed by more food addiction symptoms and reward-driven eating, and less mindful eating. These results are consistent with the hypothesis that individuals who are more sensitive to the rewarding aspects of eating may have alterations in endogenous opioid function similar to those seen in drug-addicted individuals (Volkow et al., 2012, 2013). Hence, naltrexone-induced cortisol responses may identify obese women who have underlying alterations in central opioidergic activity that drive hedonic eating.

Can responses to naltrexone predict who will benefit from different types of weight loss interventions? Our results suggest that women with larger nausea and cortisol responses to naltrexone, which presumably reflect greater alterations in endogenous opioidergic activity, may particularly benefit from mindfulness-based weight-loss programs. Specifically, among women who reported nausea or evidenced larger cortisol responses to naltrexone ingestion,

mindfulness participants reported greater reductions in food addiction symptoms than control participants. Furthermore, mindfulness participants who reported nausea also tended to report greater reductions in binge eating symptoms and reward-based eating than control participants. These findings echo promising earlier findings that mindfulness training may be particularly potent for decreasing eating in response to craving, emotions, and hedonic drive (Bowen & Marlatt, 2009; Kristeller & Wolever, 2010; Kristeller et al., 2013).

Similar to Daubenmier and colleagues (2014), we found that naltrexone-induced nausea evidenced a statistical trend in predicting weight change following a mindfulness-based intervention for weight loss. At the 6-month assessment, participants who had reported nausea lost 4.69 kg in the mindfulness arm compared to 1.81 kg in the active control arm. In contrast, there were minimal between-arm differences in 6-month weight loss among participants who did not endorse nausea. These trends suggest that mindfulness-based diet and exercise interventions, relative to standard diet and exercise interventions, may promote more weight loss and improved regulation of eating for individuals with presumably altered endogenous opioidergic activity and the related experience of greater hedonic drive. Our data also suggest that individuals without strong nausea or cortisol responses to naltrexone may show improvements in hedonic eating and weight loss regardless of adjuvant mindfulness training.

The association between emotional eating and naltrexone-induced cortisol responses may not be robust across samples. Daubenmier and colleagues (2014) reported a statistically significant correlation of r=.33; in the current study, we did not observe a statistically significant association (r=.05). Participants in both arms reported similarly high levels of emotional eating. Emotional eating as indexed by the DEBQ, however, does not explicitly assess the hedonic and addictive drive that is characteristic of reward-driven and addictive behavior, but may better reflect heightened stress-induced eating. Although speculative, the association between emotional eating and naltrexone-induced cortisol changes may reflect heightened stress reactivity rather than reward-driven eating. The current sample was less psychologically stressed compared to the pilot sample [Daubenmier and colleagues' (2014) sample reported greater perceived stress (19.0) as measured by the Perceived Stress Scale (PSS; Cohen, Kamarck, & Mermelstein, 1983) than the present sample (14.3)], which may partly explain the non-statistically significant relationship between emotional eating and cortisol responses in the current study.

Further research should seek to understand associations among stress reactivity and cortisol responses to naltrexone, which is well underway in other research on addictions. For example, researchers investigating alcohol misuse report that blunted HPA axis stress responses correlate with alcohol craving and relapse. They have postulated that that the efficacy of naltrexone in preventing alcohol relapse may result from its increasing HPA axis activity (Adinoff, Irnanmanesh, Veldhuis, & Fisher, 1998; Adinoff, Junghanns, Kiefer, & Krishnan-Sarin, 2005; Lovallo et al., 2012). In support of this idea, Kiefer and colleagues (2006) found that following alcohol withdrawal, not only were individuals with low baseline cortisol significantly more likely to relapse if they ingested a placebo rather than naltrexone, but also that decreases in plasma cortisol were significantly correlated with shorter periods of abstinence. Thus, low cortisol may be a risk factor for substance misuse, and increasing

cortisol may represent action on a marker or a mechanism of improved abilities to abstain from substance misuse. Given neurobiological evidence that food can be an addictive substrate (e.g., Davis et al., 2011; Volkow, Wang, Tomasi, & Baler, 2013), and evidence of blunted cortisol among humans and rodents who engage in stress-induced eating of hyperpalatable comfort foods (Tomiyama, Dallman, & Epel, 2011; Tryon, DeCant, & Laugero, 2013; van Strien, Roelofs, & de Weerth, 2013), it is possible that these processes may also apply in the case of food addiction.

We note that whereas naltrexone appears to be an efficacious monotherapy for alcohol addition (Anton et al., 2014; Srisurapanont & Jarusuraisin, 2005) it does not appear to be so for obesity (Billes, Sinnayah, & Cowley, 2014). Naltrexone in combination with bupropion, however, appears to have longer-term effects on weight loss (Caixàs, Albert, Capel, & Rigla, 2014). Researchers have posited that μ opioidergic blockade within the hypothalamic melanocortin and mesocorticolimbic dopamine systems may be a key mechanism of action of naltrexone in the treatment of obesity (e.g., Caixàs et al., 2014), and have not devoted specific focus to mechanism via the HPA axis pathway. Naltrexone's effect of increasing cortisol via alterations in opioidergic activity; however, suggests a potential mediating role of the HPA axis in naltrexone's neurobiological effects (Ray, MacKillop, Leggio, Morgan, & Hutchison, 2009). To our knowledge, no studies have examined long-term effects of naltrexone on HPA function in the context of hedonic eating or obesity.

Nausea showed positive, albeit weak, associations with hedonic eating behavior in this study, and no statistically significant association with adiposity. This contrasts with the earlier pilot study (Daubenmier et al., 2014), which found larger associations. Of note, there are several differences between the two samples: On average, the present sample was more obese and less psychologically stressed, and the present sample included post-menopausal women. These factors may impinge on associations between naltrexone-induced nausea and hedonic eating behavior, and deserve further attention. In addition, the naltrexone-induced cortisol increases and nausea were not highly correlated, as found in earlier studies (e.g., Daubenmier et al., 2014; Roche and King, 2015). Opioidergic systems governing subjective responses such as nausea may be separate from hypothalamic opioid tone. Indeed, the gastrointestinal tract is home to several endogenous opioidergic actions, and direct action on this opioidergic system could contribute to naltrexone-induced nausea (Holzer, 2009; Roche & King, 2015).

Although these findings require further validation, our data suggest that a single ingestion of oral naltrexone may identify women who will derive greater benefit from interventions that include mindfulness training, which targets hedonic eating.

Data and analyses we presented here have several methodological strengths and limitations. First, we collected data in the context of a rigorous randomized controlled trial (Daubenmier et al., Under Review). Additionally, all participants in this study were obese (mean BMI=35.8) whereas those in the pilot study (mean BMI=31.4; Daubenmier et al., 2014) were overweight or obese (BMI>25,), and therefore we are better able to generalize to obese women who are likely to participate in weight management programs. These analyses only examined women. Future research should carefully investigate these processes in men, as

men have demonstrated weak or non-existent naltrexone-induced cortisol increases (Roche et al., 2010, 2013; Roche & King, 2015). Further research could specifically explore the role of menstrual cycle phase on associations between naltrexone responses and hedonic eating (Roche and King, 2015). Furthermore, to better unpack associations between hedonic eating and the endogenous opioidergic system, future studies could focus on individuals who self-identify as food addicted (e.g., Gearhardt et al., 2009).

To obtain comparison baseline data on nausea and other variables, we did not randomize the order of the placebo and naltrexone pills; however, both participants and study staff believed the order to be randomized, and thus expectations likely did not drive self-reported nausea. The sub-study study took place outside of the laboratory and required participants to ingest naltrexone orally at home. This design allowed us to assess women in their typical environments (i.e., in the context of the cues for food cravings that they most often encounter) and likely afforded a more realistic reflection of their day-to-day lives. However, the lack of a controlled study environment may have introduced other sources of error.

To better understand how naltrexone may impact food preferences and eating behavior, future studies should assess palatable food intake following naltrexone ingestion, both acutely and hours later. Immediate assessment of post-stressor food intake may not provide the optimal resolution of measurement, as increased eating following a stressor (e.g., laboratory stressor task or drug challenge) may not be immediate, but rather delayed (Nieuwenhuizen & Rutters, 2008). Specifically, CRH exerts an anorectic effect at the beginning of the stress response, whereas glucocorticoids (GCs) increase appetite following prolonged HPA activation. This may account for mixed findings regarding stress-induced cortisol changes and in-laboratory, post-stressor eating (e.g., Newman, O'Connor, & Conner, 2007; van Strien et al., 2013). Hence, future studies should consider assessing eating behavior at a variety of resolutions, including the immediate hours after, and the full 24-hour period following, naltrexone ingestion. Ideally, assessments would take place both within and outside of the laboratory (e.g., Newman et al., 2007) using repeated measures and 24-hour dietary recalls. Future study designs may also benefit from randomizing the order in which participants ingest study medications.

Of note, naltrexone-induced cortisol and nausea changes are indirect measures of central opioid activity (Davis & Loxton, 2014). To better understand these functional measures, further investigation of the role of the central opioidergic system in hedonic eating could validate naltrexone-induced cortisol and nausea responses against opioid receptor binding potential using PET in samples of individuals reporting more and less hedonic eating. Additionally, examining how external substances, such as food or drugs, impact associations between the endogenous opioid system and the HPA axis may provide important clues about associations between addiction and stress. Last, although results we report here mirror those of the earlier pilot study, many effects were of marginal statistical significance. We speculate that using a more specific μ opioidergic antagonist might induce stronger withdrawal effects that correlate with eating behavior.

Conclusion

These findings replicate previous pilot results suggesting that cortisol responses and, to some extent, nausea responses following acute opioidergic blockade may be important biomarkers of hedonic eating drive among obese women. In this study, women who experienced naltrexone-induced cortisol increases or nausea reported larger reductions in hedonic eating and tended to lose more weight in the mindfulness compared to the standard weight loss program. These findings hold important implications for treatment matching. Obese individuals with presumably altered endogenous opioidergic activity – that is, those who experience naltrexone-induced cortisol increases or nausea – may represent a distinct subgroup of individuals whose success in behavioral weight loss interventions is bolstered by the addition of mindfulness training that targets hedonic eating.

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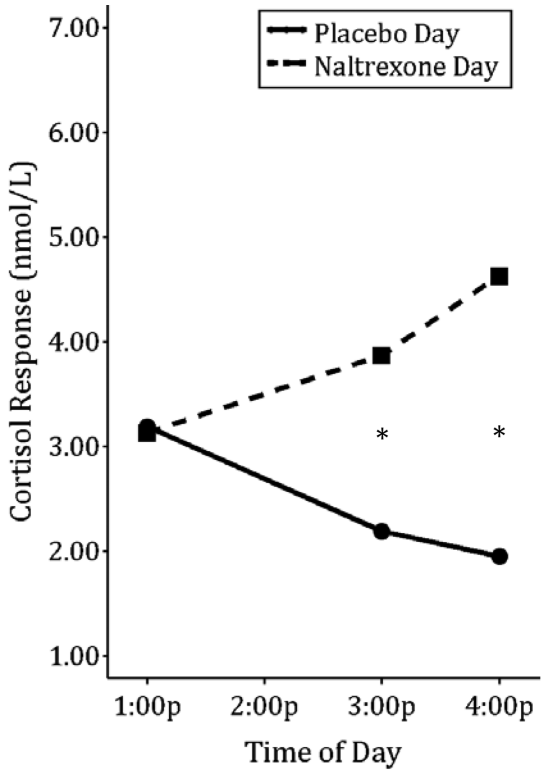
Highlights

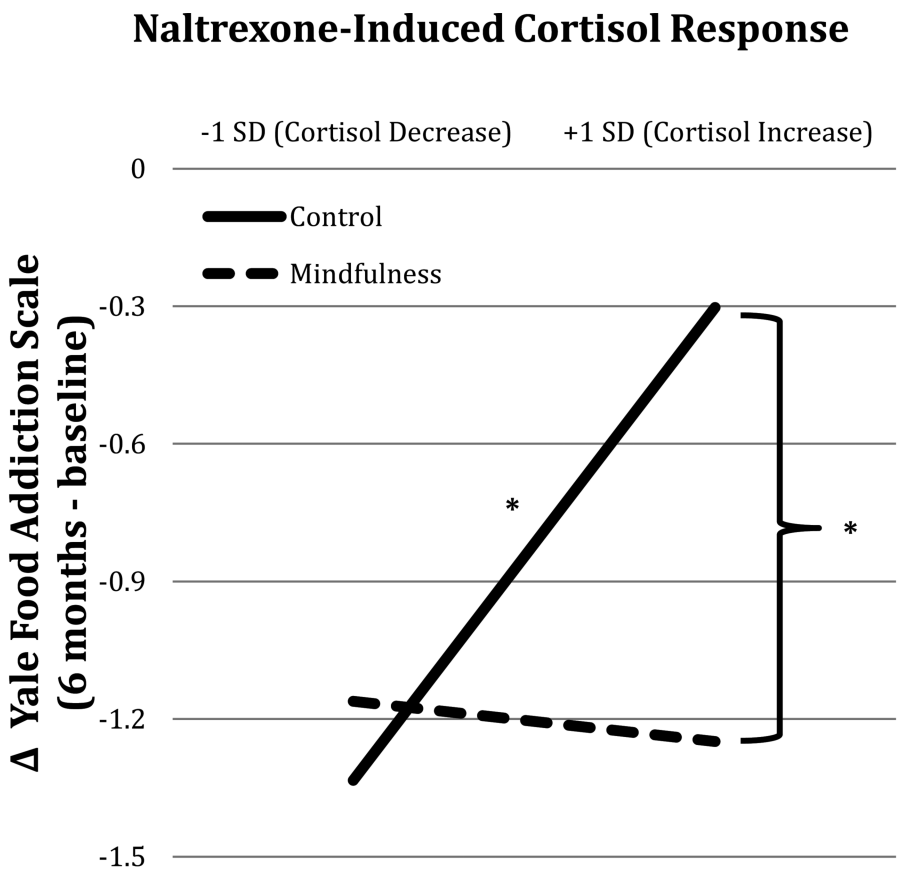
- We examined acute cortisol and nausea responses to naltrexone
- Naltrexone responses were associated with measures of hedonic eating
- Naltrexone responses may identify greater opioid-mediated hedonic eating drive
- A mindfulness vs. standard weight loss program may improve food addiction



Note. * p <. 01. Statistically significant Day*Time interaction indicated by repeated measures ANOVA.

* Indicates statistically significant differences (p < .001) within timepoint using Wilcoxon Signed Rank Tests.

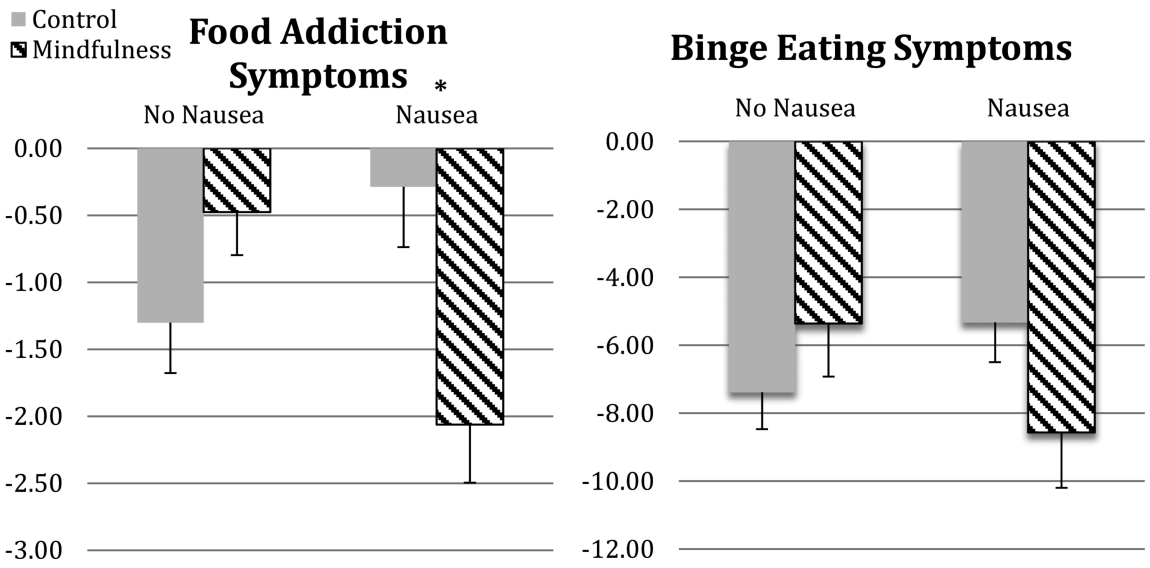
Figure 1.
Naltrexone-induced cortisol increases from 1 PM to 4 PM on placebo and naltrexone days at baseline.



Note. * p <.05. Graph depicts change in food addiction symptoms from baseline to 6 months.

X-axis depicts -/+ 1 SD below and above the mean naltrexone-induced cortisol response, respectively.

Figure 2.
Interaction of naltrexone-induced cortisol response and treatment arm (active control vs. mindfulness) as a predictor of changes in self-reported food addiction symptoms.



Note. All graphs depict change from baseline to 6-month assessment.

**p* = .024. Error bars represent standard errors of the mean. Food Addiction Symptoms=Yale Food Addiction Scale; Binge Eating Symptoms=Binge Eating Scale.

Figure 3.
Interaction of naltrexone-induced nausea (present vs. absent) and treatment arm (active control vs. mindfulness) as a predictor of changes in self-report measures of food addiction and binge eating symptoms.

Table 1

Naltrexone sub-study participant characteristics, *N*=88.

Variable or Scale	***Mean* (SD) or N (%)**			***p***
	Full Sample (*N*=88)	**Mindfulness (*n*=45)**	**Active Control (*n*=43)**	
Age (years)	46.69 (13.24)	46.52 (14.06)	46.86 (12.5)	.903
Weight (kg)	94.48 (12.61)	94.2 (10.41)	94.78 (14.68)	.832
BMI (kg/m^2)	35.81 (3.77)	35.51 (3.43)	36.12 (4.11)	.448
Race/Ethnicity (N and %)				
White	54 (61.4%)	29 (64.4%)	25 (58.1%)	.662[a]
Other	5 (5.7%)	4 (8.9%)	1 (2.3%)	-
Black	9 (10.2%)	4 (8.9%)	5 (11.6%)	-
Latino	14 (15.9%)	5 (11.1%)	9 (20.9%)	-
Asian/Pacific Islander	5 (5.7%)	3 (6.7%)	2 (4.7%)	-
Native American	1 (1.1%)	0 (0.0%)	1 (2.3%)	-
Menopausal status (N and % Postmenopausal)	40 (45.5%)	19 (42.4%)	21 (48.8%)	.341[a]
Hedonic Eating Measures				
Binge Eating Scale (BES)	16.76 (6.99)	16.98 (6.88)	16.52 (7.18)	.757
Yale Food Addiction Scale (YFAS)	2.95 (1.64)	2.97 (1.71)	2.93 (1.59)	.893
Reward-based Eating Drive (RED) Scale	0.07 (0.60)	0.19 (0.63)	−0.06 (0.54)	
Emotional Eating subscale, Dutch Eating Behavior Questionnaire (DEBQ)	3.4 (0.87)	3.43 (0.86)	3.37 (0.9)	.764
Mindful Eating Questionnaire (MEQ)	2.58 (0.33)	2.59 (0.35)	2.57 (0.32)	.828
Placebo-induced Cortisol response (4 PM – 1 PM)	1.13 (4.05)	−1.02 (4.63)	1.24 (3.40)	.799
Naltrexone-induced Cortisol response (4 PM – 1 PM)	2.79 (6.38)	3.20 (7.22)	2.34 (0.82)	.533
Nausea Response, Naltrexone Day (present)	38 (43.2%)	19 (42.2%)	19 (44.2%)	1.00[a]
Nausea Response, Placebo Day (present)	15 (17.0%)	8 (17.8%)	7 (16.3%)	1.00[a]

Note. BMI=Body Mass Index.

[a]Result of Chi-Square test.

Table 2

Means and standard deviations of baseline weight, self-report eating measures, and naltrexone-induced cortisol response by nausea group (*N*=88).

Variable or Scale	*Mean* (SD) No Nausea (*n*=50)	*Mean* (SD) Nausea (*n*=38)	*Mean* Diff	95% CI	*p*
BMI (kg/m^2)	35.86 (3.89)	35.74 (3.65)	0.12	(−1.50, 1.75)	.878
Hedonic Eating Measures					
Binge Eating Scale	15.73 (6.74)	18.11 (7.17)	−2.39	(−5.36, 0.58)	.113
Yale Food Addiction Scale	2.72 (1.55)	3.26 (1.73)	−0.54	(−1.24, 0.16)	.126
Reward-based Eating Drive Scale	−0.03 (0.60)	0.19 (0.58)	−0.23	(−0.49, 0.02)	.074
Emotional Eating subscale, Dutch Eating Behavior Questionnaire (DEBQ)	3.28 (0.89)	3.55 (0.84)	−0.27	(−0.64, 0.10)	.154
Mindful Eating Questionnaire	2.61 (0.35)	2.53 (0.31)	0.08	(−0.07, 0.22)	.291
Naltrexone-induced cortisol response (4 PM – 1 PM)	1.59 (4.31)	4.35 (8.16)	−2.76	(−5.68, 0.16)	.064

Note. Degrees of freedom (*df*) for all comparisons were 86.

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Table 3

Treatment arm (mindfulness vs. active control) × baseline naltrexone-induced Cortisol (4 PM – 1 PM) predicting weight and self-report hedonic eating measures at 6 months (*N*=88).

	Outcome: Yale Food Addiction Scale				Outcome: Reward-based Eating Drive Scale			
Variable	***β***	**SE(*b*)**	***b* (95% CI)**	***p***	***β***	**SE(*b*)**	***b* (95% CI)**	***p***
Intercept		0.33	1.31 (0.66, 1.97)	1.58×10^{-4}		0.09	0.01 (−0.18, 0.20)	.911
Outcome at baseline	0.30	0.08	0.22 (0.05, 0.38)	.010	0.54	0.10	0.54 (0.34, 0.75)	2.00×10^{-6}
Δ Cortisol	0.42	0.04	0.08 (0.01, 0.15)	.034	0.23	0.02	0.02 (−0.01, 0.05)	.183
Treatment Arm	−0.04	0.31	−0.10 (−0.71, 0.52)	.757	−0.07	0.13	−0.08 (−0.34, 0.18)	.540
Δ Cortisol × Treatment Arm	−1.94	0.04	−0.08 (−0.17, 0.003)	.057	−0.01	0.02	−0.01 (−0.05, 0.02)	.495
			Full Model R^2 = .19				Full Model R^2 = .33	

	Outcome: Binge Eating Scale				Outcome: Weight (Kg)			
Variable	***β***	**SE(*b*)**	***b* (95% CI)**	***p***	***β***	**SE(*b*)**	***b* (95% CI)**	***p***
Intercept		1.73	1.99 (−1.46, 5.44)	.254		4.47	1.89 (−7.02, 10.80)	.674
Outcome at baseline	0.58	0.09	0.49 (0.32, 0.66)	2.45×10^{-7}	0.92	0.05	0.95 (0.86, 1.04)	5.58×10^{-31}
Δ Cortisol	0.13	0.15	0.11 (−0.18, 0.40)	.454	0.05	0.15	0.09 (−0.21, 0.40)	.533
Treatment Arm	0.02	1.30	0.28 (−2.31, 2.87)	.830	−0.05	1.32	−1.24 (−3.87, 1.39)	.349
Δ Cortisol × Treatment Arm	−0.22	0.18	−0.22 (−0.58, 0.14)	.228	−0.08	0.19	−0.19 (−0.56, 0.19)	.326
			Full Model R^2 = .34				Full Model R^2 = .87	

Note. All models account for outcome at baseline. Treatment arm dummy coded as active control (0) and mindfulness (1). Δ Cortisol quantified as (4 PM – 1 PM). Full Model ΔR^2 presented after adding interaction term to model.

Table 4

Treatment arm (mindfulness vs. active control) × baseline naltrexone-induced nausea (present vs. absent) predicting weight and self-report hedonic eating measures at 6 months (*N*=88).

	Outcome: Yale Food Addiction Scale				Outcome: Reward-based Eating Drive Scale			
Variable	***β***	**SE(*b*)**	***b* (95% CI)**	***p***	***β***	**SE(*b*)**	***b* (95% CI)**	***p***
Intercept		0.39	1.12 (0.35, 1.89)	.005		0.11	−0.04 (−0.25, 0.17)	.682
Outcome at baseline	0.40	0.09	0.29 (0.11, 0.45)	.001	0.56	0.10	0.56 (0.35, 0.76)	8.35×10^{-7}
Nausea	0.21	0.40	0.53 (−0.28, 1.33)	.199	0.23	0.17	0.27 (−0.05, 0.60)	.105
Treatment Arm	0.04	0.37	0.10 (−0.64, 0.83)	.794	0.01	0.15	0.01 (−0.29, 0.30)	.968
Nausea × Treatment Arm	−0.37	0.58	−1.09 (−2.25, 0.07)	.065	−0.21	0.23	−0.29 (−0.75, 0.17)	.219
			Full Model R^2 = .18				Full Model R^2 = .33	

	Outcome: Binge Eating Scale				Outcome: Weight (Kg)			
Variable	***β***	**SE(*b*)**	***b* (95% CI)**	***p***	***β***	**SE(*b*)**	***b* (95% CI)**	***p***
Intercept		1.76	1.35 (−2.17, 4.86)	.447		4.50	0.80 (−8.17, 9.77)	.860
Outcome at baseline	0.57	0.08	0.48 (0.31, 0.65)	2.55×10^{-3}	0.92	0.05	0.96 (0.86, 1.04)	1.86×10^{-31}
Nausea	0.23	1.66	2.67 (−0.64, 5.98)	.113	0.06	1.70	1.54 (−1.85, 4.93)	.368
Treatment Arm	0.11	1.49	1.25 (−1.72, 4.21)	.405	−0.04	1.55	−1.08 (−4.18, 2.01)	.488
Nausea × Treatment Arm	−0.30	2.31	−4.18 (−8.78, 0.42)	.074	−0.06	2.36	−1.85 (−6.56, 2.87)	.438
			Full Model R^2 = .36				Full Model R^2 = .86	

Note. All models account for outcome at baseline. Treatment arm dummy coded as active control (0) and mindfulness (1).

Full Model ΔR^2 presented after adding interaction term to model.