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Effect of the CRF₁-receptor antagonist pexacerfont on stress-induced eating and food craving

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Abstract

Rationale—In rodents, antagonism of receptors for corticotropin-releasing factor (CRF) blocks stress-induced reinstatement of drug or palatable food seeking.

Objective—To test anticraving properties of the CRF₁ antagonist pexacerfont in humans.

Methods—We studied stress-induced eating in people scoring high on dietary restraint (food preoccupation and chronic unsuccessful dieting) with body-mass index (BMI) >22. In a double-blind, between-groups trial, 31 “restrained” eaters were stabilized on either pexacerfont (300 mg/day for 7 days, then 100 mg/day for 21 days) or placebo. On day 15, they underwent a math-test stressor; during three subsequent visits, they heard personalized craving-induction scripts. In each session, stress-induced food consumption and craving were assessed in a bogus taste test and on visual analog scales. We used digital video to monitor daily ingestion of study capsules and nightly rating of food problems/preoccupation on the Yale Food Addiction Scale (YFAS).

Results—The study was stopped early due to an administrative interpretation of US federal law, unrelated to safety or outcome. The bogus taste tests suggested some protective effect of pexacerfont against eating after a laboratory stressor ($r_{\text{effect}} = 0.30$, 95 % CL = -0.12 , 0.63 , Bayes factor 11.30). Similarly, nightly YFAS ratings were lower with pexacerfont than placebo ($r_{\text{effect}} = 0.39$, CI 0.03 , 0.66), but this effect should be interpreted with caution because it was present from the first night of pill ingestion, despite pexacerfont’s slow pharmacokinetics.

Conclusions—The findings may support further investigation of the anticraving properties of CRF₁ antagonists, especially for food.

Keywords

Craving; Stress-induced eating; Dietary restraint; CRF₁ antagonists; Bogus taste test

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

We set out to prevent stress-driven compulsive behavior with pexacerfont, an antagonist at the CRF₁ subtype of receptors for the neurotransmitter corticotropin-releasing factor (CRF). Pexacerfont has been tested in clinical trials for mood and anxiety disorders and was found ineffective for those conditions, though benign in its side-effect profile (Binneman et al. 2008; Coric et al. 2010; Kunzel et al. 2003; Zobel et al. 2000). In the rat reinstatement model of addiction relapse, CRF₁-receptor antagonists prevent stress-induced resumption of responding for heroin, cocaine, alcohol, and nicotine (Mantsch et al. 2016; Shaham et al. 2000)—and also for palatable food (Ghitza et al. 2006; Nair et al. 2009). When we started the current study, those reinstatement findings had not yet been translationally tested in humans. Each of them was of potential clinical interest. We focused on stress-induced eating rather than on stress-induced drug use because we had no safety data on interactions of pexacerfont with drugs of abuse.

We also assessed pexacerfont's effects on one of the likely mediators of stress-induced eating: craving. Craving is experienced in many of the disorders that involve compulsive or excessive behavior, such as gambling disorder (Goudriaan et al. 2010), compulsive shopping (Potenza 2014), and eating disorders (Brooks et al. 2012), and its neural substrates may be similar across all those conditions (Goudriaan et al. 2010). Even when craving does not lead to a compulsive behavior, it can be an unwanted distraction (Green et al. 2000) and is therefore an appropriate target for prevention.

Our main outcome measure, however, was not craving but actual eating—because stress could increase eating with no accompanying increase in consciously experienced craving (for example, stress could change the time horizons for decision making, such that immediate rewards are given priority over delayed consequences; Starcke and Brand 2012). Our measure of eating was the bogus taste test, in which foods presented in the guise of a taste test are surreptitiously weighed before and after participants taste them (Polivy et al. 1988).

To ensure that the participant population was one in which stress-induced eating was likely to occur and be problematic, we enrolled people scoring high on a trait called dietary restraint (Heatherton et al. 1991; Herman and Polivy 1980; Mitchell and Epstein 1996; Wardle et al. 2000). The terminology is counterintuitive: restrained eaters are chronic unsuccessful dieters who report a troubling preoccupation with food. Although dietary restraint may predict unhealthy weight gain (Klesges et al. 1992), it is not synonymous with obesity (Epstein and Shaham 2010; Rodin 1981) and is not an eating disorder. Rather, it can be thought of as a statistically “normal” (Polivy and Herman 1987) but maladaptive trait that contributes to a spiral of unhealthy eating and stress (Nieuwenhuizen and Rutters 2008). We hypothesized that in restrained eaters, pexacerfont would protect against stress-induced eating and food craving.

Materials and methods

Participants and setting

The study took place at the outpatient treatment-research clinic of the NIDA Intramural Research Program (IRP) in Baltimore.

We recruited healthy, adult “restrained” eaters (assessed by the Dietary Restraint Scale (Herman and Polivy 1980)). Anticipating maximum dropout of 20 %, we set a ceiling of 116 enrollees in order to have 90 completers. Participants gave written informed consent as approved by the Institutional Review Board of the NIDA IRP.

Inclusion criteria were as follows: body-mass index (BMI) $>22 \text{ kg/m}^2$; score of 15 or higher on the Dietary Restraint Scale, with endorsement of the item “Do you give too much time and thought to food?”; age 21–65 years; for women of childbearing potential, negative pregnancy test and agreement to use contraception for 6 months after randomization; for men, agreement not to conceive a child or donate sperm for 6 months after randomization.

Among the exclusion criteria were diabetes, type 1 or 2; ischemic heart disease; uncontrolled hypertension; allergies to foods used in the study; history of cerebrovascular accident or transient ischemic attack; past or current eating disorders, psychotic disorder, or bipolar disorder; current mood or anxiety disorder; past or current substance-use disorder except nicotine dependence; urine positive for illegal drugs; liver, thyroid, adrenal, or pituitary pathology; significant neurological disorders; use of medications that induce or inhibit CYP3A4; and dietary restrictions or food aversions that would interfere with laboratory assessment of eating.

General procedures

This was a randomized, double-blind, placebo-controlled study with two groups. Pexacerfont or placebo (obtained from Bristol-Meyers Squibb, New York, NY, USA) was administered on an outpatient basis (with video-based compliance monitoring) for up to 28 days. After day 14 of pexacerfont or placebo, each participant attended laboratory sessions. The schedule of events is shown in Table 1.

Immediately after signing informed consent, participants were randomized at a 1:1 ratio to placebo or pexacerfont. Randomization was stratified by sex, BMI, and baseline score on dietary restraint. Randomization was carried out by the NIDA IRP pharmacy, insulated from staff interacting with participants.

Based on the known pharmacokinetics of pexacerfont, participants randomized to pexacerfont received a loading dose of 300 mg to be taken once every evening for 7 days, followed by a maintenance dose of 100 mg once every evening for 21 days (Coric et al. 2010). Participants received written instructions about missed doses and pharmacokinetic interactions. To document adherence, each participant was lent a small digital camera and told to record time-stamped daily videos as he or she swallowed the pills. Each participant was also given copies of a daily version of the Yale Food Addiction Scale (YFAS) (Gearhardt et al. 2009). Participants were asked to make a time-stamped video of the completed YFAS every evening.

Visit 2, approximately 1 week after the first day of pexacerfont/placebo, was an interview to develop personalized stress- and food-related imagery scripts for each participant, for use in later visits (4 through 6, where a secondary set of outcome measures was to be collected). The methodology for script development was originated by Lang and colleagues (Miller et

al. 1987) and later adapted by Sinha and colleagues to study stress-induced drug craving (Sinha et al. 1999, 2000, 2006).

Visit 3, on day 15 of pexacerfont/placebo, was a laboratory stress session at which we collected data on the primary outcome, stress-induced eating as assessed by the bogus taste test procedure (Polivy et al. 1988). Participants were asked to consume only water for 12 h before arriving at 9:00 AM. On arrival, they had their height and weight checked and provided a blood sample (for levels of pexacerfont, thyroid hormones, stress-related hormones, and liver enzymes, and for chemistries and blood count) and a urine sample (for levels of proteins and glucose and for pregnancy testing in women). Their video was checked to ensure they had taken their study pill the night before. They were served a standardized light breakfast, generally no later than 10:00 AM, to allow time before the bogus taste test. At approximately 11:30 AM, participants underwent the computerized version of the Paced Auditory Serial Addition Task (PASAT-C) (Lejuez et al. 2003), a standard stressor in which the participant has to add pairs of successively presented digits. After entering each sum, the participant must then ignore that sum and add the following digit to the previous digit. For example, the correct answers to the series of 7, 8, 4, 5, and 1 would be 15, 12, 9, and 6.

Immediately before and after the PASAT-C, participants responded to the written prompt “Please rate how much stress you are feeling AT THIS MOMENT” on a visual analog scale marked 0–100.

The bogus taste test occurred approximately at noon, immediately after the PASAT-C stress rating. The researcher presented four bowls of food: Little Debbie brownies, Swedish fish candy, Lay’s Classic potato chips, and Totino’s cheese pizza rolls. Participants were asked to rate the sensory properties of the foods while the researcher left the room for 30 min. The outcome of interest was not the ratings but the amount of food consumed, as determined by surreptitious weighing of the food before and after the session. Prior work has shown that restrained eaters are especially prone to experimentally induced increases in consumption in bogus taste tests (Guerrieri et al. 2009). After the bogus taste test, participants were asked how much they craved each of the four types of food “AT THIS MOMENT?” on a 1–10 scale.

After providing those ratings, participants were given 10 min of guided relaxation, which was repeated until stress and craving returned to within one point of presession levels. Participants were then discharged.

During the 2 weeks after the PASAT-C session, each participant returned for three imagery script sessions, intended to explore whether any anticraving effect of pexacerfont was specific to stress-induced or cue-induced craving. Daily pexacerfont/placebo continued until the day of the third session. The stress-related, food-related, and neutral scripts were presented on successive days (consecutive days whenever possible), one script per day, in a sequence counterbalanced across participants. A bogus taste test occurred after each script; the four foods in all script sessions were M&Ms, Famous Amos chocolate chip cookies, Cheez-It baked crackers, and Orville Redenbacher’s Movie Theater Butter popcorn.

Kilocalories consumed were the main outcome measure. Food craving was assessed on ten-point scales after the bogus taste test.

Approximately 1 week after the last script session, participants had a follow-up visit for general safety monitoring, a urine pregnancy test (for women), and laboratory assessment (for levels of thyroid hormones, stress-related hormones, other hormones, and liver enzymes, and for chemistries and blood count).

We conducted a phone interview 4 weeks after the last day of study pills to assess adverse events, give safety reminders, and fully debrief each participant about the bogus taste test. All participants said they had no concerns about the deception in the bogus taste test, and all reaffirmed consent for their data to be used.

We had to stop enrollment early because, in 2014, the Office for Human Research Protections (OHRP) informed our IRB that its reading of the US Federal regulations known as the Common Rule would henceforth prohibit the use of deception (such as the bogus taste test) in any protocol that includes a “more than minimal risk” component, even when the deception is entirely unrelated to the risky elements of the protocol and entirely unrelated to whether participants can assess the risks. A review of this interpretation of the Common Rule was expected, but after several months with no review, we terminated the study.

Data analysis

Data from the session days were analyzed by analysis of covariance (ANCOVA). The classification variable was drug (pexacerfont vs. placebo), and the covariate was baseline level of dietary restraint.

Nightly ratings on the YFAS were analyzed by repeated-measures regression (SAS Proc Mixed). The between-subjects factor was Group (pexacerfont vs. placebo) and the within-subjects factor was Day (1–35). Baseline scores on the full version of the YFAS were used as a covariate.

The criterion for statistical significance was 0.05, two-tailed.

We intended to run enough participants (45 evaluable per group) to provide 80 % power to detect effects >0.60 (Cohen's d) at a two-tailed alpha of 0.05. This would have applied to any difference tested across pexacerfont groups. We had to stop enrollment early, as noted above. To help interpret main results that did not reach an alpha of 0.05, we calculated Bayes factors (Dienes 2014). The Bayes factor indicates how strongly the data favor the alternative hypothesis over the null; Bayes factors greater than 3.0 or less than 0.3 are conventionally taken as strong evidence for the alternative or the null, respectively; values in between are inconclusive. Bayes factors do not use investigator estimates of prior probabilities; instead, they use investigator estimates of hypothesized means. We set our estimates in accordance with our a priori power analysis: our hypothesized mean for an effect of pexacerfont was 0.6 standard deviations away from the observed mean for the placebo group; our hypothesized standard deviation was the recommended default of $mean/2$; our theorized distribution was half-normal (see Dienes 2014, for a description). We did not calculate Bayes factors for

comparisons not driven by a priori hypotheses (e.g., for amounts of individual foods eaten, or rates of adverse events).

Wherever possible, we also report effect-size r values (r_{effect}) and their associated 95 % confidence intervals for F tests; r_{effect} can be calculated only when numerator $df = 1$. We accompany these with counternull values, which say, essentially, “The evidence that our effect is different from 0 is exactly as strong or weak as the evidence that our effect is different from (a specified larger effect)” (Rosenthal and Rubin 1994).

Results

Of the 31 enrolled participants, 13 were randomized to pexacerfont and 18 to placebo. The PASAT-C session, where we obtained our main outcome measures, was completed by 12/13 of the pexacerfont participants and 13/18 of the placebo participants. All six sessions were completed by 10/13 of the pexacerfont participants and 13/18 of the placebo participants. There was no group difference in retention, log-rank chi-squared = 0.59, $p = 0.44$. The actual power achieved with our sample size for the PASAT-C session (12 pexacerfont, 13 placebo) was 80 % power to detect effects > 1.17 (Cohen’s d) at a two-tailed alpha of 0.05. To detect the originally stated effect size of interest, a $d > 0.60$, our power was reduced to 30 %.

Demographics and other baseline data by group are shown in Table 2. We found no significant differences between groups on any of these measures.

PASAT-C session

Food-weight data for one of the pexacerfont participants were lost due to a technical error, leaving a sample size of 24 for the bogus taste test. Across all those 24 participants, the PASAT-C significantly increased ratings of stress (mean $\pm$ SEM change score 25.5 ± 4.9 —from a pre-task mean of 7.8 ± 2.4 to a post-task mean of 33.4 ± 6.0 , $t[22] = 5.15$, $p < 0.0001$). The increase in stress was of almost identical magnitude between groups, with change scores of 24.8 ± 6.5 and 26.5 ± 8.0 for the placebo and pexacerfont groups, respectively ($t[22] = 0.17$, $p = 0.87$).

In the post-PASAT bogus taste test, the pexacerfont group ($n = 11$) and placebo group ($n = 13$) were not shown to differ at the 0.05 alpha level in the total number of kilocalories consumed, either by t test or in the planned ANCOVA controlling for dietary restraint (mean $\pm$ SEM: pexacerfont, 876 ± 143 ; placebo, 1171 ± 144 , $F[1,21] = 2.11$, $p = 0.16$, $r_{\text{effect}} = 0.30$, 95 % CL = $-0.12, 0.63$, counternull $r_{\text{effect}} = 0.55$) (Fig. 1). However, the Bayes factor for this comparison was 11.30, indicating strong support for the hypothesis that pexacerfont would reduce stress-induced eating. One participant in each group ate an especially large amount (more than 500 g), but with those two participants omitted, the absolute size of the group difference did not diminish (pexacerfont, 773 ± 110 ; placebo, 1087 ± 128 , $F[1,19] = 2.23$, $p = 0.15$, $r_{\text{effect}} = 0.32$, 95 % CL = $-0.12, 0.65$, counternull $r_{\text{effect}} = 0.58$), and the Bayes factor actually increased (from 11.30 to 72.09), again supporting the hypothesis that pexacerfont group would reduce stress-induced eating.

Ratings of craving (on a 1–10 scale) were obtained from all 25 participants who underwent the session (Fig. 2a–d). Because craving is food-specific (Fedoroff et al. 2003), we analyzed these ratings by food rather than aggregating them (see supplementary Fig. S1a–d for the corresponding measures of actual consumption, which were similar to the craving ratings). For brownies, craving was lower in the pexacerfont group (2.17 ± 0.49) than in the placebo group (4.77 ± 0.86), $F(1,22) = 6.82$, $p < 0.02$, $r_{\text{effect}} = 0.49$, 95 % CL = 0.12, 0.74, counternull $r_{\text{effect}} = 0.79$. There were nonsignificant differences in the same direction (favoring pexacerfont) for Swedish-fish candies ($r_{\text{effect}} = 0.28$, 95 % CL = -0.13 , 0.61, counternull $r_{\text{effect}} = 0.52$) and chips ($r_{\text{effect}} = 0.06$, 95 % CL = -0.34 , 0.44, counternull $r_{\text{effect}} = 0.12$), but a small non-significant difference in the opposite direction for pizza bites ($r_{\text{effect}} = 0.01$, 95 % CL = -0.39 , 0.40, counternull $r_{\text{effect}} = 0.02$). For Swedish-fish candies, the Bayes factor (7.00) supported a craving-reduction effect for pexacerfont; for the other two types of food, the Bayes factors (1.71 and 1.68) suggested that the findings were inconclusive.

Script Sessions

Twenty-three participants completed all three of these sessions.

In the bogus taste tests, the main effect of script type on kilocalories consumed was in the expected direction but was not statistically significant (neutral, 455 ± 100 ; food, 469 ± 87 ; stress, 547 ± 129 ; $F(2,42) = 0.38$, $p = 0.69$, mixed model controlling for baseline dietary restraint) (Fig. 3). There was a tendency for the pexacerfont group to eat fewer kilocalories than the placebo group overall; it was not statistically significant, but the confidence interval and counternull suggested a group difference (pexacerfont, 320 ± 367 ; placebo, 621 ± 100 ; $F(1,20) = 2.60$, $p = 0.12$, $r_{\text{effect}} = 0.34$, CI -0.08 , 0.66, counternull $r_{\text{effect}} = 0.61$). We did not calculate a Bayes factor because we had made no a priori hypothesis about an effect size.

A selective effect of pexacerfont on cue- or stress-induced eating would have been reflected in a Group $\times$ Script interaction—but this interaction was not statistically significant, $F(2,42) = 1.08$, $p = 0.35$ (Fig. 3). Bayes factors for difference scores suggested that the data were inconclusive (stress-script eating minus neutral-script eating in pexacerfont vs. placebo, Bayes factor = 0.48; food-script eating minus neutral-script eating in pexacerfont vs. placebo, Bayes factor = 0.85).

Nightly ratings of food problems/preoccupation on the YFAS

Nightly self-ratings on the YFAS were available for 30 participants and were confirmed by time-stamped video to have been filled out at the scheduled times. Even after controlling for baseline scores obtained during study screening (which had been nonsignificantly lower in the participants randomized to pexacerfont, $r_{\text{effect}} = 0.16$, CL -0.21 , 0.49, counternull $r_{\text{effect}} = 0.31$), nightly YFAS scores were lower in pexacerfont participants than in placebo participants (least-squares means: pexacerfont, 1.59 ± 0.30 ; placebo, 2.49 ± 0.27 ; $F(1,27) = 4.83$, $p < 0.04$, $r_{\text{effect}} = 0.39$, CI 0.03, 0.66, counternull $r_{\text{effect}} = 0.68$). However, this difference was present from the first night of intervention (when participants had taken only an initial loading dose of pexacerfont) and did not increase over time (Group $\times$ Day interaction: $F(29,671) = 0.51$, $p = 0.99$) (Fig. 4).

Study-drug compliance

The 13 participants randomized to pexacerfont showed video confirmation of capsule consumption on a total of 285 person-days (mean 21.9, median 2, range 8–27). This is a mean confirmed compliance rate, not counting post-dropout days, of 94 % (median 93 %, range 85–100 %). On 5 % of days, the capsule was not taken; on the remaining 1 %, there were video malfunctions. Compliance was similar in the 18 participants randomized to placebo except for one participant who did not return to the clinic after her first placebo capsule (Fig. 5).

Adverse events

At least one AE was reported by 11/13 participants in the pexacerfont group and 13/18 in the placebo group (Fisher exact $p = 0.67$). The mean number of reported AEs per capsule-taking day was 0.12 ± 0.04 in the pexacerfont group and 0.07 ± 0.01 in the placebo group, $t(29) = 1.39$, $p = 0.17$, $r_{\text{effect}} = 0.25$, $CI = -0.11, 0.55$, counternull $r_{\text{effect}} = 0.47$.

The prevalence of specific categories of AEs is shown in Tables 3 and 4, separated by the study physician's determination of likely relatedness to study participation. Across the whole study, only two people in the pexacerfont group (and two in the placebo group) reported either nausea or decreased appetite as an adverse event. Deletion of data from those two pexacerfont participants (leaving the data from the two placebo participants) decreased but did not eliminate group differences; e.g., the Bayes score for the main PASAT-C finding decreased to 5.81.

Figure 6 shows the time course, relative to pexacerfont, of the nine AEs that were classified as “possibly related to study participation” in the five pexacerfont participants who reported them. Four of the five participants remained on pexacerfont, and four of the nine AEs resolved while pexacerfont was still being administered.

Discussion

Before we discuss the implications of the results, we want to address their reliability. Having had to stop the study early, we initially viewed the results as promising but inconclusive. We calculated Bayes factors with the expectation that they would fall into the “inconclusive” range. Instead, the Bayes factors strongly supported rejection of the null hypothesis. We conclude that pexacerfont may have protected chronic dieters against stress-induced craving and eating—but we offer that conclusion with several notes of caution.

One note of caution is that Bayes factors reflect what goes into their calculation. Although they are not manipulable by estimates of prior probabilities (they do not use prior probabilities at all), they *are* determined by the size of hypothesized effect, which is chosen by the investigator. We set the size of our hypothesized effect (a Cohen's d of 0.60) before we collected any data, but if we had chosen a larger one, our Bayes factors would be smaller. Yet, even with a hypothesized effect as large as $d = 1.0$, the Bayes factor for our main outcome is only reduced from 11.30 to 6.07, well above the 3.0 threshold for rejection of the null hypothesis. Probably a greater concern is our small sample sizes, because small samples are prone to false positives as well as false negatives (Button et al. 2013). Bayes factors are

not believed to be vulnerable to those problems (Dienes 2014), but of course no statistical procedure can replace replication with a larger sample size.

Another note of caution is that one of the largest effects we found in our study is also one of the most puzzling. Nightly ratings of food problems/preoccupation on the YFAS were lower in participants randomized to pexacerfont than in those randomized to placebo. This group difference was present from the first day of capsule ingestion, when, based on our prior findings in alcoholics, we infer that plasma levels of pexacerfont were probably no greater than 21 % of their eventual steady-state level—very likely not sufficient for a behaviorally active degree of brain receptor occupancy (Kwako et al. 2015; Schwandt et al. 2016). One possibility is that our finding merely reflected some preexisting difference between groups, but if so, that difference was not detected in precapsule baseline ratings on the YFAS. A more interesting possibility is that this was a true effect of pexacerfont, mediated by peripheral CRF₁ receptors (Stengel and Tache 2009), and not accounted for by reports of problematic appetite suppression or nausea.

We had hoped to show some behavioral specificity of pexacerfont's anticraving effects by using stress-imagery scripts and food-imagery scripts in addition to a standard stressor. The scripts themselves (especially the food script) were less effective than we had intended, so we were unable to draw mechanistic conclusions from this aspect of our study; we found only that eating during the sessions was less in the pexacerfont group overall.

We did find, unexpectedly, that pexacerfont seemed to exert a preferential effect on craving for sweet foods rather than salty or savory foods, based on some of the food-specific craving ratings (and perhaps some of the eating choices; see Fig. S1) in the laboratory sessions. We do not know of a mechanism for this finding, so we think it should be interpreted with caution until it is replicated.

In a randomized trial that ran concurrently with ours, using 51 anxiety-prone alcoholics (26 on pexacerfont, 25 on placebo), pexacerfont showed no indication of an anticraving effect after presentation of alcohol imagery or stress imagery scripts (Kwako et al. 2015). One key difference between that study and ours is that there was no measure of alcohol self-administration to compare with our bogus taste test for food. The alcoholics' knowledge that alcohol was not available during the sessions could have led either to more craving (MacKillop and Lisman 2005) or less craving (Papachristou et al. 2012), but we cannot readily say how it might have suppressed an effect of pexacerfont.

With all those cautions in mind, we believe our findings support further investigation of the anticraving effects of pexacerfont or another CRF₁-receptor antagonist. Participants accepted the drug well (as verified by nightly time-stamped videos of pill-taking adherence), and the side-effect profile was, as expected from prior studies, benign. Whether the current results are taken to be promising (as the Bayes factors indicate) or too preliminary to interpret (as some readers will conclude regardless of the Bayes factors), the rationale for replication remains.

If pexacerfont does decouple stress from compulsive eating, as we have previously shown the alpha-adrenergic agonist clonidine to decouple stress from drug craving (Kowalczyk et

al. 2015), it could help prevent emotionally driven episodes of dietary excess. As we have argued elsewhere, emotionally driven eating cannot be glibly equated with obesity (Epstein and Shaham 2010), but may contribute to the development or maintenance of obesity, and may also be inherently unhealthy and distressing (Polivy and Herman 1999). We do not suggest that it should be invariably “medicalized” through pharmacological treatment, but we do think the availability of a pharmacological treatment could be part of a broader public health effort to inculcate eating habits that are based on awareness of one’s own hunger and satiety rather than on emotional and external influences (McFarlane et al. 1999; Schachter 1968). One first step might be to replicate our results in a larger and more diverse sample (the sample in this study comprised mostly overweight to obese African American women).

However, any replication attempt focused on eating, at least in the USA, will probably not be able to include the bogus taste test—arguably the gold-standard outcome measure for laboratory studies of the psychology of eating—without a simple revision to the Common Rule, clarifying that a “deceptive” procedure can be used in a study that also includes an experimental medication. Revisions to the Common Rule are now being legislatively considered for the first time in 25 years (Joffe and Magnus 2016; Lynch et al. 2016), but they do not include this clarification. This is especially unfortunate because, in light of negative findings in alcoholics with pexacerfont (Kwako et al. 2015) and another CRF₁ antagonist, verucerfont (Schwandt et al. 2016), our results suggest that any anticraving effect of pexacerfont might be greater for palatable food than for drugs of abuse.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.

Kilocalories (kcal) of four snack foods eaten in the 30-min bogus taste test immediately after the PASAT-C stressor. *Each circle* shows data from a single participant, with the group means displayed as *horizontal lines*. The means are also shown, with SEMs, in the *inset bar graph* (with the *y-axis truncated*). A total of 4000 kcal of food was available

Craving after PASAT-C stressor

Fig. 2.

Ratings of craving (“Is this food causing you to have any food cravings right now?”) for each of four snack foods after the 30-min bogus taste test in the PASAT-C stressor session. Each circle shows data from a single participant, with the group means displayed as horizontal lines. The means are also shown, with SEMs, in the inset bar graphs (with the y-axis truncated). The asterisk marks a group difference of $p < 0.05$. The scale was anchored at 1 and 10 with “none” and “most possible”

Fig. 3.

Kilocalories (kcal) of four snack foods eaten in the 30-min bogus taste test immediately after each of three imagery scripts (neutral, food, or stress) in three separate sessions. *Each filled circle* shows data from a single participant, with the group means displayed as *horizontal lines*. The means are also shown, with SEMs, in the *inset bar graph* (with the *y-axis* truncated). A total of 4000 kcal of food was available

Fig. 4.

Mean ($\pm$ SEM) nightly ratings of food problems/preoccupation on the Yale Food Addiction Scale (YFAS) during maintenance on pexacerfont or placebo. Scores were the sum of ten items such as “I ended up eating much more than I had planned,” “I worried about not eating certain types of food or cutting down on certain types of food,” and “My behavior with respect to food and eating caused me significant distress,” all in a time frame of the past 24 h

Compliance with pill ingestion

Pill compliance by day: pexacerfont group (Days are on horizontal axis)																													
Participant																													
1	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	
2	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	.	
3	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	.	
4	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	.	
5	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	N	Y	N	Y	Y	Y	Y	Y	Y	.	
6	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	.	
7	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	.	
8	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	.	
9	Y	Y	Y	Y	0	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	.	
10	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	.	
11	Y	Y	Y	0	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	.	
12	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	.	
13	Y	Y	Y	Y	Y	Y	Y	Y	N	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29

Pill compliance by day: placebo group (Days are on horizontal axis)																													
Participant																													
1	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	.	
2	Y	N	Y	0	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	.	
3	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	0	Y	Y	Y	Y	Y	Y	Y	.	
4	Y	Y	Y	0	Y	0	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	0	Y	Y	Y	Y	Y	Y	.	
5	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	0	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	.	
6	Y	Y	0	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	.	
7	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	.	
8	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	0	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	.	
9	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	.	
10	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	.	
11	Y	Y	Y	Y	Y	Y	0	Y	Y	Y	Y	Y	Y	Y	Y	Y	0	0	Y	Y	Y	Y	Y	Y	Y	Y	Y	.	
12	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	0	Y	Y	Y	Y	.	
13	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	.	
14	Y	Y	Y	Y	N	0	0	0	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	.	
15	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	.	
16	Y	Y	Y	Y	Y	Y	0	Y	0	N	Y	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	
17	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	
18	Y	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29

Y: verified video ingestion of pill
N: pill not taken
0: video malfunction

Fig. 5.

Raster display of video-confirmed compliance with study-pill ingestion. *Each row* shows daily data for one participant

Times Courses of Possibly Related AEs in the Pexacerfont Group

Fig. 6.

Raster display of the time courses of adverse events classified as possibly related to pexacerfont. *Each row* shows daily data for one participant

Table 1

Schedule of events

Phase	Visit/day	Events
Screening	Before day 1	Psychiatric and medical <i>evaluation</i> under a separate screening protocol; blood draws for safety-related labs.
Pexacerfont/placebo induction (days 1–28), with daily video self-recording of protocol adherence, plus home administration of the daily version of the Yale Food Addiction Scale every evening (video continues through day 35 for Food Addiction Scale completion)	(Visit 1) day 1 (Visit 2) day 6, 7, 8, or 9 (Visit 3) day 15 (range 15–19)	<i>Randomization</i> ; first day of <i>study drug</i> : 1 week of take-home doses given (plus two extra days of medication). <i>Script-development interview</i> (and pill count) Another week of take-home doses given (plus two extra days of medication). <i>Main stress session</i> <i>Manipulation</i> : PASAT-C math stressor <i>Outcome measures</i> : eating (kcal) in bogus taste test; stress and craving ratings Several days of take-home doses given (depending on date of next session).
	(Visits 4, 5, and 6) days 16–28 (target days 16, 18, and 20)	<i>Three script-session visits</i> <i>Manipulation</i> : Exposure to stress-related, food-related, and neutral/relaxing scripts, in counterbalanced order. <i>Outcome measures</i> : eating (kcal) in bogus taste test; stress and craving ratings. Several days of take-home doses given on visits 4 and 5
Post-study drug follow-up	Follow-up visit (day 35 ± 4) Follow-up phone calls: (1) day 56 ± 4; (2) 3 months after last dose; (3) 6 months after last dose	Medical evaluation (lab tests and interview with physician) prior to study discharge. Phone interview with study clinician to collect adverse-event information with option to speak with study physician. Reminders about drug interactions, birth control, etc.

Table 2

Demographics and baseline data by group

	Placebo (<i>n</i> = 18)		Pexacerfont (<i>n</i> = 13)	
	Mean	SD	Mean	SD
Age (years)	32.8	10.7	30.8	8.3
BMI	36.4	8.3	33.0	11.4
Dietary restraint score (min. 15 for entry)	19.8	3.8	20.5	2.3
Yale Food Addiction Scale score	7.8	4.2	6.5	4.3
	<i>N</i>	%	<i>N</i>	%
Sex				
Male	3	17%	3	23%
Female	15	83%	10	77%
Race				
African American	10	55%	10	77%
European American	5	28 %	2	15%
More than one or not reported	3	17%	1	8%

Table 3

Possibly or probably study-related adverse events by group

	Placebo (<i>n</i> = 18)		Pexacerfont (<i>n</i> = 13)	
	Number of pts	Number of reports	Number of pts	Number of reports
Fatigue	2	2	2	2
Nonmigraine headache	1	1	2	2
Nausea	0	0	1	2
Pharyngitis	0	0	1	1
Dizziness	1	1	0	0
Decreased appetite	0	0	1	1
Elevated CCK	1	1	0	0
Elevated TSH	1	1	1	1
Total	6	6	8	9

Table 4

Nonstudy-related or unlikely study-related adverse events by group

	Placebo (<i>n</i> =18)		Pexacerfont (<i>n</i> = 13)	
	Number of pts	Number of reports	Number of pts	Number of reports
Upper respiratory infection	2	3	2	2
Migraine	0	0	1	4
Allergic rhinitis	1	1	1	2
Elevated blood pressure	1	1	1	1
Nausea	2	2	0	0
Menstrual irregularity	1	1	1	1
Back pain	1	1	1	1
Allergic reaction to nonstudy drug	0	0	1	1
Sinus tachycardia	0	0	1	1
Toothache	1	1	0	0
Sinusitis	0	0	1	1
Altered taste	0	0	1	1
Dry mouth	0	0	1	1
Insomnia	1	1	0	0
Flatulence	0	0	1	1
Vomiting/diarrhea	1	1	0	0
Gastroenteritis	1	1	0	0
Abnormal CBC	0	0	1	1
Musculoskeletal pain	0	0	1	1
Nonmigraine headache	1	1	0	0
Paresthesia	1	1	0	0
Depression	1	1	0	0
Cough	1	1	0	0
Trauma	0	0	1	1
Total	16	17	16	20