

Opioid partial agonist buprenorphine dampens responses to psychosocial stress in humans



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KEYWORDS

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Summary Pre-clinical and clinical evidence indicates that opioid drugs have stress-dampening effects. In animal models, opioid analgesics attenuate responses to isolation distress, and in humans, opioids reduce stress related to anticipation of physical pain. The stress-reducing effects of opioid drugs may contribute to their abuse potential. Despite this evidence in laboratory animals, the effects of opioids on responses to psychosocial stress have not been determined in humans. Here we examined the effects of buprenorphine, a μ -opioid partial agonist used to treat opioid dependence and pain, on subjective and physiological responses to a stressful public speaking task in healthy adults. We hypothesized that buprenorphine would reduce subjective and physiological stress responses. Healthy adult volunteers ($N=48$) were randomly assigned to receive placebo, 0.2 mg sublingual buprenorphine, or 0.4 mg sublingual buprenorphine in a two-session study with a stressful speaking task (Trier Social Stress Test; TSST) and a non-stressful control task. During the sessions, the participants reported on their mood states, provided subjective appraisals of the task, and measures of salivary cortisol, heart rate, and blood pressure at regular intervals. Stress produced its expected effects, increasing heart rate, blood pressure, salivary cortisol, and subjective ratings of anxiety and negative mood. In line with our hypothesis, both doses of buprenorphine significantly dampened salivary cortisol responses to stress. On self-report ratings, buprenorphine reduced how threatening participants found the tasks. These results suggest that enhanced opioid signaling dampens responses to social stress in humans, as it does in laboratory animals. This stress-dampening effect of buprenorphine may contribute to the non-medical use of opioid drugs.

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1. Introduction

In addition to their well-known actions as analgesics, opioid drugs have stress-dampening effects. Early studies in humans showed that opioids reduce responses to the anticipation of pain, also known as anticipation stress (Hill et al., 1952, 1955) and even before the discovery of opioid receptors, they were known to act centrally to reduce the release of adrenocorticotrophic hormone (ACTH) and cortisol (Eisenman et al., 1958, 1961). In animals, opioid analgesics also diminish responses to social stress. For example, μ -opioid agonists dampen behavioral and physiological responses to isolation stress, such as distress vocalizations and hypothalamic–pituitary–adrenal (HPA) axis reactivity in guinea pigs, rhesus macaques, puppies, and rat pups (Herman and Panksepp, 1978; Panksepp et al., 1978; Kalin et al., 1988; Stein et al., 2007; Wilson and Junor, 2008). Conversely, antagonists at the μ -opioid receptor increase behavioral measures of separation distress (Panksepp et al., 1978). Despite this pre-clinical and clinical evidence, the effect of a μ -opioid agonist on responses to psychosocial stress has not yet been tested in healthy humans.

The endogenous opioid system is involved in the neuroendocrine response to stress. Stress activates the sympathetic nervous system and HPA axis. The former results in an increase in heart rate and blood pressure. The latter is activated as the hypothalamus releases corticotrophic releasing hormone (CRH), which stimulates the production of ACTH from the anterior pituitary, leading to the release of cortisol from the adrenal glands. The endogenous opioid endorphin shares a common precursor with ACTH, and when cortisol release is stimulated, endorphins are also produced (Guillemin et al., 1977; Bodnar, 2013). Thus, the opioid system and the HPA axis are physiologically intertwined.

Several other lines of evidence implicate endogenous opioids in the response to stress. Although opioid receptors are distributed widely throughout the brain in regions involved in motor, somatosensory, and limbic processing (Mansour et al., 1995; Simonin et al., 1995; Peckys and Landwehrmeyer, 1999), they are densely expressed in regions of the brain involved in the stress response including the bed nucleus of the stria terminalis, central amygdala, and paraventricular nucleus of the hypothalamus (Mansour et al., 1995; Simonin et al., 1995; Peckys and Landwehrmeyer, 1999). In laboratory animals, exposure to stress leads to the up-regulation of δ - and μ -opioid receptor expression in some of these areas, such as the hypothalamus (Drolet et al., 2001; Yamamoto et al., 2003), and mice lacking the μ -opioid receptor gene (*OPRM1*) exhibit reduced cortisol responses to stress (Ide et al., 2010; Komatsu et al., 2011). Further, μ -opioid agonists reduce isolation distress vocalizations (Herman and Panksepp, 1978; Stein et al., 2007), responses to predator odors (Wilson and Junor, 2008), anxiety-like behavior in the elevated plus maze (Kahveci et al., 2006), and fear acquisition (Good and Westbrook, 1995). In humans, polymorphisms in the μ -opioid receptor gene (*OPRM1*) predict cortisol responses to social stress (Chong et al., 2005). In heroin-dependent individuals, administration of heroin reduces amygdala response to fearful faces (Schmidt et al., 2013) and lowers cortisol levels (Kreek and Hartman, 1982). Finally, one study conducted

with healthy, non-dependent human volunteers showed that buprenorphine reduces the ability to recognize fearful facial expressions, consistent with its possible role in reducing social stress (Ipser et al., 2013). Thus, there is accumulating evidence that opioid drugs reduce reactivity to stressful stimuli, and it has been suggested that the anxiolytic or stress-dampening effects of buprenorphine may contribute to its efficacy in treating opioid addiction, independently of its role as a replacement therapy (Kosten et al., 1990; Maremmani et al., 2006).

No previous studies have examined the effect of an opioid agonist on responses to an acute psychosocial stressor in healthy, non-dependent individuals. Here we assessed the effect of relatively low doses of buprenorphine on physiological and subjective responses to a stressful speaking task in healthy human volunteers. We hypothesized, based on its action as a partial μ -opioid agonist and κ -antagonist, that buprenorphine would dampen the effects of social stress.

2. Materials and methods

2.1. Study design

This study used a mixed within- (stress vs. no-stress) and between-subjects (0, 0.2 mg, 0.4 mg buprenorphine) design. Healthy adult volunteers were randomly assigned to receive placebo, 0.2 mg buprenorphine, or 0.4 mg buprenorphine, under double-blind conditions, on each of two sessions; a stress and a non-stressful control session. The 4.5-h laboratory sessions were conducted 7 days apart. 90 min after ingesting the drug, volunteers participated in a stressful public speaking task or a non-stressful control task, in randomized, counterbalanced order. Responses to the drug and the stress were assessed at regular intervals, including mood, subjective drug effects, salivary cortisol, and heart rate and blood pressure. The primary outcome measures were self-reported anxiety and cortisol levels.

2.2. Participants

Healthy adult participants ($N = 48$, 16 female) were recruited through flyers around the University of Chicago campus and surrounding community and online advertisements. Prior to the study, participants underwent a screening session including a physical examination, electrocardiogram, self-reported drug use history, and modified structural clinical interview for the DSM-IV (SCID; First et al., 2012). Inclusion criteria were: fluency in English, BMI between 19 and 30, no regular medications, no past year history of a DSM IV axis I disorder, and no history of opiate abuse. Women were tested during the follicular stage of their menstrual cycle (days 2–14) to control for effects of hormonal fluctuations on stress responses (Kirschbaum et al., 1999).

2.3. Drug

Participants were randomly assigned to receive 0.2 mg or 0.4 mg of sublingual (sl) buprenorphine (Temgesic®, Reckitt Benckiser Pharmaceuticals) or placebo (Splenda® sucralose tablet). Buprenorphine is a μ -opioid partial agonist and

κ -opioid antagonist that is used to treat moderate to severe pain and opioid dependence. Peak plasma concentrations occur 90–360 min after ingestion (Mendelson et al., 1997).

2.4. Procedure

Volunteers first attended a 1-h orientation session during which they provided informed consent and were familiarized with the study procedure. They were told that they might receive placebo, a sedative, a stimulant, a marijuana-like substance, an opioid antagonist, or an opioid analgesic during the two study sessions. Participants were asked to refrain from alcohol and recreational drug use for 48 h before each session, and compliance was verified using breath alcohol (Alcosensor III, Intoximeters, St. Louis, MO) and urine tests (ToxCup, Branan Medical, Irvine, CA) at the start of each session. All procedures were approved by the University of Chicago Institutional Review Board and were carried out in accordance with the Declaration of Helsinki.

Participants attended two study sessions (stress and no-stress) conducted from 1200 h to 1600 h, 7 days apart. Upon arrival in the laboratory they provided breath and urine samples to rule out recent drug use or pregnancy, and then completed baseline mood and drug effect questionnaires. At 1230 h, participants consumed a tablet of 0.2 mg sl buprenorphine, 0.4 mg sl buprenorphine, or placebo (a matching sucralose tablet). Subjects were randomly assigned to one of the drug conditions, and received the same tablets on both sessions. During the next hour, they were allowed to relax, read, or watch a movie. An hour and 30 min after drug administration, they were given instructions for the Trier Social Stress Test (TSST; Kirschbaum et al., 1993) or no-stress task. The TSST is a widely implemented procedure for inducing psychosocial stress in a laboratory setting (Kudielka et al., 2007). During the TSST, participants were given 10 min to prepare and then gave a 5-min speech for a mock job interview, in front of two interviewers and a video camera. They also performed 5 min of mental arithmetic. During the non-stressful control session, participants were given 10 min to think about their favorite book or movie, then spoke about it with a research assistant for 5 min, and then played a 5-min game of solitaire. Immediately before and after the tasks, participants completed a pre- and post-task appraisal questionnaire, assessing how threatening and challenging they found the task, in addition to how satisfied they were with their performance. At baseline (15 min before drug administration), 60, 120, 150, 180, and 210 min after drug administration, participants answered drug effect and mood questionnaires, and had their heart rate and blood pressure measured. Salivary cortisol samples were collected at baseline, 60 min after drug administration, and 10, 20, and 60 min after the stress or control task.

2.5. Measures

2.5.1. Mood and subjective effects of drug and stress

Participants completed the Profile of Mood States (POMS; McNair et al., 1971) questionnaire at 6 points throughout the session. This questionnaire consists of 72 adjectives, comprising eight subscales; Tension–Anxiety,

Depression–Dejection, Anger–Hostility, Vigor, Fatigue, Confusion, Friendliness, Elation. Participants also completed the drug effects questionnaire (DEQ; Fischman and Foltin, 1991), which is comprised of five visual analog scales (VAS) from 0 to 100 on which participants indicate how much they like, feel, dislike and want more of the drug, as well as how ‘high’ they feel. A VAS assessing nausea was also included with this questionnaire. These questionnaires were completed at baseline (15 min before drug administration) and at 60, 120, 150, 180, and 210 min after tablet administration. Immediately before performing the verbal tasks, participants completed the Primary Appraisal Secondary Appraisal rating scale (Gaab et al., 2005) to rate their perception of the tasks before completing them. Immediately after the verbal tasks, participants completed VAS ratings of how stressful and challenging they found task, in addition to how satisfied they were with their performance.

2.5.2. Physiological measures

Heart rate was measured continuously using a Polar® S610 monitor (Polar Electro Inc., Lake Success, NY) and blood pressure was measured using a portable monitor (Critikon Dinamap Plus Vital Signs Monitor, GE Healthcare Technologies, Waukesha, WI) before and 60 min after drug administration, and at 10, 20 and 60 min after the tasks. Saliva samples were collected using Salivette® cotton wads (Sarstedt Inc., Newton, NC). Samples were analyzed by the Core Laboratory at the University of Chicago Hospitals General Clinical Research Center for levels of cortisol (Salimetrics LLC, State College, PA, sensitivity = 0.003 $\mu\text{g/dL}$).

2.5.3. Task performance

During the TSST, the number of pauses during the speech was recorded, in addition to the number of mistakes made in the arithmetic task.

2.6. Statistical analyses

Analyses were conducted using SPSS version 16.0 for Windows. Missing cases (due to equipment malfunction or other data collection problems) were deleted list wise, which led to smaller sample sizes for some analyses. To verify that the three groups were matched, we compared demographic information and baseline measures between the groups using a one-way analysis of variance (ANOVA). To assess the effects of buprenorphine on cardiovascular, hormonal, and subjective measures before the tasks, we compared the change from baseline to measures taken before the task instructions, averaging across the stress and control sessions for each subject. To do this, we used a one-way ANOVA and Dunnett’s test for post hoc multiple comparisons. Drug effects during the no-stress control session provided another measure of the direct effect of the drug, and these were analyzed using two-factor ANOVA for repeated measures, with time as the within-subjects factor and treatment group as the between-subjects factor. Responses to stress were analyzed using repeated measures ANOVAs, with task (TSST vs. control) and time as within-subjects factors, and treatment group as between-subjects factors. Significant interactions were further investigated by two-way (Group $\times$ Task) ANOVA and

one-way (Group) ANOVA at each time point during stress. In addition, AUC values were calculated and compared using two-factor (Task $\times$ Group) repeated measures ANOVA and post hoc Dunnett's tests to correct for multiple comparisons. Repeated-measures ANOVAs were performed with Greenhouse–Geisser correction where violations of sphericity were observed. Differences were considered to be significant if $p < 0.05$.

3. Results

3.1. Demographics and baseline differences

Participants were mostly Caucasian (79%) and in their 20s (23.4 years of age ± 3.6). The groups did not differ on demographic characteristics, trait anxiety as measured by the State-Trait Anxiety Inventory (STAI; [Spielberger, 1970](#)), or drug use history, or on baseline measures of mood (POMS), heart rate, blood pressure, or salivary cortisol ([Table 1](#)).

3.2. Drug effects

In the analysis of the pre-task (post-dosing) measure from both sessions, neither dose of buprenorphine altered blood pressure, heart rate, or cortisol levels. Buprenorphine began to increase ratings of "feel drug" and "feel high" before the task, and these effects reached statistical significance later in the session. During the non-stressful control session, buprenorphine (relative to placebo) significantly increased ratings of "feel drug" [Group $F(2,45) = 7.3$, $p < 0.01$, $\eta^2 = 0.27$; 0 vs. 0.4 mg, $p < 0.001$, 0 vs. 0.2 mg $p < 0.05$, peak at 120 min] and "dislike effect" [Group $F(2,45) = 6.0$, $p < 0.01$, $\eta^2 = 0.24$; 0 vs. 0.4 mg, $p < 0.01$, 0 vs. 0.2 mg, $p < 0.05$, peak at 150 min]. Only the higher dose significantly increased ratings of "feel high" [Group $F(2,45) = 5.5$, $p < 0.01$, $\eta^2 = 0.22$; 0 vs. 0.4 mg, $p < 0.01$, peak at 120 min] and nausea [Group $F(2,45) = 9.2$, $p < 0.001$, $\eta^2 = 0.29$; 0 vs. 0.4 mg, $p < 0.001$, peak at 150 min]. The lower dose did not significantly increase ratings of "feel high".

3.3. Subjective effects of the stress task

Effects of stress. Stress was expected to increase anxiety and negative mood, and it produced these anticipated subjective effects. In all groups, it increased POMS anxiety [Task $F(1,44) = 8.5$, $p < 0.01$, $\eta^2 = 0.17$], anger [Task $F(1,44) = 16.4$, $p < 0.001$, $\eta^2 = 0.28$], depression [Task $F(1,44) = 5.9$, $p < 0.05$, $\eta^2 = 0.12$], and confusion [Task $F(1,44) = 5.1$, $p < 0.05$, $\eta^2 = 0.10$]. On the pre-task appraisal questionnaire participants rated the TSST as significantly more threatening [Task $F(2,45) = 16.3$, $p < 0.001$, $\eta^2 = 0.51$] and challenging [Task $F(2,45) = 31.2$, $p < 0.001$, $\eta^2 = 0.41$] than the control task, and they were less confident in their ability to perform the task [self efficacy; Task $F(2,45) = 5.14$, $p < 0.01$, $\eta^2 = 0.27$]. On the post-task questionnaire, participants were less satisfied with their performance on the task [Task $F(2,45) = 21.2$, $p < 0.001$, $\eta^2 = 0.32$] on the stress session, compared to the no-stress condition.

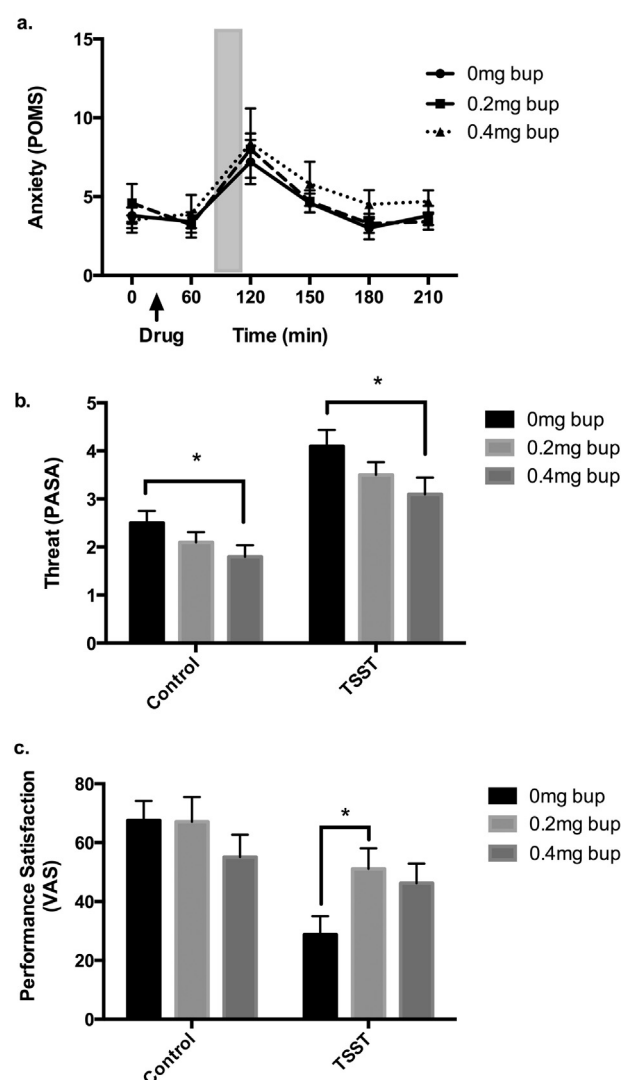


Figure 1 The effect of buprenorphine on subjective responses to stress as measured by (a) POMS anxiety, (b) threat appraisal, and (c) performance satisfaction. Shaded area indicates the time during which the TSST took place. Bars depict mean $\pm$ SEM. Asterisks indicate significant difference, $p < 0.05$.

Effects of buprenorphine. Buprenorphine did not affect ratings of anxiety after stress ([Fig. 1a](#)). However, on the pre-task appraisal questionnaire, buprenorphine dose-dependently decreased ratings of how threatening subjects expected the tasks to be (both control and stress tasks) [Group $F(2,45) = 3.7$, $p < 0.05$, $\eta^2 = 0.14$] ([Fig. 1b](#)). On the post-task appraisal, both doses increased participants' reports of their satisfaction with their performance on the stress task immediately after the task, and this was marginally significant ([Fig. 1b](#); Task $\times$ Group $F(2,45) = 3.85$, $p < 0.055$, $\eta^2 = 0.17$). The drug did not significantly affect performance on the task, as assessed by total number correct and number of restarts on the arithmetic task and number of pauses during the speech (Group $F(2,47) = 1.10$, $p = 0.35$, $\eta^2 = 0.05$; Group $F(2,47) = 0.04$, $p = 0.96$, $\eta^2 = 0.002$; Group $F(2,47) = 0.89$, $p = 0.42$, $\eta^2 = 0.04$).

Table 1 Demographic and baseline characteristics of participants in each drug group.

	0 mg	0.2 mg	0.4 mg
N (male/female)	18 (12/6)	15 (9/6)	15 (11/4)
Race N (%)			
European American	72	86	79
African American	6	7	14
Asian American	22	7	7
Age (years)	22.8 ± 3.6	23.1 ± 3.2	24.4 ± 4.0
BMI (kg/m ²)	22.6 ± 1.8	22.2 ± 2.1	22.9 ± 2.6
Education (years)	15.4 ± 1.3	14.9 ± 1.5	15.1 ± 1.3
Current drug use			
Caffeine (servings/day)	0.8 ± 1.3	0.9 ± 1.6	0.7 ± 1.4
Alcohol (drinks/week)	5.2 ± 5.9	3.9 ± 2.6	6.8 ± 4.6
Lifetime opioid use (mean number of times used)	1.4 ± 2.3	2.6 ± 3.9	4.1 ± 5.6
State Trait Anxiety Inventory (STAI)	31.5 ± 7.5	35.2 ± 9.7	32.3 ± 5.8
POMS anxiety	3.7 ± 2.1	4.6 ± 3.1	3.3 ± 2.0
Systolic blood pressure (mmHg)	114.4 ± 9.5	114.1 ± 13.1	114.5 ± 9.5
Heart rate (bpm)	70.6 ± 10.8	73.4 ± 11.8	68.4 ± 10.0
Cortisol (μL/dL)	0.24 ± 0.13	0.20 ± 0.10	0.18 ± 0.10

3.4. Physiological effects of the stress task

Effects of stress. As expected, the TSST significantly increased systolic blood pressure [Task $F(1,44) = 19.2$, $p < 0.001$, $\eta^2 = 0.30$], diastolic blood pressure [Task $F(1,44) = 9.2$, $p < 0.01$, $\eta^2 = 0.17$] and heart rate [Task $F(1,35) = 18.8$, $p < 0.001$, $\eta^2 = 0.40$] in each of the three treatment groups, compared to the control task.

Effects of buprenorphine. Both doses of buprenorphine completely blocked the increase in salivary cortisol seen after the TSST in the placebo group [Fig. 2; Task $\times$ Group $F(2,44) = 3.3$, $p < 0.05$, $\eta^2 = 0.15$]. Buprenorphine did not affect blood pressure or heart rate increases in response to stress.

4. Discussion

In this study, we assessed the effects of buprenorphine, a μ -opioid partial agonist, on physiological and subjective responses to a stressful speaking task in healthy human volunteers. In accordance with our hypothesis, we found that both doses of buprenorphine attenuated cortisol responses to the task and some measures of emotional stress (i.e., pre-task perceptions of threat and post-task ratings of satisfaction with their performance). This is the first study to show that an opioid drug reduces responses to acute psychosocial stress in a healthy human population, extending findings with laboratory animals and clinical populations showing that the opioid system is involved in mediating responses to stress.

The main result of this study is that even at low doses, buprenorphine blunts cortisol responses to stress. Over the last decade, use of prescription opioids has dramatically increased, particularly among adolescents and young adults (Compton and Volkow, 2006). One major theory explaining addiction is the self-medication hypothesis, according to which individuals are drawn to consume particular types of drugs, including opioids, to relieve the discomfort of

deficits in their social environment, low self esteem, or negative mood states (Schuman-Olivier et al., 2010). Thus, one reason for the increased non-medical use of opioids especially among adolescents, may be their propensity to reduce

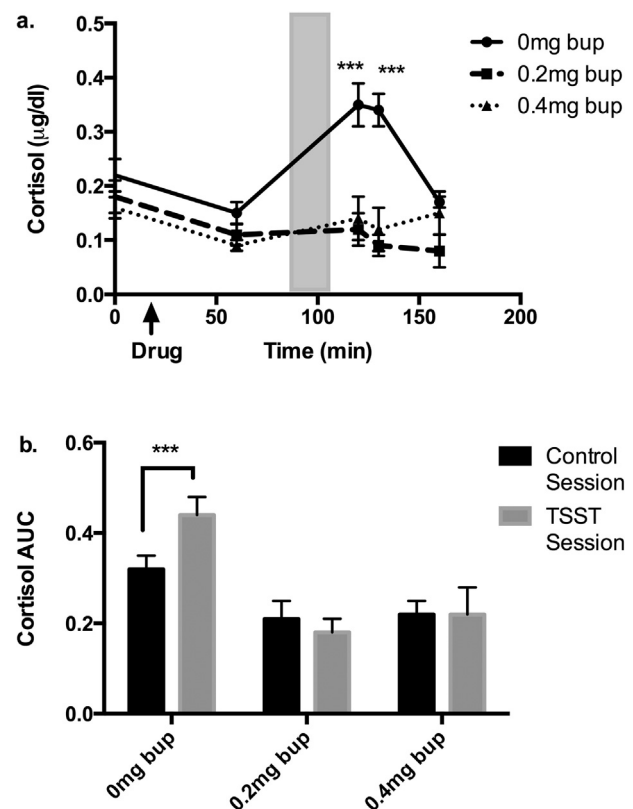


Figure 2 The effect of buprenorphine on cortisol responses to stress depicted (a) across the TSST session and (b) as the area under the curve (AUC) of the TSST as compared to the control session. Shaded area indicates the time during which the TSST took place. Bars depict mean $\pm$ SEM. Asterisks indicate a significant difference, $p < 0.001$.

the adverse consequences of social instability and increased social stress. The present results support this idea that opioid drugs may relieve some of the discomfort of social stress.

The effects of buprenorphine on subjective responses to stress were mixed. Although the drug did not reduce momentary ratings of anxiety, either alone or after stress, both doses of buprenorphine decreased subjects' anticipatory evaluations of how stressful they expected the task to be, and after the task it increased the ratings of how satisfied they were with their performance on the task. Thus, the drug specifically dampened subjects' evaluations of the stress task. It is not clear why the evaluations were affected while momentary ratings of anxiety were not. It is possible that participants' direct evaluations of the task are a more precise or sensitive index of the anxiolytic effect than assessment of fluctuations in current mood states. Another potential interpretation of this result is that participants in the 0.4 mg group experienced increased anxiety due to subjective drug effects. While we did not observe any significant drug effects on other scales of the POMS, participants who received a higher dose of the drug reported increases in nausea and ratings of "feel drug", which may have contributed to reports of anxiety, and obscured any effects of the drug on anxiety related to the task.

The observed stress-blunting effect of buprenorphine is most likely related to its actions at μ -opioid receptors, but there is the possibility that some component may also be due to its secondary effect as an antagonist at the κ -opioid receptor (Leander, 1987). In rodents, exogenously administered μ -opioid agonists reduce behavioral manifestations of anxiety in response to stress (Herman and Panksepp, 1978; Kahveci et al., 2006; Stein et al., 2007; Wilson and Junor, 2008), but antagonism at the κ receptor has similar anxiolytic effects; mice lacking the κ receptor and those pretreated with a κ receptor antagonist fail to develop conditioned place aversion in the context of repeated physical stressors, such as foot shocks (Land et al., 2008). Further, the effects of pharmacological activation of the HPA axis on conditioned place aversion can be blocked by an administration of a κ -antagonist (Land et al., 2008). The κ receptor has also been shown to mediate responses to social stressors, and the administration of a κ -antagonist reduces behavioral responses to social defeat stress in rodents (McLaughlin et al., 2005; Funk et al., 2014). It may be that the combined actions of buprenorphine at the κ receptor and μ receptor contribute to the stress-blunting effects of low doses we observed in this study.

Our study has several limitations. First, the sample was small, which made it difficult to study individual differences, including sex differences, in the stress-blunting effects of buprenorphine. An understanding of such individual differences may help to guide practice to target at-risk patients. Second, we tested only two doses of the drug. Although the doses we used were the lowest commercially available doses, it is possible that stress-dampening effects might be detected at even lower doses. Finally, the participants were limited to healthy young adults, and it is not known whether an opioid drug would effectively reduce responses to stress in clinical populations of either anxious individuals or drug-users. Finally, we used a drug with actions at two opioid receptor subtypes, and so it is difficult to attribute our findings to either μ or κ receptor types. This will be

resolved in future studies with more specific pharmacological agents.

One important alternative interpretation of our results is that the effects of buprenorphine on stress may be mediated by its effects on reward, or feelings of euphoria. This is unlikely given the observation that the stress-blunting effects occurred even at the 0.2 mg dose, which did not produce significant ratings of "feel high". Another interpretation might be that the observed effects were secondary to more general sedation, but neither dose affected subjects' performance on the task, suggesting that the stress-dampening effects were relatively specific. Buprenorphine is currently used sublingually in opioid replacement therapy at doses ten to forty times those used in this study (4–16 mg sl). Here we showed that a relatively low dose (0.2 mg sl) of buprenorphine, one that does not produce euphoria, substantially reduces cortisol responses to stress. Interestingly, this stress-dampening effect may also be valuable during treatment for opioid users, to prevent relapse. Stress is a known precipitant of relapse in opioid addicts (Sinha, 2001; Lijffijt et al., 2014; Spanagel et al., 2014), and dysregulation of the HPA axis is a hallmark of opioid withdrawal (Zhang et al., 2008). While buprenorphine is used clinically at higher doses in opioid replacement therapy, our results suggest that even at low doses, the drug has stress-blunting effects that may contribute to its efficacy in preventing relapse in vulnerable populations.

Our findings are in line with a body of pre-clinical evidence implicating the opioid system in stress responses, and suggesting that opioid agonists reduce stress responses. Other questions for future investigation include the pharmacological mechanism through which buprenorphine exerts its stress-blunting effects, and whether this effect is specific to the type of stressor individuals experience; the TSST differs from physiological stressors, for example, such as hunger, sleep-deprivation, or pain. It will also be important to investigate how the drug acts on stress in clinical populations, such as those in recovery from dependence.

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Conflict of interest statement

None declared.

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