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REGULAR RESEARCH ARTICLE

Effects of Buprenorphine on Responses to Emotional Stimuli in Individuals with a Range of Mood Symptomatology

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Abstract

Background: The opioid drug buprenorphine has been shown to modify responses to emotional stimuli and may have antidepressant properties. In preclinical studies, it shows antidepressant-like and anxiolytic-like effects, and a handful of clinical studies suggest it may reduce symptoms of depression in patients. We have shown that low doses of buprenorphine reduce responses to negative emotional stimuli in healthy adults. Here we extended these findings to individuals with symptoms of depression and anxiety.
Methods: We examined the effects of buprenorphine on attention to emotional facial expressions and ratings of and psychophysiological responses to emotional images in adults with a range of mood symptomatology. Volunteers (n = 38) were recruited with low, mild, moderate, and severe scores on the Depression-Anxiety-Stress Scale. They attended 2 laboratory sessions during which they received either placebo or 0.2 mg sublingual buprenorphine in randomized order under double-blind conditions. During peak drug effect, participants completed a visual attention task assessing responses to emotional faces and a picture-rating task assessing responses to emotional images with and without social content.
Results: Buprenorphine reduced attention to fearful facial expressions as it did in our previous study, and the emotion-specific effect was especially pronounced in individuals with high Depression-Anxiety-Stress Scale scores. The drug also increased ratings of positivity of images with social content, but this effect was less strong in individuals with higher Depression-Anxiety-Stress Scale scores.
Conclusions: These results suggest low doses of buprenorphine may reduce some dimensions of responses to negative emotional stimuli in individuals high on depression or anxiety, while leaving other dimensions unaffected.

Keywords: buprenorphine, opioids, depression, anxiety, psychophysiology

Introduction

Buprenorphine, a mu-opioid partial agonist and kappa antagonist, has received attention recently for its possible role as a mood regulator. In preclinical studies with rodents, buprenorphine shows antidepressant-like and anxiolytic-like effects on the forced swim test and novelty-induced hypophagia paradigms (Falcon et al., 2014, 2016). Early studies suggested that buprenorphine might be effective as an antidepressant in patients with treatment-resistant depression disorders (e.g., Emrich et al., 1982; Bodkin et al., 1995). In patients treated for opioid dependence, Kosten et al. (1990) noted that buprenorphine significantly

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Significance Statement

This study investigates the effects of a potential opioid antidepressant medication, buprenorphine, on responses to emotional stimuli in adults with a range of mood symptomatology. It is the first study to assess the effects of this drug on emotion processing in this study population in a controlled laboratory setting, and it lays the foundation for future investigations of novel opioid-based therapies for disorders of emotion processing.

reduced symptoms in depressed opioid dependent patients. Extending these findings beyond opioid users, Bodkin et al. (1995) reported notable improvement in non-drug-abusing patients with refractory depression after just a single week of treatment with buprenorphine. Several more recent reports support the efficacy of opioids in treating depression and anxiety (Nyhuis et al., 2008; Norelli et al., 2013; Karp et al., 2014; Schatzberg, 2015; Yovell et al., 2015; Kosten, 2016). For example, Yovell et al. (2015) found that low doses of buprenorphine reduced suicide ideation in suicidal adults, and Norelli et al. (2013) reported 6 cases in which buprenorphine reduced nonsuicidal self-injury. Karp et al. (2014) conducted an open label study with buprenorphine (mean dose 0.4 mg/d), in which adults with treatment-resistant depression reported a sharp decline in depressive symptoms. Finally, Sullivan (2016) has noted that because depression is a risk factor for initiation and maintenance of opioid use, the drug may be used in part to self-medicate depression. Thus, buprenorphine may have a role in treating mood disorders. Yet, the emotional processes by which it has a therapeutic effect are not known.

Several controlled laboratory studies have investigated the effects of buprenorphine on emotion processing in healthy volunteers. For example, buprenorphine reduces the ability to recognize fearful faces (Ipser et al., 2013) and enhances memory for postively valenced emotional stimuli (Syal et al., 2015). Further, we have recently shown that buprenorphine reduces responses to both psychosocial stress (Bershad et al., 2014) and other types of negative affective stimuli (Bershad et al., 2016). These tasks shed light on how drugs produce antidepressant effects: drugs with known antidepressant efficacy such as serotonin reuptake inhibitors (SSRIs) modulate responses to emotional stimuli on these and related tasks (Harmer et al, 2003). Notably, these effects with SSRIs are evident even after a single dose, predating and predicting their therapeutic effectiveness after several weeks of treatment (Harmer et al., 2003). In the present study, we extended our previous findings with buprenorphine by examining its effects on emotion processing in individuals with symptoms of depression. We recruited non-treatment-seeking volunteers who reported low to high symptoms of depression and anxiety and studied their responses to a single dose of buprenorphine (0.2 mg) or placebo on emotion-processing tasks. We hypothesized that buprenorphine would dampen reactivity to negative emotional stimuli and that this effect would be most pronounced in individuals reporting the most severe mood symptoms.

In addition to obtaining subjective reports of "feeling states" and performance on behavioral tasks, we also collected objective measures of emotional reactivity using psychophysiological indices of facial electromyography (EMG) and electrooculography (EOG) (Blascovich et al., 2011). Facial EMG is based on the fact that the *zygomaticus major* (zygomatic, "smile") muscle is activated by pleasant stimuli, while the *corrugator supercilii* (corrugator, "frown") muscle is reciprocally deactivated by positive stimuli and activated by negative stimuli (Larsen et al., 2003). EMG is sensitive even to images that are presented too quickly to consciously be perceived, and such images can evoke responses in the zygomatic and corrugator muscles (Dimberg et al., 2000). This suggests that these physiological indices may be more sensitive measures of emotional responses than self-report indices. Finally, another important component of emotional responding is immediate visual attention to stimuli with positive or negative content (McCabe et al., 2000). Attention to emotionally valenced stimuli can be objectively assessed using EOG and a visual probe task (Wardle et al., 2012), measuring initial gazes toward faces expressing negative and positive emotions vs neutral faces. Together, these psychophysiological metrics augment self-report indices in human laboratory studies and provide a more complete picture the effects of buprenorphine on reactivity to affective stimuli.

Methods

Study Design

This study used a 2-session, within-subjects, double-blind design in which young adults with a range of scores on a psychiatric rating scale received either buprenorphine (0.2 mg sublingual) or placebo in randomized order during two 4-hour laboratory sessions. Outcome measures included ratings of mood states and emotional images with social or nonsocial content, psychophysiological responses to emotional images, and visual attention to emotional faces.

Participants

Healthy volunteers (n = 38) aged 18 to 40 years were recruited from the University of Chicago and surrounding area. We recruited participants with low, mild, moderate, and high scores on the Depression Anxiety Stress Scale (DASS-21; Lovibond and Lovibond, 1995; see below). At a preliminary screening session, participants underwent a physical and psychiatric screening, which included an in-person psychiatric interview and detailed drug use history questionnaire, electrocardiogram, and completion of the DASS-21. Exclusion criteria included Major Axis I psychiatric disorders, including Major Depression (DSM 2015; APA 2013), serious medical condition, history of cardiac or liver disease, current or past substance abuse, individuals using any contraindicated medications, and individuals with a previous negative reaction to buprenorphine. Women who were pregnant, planning to become pregnant, or lactating were excluded. Inclusion criteria were: a fluency in English, a high school education, and BMI between 19 and 30 kg/m^2.

Study Drug

At each session, participants received 2 sublingual tablets, either a drug and a placebo tablet or 2 placebo tablets. In the drug condition, they received 0.2 mg buprenorphine (Temgesic, Indivior) and a physically similar placebo (Splenda sucralose tablet), and in the placebo condition they received 2 placebo tablets. The

tablets were identical in size and shape, and the placebo tablet helped to mask taste cues in the drug condition. The drugs were administered in counterbalanced order at 2 sessions under double-blind conditions. Buprenorphine is a mu-opioid partial agonist and kappa-opioid antagonist that is used to treat moderate to severe pain and opioid dependence. Notably, the dose used in this study was less than one-twentieth that used in opioid replacement therapy. This dose has been shown to improve memory for social reward (Syal et al., 2015), reduce recognition of fear (Ipser et al., 2013), and reduce attention bias to emotive faces and responses to emotional images (Bershad et al., 2016) without producing appreciable subjective effects or nausea. In our previous study (Bershad et al., 2014), a higher dose of buprenorphine (0.4 mg) produced significant nausea in the majority of participants. Peak plasma concentrations of the drug occur 90 to 360 minutes after ingestion (Mendelson et al., 1997).

Session Procedures

Orientation

During a 1-hour orientation session, participants were provided with information about the study and gave informed consent. The study was approved by the University of Chicago Institutional Review Board. Participants were told the goal of the study was to examine the effects of drugs on mood, perceptions, and behavior. To minimize expectancy effects, they were informed that they could receive a stimulant drug such as amphetamine, a sedative drug such as valium, an opioid such as buprenorphine, or placebo.

Study Sessions

Participants completed two 4-hour sessions from 1:00 PM to 5:00 PM. The sessions were separated by at least 2 days and were conducted in a comfortably furnished room containing chairs, a desk, computer, a television, video player, and reading materials. During the sessions, the participants were allowed to watch movies, read, or relax when not completing study questionnaires or tasks. Subjects were asked to abstain from drugs and alcohol for 48 hours before each session, and compliance was verified at the start of each session with a urine drug (ToxCup, Branan Medical Corporation) and breathalyzer tests (AlcosensorIII, Intoximeters). Women were also tested for pregnancy before each session (AimStickPBD, hCG professional, Craig Medical Distribution). After these tests, participants completed baseline measures for their mood and cardiovascular state (see below for mood and cardiovascular measures). At 1:30 PM, participants took 2 sublingual tablets, either 0.2 mg of buprenorphine and placebo or 2 placebo tablets. Participants then relaxed for 1 hour, and subjective and cardiovascular measures were collected again at 2:00 PM and 2:30 PM. At 2:45 PM, psychophysiological sensors were placed to collect electromyographic data, and participants completed the emotional images task and attentional bias task in randomized order. At 4:00 PM, the psychophysiological sensors were removed and subjective and cardiovascular measures were re-assessed at 4:30 PM and 5:00 PM. Participants then completed an end of session questionnaire and left the laboratory at 5:15 PM.

Behavioral Tasks

Emotional Images Task

Positive, negative, and neutral emotional images with and without social content were taken from the International Affective Picture System (Lang et al., 1999), as described in Wardle et al., 2012. Two different sets of these images matched for valence and arousal were prepared, one for each session, to minimize habituation across sessions. Social stimuli depicted 2 people or parts of people interacting, whereas nonsocial stimuli contained no images of people or parts of people. Thus, each set consisted of 6 subsets: social/negative, social/neutral, social/positive, nonsocial/negative, nonsocial/neutral, and nonsocial/positive. Further, each subset contained 9 images, 3 each of mild, moderate, and extreme intensity. Images were presented using E-Prime 2.0 software (Psychology Software Tools) in randomized order with no more than 2 pictures of consistent valence appearing consecutively. Each image presentation began with a 3-second fixation cross and a 6-second presentation followed by a 3-second fixation mark. Subjects rated each image immediately after its presentation using an evaluative space grid (Larsen et al., 2009), which allowed for independent evaluations of emotional valence in both positive and negative dimensions ("0": not at all; "4" extreme). Emotional reactivity to images was determined through EMG of corrugator and zygomatic musculature. EMG measures of facial muscle activity (corrugator and zygomatic muscles) are indicative of affective responses to emotional stimuli and can provide a more objective measure of emotional reactivity than subjective reports alone (Dimberg et al., 2000). Highly positive stimuli increase activity in the zygomatic, or "smile" muscle, and relax the corrugator ("frown") muscle. Negative stimuli activate the corrugator muscle. EMG was measured with 4 mm Ag/AgCl electrodes precisely placed on the cheek and left brow. An 8-mm Ag/AgCl ground sensor was placed on the subject's forehead. Signals were amplified, filtered through a 10- to 500-Hz band pass, digitized, refiltered, rectified, and then integrated over 20 milliseconds using EMG100C amplifiers, an MP150 Data Acquisition System, and Acqknowledge software from Biopac Systems (Goleta).

Attention Bias Task (ABT)

The ABT was adapted from Garner et al. (2006). Participants were shown pairs of faces, one on each side of the screen. Each pair contained one neutral face and one emotional expression face using the same actor. The emotional expressions were collected from the standardized Karolinska set (Goeleven et al., 2008). Each face pair presentation consisted of a 1-second pre-picture fixation, then a 2-second picture presentation. To distract the participants from the purpose of the task, a probe (either a square or a circle) was presented following the 2-second onset of the face pair, and the participants were asked to indicate whether the shape presented was a square by pressing one keyboard key or if it was a circle by pressing a different key. After a response, or 10 seconds elapsed, an intertrial interval of 750 to 1250 milliseconds began, followed by another trial. EOGs were used to quantify which face was initially fixated on in each trial. EOGs were collected using a 4-mm silver/silver chloride electrode attached 1.5 cm from the outer canthus of each eye. The application and data collection process was the same as the EMG application and collection detailed above. Trained, blinded scorers discarded trials in which the gaze was not centrally fixed prior to the trial, initial fixation was <100 milliseconds after picture onset, or noise obscured eye movements.

Cardiovascular Measures

Heart rate and blood pressure were monitored with portable monitors (Omron 10 Plus, Omron Healthcare) 5 times during the session (-15, 30, 60, 180, and 240 minutes post drug

administration). Mean arterial pressure was calculated using the formula: (systolic BP+2 x diastolic BP)/3.

Subjective Questionnaires

DASS

The DASS-21 (Lovibond and Lovibond, 1995) is a reliable 21-item questionnaire that provides an assessment of negative affect along 3 dimensions: depression, anxiety, and stress, experienced over the prior week. Each question is scored from 0 to 3, with higher scores indicating more symptoms. We recruited subjects with a range of scores on this questionnaire. Scores on the DASS are categorized based on responses on the subscales (Table 1; Lovibond and Lovibond, 1995). Thus, low or normal scores are 0 to 9 on the depression subscale, 0 to 7 on the anxiety subscale, and 0 to 14 on the stress scale; mild scores are 10 to 13 on depression or 8 to 9 on anxiety or 15 to 18 on the stress scale; moderate scores are 14 to 20 on depression or 10 to 14 on anxiety or 19 to 25 on the stress scale; and severe scores are 21 to 27 on depression or 15 to 19 on anxiety or 26 to 33 on the stress scale. We used this grouping strategy to recruit subjects with a wide range of scores, but on most measures during data analysis we treated DASS scores as a continuous variable. Because the scores on the 3 dimensions (depression, anxiety, and stress) were highly correlated, we used the sum for the entire DASS for each subject.

Drug Effects Questionnaire (DEQ)

The DEQ consists of 6 questions on a visual analog scale assessing subjective drug effects. Subjects were asked to rate the extent they felt a drug effect, whether they liked or disliked the drug effect, if they felt high, and if given a choice, would they want more of the drug.

Statistical Analysis

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 4 groups (normal, mild, moderate, severe) were matched, we compared demographic information and baseline measures between the groups using a 1-way analysis of variance (ANOVA) and chi-squared tests where appropriate (Table 2). Subjective effects of the drug were assessed using a 2-way ANOVA, with dose and time as within-subject factors and DASS score as a covariate. The ABT and Emotional Images Task were analyzed with mixed ANOVAs, with dose and valence as within-subject factors and DASS group as a covariate. Significant main effects and interactions were followed with posthoc *t* tests. Values $<P=.05$ were considered significant.

Results

Participant Characteristics

Participants were mostly Caucasian (53%) with a mean age of 24 years and an average of 15 years education. The DASS groups did not differ on any demographic or substance use characteristics (Table 2).

Table 1. DASS Scoring and Groups

	Depression	Anxiety	Stress
Normal	0–9	0–7	0–14
Mild	10–13	8–9	15–18
Moderate	14–20	10–14	19–25
Severe	21–27	15–19	26–33

Subjective and Physiological Effects of Buprenorphine

Buprenorphine slightly increased ratings of "feel drug" (Figure 1: time x drug $F[4,132]=3.4$, $P < .05$, $\eta\rho^2=0.09$; peak at 180 minutes), "like drug" (time x drug $F[4,132]=5.2$, $P<.001$, $\eta\rho^2 = 0.14$; peak at 180 minutes), and "want more" (time x drug $F[4,132]=3.0$, $P<.05$, $\eta\rho^2 = 0.08$; peak at 180 minutes). Buprenorphine did not significantly affect ratings of "feel high," or "dislike drug." Buprenorphine did not exert significant effects on heart rate or blood pressure. DASS scores did not significantly predict subjective drug responses.

Table 2. Demographic and Lifetime Nonmedical Drug Use Based on DASS Scores (n=38)

	Mean (SEM) or Percent (n)			
Category	Normal (n=9)	Mild (n=8)	Moderate (n=10)	Severe (n=11)
Gender				
Male/female	3/6	3/5	4/6	5/6
Age	25.26 (3.87)	21.75 (5.55)	25.00 (6.67)	22.63 (3.20)
Education	16.44 (2.60)	14.25 (0.71)	15.00 (1.41)	15.09 (1.04)
BMI	24.73 (4.22)	23.03 (2.85)	24.73 (2.92)	23.63 (2.87)
Depression	1.44 (1.13)	5.75 (1.39)	7.30 (2.16)	12.10 (3.62)
Anxiety	0.67 (0.50)	3.13 (1.89)	3.10 (2.64)	5.27 (5.10)
Stress	2.56 (2.70)	5.25 (3.33)	6.70 (3.77)	8.00 (4.76)
Race				
Caucasian	44.4% (4)	37.5% (3)	50.0% (5)	72.7% (8)
African-American	22.2% (2)	12.5% (1)	30.0% (3)	27.3% (3)
Asian	11.1% (1)	0.0% (0)	10.0% (1)	0.0% (0)
Other	22.2% (2)	50.0% (4)	10.0% (1)	0.0% (0)
Lifetime drug use				
Marijuana	55.5% (5)	75.0% (6)	60.0% (6)	90.9% (10)
Opiates	11.1% (1)	12.5% (1)	0.0% (0)	18.2% (2)
MDMA	22.2% (2)	12.5% (1)	20.0% (2)	18.2% (2)
Hallucinogens	22.2% (2)	62.5% (5)	30.0% (3)	45.5% (5)
Stimulants	22.2% (2)	25.0% (2)	10.0% (1)	54.5% (6)
Sedatives	22.2% (2)	0.0% (0)	10.0% (1)	18.2% (2)

The groups did not differ on any measure except for DASS-21 scores.

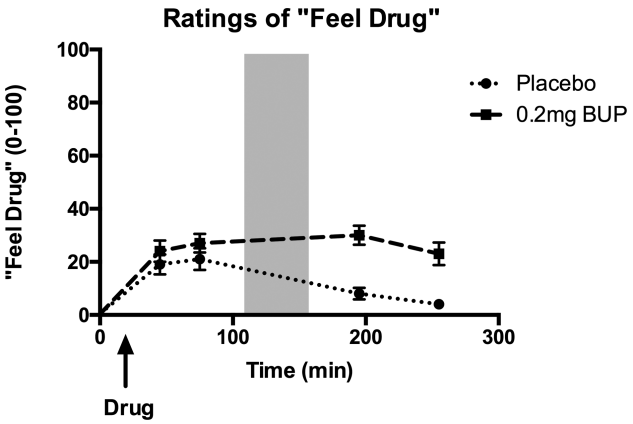

Figure 1. Mean (± SEM) ratings of "feel drug" throughout the sessions during placebo sessions (circles, dotted line) and after buprenorphine (0.2 mg; squares, dashed line). Shaded area indicates the time during which the tasks took place.

ABT

Buprenorphine slightly decreased the number of first gazes toward emotive faces overall (drug F[1,32]=8.0, $P< .01$, $\eta\rho^2 = 0.20$), but this effect was most pronounced for first gazes toward fearful expressions compared with other emotions (type x drug F[3,96] = 4.8, $P < .05$, $\eta\rho^2 = 0.09$; fear vs happy $P < .05$). Strikingly, the effects of buprenorphine on visual orienting toward emotional faces were strongest in individuals with high DASS scores (Figure 2; drug x DASS score F[1,32]=8.6, $P<.01$, $\eta\rho^2=0.21$) such that buprenorphine most dramatically reduced first gazes toward fearful faces in these individuals (Figure 3; type x drug x DASS score F[3,96]=4.1, $P<.01$, $\eta\rho^2=0.11$; fear vs happy, $P<.01$).

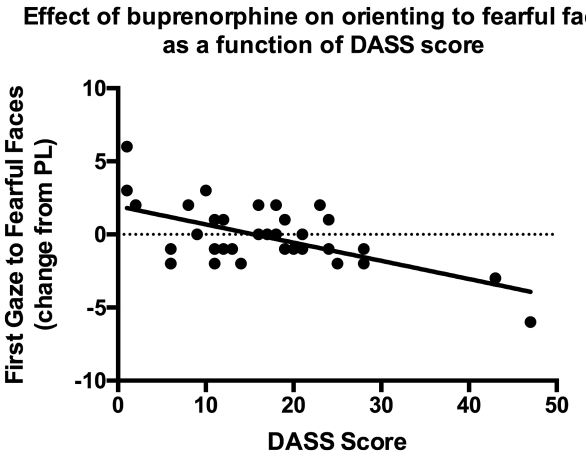

Figure 2. Number of initial gazes toward fearful faces for individual subjects after buprenorphine minus placebo, as a function of total DASS score. Dashed line signifies no difference between buprenorphine and placebo sessions, solid line indicates correlation (r=-0.6, p<0.001).

Emotional Images Task

Data from 2 subjects were excluded because of equipment malfunction during the task, and from one subject because they did not complete the task as directed. The task produced its expected effects on affective ratings and corrugator reactivity as measured by facial EMG. That is, subjects rated positive images more positively and negative images more negatively than neutral images (valence F[2,34]=33.5, $P<.001$; $\eta\rho^2 =0.67$; positive > neutral $P<.001$, negative < neutral $P<.001$). Corrugator activity increased with responses to negative images compared with neutral ones (valence F[2,34]=3.8, $P<.05$; $\eta\rho^2 =0.18$; negative > neutral $P<.01$).

As we previously showed, buprenorphine selectively enhanced positivity ratings of images with social content (Figure 4; Drug x social F[1,34]=8.4, $P<.01$; $\eta\rho^2=0.20$; social > nonsocial on buprenorphine: $P=.06$). This effect was slightly less pronounced in individuals with higher DASS scores (drug x social x DASS score F[1,34]=10.3, $P<.01$; $\eta\rho^2=0.23$). Neither buprenorphine nor DASS score affected corrugator or zygomatic responses to emotional images.

Drug Identifications

After receiving the dose of buprenorphine, 4 participants correctly guessed they had received an opioid drug. Of the remaining participants, 23 guessed they had received a sedative, 5 guessed they had received a stimulant, and 6 guessed placebo.

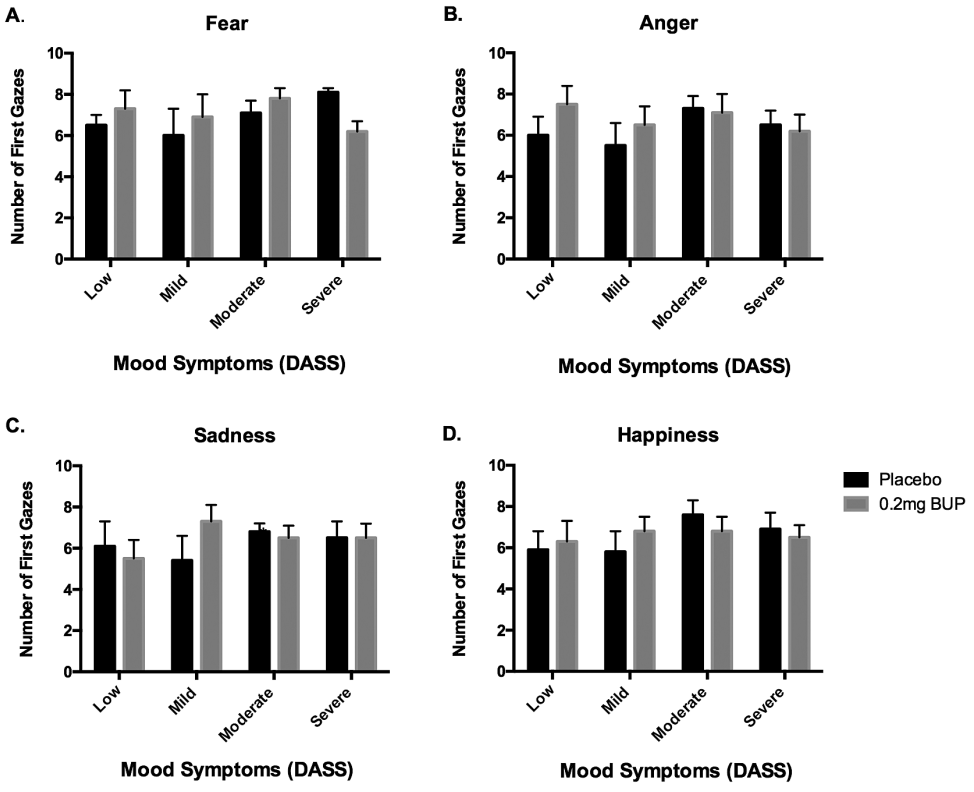

Figure 3. Mean (± SEM) number of initial gazes after placebo and buprenorphine (0.2 mg) toward faces depicting fear, anger, sadness, and happiness, separated by DASS scores (Low N=9; Mild N=8, Moderate N=10, Severe N=11). DASS score was treated as a continuous variable for statistical analyses.

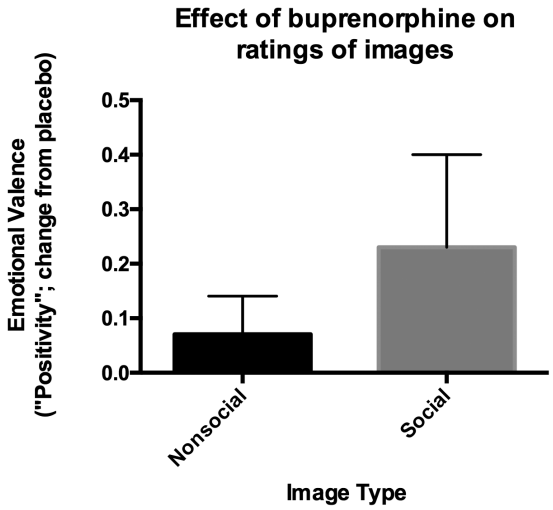

Figure 4. Mean (± SEM) difference scores (buprenorphine minus placebo) on positivity ratings of images with and without social content for all subjects together. The DASS groups did not differ on this measure.

During the placebo session, 20 participants correctly guessed placebo, 2 guessed an opioid drug, 10 guessed a sedative, and 6 guessed they had received a stimulant. The drug identifications were not related to DASS scores.

Discussion

In this study, we aimed to assess the effects of buprenorphine on behavioral and subjective responses to emotional stimuli in volunteers with a range of mood symptoms, from low to high. Extending our previous findings with nonsymptomatic volunteers, we found that buprenorphine reduced initial orienting toward fearful facial expressions and increased ratings of positivity of images with social content. Importantly, both these effects were more pronounced in individuals with high depression and anxiety scores. Additionally, we replicated our earlier finding that buprenorphine increased ratings of positivity of images with social content. On this measure, however, individuals with higher DASS scores seemed to be less sensitive to the effect. It is notable that we detected these behavioral effects of buprenorphine on emotional reactivity at a very low dose, a dose that did not increase ratings of euphoria or "feel high."

The main result of this study is that buprenorphine reduces attention to fearful faces most strongly in individuals with high scores on the DASS. This finding provides further support for the idea that the drug may have antidepressant properties. The profile of effects resembles the effects of single doses of standard SSRI antidepressant drugs, which decrease recognition of fearful facial expressions in individuals with depression (Bhagwagar et al., 2004) and reduce amygdala responses to such faces (Murphy et al., 2009). Although the therapeutic effects of SSRIs take weeks to develop, single doses of these drugs produce behavioral effects on tasks such as those used here, and these acute effects are predictive of the therapeutic effectiveness that develops weeks later (Warren et al., 2015). To the extent that the effects of buprenorphine resembled the effects of a known antidepressant, our findings with buprenorphine suggest that it may have similar therapeutic effects. Our findings are also in line with results from rodent models showing that the effects of buprenorphine on time to immobility in the forced swim test resemble those of standard SSRIs (Falcon et al., 2014).

Another, somewhat surprising, result of this study was that individuals with high DASS scores do not respond as strongly to the enhancing effects of buprenorphine on positivity ratings of social images. We and others have reported that low doses of buprenorphine not only reduce responses to negative stimuli but also enhance reactivity to positive stimuli (Syal et al., 2015; Bershad et al., 2016). This is consistent with studies in nonhuman animals that suggest that opioids are involved in socially rewarding activities such as play behavior (Panksepp et al., 1985; Vanderschuren et al., 1995a, 1995b; Trezza et al., 2010). The fact that buprenorphine did not enhance positive responses more strongly in individuals with high DASS scores was unexpected, given that some other antidepressants acutely increase responses to positive stimuli (Harmer et al., 2003, 2009). It remains to be determined which behavioral responses are critical to predicting antidepressant effectiveness, dampening responses to negative stimuli, or enhancing responses to positive stimuli (Pizzagalli, 2014).

One question raised by this study is what is the optimal selection of participants to study potential antidepressant effects. Our first study used healthy asymptomatic volunteers (Bershad et al., 2016), while this study used participants with a range of scores on the DASS, which included symptoms of both anxiety and depression. While anxiety and depression are classified as separate disorders, there is a great deal of overlap between the two (Lovibond and Lovibond, 1995), and the opioid system seems to be involved in both anxiety and depressed mood. For example, individuals high on either depression or anxiety exhibit heightened reactivity to negative facial expressions (Warren et al., 2015). Furthermore, the opioid system seems to be involved in both anxiety and depression-related processes. A polymorphism in the opioid receptor (*OPRM1*) that results in reduced mu-opioid signaling both increases the likelihood of developing depression following social rejection and also alters anxiety-like responses to various stressors (Chong et al., 2005; Slavich et al., 2014). Thus, our results and those from other groups suggest that the opioid system is involved in negative affective responses broadly, beyond the boundaries of a specific DSM disorder. In the present study, we had the capability to investigate separate contributions of symptoms of either anxiety or depression, using the DASS scales. However, the participants scores on all 3 scales were highly correlated ($r = 0.4–0.8$), and so we used a total DASS score for the analyses. A future direction of this work will be to examine the effects of buprenorphine in more severely symptomatic individuals, such as those with a clinical diagnosis of a DSM-V mood disorder.

It is not yet clear how buprenorphine's mechanism of action contributes to its effects on emotion processing. Two recent studies attempted to create a functional kappa antagonist by combining buprenorphine with a mu opioid antagonist, assessing its effects in patients with major depression who had not responded to previous antidepressant medications (Ehrich et al., 2015; Fava et al., 2016). In both studies, patients exhibited improved outcome on 3 standard clinical measures of depression, suggesting pure kappa antagonism may be sufficient to reduce negative mood, even in the absence of mu effects. Other studies, however, have suggested that it is a combination of mu and kappa mechanisms that make buprenorphine effective (Lutz and Kieffer, 2013a, 2013b), and there is a long history of using mu-agonists in the treatment of depression before the development of SSRIs (Emrich et al., 1982). Although both receptor systems seem to be involved in mediating emotional responses, the relative contributions of the MOR and KOR actions in the antidepressant effect of buprenorphine remain to

be determined (Sher, 1998; Ehrich et al., 2015; Balon, 2016; Fava et al., 2016; Li et al., 2016).

A few limitations warrant consideration. While the stimuli in controlled laboratory studies like the one described here are modeled after real-world social encounters, they are not as salient or immersive as a real-world experience might be. Images of emotional faces allow us to isolate dimensions of behavior we might not otherwise be able to (e.g., visual attention), but they lack the intensity of actual social interaction. Furthermore, we tested only a single dose of buprenorphine, and it may be the case that multiple different doses exert different effects on socio-emotional processing. While there are limitations to the study presented here, it provides further evidence in support of the effectiveness of buprenorphine in dampening responses to negative emotional stimuli in individuals with mood symptomatology.

In summary, in this study we tested the effects of buprenorphine on responses to 2 emotion-processing tasks in individuals with low to high anxiety and depression symptoms. We replicated our previous findings, showing that buprenorphine reduces attention to fearful faces and enhances ratings of positivity of images with social content. Further, we found that individuals with high DASS scores exhibited a more pronounced buprenorphine-induced decrease in attention to fearful faces. Individuals with greater mood symptomology also exhibited less response to buprenorphine on ratings of social images, suggesting that while the drug may act to reduce responses to negative emotional stimuli in clinical populations, it may not be as effective at increasing positive emotional responses. Antidepressant effects could result from both decreases in negative affective responses, or increases in positive affective responses. It remains to be determined which of these, and which measures of emotion processing, are most related to clinical response.

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