Archival Report

Low-Dose Augmentation With Buprenorphine for Treatment-Resistant Depression: A Multisite Randomized Controlled Trial With Multimodal Assessment of Target Engagement

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ABSTRACT

BACKGROUND: The experimental therapeutics approach that combines a placebo-controlled clinical trial with translational neuroscience methods can provide a better understanding of both the clinical and physiological effects of pharmacotherapy. We aimed to test the efficacy and tolerability of low-dose augmentation with buprenorphine (BPN) for treatment-resistant depression, combined with multimodal assessment of target engagement.

METHODS: In this multisite randomized clinical trial, 85 participants ≥50 years of age with a major depressive episode that had not responded to venlafaxine extended release were randomized to augmentation with BPN or placebo for 8 weeks. The primary outcome measure was the Montgomery–Åsberg Depression Rating Scale. In addition, three linked experiments were conducted to test target engagement: 1) functional magnetic resonance imaging using the monetary incentive delay task, 2) brain positron emission tomography of healthy participants using a novel kappa opioid receptor antagonist tracer [^{11}C]LY2795050, and 3) transcranial magnetic stimulation measure of cortical transmission after daily BPN administration.

RESULTS: The mean ± SD dosage of BPN was 0.59 ± 0.33 mg/day. There were no significant differences between the BPN and placebo groups in Montgomery–Åsberg Depression Rating Scale changes over time or adverse effects. BPN administration had minimal effects on functional magnetic resonance imaging blood oxygen level–dependent responses in regions involved in reward anticipation and response, no significant displacement of kappa opioid receptor radioligand in positron emission tomography imaging, and no significant changes in transcranial magnetic stimulation measures of inhibitory and excitatory cortical transmission.

CONCLUSIONS: Our findings suggest a lack of clinical effect of low-dose BPN augmentation and lack of target engagement with this dosage and physiological probes.

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At least one third of patients with major depressive disorder (MDD) do not respond to an antidepressant trial of adequate dosage and duration (1). Augmentation pharmacotherapy is a favored second or third step for the treatment of MDD, and a remission rate of 44% has been reported with aripiprazole augmentation in older patients with MDD who did not respond to venlafaxine extended release (XR) (2). However, the clinical effects of augmentation strategies may not be experienced for at least 6 to 8 weeks (1). Agents of novel mechanism with an acceptable safety and tolerability profile that lead to more rapid clinical benefit are needed.

The opioid system is a novel antidepressant target. Both rodent (3,4) and human (5,6) studies have characterized the expression of endogenous opioid system peptides and G-protein–coupled receptors in the limbic and paralimbic regions, which are centrally involved in the modulation of mood, motivational, autonomic, stress, and neuroendocrine responses. These processes are linked with monoaminergic circuits and dysregulated in MDD. Animal studies have also suggested age-related changes in the opioid system, including changes in density and binding affinity for μ opioid receptors (ORs) and kappa ORs (κ-ORs) (7–9). Repurposing Food and Drug Administration–approved opioid medications that may have antidepressant effects is an attractive approach, leveraging existing discoveries to rapidly advance treatment options in a cost-effective and efficient way.

Buprenorphine (BPN) is both a μ-OR partial agonist and a κ-OR antagonist, with putative antidepressant effects in both human and rodent studies (3,5,6,10–12). In open-label studies, low-dose BPN led to rapid antidepressant effects (13), and a placebo-controlled randomized controlled trial described rapid reduction in suicidal ideation for those receiving low-dose BPN (mean dosage of 0.45 mg/day) (14). However, BPN combined with samidorphan, a potent μ-OR antagonist, did not demonstrate statistically significant superiority over placebo (PBO) (15). Thus, we conducted a proof-of-concept study to investigate low-dose BPN as an augmentation to antidepressant pharmacotherapy. We combined a randomized placebo-controlled clinical trial with translational neuroscience methods to better understand both the clinical and physiological effects of BPN (16). This experimental therapeutics approach can provide actionable data with both positive and negative results and can guide future experiments by informing dosing, physiological target selection, and clinical trial design.

A multimodal suite of target engagement strategies were conducted across the three sites: 1) a positron emission tomography (PET) brain imaging study in healthy participants, using the novel κ-OR antagonist tracer [^{11}C]LY2795050 before and after ∼2 weeks of daily low-dose BPN; 2) a task-based functional magnetic resonance imaging (fMRI) study examining the effects of BPN on the brain reward system using the monetary incentive delay (MID) task, which examined brain activation patterns during anticipatory and consummatory phases of monetary reward processing (17); and 3) a motor cortex transcranial magnetic stimulation (TMS) neurophysiology study measuring GABAergic (gamma-aminobutyric acidergic) and glutamatergic neurotransmission before and after BPN treatment to test the engagement of other depression-related neurotransmitter systems. In this paper, we present the results of the clinical trial and of these novel assessments. We hypothesized that BPN will have an antidepressant effect, supported by evidence of molecular target engagement on PET (decrease in κ-OR binding with κ-OR antagonist tracer), functional engagement on fMRI (difference in reward circuit activation after BPN administration), and engagement of GABA and glutamate neurotransmission on TMS measures.

METHODS AND MATERIALS

BPN Augmentation Clinical Trial

Study Design. This study was conducted as a part of the IRLGRey-B (Incomplete Response in Late-Life Depression: Getting to Remission with Buprenorphine) study, a multisite, placebo-controlled, randomized clinical trial funded by the National Institute of Mental Health. The methods have been described in detail previously (18). During phase 1, all participants received open-label venlafaxine XR for 12 to 16 weeks (target dosage: minimum 150 mg/day, maximum 300 mg/day) to prospectively determine treatment resistance. With remission defined as a score ≤10 for two consecutive assessments on the Montgomery–Åsberg Depression Rating Scale (MADRS) at the end of phase 1, nonremitters were eligible for phase 2, which consisted of venlafaxine XR augmented with low-dose BPN or matching PBO for 8 weeks. This report focuses on clinical findings and multimodal experiments during BPN versus PBO augmentation (phase 2).

Participants. Participants were recruited from three academic centers (Centre for Addiction and Mental Health, Toronto, Ontario, Canada; University of Pittsburgh, Pittsburgh, PA; Washington University in St. Louis, St. Louis, MO) from July 2009 to July 2014.

Participants 50 years and older with a diagnosis of MDD confirmed using the Structured Clinical Interview for DSM-IV and a MADRS score ≥15 at baseline were eligible for the study.

Exclusion criteria included the following: dementia; lifetime diagnosis of bipolar disorder, schizophrenia, or other psychotic disorders; current psychotic symptoms; lifetime history of opiate abuse or dependence; abuse or dependence on alcohol or other substances within the past 3 months; high risk for suicide and unable to be managed safely in the clinical trial; contraindication to venlafaxine XR or BPN; taking psychotropic medications that cannot be safely tapered and discontinued prior to study initiation (with exception of benzodiazepines up to 2 mg/day lorazepam equivalent, other sedative-hypnotics, and gabapentin if prescribed for nonpsychiatric indication); inability to provide consent or communicate in English; inability/refusal to identify an emergency contact; noncorrectable clinically significant sensory impairment; unstable physical illness; concomitant use of strong or moderate CYP3A4 inhibitor; severe pain; significant hepatic or renal impairment; pregnancy; and any safety concerns that would preclude MRI/PET/TMS (site specific).

All participants provided written informed consent. The study was approved by the institutional review boards at each respective site. This study was registered on ClinicalTrials.gov (NCT02176291, NCT02181231, NCT02263248).

Randomization and Blinding. Phase 1 nonremitters were randomized 2:1 to BPN or PBO augmentation to venlafaxine XR (at the same dose as at the completion of phase 1), using permuted block randomization. The randomization sequence was generated by an external consultant otherwise not involved in the study. Participants, clinical assessors, and investigators were blinded to the randomization.

Interventions. BPN (or matching PBO pills) was started at 0.2 mg/day, administered sublingually, and increased by 0.2 mg/day each week, based on depressive symptom severity and tolerability, to a maximum of 1.2 mg/day. These dosages were based on previous BPN studies for treatment-resistant depression in younger (0.15–1.8 mg/day) and older adults (0.2–1.6 mg/day) (13,19). Study medication was dispensed in blister packs, and participants were instructed to return all unused medication in the blister pack at each visit. Adherence to pharmacotherapy was assessed using self-report data and pill counts.

Assessments and Outcomes. The primary outcome measure was MADRS, which was administered weekly by a rater blinded to group allocation. Tolerability and safety were monitored weekly with assessment of orthostatic vital signs and weight, assessment of suicidality using the Scale for Suicidal Ideation (20), and assessment of adverse effects using the self-reported Antidepressant Side Effect Checklist (21). Comorbid physical illness at baseline was measured with the Cumulative Illness Rating Scale for Geriatrics (22).

Statistical Analyses of Clinical End Points. Baseline differences in demographic and clinical characteristics between BPN and PBO groups were tested using analysis of variance techniques for continuous variables and logistic regression for categorical variables. For the primary efficacy outcome, Fisher's exact test was used to compare proportions of remitters (MADRS score ≤10) in each treatment group. We also compared the trajectories (change of MADRS score over time) between BPN and PBO using polynomial mixed-effects longitudinal models. Safety outcomes were compared using mixed-effects modeling to compare Antidepressant Side Effect Checklist scores between the two treatment groups over time. Statistical analyses of the clinical end points were performed using SAS versions 9.2 and 9.3 and R version 2 or later.

fMRI to Examine Effect of BPN in the Brain Reward System During the MID Task

Trial participants with MDD and healthy control subjects (age >21) underwent task-based fMRI at Washington University in St. Louis. The enrollment process and outcomes are illustrated in Figure 1. Trial participants with MDD were recruited and treated as described above.

Healthy adults were recruited from the community via flyers and word-of-mouth to complete both the fMRI and PET scans at Washington University in St. Louis. These healthy control subjects were 21 years of age and older, male or female, medically stable, and not currently taking opioids. They received 0.2 mg oral BPN (open label) approximately 24 hours after the baseline assessment and scan. Over the next week, the dosage was titrated up to 1.2 mg/day based on tolerability. Control participants continued receiving 1.2 mg/day over the second week, mimicking the administration of BPN in the clinical trial.

Trial participants and control subjects had two fMRIs, first at baseline before receiving BPN (visit 1) and then after receiving BPN (visit 2). For control subjects, scans were repeated after ~2 weeks (mean ± SD = 14.0 ± 7.3 days; range, 7–27 days) of BPN administration. For trial participants, scans were repeated after receiving BPN for 8 weeks. A modified version of the MID task (23) was used. The fMRI task analysis studied the effects of BPN on the neural reward system. Therefore, only participants from the clinical trial who received BPN (unblinded for analysis) were included in the analysis. See the Supplement for further description of the MRI protocols.

We examined six regions of interest (ROIs) defined a priori, which were extracted from a published meta-analysis of
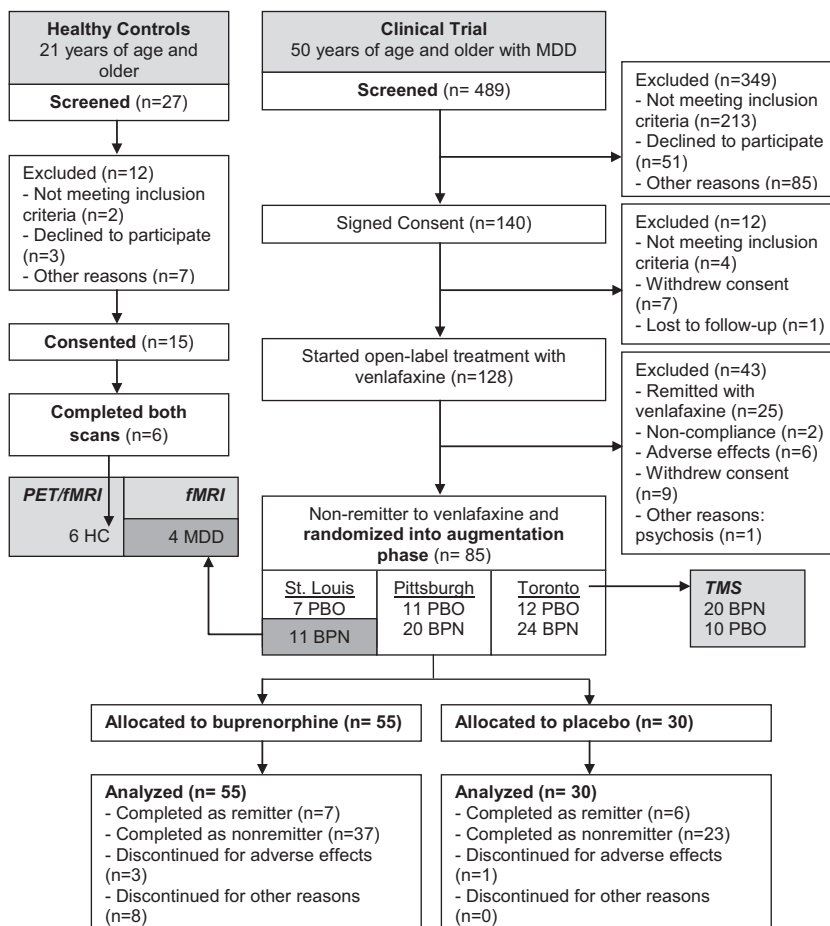

Figure 1. Enrollment and outcomes. BPN, buprenorphine; fMRI, functional magnetic resonance imaging; HC, healthy control; MDD, major depressive disorder; PBO, placebo; PET, positron emission tomography; TMS, transcranial magnetic stimulation.

reward processing (24): left caudate, left middle frontal gyrus, right anterior cingulate, right frontal lobe, right middle frontal gyrus, and right caudate. We used repeated-measures analysis of variance to test whether there were changes in activity at any of these six ROIs before and after receiving BPN.

In the analysis, time (8 time points spanning 16.8 s during the task) and visit (visit 1 or 2) were defined as within-subject factors. We focused on examining reward cue (and not loss cue) and win outcome only (and not in contrast to loss outcome), and these conditions were examined separately. These conditions were chosen based on studies examining brain activation changes in reward anticipation and reward outcome during monetary reward processing (25). In the case of a significant visit-by-time interaction, we subsequently examined whether the effect of time (signifying a response to the task) was significant at either visit 1 or 2. We also plotted the brain voxel's time course to examine the shape of the hemodynamic response. Results that indicated a significant visit-by-time interaction, an effect of time at either visit 1 or 2, and a time course resembling the hemodynamic response were considered meaningful and interpretable.

PET With [¹¹C]LY2795050 in Control Participants to Assess the Effect of BPN on κ-OR Binding

Control participants who completed the task-based fMRI at Washington University in St. Louis also underwent PET imaging with radioligand [¹¹C]LY2795050 to determine the effect of daily low-dose BPN administration on κ-OR binding. In vivo PET experiments in humans have shown that [¹¹C]LY2795050 imaging is reproducible and reliable in brain ROIs with moderate to high κ-OR density (26,27). The PET studies were approved by the United States Food and Drug Administration (IND 130774 and RDRC #796L).

During a baseline [¹¹C]LY2795050 PET and MRI session, 167 to 403 MBq of [¹¹C]LY2795050 was given intravenously followed by a 90-minute dynamic emission scan. Scans were repeated after ~2 weeks of BPN administration, as described in fMRI methodology earlier. See the Supplement for further information regarding PET/MRI acquisition.

We used the semiquantitative standard uptake value ratios over a 30- to 90-minute postinjection window with the cerebellum as a reference region to compare [¹¹C]LY2795050 binding in various ROIs between pre-BPN administration and post-BPN administration. In this analysis, ROIs were defined using FreeSurfer (28) for 13 regions, averaged over left and right hemispheres: amygdala, insula, rostral anterior cingulate cortex, pallidum, putamen, medial temporal cortex, superior frontal cortex, lingual gyrus, hippocampus, caudate, precuneus, thalamus, and cerebellum.

TMS Assessment of BPN or PBO Effects on Cortical Excitability, Inhibition, and Plasticity

TMS is a noninvasive procedure that can be used to stimulate cortical regions (29). When TMS is applied at a sufficient intensity over the motor cortex, it activates descending pyramidal corticospinal neurons, resulting in a motor-evoked potential that can be measured using electromyography (30,31). Paired-pulse TMS can be used to index cortical GABA receptor–mediated inhibitory neurotransmission and glutamate receptor–mediated excitatory neurotransmission (32,33). In addition, TMS combined with peripheral nerve stimulation can also be used to assess cortical plasticity, akin to long-term potentiation (34,35).

Trial participants (age ≥50 with a diagnosis of MDD) at the Centre for Addiction and Mental Health (Toronto, Ontario, Canada) underwent TMS at three time points: 1) baseline (before exposure to BPN or PBO), 2) within 7 days of exposure to BPN or PBO augmentation, and 3) after 8 weeks of BPN or PBO augmentation. Cortical inhibition was indexed with cortical silent period and paired-pulse short-interval intracortical inhibition. Cortical facilitation was measured using paired-pulse intracortical facilitation. Long-term potentiation–like cortical plasticity was measured using paired associative stimulation. See the Supplement for additional details on these four TMS measures.

TMS analyses were completed using SPSS Statistics 26.0 (IBM Corp.) according to the intention-to-treat principle. Measures that did not satisfy normality assumption based on the Shapiro-Wilk test were log-transformed. Groups (BPN vs. PBO) were compared using a mixed analysis of variance, with treatment group as a between-subjects factor and time (baseline, week 1, final) as a within-subjects factor.

RESULTS

Randomized Clinical Trial

Of the 128 participants who started open-label treatment with venlafaxine XR, 18 discontinued the study and 25 remitted. A total of 85 did not remit, and 55 were randomized to BPN and 30 to PBO (Figure 1). Baseline demographic and clinical characteristics of randomized participants are summarized in Table 1.

The average daily dose ± standard deviation of BPN was 0.59 ± 0.33 mg. Seven of the 55 (12.7%) participants randomized to BPN and 6 of the 30 (20%) randomized to PBO were remitters at the end of the randomized trial. These two proportions did not differ significantly (odds ratio 0.59, 95% confidence interval 0.17–2.0, $p = .41$).

A plot of mean MADRS scores over time is shown in Figure S1. Based on the significance of the fixed effect polynomial coefficients, a cubic model best fit the trajectory of MADRS scores during the trial. The model indicates improvement in both treatment arms over time ($F_{3,443} = 12.32$, $p < .01$). However, there were no significant differences between the treatment groups in the MADRS trajectories over time ($F_{3,443} = 0.26$, $p = .85$).

Similarly, there was not a significant overall effect of time or a difference in the effect of time between the two treatment groups for adverse effects as measured with the Antidepressant Side Effect Checklist.

fMRI to Examine Effects of BPN in the Brain Reward System

Ten participants (4 midlife to older adults with MDD and 6 healthy control subjects) underwent scans before and after BPN administration and were included in the analysis. In the analysis of six ROIs defined a priori (24) to examine the effect of BPN on brain activation patterns in the gain cue and win outcome conditions (Table S2), the only significant effect was in one region in the win outcome condition, with the right

Table 1. Demographic and Baseline Clinical Characteristics of Participants in the Clinical Trial

	BPN (n = 55)	PBO (n = 30)	p Value
Demographic Characteristics			
Age at Baseline, Years, Mean (SD)	64.6 (8.6)	66.5 (7.9)	.91
Education, Years, Mean (SD)	15.3 (2.7)	15.2 (2.9)	.91
Female[a], n (%)	31 (56.4%)	21 (70.0%)	.22
Race, n (%)			.71
Asian	1 (1.8%)	0 (0%)	
Black	4 (7.3%)	1 (3.3%)	
Other or multiple	1 (1.8%)	1 (3.3%)	
White	49 (87.8%)	28 (93.3%)	
Clinical Characteristics			
BMI[a], Mean (SD)	29.2 (6.0)	29.9 (5.4)	.64
MADRS[a], Mean (SD)	22.7 (6.5)	20.4 (6.3)	.13
CIRS-G[a], Mean (SD)	5.0 (2.6)	6.2 (1.9)	.01
SSI, Median [Min, Max]	0 [0, 20]	0 [0, 12]	.66

BMI, body mass index; BPN, buprenorphine; CIRS-G, Cumulative Illness Rating Scale for Geriatrics; MADRS, Montgomery–Åsberg Depression Rating Scale; Max, maximum; Min, minimum; PBO, placebo; SSI, Scale for Suicidal Ideation.

[a]Indicates variables that had statistically significant (p < .05) site differences. Baseline demographic and clinical characteristics by site can be found in the Supplement (Table S1).

middle frontal gyrus showing a visit-by-time interaction (Z = 3.20, p < .01) with a significant time effect during at least 1 visit. There was a main time effect both at visit 1 (p < .05, Z = 2.07) and at visit 2 (p < .01, Z = 3.32) in the win outcome condition (Figure 2). The pattern of activation in this region suggested sustained activation at baseline (visit 1) but an initial increase followed by a rapid decrease in the bold signal after BPN (visit 2).

PET With [^{11}C]LY2795050 to Assess the Effect of BPN on κ-OR Binding

Six control participants (5 men and 1 woman) ages 23–41 (mean ± SD: 30.3 ± 7.8 years) completed both baseline and post-BPN MRI/PET scans. All 6 participants were taking 1.2
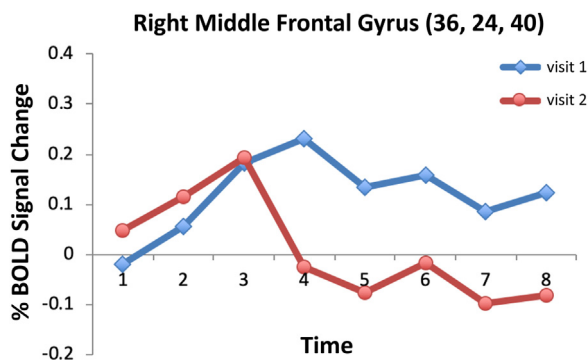
Figure 2. Time courses in the right middle frontal gyrus showed a significant visit by time interaction (p < .01), with significant effects of time at visit 1 (p < .05) and visit 2 (p < .01) in the win outcome condition. BOLD, blood oxygen level–dependent.

mg/day of BPN at the time of the post-BPN scan. Mean injected dose ± SD of [^{11}C]LY2795050 was 266 ± 67 MBq at baseline and 355 ± 52 MBq after BPN administration. Because of the small sample size and lack of evident differences, we do not report inferential statistics on pre-post differences. Therefore, engagement of κ-OR after about 2 weeks (range, 7–27 days) of BPN administration was not detected by PET with [^{11}C]LY2795050. Figure 3 shows [^{11}C]LY2795050 standard uptake value ratios before and after BPN in the 6 participants studied.

TMS Protocols to Assess the Effect of BPN or PBO on Cortical Transmission

A total of 30 participants (20 randomized to BPN and 10 to PBO) completed TMS measurements, and 28 (18 BPN, 10 PBO) were included in the analysis owing to missing data. The four TMS measures over time in each treatment group are shown in Figure 4.

There were no significant changes in any of the four TMS measures over time (short-interval intracortical inhibition: $F_{2,24}$ = 0.37, p = .70; intracortical facilitation: $F_{2,24}$ = 0.61, p = .55; cortical silent period: $F_{2,24}$ = 1.11, p = .32; maximum paired associative stimulation: $F_{2,24}$ = 0.06, p = .94). Similarly, there were no significant interactions between group and time (short-interval intracortical inhibition: $F_{2,24}$ = 0.18, p = .83; intracortical facilitation: $F_{2,24}$ = 0.16, p = .85; cortical silent period: $F_{2,24}$ = 0.14, p = .79; maximum paired associative stimulation: $F_{2,24}$ = 1.11, p = .34).

DISCUSSION

We conducted an 8-week multisite, randomized, PBO-controlled trial of low-dose BPN augmentation pharmacotherapy in adults age 50 and older with treatment-resistant depression, and we used a multimodal approach to examine target engagement. The key results were 1) the effects of low-dose BPN and PBO on depression were small and did not differ, 2) low-dose BPN was well tolerated with no significant differences in adverse effects between BPN and PBO, 3) BPN had minimal effects on fMRI bold responses in regions involved in reward anticipation and response during the MID task, 4) PET imaging in healthy control subjects did not show significant displacement of the κ-OR radioligand by low-dose BPN, and 5) low-dose BPN did not significantly affect TMS measures of plasticity or inhibitory and excitatory cortical transmission in depressed midlife and older participants.

This study did not show clinical effects of low-dose (mean = 0.59 ± 0.33 mg/day) BPN after 8 weeks; there were no significant differences between the treatment groups in the proportions of remitters or in the MADRS trajectories over time. It is possible that the dosage of BPN was too low. A previous randomized, placebo-controlled trial of low-dose BPN/samidorphan showed no difference in MADRS score changes in the group that received BPN/samidorphan 0.5 mg/0.5 mg compared with PBO and numerically greater but not statistically significant improvement in those who received 1 mg/1 mg (15). The low dosage of BPN may also explain the lack of target engagement. The specific clinical characteristics of our sample may also explain the lack of clinical effect observed. For one, we excluded patients with moderate to severe chronic pain to minimize an analgesic
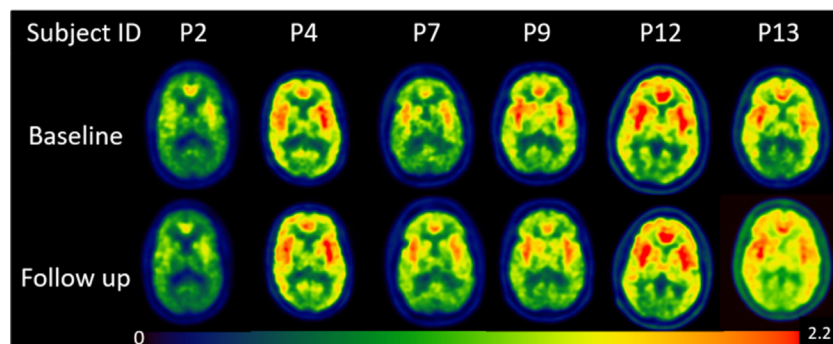
Figure 3. [^{11}C]LY2795050 standard uptake value ratios (SUVRs) in brains (similar axial slices shown) of 6 healthy participants who received buprenorphine over 2 weeks. Baseline positron emission tomography scans took place approximately 24 hours before first buprenorphine dose. Follow-up positron emission tomography scans took place approximately 2 weeks after baseline. SUVR images as shown were calculated using cerebellum gray matter as the reference region and over a 30- to 90-minute postinjection window. It is used as a semiquantitative assessment of tracer binding to kappa opioid receptors in the brain. Warmer color and higher SUVR values reflect more tracer uptake and suggest a higher relative concentration of unoccupied kappa opioid receptors compared with the reference region. Because of the small sample size and lack of evident differences, we did not conduct inferential statistics on pre-post differences. The lack of differences in [^{11}C]LY2795050 SUVR between baseline and follow-up scans in any regions of interest suggests no changes in unoccupied kappa opioid receptor concentration in the brain after buprenorphine treatment.

effect that could have confounded an antidepressant effect. We also excluded patients with a history of opioid misuse or current misuse of other substances to minimize the risk of triggering BPN misuse. Patients living with comorbid pain and MDD or those with MDD and substance misuse may be more likely to experience an antidepressant effect from BPN given the dysregulation of the opioid systems in these populations (36).

The fMRI experiment using an MID task showed minimal to no effects of BPN administration on the activation of regions associated with reward anticipation and response to either reward cues or reward outcomes. In the reward outcome, the right middle frontal gyrus (x, y, z of 36, 24, 40) showed a pattern of initial rise but rapid fall in the bold signal in the post-BPN condition, potentially suggesting a blunted response.
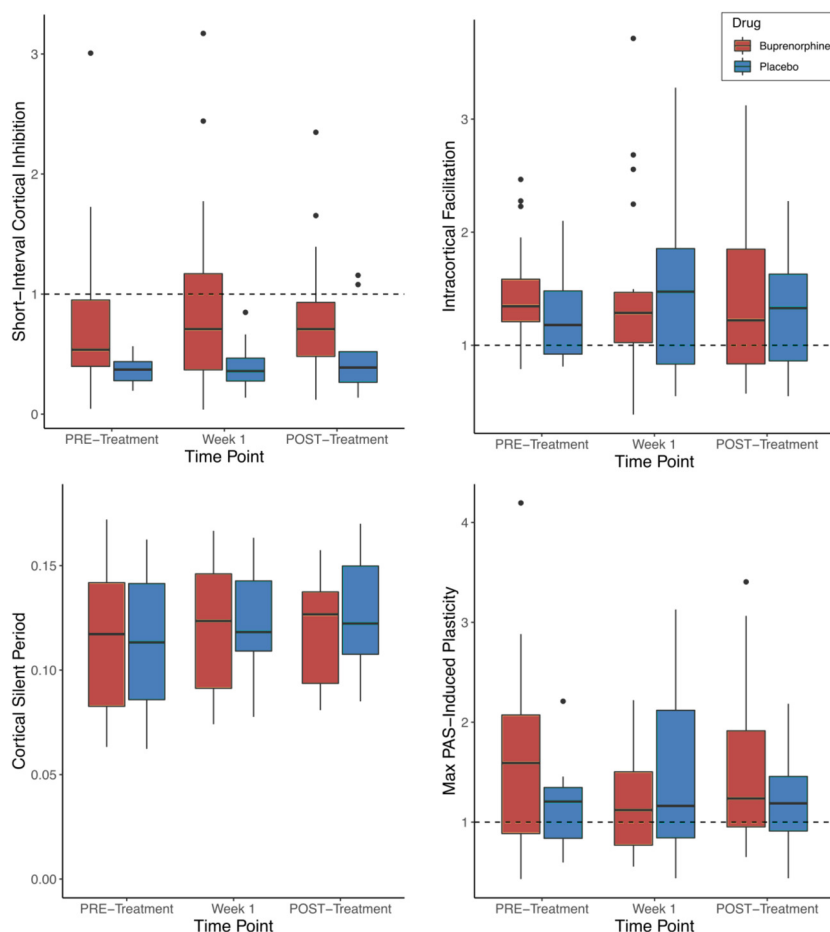
Figure 4. Transcranial magnetic stimulation measures (mean ± SEM) over time by treatment group. Short-interval intracortical inhibition and intracortical facilitation are expressed as the ratio of the mean conditioned motor-evoked potential (MEP) amplitude to the mean unconditioned MEP amplitude. Cortical silent period duration is in seconds. Maximum paired associative stimulation (PAS) is expressed as the ratio of the maximum mean MEP amplitude at any post-PAS time point to the mean pre-PAS MEP amplitude. There was no significant change in any transcranial magnetic stimulation measures over time and no significant interaction between group and time.

Overall, BPN had very limited effects on brain activation patterns in the regions studied, contrary to our hypotheses that BPN would activate regions with established involvement in reward processing. These results are consistent with our previous study (18) that examined the neural effects of BPN using a gambling task (probing striatal and reward-related regions) and also showed no changes in reward circuitry elicited by the reward responsivity task.

PET imaging of healthy adults did not show a decrease in κ-OR binding after 7 to 27 days of BPN compared with before BPN, which would be expected if κ-OR was occupied by BPN. This negative result suggests that BPN at a dosage of up to 1.2 mg/day does not meaningfully engage κ-OR. However, this negative result could also be due to the semiquantitative standard uptake value ratio method we used not being sensitive enough to detect subtle differences in binding. While full kinetic analysis would be ideal to quantitatively assess the true κ-OR binding and occupancy, we were unable to obtain adequate data to characterize the arterial radiotracer concentration. In addition, κ-OR is ubiquitous in the brain, and an ideal reference region does not exist. However, given its lowest receptor density and smallest response to blockers, we used the cerebellum as the pseudo reference in this study (27). In a reference-free standard uptake value analysis, we also did not detect any regional changes before and after BPN in these subjects. In addition, we evaluated κ-OR binding after subchronic daily dosing of BPN to simulate the effect of clinical treatment; however, it is possible that adaptive changes (i.e., upregulation of κ-OR with subchronic BPN) obscured the effect of BPN on κ-OR (37). Examining PET changes after a single dose of BPN may be more sensitive to demonstrate target engagement.

Previous TMS evidence suggests that mechanisms in the motor cortex that are mediated by GABA and glutamate receptors are impaired in depression (38,39). Despite prior evidence of interactions between opioid, GABA, and glutamate systems (40), we did not observe any significant changes in TMS measures of cortical inhibition, facilitation, or plasticity after either BPN or PBO augmentation. Similarly, our previous study of open-label venlafaxine in older adults with MDD did not show an effect of venlafaxine on these cortical measures (41). Our findings suggest that low-dose augmentation of venlafaxine with BPN does not further engage GABAergic and glutamatergic mechanisms in the cortex. These findings are specific to the motor cortex and could differ in other cortical regions more closely linked with the neurobiology of depression.

Limitations of this study include relatively small sample sizes, particularly for the linked experiments (i.e., fMRI, PET, and TMS), and the heterogeneity of the participants (e.g., differences in the age cutoff) and duration of BPN treatment for these three target engagement substudies. As stated earlier, some of the exclusion criteria (including moderate or severe pain or substance misuse) may also limit the interpretation of our results. Finally, we did not use a dose-finding lead-in phase to determine the BPN dosage needed to achieve a physiological effect, using measures such as cold-pressor threshold or pupil dilation (42), and we do not have plasma levels of BPN and its metabolites.

Our findings of a lack of clinical effect and target engagement support the National Institute of Mental Health

recommendation (43) to start development of pharmacological interventions by adequately testing mechanisms of action and demonstrating dose-dependent neurophysiological effects before proceeding with large clinical trials. This experimental medicine and target engagement approach aims to integrate clinical and physiological biomarkers to inform next steps in discovery. For example, if we had observed the expected findings across all dimensions (clinical measures, functional engagement using fMRI, molecular target engagement by PET, and neurophysiological evidence of the engagement of GABA and glutamate neurotransmission), it would be a clear "go" signal for further studies of BPN in midlife and older patients with MDD. In contrast, the results of this study would suggest "no go" with this dosage and physiological probes. However, given the well-supported connection between the opioid system and depression, the growing literature on the use of κ-OR antagonists and improved mood, and the current mental health and substance use crises, there is still a need to study novel agents modulating the opioid system. Future studies using larger doses of BPN, other probes of target engagement, and samples with different characteristics may be warranted.

ARTICLE INFORMATION

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