Buprenorphine in Combination with Samidorphan (ALKS 33) Results in Antidepressive-Like Effects in Two Distinct Rat Models

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P.2.a.010

INTRODUCTION

- The endogenous opioid system regulates mood and is dysregulated in patients with depressive illness.
- The use of μ-opioid agonists for the treatment of central nervous system (CNS) diseases and mood disorders such as major depressive disorder (MDD) has been hampered by their abuse liability and overdose potential.
- One strategy to increase the utility of opioids is balanced neuromodulation of μ-opioid agonist activity.
- ALKS 5461 represents a novel treatment for depression that combines buprenorphine (BUP) and samidorphan (SAM), a potent full μ-opioid antagonist. Both BUP and SAMI have similar activity at δ and κ receptors
- In a recent phase 2 clinical trial in MDD, ALKS 5461 was superior to placebo on a range of depressive symptoms.
- It is hypothesized that this combination results in balanced neuromodulation that regulates the pharmacodynamic effects of the agonist to minimize its potential for abuse and overdose while preserving therapeutic efficacy in the treatment of depression.
- Previously, it has been demonstrated that co-administration of BUP and SAM dose-dependently attenuated buprenorphine-induced elevations of extracellular dopamine and serotonin in the nucleus accumbens and medial prefrontal cortex of rats (Deaver, et. al., ACNP, 2013: See Figure 2).
- Here, we used two models to examine the anxiolytic and antidepressant-like effects of this combination in rats.
- In the first model, an anxiogenic/depressive-like state was induced with chronic corticosterone treatment and saccharin consumption was measured.
- In the second model, the forced swim test, Wistar Kyoto (WKY) rats were used because they display a number of behavioral and hormonal deficits that are often described as depression-like features and are used in nonclinical models of learned helplessness.

METHODS

Drugs and Animals:

- Samidorphan was synthesized by Cambridge Major Laboratories (Germantown, WI). Buprenorphine (Buprenex®, 0.3 mg/mL) was purchased from Butler Schein Animal Heath Supply (Chicago, IL).
- Rats were purchased from Charles River Laboratories (Raleigh, NC).

Saccharin Consumption Test:

- Male Sprague Dawley (SD) rats (n=30) were implanted with two 100 mg slow-release corticosterone pellets (#G-111, Innovative Research America, Sarasota, FL).
- Rats were then individually housed to allow measurement of individual saccharine and water consumption (two bottle choice).
- On Day 7, rats were tested to confirm a reduction in saccharin consumption and then assigned to treatment groups using a complete random block design based on this consumption.
- On Day 14, rats were treated subcutaneously (SC) with a) 0.9% saline, 1 mL/kg; b) buprenorphine (0.1 mg/kg) in combination with 0.3 mg/kg samidorphan; or c) buprenorphine (0.1 mg/kg) in combination with 3 mg/kg samidorphan.
- Rats were then returned to their home case for a second test.
- Saccharin consumption was calculated based on the change in bottle weights during the 16.5-hour overnight access and calculated in grams.

Forced Swim Test:

- Male WKY rats (n = 8/group) were randomly assigned to one of three treatment groups.
- The swim chambers were 45 cm x 20 cm (H x D) and filled to 29 - 31 cm with water (24 - 26°C) for each test.
- On Day 1, rats were placed in the water-filled tanks for 15 minutes, then removed, towel dried, and placed in a warm enclosure for 15 minutes before being returned to the vivarium.
- Following the initial swim, rats received three injections of a) 0.9% saline for injection (1 mL/kg, SC); b) buprenorphine (0.1 mg/kg) in combination with 0.3 mg/kg samidorphan, SC; or c) buprenorphine (0.1 mg/kg) in combination with 3.0 mg/kg samidorphan, SC at 1, 19, and 23 h after the first swim.
- One hour after the last injection, rats were placed in the water-filled tanks a second time for 300 seconds under the same conditions as Day 1.
- These sessions were videotaped from the side of the cylinders and were scored manually for immobility time (in seconds) over the entire 300 second period using a stop watch by a rater blinded to the treatments. Because WKY rats did not display any climbing behavior, the remaining time was used as swim time.
- A rat was judged to be immobile if it was making only movements necessary to keep its head above water.

RESULTS

FIGURE 1: Effects of BUP on extracellular concentrations of dopamine (DA) in the nucleus accumbens

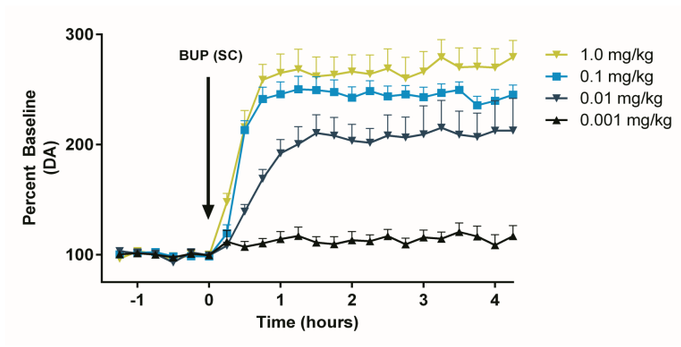

Figure 1: Subcutaneous administration of buprenorphine dose-dependently increased extracellular concentrations of dopamine in rat nucleus accumbens shell.

FIGURE 2: Effects of BUP and SAM combinations on extracellular concentrations of dopamine, its metabolites and 5-HIAA in the nucleus accumbens

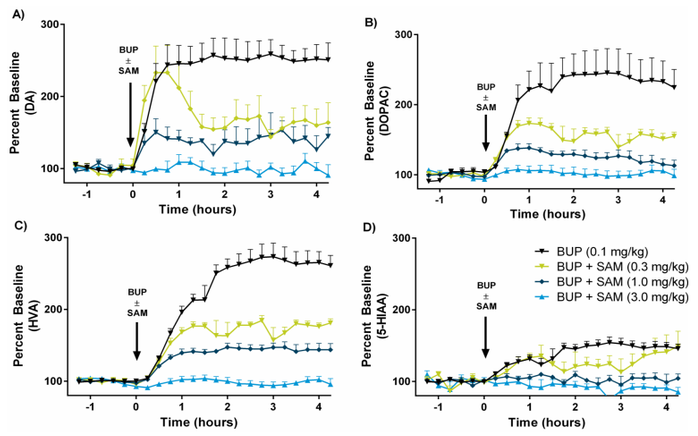

Figure 2: Concurrent administration of samidorphan dose-dependently attenuated buprenorphine-induced increases in: A) DA; B) DOPAC; C) HVA and D) 5-HIAA. Importantly, lower doses of samidorphan (0.3 mg/kg or 1.0 mg/kg) did not completely block the effects of buprenorphine on DA, DOPAC, HVA or 5-HIAA.

FIGURE 3: Effects of BUP and SAM combinations on saccharin consumption in corticosterone treated SD rats

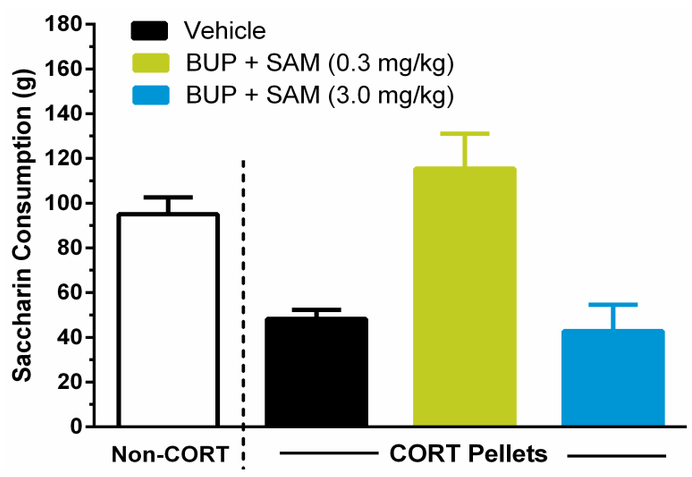

Figure 2: On Day 14 following the implantation of corticosterone (CORT) pellets, Sprague Dawley (SD) rats were treated just prior to the 16.5-hour two-bottle choice between water and saccharin. Chronic CORT decreased saccharin consumption ($t = 5.336$, $df = 17$, $p<0.001$). Among the groups treated with CORT (n = 10 per group), there was a significant effect of treatment ($F_{(2,24)} = 12.23$, $p < 0.001$) on Day 14, with rats given BUP (0.1 mg/kg, SC) in combination with SAM (0.3 mg/kg, SC), consuming more saccharin than those in the other two groups. Administration of 0.1 mg/kg BUP + 0.3 mg/kg SAM increased saccharin consumption similar to that of the non-CORT treated rats, whereas administration of 0.1 mg/kg BUP + 3.0 mg/kg SAM did not. Data are expressed as mean ± SEM.

FIGURE 4: Effects of BUP and SAM combinations in the forced swim test in WKY rats

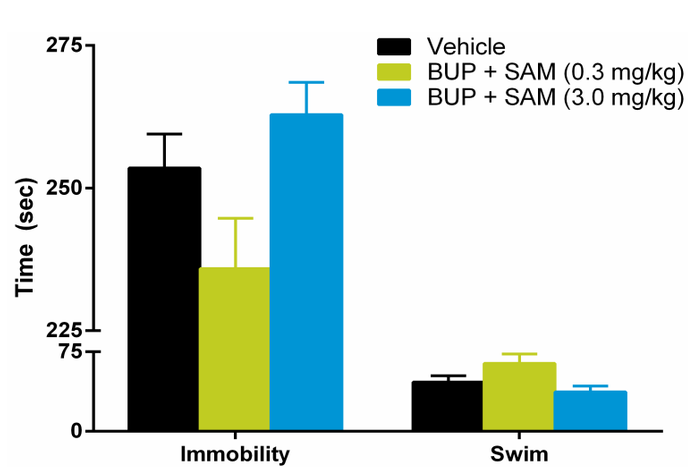

Figure 3: Rats (n = 8 per group) were treated with vehicle (1 mL/kg), 0.1 mg/kg BUP in combination with 0.3 mg/kg SAM or 0.1 mg/kg BUP in combination with 3.0 mg/kg SAMI 1, 19, and 23 hours after the first swim test and tested 1 hour after the last injection. There was an overall effect of treatment ($F_{(2, 21)} = 3.88$, $p = 0.037$) on immobility time: administration of 0.1 mg/kg BUP + 0.3 mg/kg SAM reduced total immobility time whereas administration of 0.1 mg/kg BUP + 3.0 mg/kg SAM did not. Data are expressed as mean ± SEM.

CONCLUSIONS

- Samidorphan dose-dependently attenuated buprenorphine-induced elevations in dopamine and serotonin.
- In both behavioral paradigms, the dose combination that attenuated, but did not completely block buprenorphine-induced elevations in monoamines, demonstrated anxiolytic and antidepressant-like effects in rats.
- In rats, these data suggest that a balanced neuromodulation of μ-opioid agonist activity is required to maintain efficacy in these paradigms.
- However, a potential role of δ- and κ-opioid receptors cannot be ruled out.

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All studies were funded by Alkermes, Inc.

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ALKS 5461 represents a novel treatment for depression that combines buprenorphine (a partial mu agonist) with samidorphan (a potent full mu antagonist), formerly referred to as ALKS 33. In a recent phase 2 clinical trial in Major Depressive Disorder, ALKS 5461 was superior to placebo on a range of depressive symptoms. There is a substantial body of nonclinical and pharmacologic research indicating that endogenous opioid systems regulate mood and are dysregulated in patients with depressive illness [1,2]. Additionally, opioid receptors and their endogenous ligands are expressed in areas of the brain that have been associated with regulating mood and depression, including the nucleus accumbens, prefrontal cortex, hippocampus, thalamus, caudate and amygdala [3]. Unfortunately, the use of mu opioid agonists for the treatment of CNS diseases and mood disorders such as Major Depressive Disorder has been hampered by their abuse liability and overdose potential. One strategy to increase the utility of opioids is to balance the activity of known partial or full mu opioid agonists with a pharmacologically active mu opioid antagonist. It is hypothesized that such a combination would modulate the pharmacodynamic effects of the agonist molecule so as to minimize its potential for abuse and overdose while preserving therapeutic efficacy. Previously, it has been demonstrated that co-administration of buprenorphine with samidorphan dose-dependently attenuated buprenorphine-induced elevations of extracellular dopamine and its metabolites in the nucleus accumbens and medial prefrontal cortex in rats (Deaver, et al., ACNP 2013).

Corticosterone-induced decreases in saccharin consumption and the forced swim test are models commonly used to study the antidepressant-like effects of drugs. In the first model, rats were induced into a depressive-like state with chronic exposure to corticosterone, as indicated by a decrease in saccharin consumption. In the forced swim test, Wistar-Kyoto rats were used because they are a spontaneously hypertensive strain that demonstrate endogenous hormonal and behavioral abnormalities often used in nonclinical models of behavioral despair. Antidepressant drugs reverse corticosterone-induced decreases in saccharin consumption and reduce immobility time in the forced swim test. Here, two doses of samidorphan (0.3mg/kg and 3.0mg/kg) were administered with a fixed dose of buprenorphine (0.1mg/kg) and data were analyzed using one-way analysis of variances. Buprenorphine, combined with 0.3mg/kg samidorphan, reversed corticosterone-induced decreases in saccharin consumption and decreased immobility in the forced swim test. However, when buprenorphine was combined with the higher dose of samidorphan (3.0mg/kg), the positive effects observed with the lower dose were reversed in both the saccharin consumption test and forced swim test. Thus, balanced modulation of opioid pharmacology may unlock the potential therapeutic value of known opioids by improving their safety. Together, the current data suggest that modulation of mu receptor activity plays an important role in the observed effects in these rat models of depression-like behavior.

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Disclosure statement: All authors are full time employees of Alkermes, Inc., and all studies were funded by Alkermes, Inc.

Citation: Eur Neuropsychopharmacol. 2014;24(Suppl 2):S366

Keywords

Depression: basic

Antidepressants: basic

Drug development