

Kappa opioid receptor antagonism: Are opioids the answer for treatment resistant depression?

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Abstract

Introduction: Past trials of buprenorphine (BUP) in the treatment of major depressive disorder (MDD) have displayed favorable results, although its clinical utility was limited by the risk of abuse or physical dependence. By combining BUP with samidorphan (SAM), the euphoric high is negated by an opposing mechanism, which theoretically reduces addictive-like properties while allowing the antidepressant properties to remain. As such, the objective of this article is to analyze the results of BUP/SAM premarketing clinical trials as adjunctive treatment for treatment-resistant MDD.

Methods: A comprehensive PubMed/MEDLINE search was conducted through November 9, 2017, using the following search terms: depression, samidorphan, buprenorphine, ALKS-5461. Additional data were obtained from Clinicaltrials.gov and resources included in the present study. All English-language clinical trials evaluating the combination of BUP/SAM in the treatment of MDD were included.

Results: A few premarketing studies have evaluated the efficacy and safety of BUP/SAM combination as adjunctive treatment in patients with treatment-resistant MDD. The FORWARD-1 through FORWARD-5 trials concluded (1) the most effective dosing ratio of BUP/SAM to reduce abuse potential was 1:1; (2) statistically significant changes in scores from baseline on the Montgomery-Asberg Depression Rating Scale were noted for the 2 mg/2 mg dose compared with placebo; and (3) the most commonly reported adverse effects were nausea, dizziness, and fatigue.

Discussion: Buprenorphine/samidorphan has shown favorable results for efficacy and tolerability in premarketing studies evaluating its use as adjunctive therapy for treatment-resistant MDD. Its novel mechanism targeting the opioid pathway may serve as a promising antidepressant devoid of abuse potential.

Keywords: depression, buprenorphine, samidorphan, opioid receptor antagonist

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Background

In 2015, approximately 6.7% of adults in the United States experienced a major depressive episode, which translates to an estimated 16.1 million individuals.¹ Despite numerous therapeutic options, only about one third of patients will achieve remission after the first medication trial.² In addition, after each subsequent medication trial, the likelihood of achieving remission further declines.³ These individuals who fail multiple antidepressant therapies may

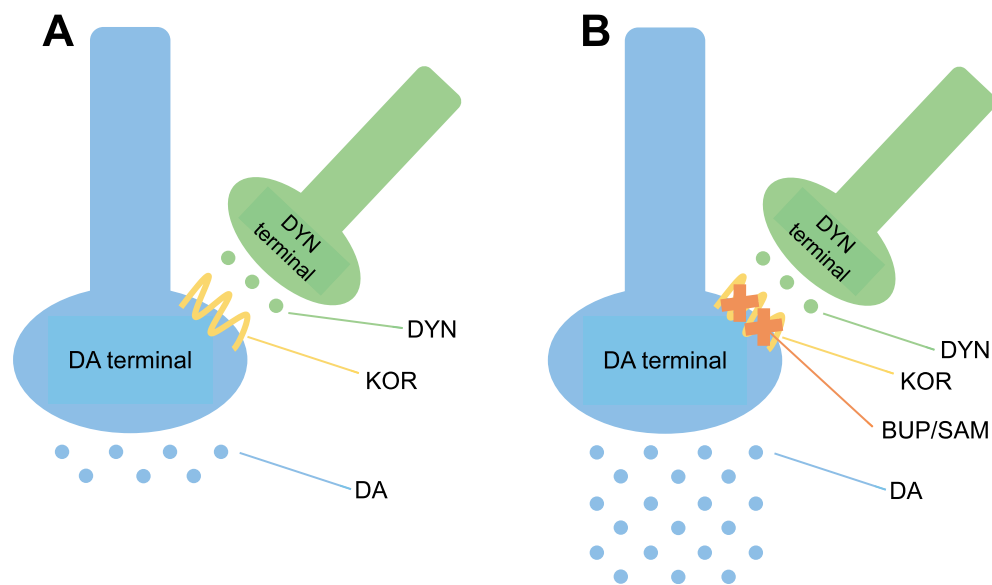


FIGURE: Mechanism of action of buprenorphine/samidorphan (BUP/SAM) (A) In the absence of kappa opioid receptor (KOR) antagonism, endogenous dynorphin (DYN) activates KOR-mediated dopaminergic inhibition, which may lead to depressive-like symptoms of dysphoria and anhedonia. (B) In the presence of KOR antagonism via BUP/SAM, KOR-mediated dopaminergic inhibition is blocked, facilitating increased dopamine (DA) release, which may lead to a reduction in depressive-like symptoms

be classified as “treatment resistant.” It is estimated that roughly half of all patients treated with antidepressants will likely experience a chronic, recurrent course of major depressive disorder (MDD), thus emphasizing the need for alternative treatments.⁴ However, most first- and second-line agents are mechanistically similar in that their primary function is to modulate the neuronal transmission of monoamines by increasing synaptic levels of serotonin, norepinephrine, and/or dopamine (DA).⁵ Even the relatively new antidepressants, such as vortioxetine, vilazodone, and levomilnacipran, have a large degree of monoamine-targeted mechanistic overlap already seen with classic antidepressants, such as selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs).⁶ This singular focus on this pharmacologic strategy has resulted in a paucity of novel antidepressants targeting subgroups of resistant depression, such as those of different underlying pathophysiology.

As such, a different etiologic hypothesis of MDD involves the opioid pathway. Prior to the development of monoamine oxidase inhibitor antidepressants in the 1950s, opioids were considered a therapeutic approach in the treatment of MDD.⁷ The endogenous peptides dynorphins (DYNs), enkephalins, endorphins, and endomorphins bind to the 3 main opioid receptors mu, delta, and kappa in the central nervous system.⁸ Endomorphins and endorphins have a high affinity for the mu opioid receptor (MOR), whereas enkephalins and DYNs have a much lower affinity.⁸ Mu opioid receptor activation is responsible for

the analgesic effects of opioids, although this also drives unwanted side effects, such as acute euphoria, respiratory depression, or physical dependence after prolonged exposure.⁸ Dynorphins display high affinity for the kappa opioid receptor (KOR) and were initially investigated to elicit analgesia similarly to MOR but with less incidence of euphoria and reinforcement.^{9,10} Incidentally, KOR agonism contributed to the mood-related side effect of dysphoria. This discovery sparked exploration into antidepressant-like effects via KOR antagonism.¹⁰

Kappa opioid receptors located within the mesolimbic region of the brain are essential for regulating mood and affective disorders.¹¹ GABAergic neurons projecting from the nucleus accumbens release DYN, which binds and activates KORs located on ventral tegmental area dopaminergic neurons to inhibit dopaminergic firing.¹² This decrease in DA transmission has been associated with dysphoria and anhedonia-related symptoms, as well as the modulation of mood and stress.¹³ Pro-DYN knockdown mice exhibited a reduction in depressive-like behavior, implicating a potential role for KOR antagonists in the treatment of MDD to prevent DYN-mediated DA depletion.¹⁴ The relationship between DYN, KOR, and DA is shown in the Figure, part A.

The role of KOR antagonism in depression has been largely explored in rodent and other animal models, primarily by using the forced swim test. The forced swim test is a behavioral test based on the learned helplessness model of depression, which can be used to evaluate the

potential antidepressant properties of a compound by measuring of immobility time.^{15,16} In theory, immobility time, or passive behavior, should reduce under antidepressant conditions.^{15,16} It has been hypothesized that induction of DYN in the nucleus accumbens promotes immobility during the forced swim test, in which case KOR antagonists would oppose this mechanism, thus signifying an antidepressant-like effect in animal models.¹⁶ The main KOR antagonists that were modeled for antidepressant properties include 5'-guanidinonaltrindole, 5'-acetaminidinoethylnaltrindole, nor-binaltorphimine, and the 4-phenylpiperidine derivative JDtic.¹⁷⁻²⁰ Although all produced reductions in immobility time on the forced swim test, they were never marketed because of concerns of slow onset, toxic drug accumulation, poor oral bioavailability, and/or cardiac toxicity.¹⁷⁻²⁰

One such KOR antagonist, a combination product of buprenorphine (BUP) and samidorphan (SAM), hereafter referred to as BUP/SAM, has been granted Fast Track designation by the US Food and Drug Administration.²¹ Samidorphan, also known as 3-carboxamido-4-hydroxynaltrexone, is a synthetic analog of naltrexone and is a potent MOR antagonist. The original compound was structurally modified to provide a 14-fold increase in binding affinity to MORs and improve oral bioavailability, given that oral administration of well-known MOR antagonists, naloxone and naltrexone, is limited by poor oral bioavailability.^{22,23} Buprenorphine is a partial MOR agonist and KOR antagonist. Given its partial agonism at MORs, it has been noted to be safer than conventional opiates, as evidenced by its "ceiling effect" of respiratory depression, subsequent lack of toxicity, and comparatively mild withdrawal profile.²⁴ When BUP and SAM are administered concurrently, SAM, like naltrexone or naloxone, acts to negate the agonistic effects that low-dose BUP has at MORs. The antagonistic properties at KORs from BUP remain, causing the combination product to act primarily as a KOR antagonist.²⁵ This contrivance has been hypothesized as the proposed mechanism of action for the new antidepressant combination product BUP/SAM, as depicted in the Figure, part B. In summary, BUP will enhance and stabilize endogenous opioid tone in areas of deficiency and hyperactivity, respectively, whereas SAM acts to negate abuse potential.

Buprenorphine has previously demonstrated antidepressant-like properties in humans in a few studies.²⁶⁻²⁹ Of the 71 patients across these 4 studies,²⁶⁻²⁹ 44 were male and 40 were opioid-addicted patients receiving maintenance treatment. The studies²⁶⁻²⁹ were conducted anywhere from 1 to 8 weeks, and BUP was initiated between 0.15 and 0.40 mg/d and titrated to 0.8 to 8.0 mg/d. All of the studies²⁶⁻²⁹ used the sublingual formulation of BUP, although 1 study²⁷ also incorporated intranasal BUP. Patients were assessed on a variety of scales, including

the Beck Depression Inventory, Six-item Short Depression Scale, Hamilton Rating Scale for Depression (HAM-D), Atypical Depression Diagnostic Scale, Profile of Mood States, Global Assessment Scale, and Montgomery-Asberg Depression Rating Scale (MADRS).²⁶⁻²⁹

The first study²⁶ conducted observed that 12 of 19 opioid-addicted, depressed patients met clinical criteria for response at the end of the 1-month study. In addition, maximal symptom reduction was observed rapidly at week 1 (n=8), week 2 (n=2), and week 3 (n=2). The second study²⁷ noted significant improvement as early as week 1, which was sustained through the end of the study at week 4. Of the 7 individuals who completed this, 4 met criteria for remission, 2 for response, and 1 for no response. The third study,²⁸ which was the smallest and shortest study, included 6 patients in a 1-week, dose-titration study. At the end of week 1, 5 of 6 patients met criteria for remission per change in HAM-D scores, whereas 4 of 6 patients met criteria for remission per change in Beck Depression Inventory scores. Lastly, 15 patients were enrolled in an 8-week, dose-titration study and were administered the MADRS weekly.²⁹ There were 8 patients who met criteria for response at the end of the study (mean MADRS=9.5); however, at week 16 telephone follow-up, which occurred after BUP discontinuation at week 8, mean MADRS scores rose back to 17.8, indicating the need for long-term treatment.

Despite the limitations of these studies, such as small sample size, short duration, lack of information regarding description of study design, variability in patient assessment, and failure to report side effects or pertinent statistics, BUP was able to demonstrate rapid onset of antidepressant action. The combination of findings among KOR antagonists in rodent models coupled with preliminary findings of BUP as a rapid-acting antidepressant serve as a strong pharmacologic rationale for the development of BUP/SAM. As such, the objective of this article is to analyze the results of BUP/SAM premarketing clinical trials as adjunctive treatment for treatment-resistant MDD.

Methods

A comprehensive PubMed/MEDLINE search was conducted through November 9, 2017, using the following search terms: depression, samidorphan, buprenorphine, ALKS-5461 (developmental code name). All English-language clinical trials evaluating the combination of BUP/SAM in the treatment of MDD on human participants were included. Two researchers conducting this search yielded 2 unique results from search terms, of which both were included. Three additional trials were included that were obtained from Clinicaltrials.gov and resources included in the present study.

TABLE: Summary of premarketing clinical trials evaluating buprenorphine/samidorphan (BUP/SAM)

Design	Assessment	Results
FORWARD-1 ²⁵		
- DB, R, PC, crossover study - BUP 8 mg + SAM 0 mg, 1 mg, 4 mg (n = 6) - SAM 0 mg, 8 mg, 16 mg (n = 7) 1-wk, DB, R, PC, parallel-group, multiple-dose study - BUP/SAM ratio 8:1 (n = 14) - BUP/SAM ratio 1:1 (n = 14)	- Objective blockade: pupillometry - Subjective blockade: VAS and 16-item opiate agonist scale HAM-D, MADRS	- Ratios ~8:1 and 1:1 achieved intermediate and maximal levels, respectively, of blockade - Most common ADEs were N/V, dizziness, fatigue - In general, ADEs improved as ratio approached 1:1 - No clinically significant changes otherwise - Significant improvement for dose ratio of 1:1 - Greater self-reported VAS scores in 8:1 group in first 3 days for “high” and “sedation” - Most common ADEs were dizziness, N/V, sedation, constipation, fatigue - No clinically significant changes otherwise
FORWARD-2 ³⁰		
- DB, R, PC, SPCD study - BUP/SAM 2 mg/2 mg (n = 47^a) - BUP/SAM 8 mg/8 mg (n = 41^a)	HAM-D, MADRS, CGI-S, rate of response, rate of remission	- Significant improvement for 2 mg/2 mg dose - Significant rate of response/remission per MADRS for 2 mg/2 mg dose - Most common ADEs were N/V, headache, dizziness, sedation - No clinically significant changes otherwise
FORWARD-3 ^{31,32,b}		
- DB, active-controlled, 4-wk placebo run-in phase followed by 6-wk DB efficacy phase - BUP/SAM 2 mg/2 mg (n = 164^a)	MADRS	- No significant improvement for 2 mg/2 mg dose - Most common ADEs were nausea, headache, constipation, dry mouth - No serious ADEs occurred in active treatment group
FORWARD-4 ^{32,33,b}		
- DB, R, PC SPCD study - BUP/SAM 0.5 mg/0.5 mg (n = 115^a) - BUP/SAM 2 mg/2 mg (n = 116^a)	MADRS	- Significant improvement for 2 mg/2 mg dose; significance first noted at week 3 - Most common ADEs were N/V, constipation, dizziness, somnolence, headache - No serious ADEs occurred in active treatment group
FORWARD-5 ^{34-36,b}		
- DB, R, PC SPCD study - BUP/SAM 1 mg/1 mg (n = 125^a) - BUP/SAM 2 mg/2 mg (n = 126^a)	6-item and 10-item MADRS	- Significant improvement for 2 mg/2 mg dose for core and overall symptoms 1 mg/1 mg dose displayed symptomatic improvement but lacked significance - Most common ADEs were nausea, dizziness, and fatigue

ADE = adverse drug event; CGI-S = Clinical Global Impressions severity scale; DB = double-blind; HAM-D = Hamilton Rating Scale for Depression; MADRS = Montgomery-Asberg Depression Rating Scale; N/V = nausea/vomiting; PC = placebo-controlled; R = randomized; SPCD = sequential parallel comparison design; VAS = visual analog scale.

^aBoth groups combined.

^bFull report of studies has not been published; thus, information contained in this table may be incomplete.

Results

A series of trials—Focused On Results with a Rethinking of Depression, collectively referred to as the FORWARD trials—evaluated BUP/SAM as adjunctive treatment for MDD, and a summary of these results can be found in the Table.

FORWARD-1

The first FORWARD trial, referred to as FORWARD-1, was a 2-part study²⁵ that first evaluated the dose ratio of BUP

to SAM that was most effective at blocking opioid effects. The first portion included 13 healthy, opioid-experienced, nonaddicted, and non-treatment-seeking adults in a single-center, double-blind, randomized, placebo-controlled, crossover study. The participants were enrolled into sequential cohorts where cohort 1 (n = 6) was administered BUP/SAM dosages 8 mg/0 mg, 8 mg/1 mg, and 8 mg/4 mg, and cohort 2 (n = 7) was administered BUP/SAM 8 mg/0 mg, 8 mg/8 mg, and 8 mg/16 mg. Within-cohort doses were administered in a blinded, randomized fashion and were separated by 7- to 12-day

washout periods. Patients were assessed for subjective opioid effects via the visual analog scale (VAS) and the 16-item opiate agonist scale. The VAS is an instrument measuring level of agreement from “not at all” to “extremely” among subjective items, such as “bad effects,” “good effects,” “high,” etc. The 16-item opiate agonist scale required patients to rate the intensity of subjective effects from “no effect” to “maximum effect.” Patients were also assessed for objective opioid effects via pupillometry, which measures pupil diameter and can be used to detect miosis. Lastly, a safety assessment was conducted that included adverse drug event (ADE) monitoring, vital signs, laboratory findings, physical examinations, electrocardiogram, and pulse oximetry.²⁵

Researchers found that objectively, maximal miosis inhibition occurred at BUP/SAM doses of 8 mg/8 mg and 8 mg/16 mg ($P \leq .001$) compared with 8 mg/0 mg.²⁵ In addition, VAS and 16-item opiate agonist scale scores dose-dependently decreased with coadministration of SAM. For safety and tolerability, the most common ADEs in the BUP/SAM 8 mg/0 mg group were nausea ($n=7$), vomiting ($n=6$), dizziness ($n=1$), and fatigue ($n=1$). In general, the frequency of ADEs decreased as SAM dose increased, and there were no clinically significant changes on safety assessment measurements otherwise. Overall, the authors concluded that BUP/SAM dose ratios of ~8:1 and 1:1 achieved intermediate and maximal levels of blockade, respectively, and the medications were relatively well tolerated at these dosage ratios.²⁵

The second portion of the study²⁵ was a randomized, double-blind, placebo-controlled, parallel-group, multiple-dose study designed to evaluate the safety, tolerability, and efficacy of BUP/SAM dose ratios from the first part of the study. The participants were 32 adults with MDD per *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, criteria who must have been in a current depressive episode of at least 8 weeks with inadequate response to stable dose of SSRI or SNRI antidepressant, defined as less than 50% improvement in symptoms. Diagnoses of bipolar disorder, psychosis, and personality disorder were excluded; other exclusion criteria were risk of suicide, or diagnosis of alcohol or illicit drug dependence within the past 12 months of screening. The participants were randomized to 1 of 3 treatment cohorts for 7 days: (1) BUP/SAM 8:1 dose ratio ($n=14$), (2) BUP/SAM 1:1 dose ratio ($n=14$), or (3) placebo ($n=4$); all 3 treatment arms continued their current SSRI or SNRI therapy. Cohort 1 received BUP/SAM 2 mg/0.25 mg for 3 days followed by 4 mg/0.5 mg for 4 days. Cohort 2 received BUP/SAM 4 mg/4 mg for 3 days followed by 8 mg/8 mg for 4 days. Patients were assessed daily on safety measurements of ADE monitoring, vital signs, laboratory findings, electrocardiogram, daily VAS, Addiction Research Center Inventory-Morphine Benzodrine

Group (ARCI-MBG), and the Columbia Suicide Severity Rating Scale (C-SSRS). Patients were also assessed on efficacy measurements of HAM-D and MADRS at baseline and on day 7.²⁵

Researchers found that for efficacy, both BUP/SAM dose ratios resulted in improvement on HAM-D and MADRS from baseline to end of study.²⁵ The HAM-D and MADRS scores for BUP/SAM 8:1 at baseline were, respectively, means (SDs) of 17.5 (2.0) and 23.3 (4.1), with changes of -5.0 (6.1) and -8.5 (7.4), at the end of the study, although neither reached statistical significance. The respective HAM-D and MADRS scores for BUP/SAM 1:1 at baseline were 19.4 (2.7) and 26.4 (4.4), with a statistically significant change on HAM-D of -6.7 (3.4; $P=.032$) and a trend toward significance on MADRS -11.5 (6.5; $P=.054$). The most notable safety outcomes included that the BUP/SAM 8:1 group reported higher VAS scores compared with the BUP/SAM 1:1 group for feeling “high” and sedation. Lastly, the most notable tolerability outcomes for BUP/SAM 8:1 and 1:1, respectively, included the most common ADEs of dizziness ($n=8$ and 4), nausea ($n=4$ and 3), vomiting ($n=4$ and 2), constipation ($n=2$ and 3), sedation ($n=3$ and 1), and fatigue ($n=2$ and 1).²⁵ Of note, cohort 1 and cohort 2 each had 1 patient discontinue treatment after the first study dose because of vomiting. Lastly, upon abrupt discontinuation of study drug, no opioid withdrawal was observed. Therefore, coupled with the findings from the first portion of the study, the authors concluded the most effective and robust antidepressant effects were observed among participants in the BUP/SAM 1:1 dose ratio group.²⁵

FORWARD-2

As a follow-up to the 1-week FORWARD-1 pilot trial, the FORWARD-2 trial was a multicenter, randomized, double-blind, placebo-controlled study³⁰ that used a 2-stage sequential parallel comparison design (SPCD) to evaluate the efficacy and safety of BUP/SAM. The SPCD is one that can be used to enhance signal detection in studies with relatively small sample sizes, something the authors wanted to employ because of the high incidence of placebo response in depression trials. The SPCD in FORWARD-2 contained 2 stages, each consisting of 5 weeks, where participants received treatment for 4 weeks and then underwent a 1-week washout period. During the first stage, a larger portion of participants were randomized to placebo rather than active treatment. At the end of the first stage, the participants who met criteria for placebo nonresponse were then randomized to either the active drug arm or placebo in the second stage. The participants who were considered placebo responders remained on placebo during stage 2.³⁰

Included were adults who met *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, criteria for MDD, were in a current episode of MDD for ≤ 4 months, had a HAM-D score of ≥ 16 at screening, were receiving an SSRI or SNRI at an adequate dose for at least 8 weeks, and had an inadequate response to 1 or 2 courses of antidepressants.³⁰ There were many exclusion criteria, such as other disease states (psychosis, substance or alcohol use), improvement on HAM-D from screening to baseline visit, any lifetime history of opioid dependence, adjuvant therapy (including electroconvulsive therapy and psychotherapy), pregnancy, and suicide attempt within the past 2 years.³⁰ Participants were administered HAM-D, MADRS, and Clinical Global Impressions severity scale (CGI-S) weekly to assess primary outcome of change in HAM-D score from baseline to week 4, and secondary outcomes of change in MADRS and CGI-S score from baseline to week 4, rate of response, and rate of remission. Response was defined as $\geq 50\%$ reduction in HAM-D or MADRS scores at week 4, and remission was defined as HAM-D score ≤ 7 or MADRS score ≤ 10 at week 4. Safety and tolerability were assessed via ADE monitoring, vital signs, laboratory findings, VAS, Clinical Opiate Withdrawal Scale (COWS), ARCI-MBG, and C-SSRS.³⁰

From 31 sites within the United States, 142 participants were randomized in stage 1 to either BUP/SAM 2 mg/2 mg ($n=24$), BUP/SAM 8 mg/8 mg ($n=19$), or placebo ($n=98$).³⁰ The participants who received active drug were crossed over to placebo in stage 2, and from the placebo group in stage one, 23 participants were placebo responders and remained on placebo in stage 2. The remaining 65 participants from the original placebo group were randomized to BUP/SAM 2 mg/2 mg ($n=23$), BUP/SAM 8 mg/8 mg ($n=22$), and placebo ($n=20$).³⁰

Efficacy assessment was significant for the BUP/SAM 2 mg/2 mg group, but nonsignificant, smaller changes were observed in the BUP/SAM 8 mg/8 mg group compared with placebo.³⁰ For the BUP/SAM 2 mg/2 mg group, differences from baseline to end of week 4 were as follows: HAM-D (-2.8 , 95% confidence interval [CI] = -5.1 , -0.6 ; $P=.014$); MADRS (-4.9 , 95% CI = -8.2 , -1.6 ; $P=.004$); and CGI-S (-0.5 , 95% CI = -0.9 , -0.1 ; $P=.012$). In addition, both active treatment arms displayed a greater rate of response and remission compared with placebo in both stages according to HAM-D and MADRS, although only the BUP/SAM 2 mg/2 mg dose in stage 2 produced significantly more responders ($P=.003$) and remitters ($P=.003$) than placebo per MADRS scores.³⁰

During stage 1, 7 participants discontinued BUP/SAM 2 mg/2 mg treatment (ADE, $n=4$; lost to follow-up, $n=2$; withdrawal by patient, $n=1$), and 5 discontinued BUP/SAM 8 mg/8 mg (ADE, $n=5$; lost to follow-up, $n=1$).³⁰

During stage 2, 5 participants withdrew from BUP/SAM 2 mg/2 mg because of ADE, and 4 withdrew from BUP/SAM 8 mg/8 mg because of an ADE. The specific ADEs leading to discontinuation were not reported, although the most common ADE leading to discontinuation was vomiting (4.3%). Overall, the most common ADEs for BUP/SAM 2 mg/2 mg and BUP/SAM 8 mg/8 mg, respectively, were nausea (34.0% and 34.2%), headache (8.5% and 31.7%), dizziness (19.2% and 31.7%), vomiting (17.0% and 26.8%), and sedation (14.9% and 14.6%). Of note, 3 serious ADEs occurred including attempted suicide via drug overdose ($n=1$, placebo group), intraocular melanoma ($n=1$), and acute opioid withdrawal ($n=1$), the last two both occurring in the BUP/SAM 2 mg/2 mg group. The last patient was reportedly taking prohibited opioid medication. There was no evidence of withdrawal per COWS assessment, and VAS scores were generally neutral for all groups. The ARCI-MBG produced inconsistent results of higher scores in stage 1, but scores in stage 2 were similar to that of placebo. The emergence of suicidal ideation per C-SSRS assessment was reported to be low and similar across all groups, although exact figures were not reported. Otherwise, there were no clinically relevant safety concerns. With this, the authors concluded that although both dosage groups of BUP/SAM displayed antidepressant activity, significant treatment effects were observed in the BUP/SAM 2 mg/2 mg dosage group only. In addition, although BUP/SAM was relatively well tolerated, enhanced tolerability may be seen upon slower titration.³⁰

FORWARD-3

The first phase 3 efficacy study, the FORWARD-3 trial, was conducted as a double-blind, active-control, 4-week, placebo run-in phase followed by a 6-week double-blind efficacy phase.^{31,32} The inclusion and exclusion criteria were very similar to those of the FORWARD-2 trial.³⁰⁻³² Participants were split into 2 groups: group 1 participants had a HAM-D score of ≥ 20 at screening ($n=399$) and group 2 participants had a HAM-D score of 18 to 19 at screening ($n=30$).^{31,32} After the 4-week placebo run-in phase for group 1, placebo responders ($n=77$) were continued on placebo while placebo nonresponders ($n=297$) were randomized to either BUP/SAM 2 mg/2 mg dose ($n=149$) or placebo ($n=148$) for the 6-week efficacy phase.^{31,32} Participants in group 2 were randomized to BUP/SAM 2 mg/2 mg ($n=15$) or placebo ($n=15$) for the duration of the 10-week study and were not included in the efficacy assessment.^{31,32} Assessment of efficacy was change in MADRS score from baseline compared with placebo for group 1, and safety assessment included ADE monitoring for groups 1 and 2.^{31,32}

The change in MADRS scores from baseline to end of study were not statistically different from that of

placebo.³² In group 1, the most commonly reported ADEs in the BUP/SAM 2 mg/2 mg group were nausea ($n=13$), headache ($n=6$), constipation ($n=3$), and dry mouth ($n=3$), which occurred more commonly across the board compared with placebo. Similar ADE findings were noted in group 2. Of note, 1 undisclosed serious adverse event occurred in the placebo arm of group 1. In addition, there were no signs of withdrawal or abuse potential. With this, the authors³² concluded that efficacy results were not statistically significant and were inconsistent with previous findings. The authors concluded that this was likely due to inadequate filtering of placebo response, because only 19% of participants were identified and filtered as such. These findings prompted the employment of enhanced placebo-response filtering in follow-up phase 3 studies.

FORWARD-4

The second phase 3 efficacy study, the FORWARD-4 trial, was conducted as a randomized, double-blind, SPCD study to enhance placebo response filtering.^{32,33} The inclusion and exclusion criteria were very similar to those for the FORWARD-2 and FORWARD-3 trials.³⁰⁻³³ Participants were randomized to either placebo ($n=251$), or active treatment of BUP/SAM 0.5 mg/0.5 mg ($n=59$) or BUP/SAM 2 mg/2 mg ($n=60$) for stage 1 of SPCD.^{32,33} For stage 2, the participants receiving active treatment remained in those treatment arms.^{32,33} From the placebo arm, the 83 placebo responders were continued on placebo in stage 2 while the 168 placebo nonresponders were randomized to BUP/SAM 0.5 mg/0.5 mg ($n=56$), BUP/SAM 2 mg/2 mg ($n=56$), or placebo ($n=56$). Assessment of efficacy was change in MADRS score from baseline compared with placebo, and safety assessment included ADE monitoring for groups 1 and 2.

The changes in MADRS scores were statistically significant for the BUP/SAM 2 mg/2 mg group ($P=.028$), but not the BUP/SAM 0.5 mg/0.5 mg group.³² In addition, statistical significance was noted as early as week 3 for BUP/SAM 2 mg/2 mg group ($P=.02$).³² The most commonly reported ADEs for BUP/SAM 0.5 mg/0.5 mg and BUP/SAM 2 mg/2 mg, respectively, were nausea ($n=14$ and 17), constipation ($n=4$ and 10), dizziness ($n=4$ and 8), somnolence ($n=5$ and 6), vomiting ($n=4$ and 6), and headache ($n=7$ and 5). Of note, 1 undisclosed serious adverse event occurred in the placebo group. In addition, there were no signs of withdrawal or abuse potential. With this, the authors³² concluded that BUP/SAM 2 mg/2mg is an efficacious and safe agent when used as adjunctive treatment of MDD, a reinforcement of the FORWARD-2 trial findings. The authors³² were able to identify and filter 31% of participants as placebo responders, which is likely why these results differed from that of FORWARD-3.

FORWARD-5

The FORWARD-5 trial is the largest phase 3 safety, tolerability, and efficacy study of BUP/SAM as adjunctive treatment of MDD.³⁴⁻³⁶ The trial was designed as a randomized, double-blind, multicenter, placebo-controlled, SPCD study.³⁴⁻³⁶ Inclusion and exclusion criteria were very similar to those for the FORWARD-2 through FORWARD-4 trials.³¹⁻³⁶ Participants were randomly assigned in stage 1 to BUP/SAM 2 mg/2 mg ($n=63$), BUP/SAM 1 mg/1 mg ($n=63$), or placebo ($n=280$) for 5 weeks.³⁴⁻³⁶ At the end of stage 1, those who were originally randomized to active drug remained on active drug. In the placebo arm, placebo responders ($n=69$) remained on placebo while placebo nonresponders were randomized to BUP/SAM 2 mg/2 mg ($n=63$) and BUP/SAM 1 mg/1 mg ($n=62$).³⁴⁻³⁶ Buprenorphine/samidorphan dosing was titrated starting at 0.5 mg/0.5 mg on days 1 to 3, 1 mg/1 mg on days 4 to 7, and 2 mg/2 mg on day 8, if applicable.³⁶ Efficacy was assessed based on average of changes of 6-item MADRS (core symptoms of depression) and 10-item MADRS (overall symptoms of depression) scores, in addition to change in MADRS-10 score from baseline to end of study. Safety was assessed on COWS and the emergence of ADEs.³⁴⁻³⁶

Researchers announced that the BUP/SAM 2 mg/2 mg dose displayed statistically significant reductions on 6-item (-1.5 ; $P=.018$) and 10-item (-1.7 ; $P=.026$) MADRS scores from week 3 to end of treatment.^{35,36} In addition, the most commonly reported ADEs reported for BUP/SAM 1 mg/1 mg and 2 mg/2 mg, respectively, were nausea ($n=9$ and 17), dizziness ($n=6$ and 7), fatigue ($n=5$ and 7), vomiting ($n=3$ and 6), constipation ($n=9$ and 5), and headache ($n=4$ and 5).^{35,36} Of note, 5 serious ADEs occurred in the active drug group, although none were considered study drug related.³⁶ In addition, there were no signs of withdrawal or abuse potential.³⁶ With this, authors concluded that the BUP/SAM 2 mg/2 mg dose was efficacious and safe as adjunctive treatment in MDD.

Conclusion

Because of the high chronicity and increased risk of mortality associated with MDD, there is a need for the exploration of medications targeting novel treatment pathways in addition to serotonin, norepinephrine, and DA. Buprenorphine/samidorphan is a novel antidepressant working via the opioid receptor pathway to ultimately increase dopaminergic transmission in the mesolimbic pathway.

Past trials of BUP in the treatment of MDD were favorable in terms of antidepressant properties, albeit limited because of risk of abuse. With the addition of SAM, a MOR antagonist, this combination will theoretically

negate the concern over addictive-like properties at the MOR while maximizing potential antidepressant opioidergic activity at the KOR. Early trials of BUP/SAM identified that the ideal ratio of BUP to SAM was 1:1 to block opioid abuse liability, as measured by mu-associated properties of euphoria, drug-liking, and pupillary miosis.

Similarly, previous studies of KOR antagonists have also displayed prominent antidepressant properties; however, these agents fell short of marketing potential because of their decreased systemic availability and concerns for accumulation and toxicity. In phase 3 clinical trials of BUP/SAM, there was no evidence of withdrawal or abuse among the study participants. In addition, BUP/SAM performed well to reduce HAM-D, MADRS, and CGI-S scores, specifically with that of the BUP/SAM 2 mg/2 mg dose. The antidepressant properties were evident as early as week 3, which could pose as a unique, fast-acting property known to be atypical of traditional antidepressants. In October 2016, positive results from the FORWARD-5 trial were initially announced indicating that steps will be taken to market BUP/SAM within the United States as an adjunctive treatment option for patients with MDD. The complete, official results from the FORWARD-3 through FORWARD-5 trials have not been published as of November 2017, although the results remain anticipated.

Interpretation of the clinical trials investigating BUP/SAM are largely limited by small sample size, short duration of follow-up at less than 12 weeks, and lack of long-term follow-up. Also, using VAS scales in opioid-naïve depressed participants is considered exploratory because they are not validated in this population. In addition, participants were not allowed to have more than 2 trials of inadequate response to antidepressant therapy. Therefore, although these participants are still considered treatment resistant by definition, participants who have failed multiple antidepressants across multiple classes have not been captured in these analyses. In turn, this compromises the translation of efficacy to real-life practice. Most concerning is that patients with a history of substance abuse or alcohol dependence were excluded from the FORWARD trials; therefore, the safety and long-term effects in this patient population remain unknown. Also, full results of the FORWARD-3 through FORWARD-5 trials have yet to be published, limiting the degree of clinical interpretation. Lastly, a comparison of BUP/SAM to other agents used as adjunctive therapy in MDD, such as antipsychotics, is lacking. With this, it is difficult to assess the usefulness of BUP/SAM (1) for longer than 12 weeks of treatment, (2) in those resistant to more than 2 antidepressants, (3) in those with a history of opioid or alcohol dependence, and (4) compared with other agents used as adjunctive therapy for MDD.

Despite this, BUP/SAM has generated evidence to support its role as adjunctive therapy in the treatment of MDD. By combining a KOR antagonist with other first-line MDD options, such as an SSRI, SNRI, mirtazapine, or bupropion, there can be an increase in the neurobiologic coverage across serotonergic, noradrenergic, dopaminergic, and opioidergic pathways. Additional studies are still needed to compare BUP/SAM to other agents used as adjunctive treatment in MDD; in special populations, such as in patients with co-occurring substance abuse; and as a monotherapeutic antidepressant option. Overall, advancement in the treatment of MDD with the novel medication BUP/SAM has shown to be a progressive option in expanding our antidepressant armamentarium. Buprenorphine/samidorphan may prove to be a vital treatment option for individuals who have exhausted at least 2 classic antidepressant pharmacotherapy agents, and may lead to the dawning of a new age for antidepressant drug development.

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