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# Combination Olanzapine and Samidorphan for the Management of Schizophrenia and Bipolar 1 Disorder in Adults: A Narrative Review

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## Health Psychology Research

Schizophrenia is a debilitating psychotic disorder characterized by positive symptoms such as delusions, hallucinations, and disorganized thoughts, and negative symptoms like lack of effect or motivation. Bipolar 1 disorder (B1D) is a psychiatric illness characterized by recurrent manic episodes in alternation with depressive episodes and interspersed periods of euthymia, ultimately resulting in psychological distress and impairment of daily functioning. Effective treatments are needed for both schizophrenia and B1D to reach the treatment goals of reducing the debilitating symptomology, improving social functioning and quality of life, and increasing the chances of recovery and more favorable long-term outcomes. To date, olanzapine is one of the most efficacious atypical antipsychotics (AAPs) for the treatment of both schizophrenia and B1D and is associated with fewer extrapyramidal effects compared to other treatments. However, compared to other AAPs, olanzapine is associated with a greater chance of metabolic syndrome, limiting its clinical use and affecting treatment compliance. Samidorphan mitigates the weight gain side effects of olanzapine by antagonizing μ-, κ-, and δ-opioid receptors. The use of combination drugs to treat psychiatric conditions is an emerging field with the goal of increasing therapeutic efficacy and decreasing undesirable side effects. Clinical trials have demonstrated combination on olanzapine and samidorphan (OLZ/SAM) treatment resulted in significantly less weight gain than olanzapine monotherapy. Clinical trial patients reported improvements in symptoms of psychosis, reduced weight gain, and overall satisfaction with their treatment. OLZ/SAM has been as shown to be a safe and effective pharmaceutical option for the clinical management of schizophrenia and B1D.

## INTRODUCTION

Schizophrenia, derived from the Greek 'schizo' and 'phren' meaning 'splitting mind,' is a debilitating psychotic disorder characterized by positive symptoms such as delusions, hallucinations, and disorganized thoughts, and negative symptoms like lack of effect or motivation.[1,2] The disease has a multifactorial etiology with many associated risk factors, including maternal malnutrition, influenza during gestation, cannabis use, urbanization, and birthing complications.[1,3] The diagnosis of schizophrenia is clinical and requires the exclusion of any other potential causes of psychosis.

Although schizophrenia has a low prevalence affecting about 1% of the world's population, psychotic disorder carries a significant burden of disease.[3,4] Schizophrenia is one of the leading causes of disability and death worldwide.[3] Life expectancy is reduced by 20% in those with schizophrenia with up to 40% of schizophrenia-related deaths attributed to suicide.[1] The economic burden of the disease of schizophrenia is substantial. Annual costs are estimated to range from $94 million to $106 billion globally and more than $60 billion in the United States.[4] The economic disease

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burden is measured in direct medical, direct nonmedical, and indirect costs, with indirect costs contributing most to the overall burden. Examples of indirect costs include unemployment, income assistance, morbidity, law enforcement, and more.[4]

Bipolar 1 disorder (B1D) is a psychiatric illness characterized by recurrent manic episodes in alternation with depressive episodes and interspersed periods of euthymia, ultimately resulting in psychological distress and impairment of daily functioning.[5] While the basis of B1D has been identified as largely biological, the disease course and symptomology can vary greatly depending on psychological, and environmental social factors.[6,7] Identified risk factors for B1D include pre-existing anxiety and disruptive behavioral disorders, maternal influenza infection, preterm birth, head injury, and physical or sexual abuse.[8] The lifetime and 12-month prevalence rates for B1D are estimated to be 2.4% and 1.5%, respectively.[5]

B1D has a high comorbidity association with both chronic medical conditions and other psychiatric conditions, resulting in an increased burden of disease and worsened prognosis. Common comorbidities include anxiety, substance abuse, personality disorders, metabolic syndrome, migraine, and obesity.[5] Consequently, those with B1D are at much higher risk for premature death with an estimated loss of 10-20 potential years of life, with suicide or cardiovascular disease being the most common causes of death.[9]

The current estimated economic burden of bipolar disease in the United States is more than $195 billion annually, with 72-80% of costs being indirect rather than direct medical costs. Major drivers of the high economic burden associated with B1D include unemployment, lost work productivity for patients and caregivers, frequent psychiatric interventions, and high rate of comorbid conditions requiring clinical management.[10]

Effective treatments are needed for both schizophrenia and bipolar disorder to reach the treatment goals of reducing the debilitating symptomology, improving social functioning and quality of life, and increasing the chances of recovery.[9,11] Combination of olanzapine and samidorphan (OLZ/SAM) has been recently Food and Drug Administration (FDA) approved for the treatment of both schizophrenia and bipolar I disorder after showing statistical improvement in clinical trials.[12]

## METHODS

The present investigation is a narrative review. In 2021, a comprehensive search was performed using the PubMed database for studies related to the topic of OLZ/SAM for treatment of schizophrenia and B1D. We searched the following keywords: schizophrenia, bipolar disorder, Lybalvi, olanzapine, samidorphan. Priority for inclusion was given to recent manuscripts (within the last three years), but relevant papers older than three years were also included. An attempt to search for, use, and cite primary manuscripts whenever possible was also made. This article, therefore, is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

## EPIDEMIOLOGY, PRESENTATION, AND PATHOPHYSIOLOGY OF SCHIZOPHRENIA AND BIPOLAR 1 DISORDER

### PREVALENCE OF SCHIZOPHRENIA

Recent studies estimate the global number of individuals with schizophrenia to be 21 million people worldwide or roughly 1% of the population.[13,14] Prevalence studies have observed no sex differences amongst those affected by schizophrenia.[14,15] Higher incidence rates are reported in African-Caribbean migrants and their descendants.[1,16]

### ETIOLOGY AND RISK FACTORS OF SCHIZOPHRENIA

Schizophrenia is a heterogeneous psychiatric illness with a multifactorial cause. Factors contributing to the etiology of schizophrenia include neurobiological, genetic, psychosocial, and environmental. The neurobiological component of schizophrenia is largely related to abnormalities in neurotransmitter signaling.[1] Family and twin studies have illustrated a genetic component of schizophrenia, as well. Monozygotic twin studies have shown varying heritability rates ranging from 40%-80% with overall heritability of schizophrenia estimated to be around 80%.[13,17–19] Circumstances in which both parents are affected by schizophrenia carry an estimated 40% risk of the offspring developing schizophrenia.[1]

Certain psychosocial or environmental risk factors have a high association with the development of schizophrenia, which includes but are not limited to low birth weight, emergency cesarean section or other birthing complications, maternal infection, residing in urban areas, childhood trauma, early stress, gestational diabetes, preeclampsia, advanced paternal age, substance abuse, and comorbid psychiatric illnesses.[1,17,20,21] Recent longitudinal studies have shown a dose-effect relationship between cannabis usage and a 40% increase in the risk of development of schizophrenia.[1]

### PRESENTATION OF SCHIZOPHRENIA

Schizophrenia commonly presents in early adulthood (early-onset schizophrenia) but can also present with older age (late-onset schizophrenia).[20] Symptoms are separated into categories of positive and negative symptoms. Positive symptoms include the symptoms of psychosis, delusions, and hallucinations, as well as disorganized thought and behavior. Negative symptoms include alogia, avolition, social withdrawal, deficits in executive function, and diminished or loss of emotional expression.[13] Most people suffering from schizophrenia have significant psychosocial dysfunction resulting in impairment of daily functioning in areas of work, interpersonal relations, or self-care.[13,15] In addition, those with schizophrenia are more likely to be homeless, unemployed, or live-in poverty. Finally, schizophrenia is associated with a significantly reduced life expectancy with most deaths attributable to sequelae from comorbid illnesses.[15,22]

## PATHOPHYSIOLOGY OF SCHIZOPHRENIA

The idea of a genetic role in the development of schizophrenia is well-established. Genome-wide association studies have identified numerous genes implicated in the development of schizophrenia, including but not limited to neuregulin (NGR1), dysbindin (DTNBP1), and catecholamine O-methyl transferase (COMT) Val158Met polymorphism.[1,17] NGR1 is involved in glutamate signaling and brain development, DTNBP1 aids in the release of glutamate, and COMT regulate dopamine function.[1] While the aforementioned genes have been more widely studied thus far in relation to schizophrenia, genome-wide association studies have identified a total of 108 schizophrenia-associated loci.[21,23] It has been postulated that epigenetic changes in expression levels of the COMT polymorphism and other genetic polymorphisms may have a relationship between traumatic life events and the development of schizophrenia.[17,21,24,25] Further studies are currently exploring gene-environment interactions and their effect, if any, on schizophrenia. Additionally, a 22q11.2 chromosomal deletion has been discovered with a 30-40% associative risk of schizophrenia development.[13]

The neurobiological basis of schizophrenia is largely based on defective neurotransmitter signaling, specific hyperactivity in dopaminergic, serotoninergic, and alpha-adrenergic circuits, or hypoactivity in glutaminergic and GABAergic circuits.[1] Aberrant neural circuitry as a result of defective synaptic pruning and the associated increase in gray matter loss is associated with the cognitive deficits in schizophrenia from the resultant excitatory-inhibitory imbalance.[13,26–28] Irregular dopamine signaling in mesostriatal dopamine networks is highly associated with schizophrenia.[13] Positive symptoms are likely a result of excessive dopamine activity in the mesolimbic pathway, while negative symptoms are likely a result of reduced dopamine activity in the nigrostriatal pathway.[1,29] Finally, it has been discovered that hippocampal neurons in the CA1 region have shown increased glutamatergic activity in concordance with the developmental progression of psychotic symptoms from prodromal to syndromal as observed in longitudinal studies. The glutamate-driven hypermetabolism in specific hippocampal regions ultimately leads to reduced hippocampal volume in the brains of schizophrenia patients.[30]

## PREVALENCE OF BIPOLAR 1 DISORDER

B1D is an unpredictable fluctuating mood disorder that generally presents early in life with a mean onset age of 20 and of similar prevalence in men and women.[31] B1D affects an estimated 2.4% of the world's population or about 45 million people.[5,32] Current estimates indicate that bipolar disease is the 17th leading cause of global burden of disease behind schizophrenia and other psychiatric illnesses.[31]

## ETIOLOGY AND RISK FACTORS OF BIPOLAR 1 DISORDER

It is well-established that bipolar disorder has a heterogeneous etiology. Factors contributing to the development of B1D include family history and genetics, along with environmental, social, neuropsychological, and biological variables. Results from twin heritability studies report the heritability of B1D at around 70%[9]; however, the development of B1D also appears to be largely dependent upon interactions between genetics and environmental risk factors and not heritability alone.[8]

While there are many risk factors associated with bipolar disorder, such as pre-existing anxiety disorders, pregnancy, and birth complications, and substance abuse, very few risk factors show strong enough specificity to unequivocally link the risk to the development of the bipolar disorder.[8] An exception is the significant relationship that exists between experiencing childhood trauma and developing B1D with earlier onset and greater severity of the disease.[17,33] Although the exact mechanism has not yet been ascertained, there are numerous working theories investigating the physiologic link between exposure to stressors during neurodevelopmental stages and the development of B1D, which will be explored further in the pathophysiology section.[33]

## PRESENTATION OF BIPOLAR 1 DISORDER

Bipolar disorder has an age of onset around adolescence or early adulthood, generally after preceding subclinical symptoms have appeared. B1D presents with alternating manic and depressive episodes with euthymic episodes in between.[33] Manic episodes generally last over one week and present with characteristics such as distractibility, impulsivity, elevated mood, overconfidence, grandiosity, talkativeness, and decreased need for sleep. Depressive episodes include experiences of anhedonia, low mood, decreased energy, and feelings of hopelessness or worthlessness.[6] The culmination of symptoms presenting with B1D results in overall reduced quality of life, especially during the presence of depressive symptoms.[31,34] Patients with B1D have a significantly higher unemployment rate and divorce/separation rate as compared to the general population along with cognitive impairment affecting activities of daily living, further contributing to reduced quality of life.[31,34–36] The poor quality of life seen in patients with B1D ultimately results in reduced educational attainment and the ability to maintain employment.[31,37] B1D is currently associated with the highest suicide rate of all psychiatric illnesses with one in four individuals suffering from B1D reporting a suicide attempt, which is the largest contributor to the premature mortality seen in the disease.[38,39]

## PATHOPHYSIOLOGY OF BIPOLAR 1 DISORDER

Current evidence suggests B1D is a product of a constellation of immune-mediated inflammation in combination with abnormalities in brain structure, circuitry, neurotransmitter signaling, and intrinsic activity.[40–46] Levels of immune-regulated inflammatory markers, such as interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), interferon-γ (IFN-γ), and C-reactive protein (CRP) are elevated in patients with B1D, along with increased levels of CD4+ T cells in circulation, suggesting an association between a pro-inflammatory state and B1D.[40,47–56] Manic episodes specifically seem to coincide with state-dependent inflammatory activation and increased levels of the afore-

mentioned inflammatory markers as shown in a recent longitudinal study.[40,57]

Neuroimaging studies have shown gray matter abnormalities without consistency between patients with B1D; however, imaging has consistently shown reduced white matter volumes and alterations in white matter connections, especially in the cingulum, corpus callosum, frontal brain regions, and tracts connecting regions of the limbic system.[40,58–63] It is postulated that the diffuse white matter damage may be potentiated by a CD4+ T cell-mediated immune response causing cytotoxic effects.[40] The white matter effects are most consistently seen in the limbic system, which is involved in the modulation of homeostasis and neurotransmitter signaling in response to stress.[40,64,65] Additionally, increased amygdala volume and decreased hippocampal volume are consistently seen in patients with B1D.[40,41] The combination of effects observed in the limbic network localizes B1D pathophysiology to the limbic system as a result of the localized immune-mediated white matter damage.[40]

Neurochemical changes observed in patients with B1D include hyperactivity in the hypothalamus-pituitary-adrenal (HPA) axis, transient increases in dopamine and norepinephrine signaling, and changes in serotonin metabolism.[40,66,67] Much like the etiology of the white matter changes seen in BD, data suggests the neurotransmitter dysregulation is induced by the stress response and resultant immune-mediated inflammation.[40]

Abnormalities in functional connectivity have been observed in association with B1D in functional magnetic resonance imaging (MRI) studies, most often as functional disconnection the raphe nuclei involved in serotonin signaling and increased thalamus-sensorimotor network connectivity.[40,46,68,69]

Together, the data show that the pathophysiology of B1D is ultimately the result of immune dysregulation with a pro-inflammatory state causing white matter damage in the limbic system, leading to changes in neurotransmitter signaling and functional brain connectivity and activity, precipitating the presentation of the mania and depression seen in B1D.[40]

## CURRENT TREATMENT OF SCHIZOPHRENIA AND BIPOLAR 1 DISORDER

### CURRENT TREATMENT OF SCHIZOPHRENIA

Related to its disease complexity, there are several therapeutic options available to treat the various positive, negative, and cognitive symptoms of schizophrenia, including first-generation antipsychotics (FGAs), atypical antipsychotics (AAPs), third-generation antipsychotics, as well as other nonpharmacologic treatments such as cognitive-behavioral therapy (CBT) and exercise.[70–74]

The first pharmacologic treatments for schizophrenia were initially developed in the 1960s based on the dopamine hypothesis, which emphasized the role of excessive dopamine in the production of positive symptoms of schizophrenia.[71,74,75] The FGA chlorpromazine supports this hypothesis and was the first FDA-approved pharmacologic therapy for schizophrenia.[74,76] Chlorpromazine re-duces positive symptoms by non-selectively antagonizing dopamine-2 ($D_2$) receptors, however, it has little effect on negative and cognitive symptoms. Chlorpromazine's lack of selectivity to dopamine receptors in the mesolimbic pathway causes many side effects including parkinsonian-like extrapyramidal effects because of $D_2$ receptor antagonism in the nigrostriatal pathway. The side effects of FGAs led to the development of more selective treatment options such as AAPs and third-generation antipsychotics, which each target multiple receptor types.[74,76]

AAPs differ from FGAs by exhibiting greater antagonism at serotonin ($5\text{-}HT_{2A}$) receptors than at $D_2$ receptors in the nigrostriatal pathway and bind with higher affinity to $D_4$ than $D_2$ receptors, resulting in a lower occurrence of extrapyramidal side effects and reduction of negative symptoms.[74] Clozapine is the only FDA-approved AAP for treatment-resistant schizophrenia, which is most commonly diagnosed when patients fail to respond to at least two other antipsychotics.[73] Clozapine, however, is associated with various autonomic side effects such as hypotension and reflex tachycardia, as well as agranulocytosis, drooling, constipation and seizures.[71,74] Olanzapine and risperidone are newer AAPs, with fewer autonomic side effects and neither are associated with agranulocytosis.[71,74,77] Third generation antipsychotics such as aripiprazole, aripiprazole, and cariprazine are newer treatments that exhibit partial agonist of the $D_2$ receptor.[74,78]

Other nonpharmacologic treatments of schizophrenia such as CBT and exercise, are reported to reduce negative and cognitive symptoms of schizophrenia, which can be used in conjunction with pharmacologic therapy.[72,79] Decreased hippocampal volume is associated with impairment of executive functioning and cognition in schizophrenia.[79] Pajonk et al[79] found that three months of aerobic exercise increased hippocampal volume which also correlated with increased short-term memory test scores in patients with schizophrenia. Recently, research investigating the use of combination and multi-target drug therapies to treat schizophrenia has emerged.[74] Targeting multiple neurotransmission pathways, with multiple receptors, could potentially allow for increased therapeutic efficacy and decreased unwanted side effects.

### CURRENT TREATMENT OF ACUTE MANIA IN BIPOLAR 1 DISORDER

Lithium carbonate and chlorpromazine were among the first pharmacologic treatments for acute mania in B1D in the 1940s and 1950s, however the acceptance of lithium was delayed due to toxicity observed in patients given unregulated dosages.[80] Subsequently, the utilization of AAPs was also proven efficacious in the treatment of acute mania.[81] AAPs such as aripiprazole, asenapine, cariprazine, olanzapine, paliperidone, risperidone, and ziprasidone, as well as quetiapine (in higher doses), were authorized for treatment of dysphoric and mixed state mania.[82,83] Sodium divalproex (valproate) and carbamazepine are two anticonvulsants approved for the treatment of acute mania, however, they have not shown efficacy in long-term prophylaxis.[81,82]

## CURRENT TREATMENT OF DEPRESSION IN BIPOLAR 1 DISORDER

In patients with B1D, several studies reported that depressive episodes account for nearly three quarters of the mean proportion of weeks ill (approximately 50%), causing depression to be a major contributor to the burden of illness in B1D.[82,84,85] Current treatments for acute depressive episodes exhibit inconsistent results, and thorough investigation into long-term prophylaxis is limited. Despite a lack of evidence showing efficacy and safety, B1D-depression is often treated with antidepressants. In this regard, some clinicians utilize antidepressants only in acute treatment of B1D-depression related to concern of induction of mood switching to hypomania, mania, and mixed states.[86]

### LONG-TERM PROPHYLAXIS

Lithium has been a component of the first-line treatment of B1D for almost 60 years.[87] Along with its more prominent effects against mania and hypomania, lithium may also have long-term benefits against B1D-depression recurrence and suicide risk reduction in B1D patients.[88] Lamotrigine is an anticonvulsant that is FDA-approved for long-term B1D prophylaxis and has reportedly limited the risk of recurrence of depressive episodes, however, it lacks efficacy in managing acute mania.[89]

### TREATMENT RESISTANCE BIPOLAR 1 DISORDER

For B1D patients resistant to pharmacotherapy, nonpharmacologic therapies such as transcranial magnetic stimulation could be a promising new treatment option for reducing depressive symptoms and mania. However, current studies have reported mixed results, therefore more confirmatory research is needed.[90]

## OLZ/SAM DRUG INFO

OLZ/SAM, marketed as Lybalvi, became FDA-approved for the treatment of adults with schizophrenia and B1D on June 1, 2021.[91] OLZ/SAM is a daily oral tablet composed of multiple dose strengths of olanzapine, (5, 10, 15, 20 mg) depending on the disorder being treated, and a fixed dose of 10mg of samidorphan.[92] Specifically, OLZ/SAM treatment in B1D is used for acute management of manic/mixed episodes, maintenance monotherapy, or as an adjunct to lithium or valproate.[91] Olanzapine is one of the most efficacious AAPs in the treatment of both schizophrenia and B1D and is associated with fewer extrapyramidal effects than with FGA treatment.[93,94] However, compared to other AAPs, olanzapine is associated with a greater chance of metabolic abnormalities such as dyslipidemia, type II diabetes, and weight gain, limiting its clinical use and affecting treatment compliance.[93–97]

In studies enrolling healthy adults and adults with schizophrenia, the combination of olanzapine with samidorphan, a μ-opioid receptor antagonist, mitigated weight gain associated with olanzapine monotherapy.[94,98,99] The opioid system has been implicated in the role of mediating feeding behavior, food reward, and metabolism in many clinical and preclinical studies. For example, a decrease in weight gain was reported in μ-, κ-, and δ- opioid receptor knockout mice, despite no differences in caloric intake in μ- and κ- opioid receptor knockouts.[99] Therefore, antagonism of the opioid system by samidorphan was introduced to minimize olanzapine-induced weight gain and increase olanzapine's use as a treatment for schizophrenia and B1D.[94] However, although samidorphan decreases olanzapine-induced weight gain, it has not been shown to decrease any of the other metabolic adverse effects of olanzapine therapy, such as dyslipidemia and type II diabetes, potentially indicating a direct effect of olanzapine on metabolism.[94] Contraindications for OLZ/SAM include patients taking opioids, and patients going through acute opioid withdrawal.[100]

## OLZ/SAM MECHANISM OF ACTION

OLZ/SAM is a novel combination of olanzapine and samidorphan, that has been reported to mitigate the weight gain seen in olanzapine monotherapy.[91] Olanzapine has already been proven to be efficacious in the treatment of schizophrenia and B1D through $D_2$ receptor antagonism in the mesolimbic system and $5\text{-HT}_{2A}$ receptor antagonism in the frontal cortex.[96,101] Antagonism of $D_2$ receptors decreases positive symptoms of schizophrenia while antagonism of $5\text{-HT}_{2A}$ receptors decreases negative symptoms.[96,101] Several MRI studies also found increased activity in the prefrontal cortex during cognitive and emotional tasks in schizophrenia patients treated by olanzapine, suggesting a pattern of positive effects on cognition as well.[102]

The role of a said orphan in OLZ/SAM is to mitigate the weight gain induced by olanzapine monotherapy.[99] Samidorphan binds with high affinity to μ-, κ-, and δ-opioid receptors and primarily functions as a μ-opioid antagonist and partial agonist at κ- and δ-opioid receptors.[98,103,104] Samidorphan has been reported to decrease activation of the mesolimbic reward system when used in combination with buprenorphine in the treatment of the major depressive disorder.[105] While the mechanism of action for reducing weight gain via samidorphan is not entirely understood, opioid receptors are present throughout the mesolimbic system and their antagonism by the μ-opioid antagonist naltrexone, is observed to reduce cravings for sweet/rich foods.[98,104] Results of a 12-week, phase-II trial, found that OLZ/SAM treatment in schizophrenia patients, is associated with significantly less weight gain than olanzapine monotherapy.[106] Therefore, samidorphan inhibition of the mesolimbic reward system by μ-opioid receptor antagonism is presumed to be the source of the observed decrease in olanzapine-induced weight gain in patients administered OLZ/SAM.[98,105]

## PHARMACOKINETICS AND PHARMACODYNAMICS OF OLZ/SAM

A phase I study assessing the pharmacokinetic profile of olanzapine and samidorphan in schizophrenia patients after once-daily 14-day administration of OLZ/SAM, found that steady-state concentrations of both drugs were reached linearly after one week.[106] Olanzapine is primarily metab-

olized by cytochrome P450 (CYP) 1A2 mediated oxidation and also via direct glucuronidation by uridine 5'-diphosphate-glucuronosyltransferase 1A4.[107] Therefore, caution should be exercised with coadministration of either CYP1A2 inhibitors, such as fluvoxamine, or CYP1A2 inducers including carbamazepine or rifampin. Samidorphan is mainly metabolized by CYP3A4, consequently, caution should also be taken when co-administering CYP3A4 inducers and inhibitors.[107] Heavy smoking also induces CYP1A2 leading to increased clearance of olanzapine by 30-55% when compared to nonsmokers.[108]

Physiologically based and clinically developed pharmacokinetic models using healthy individuals and patients with schizophrenia, concluded that samidorphan did not alter the pharmacokinetics of olanzapine when co-administered across the clinical dose range (5-30mg), which is consistent with previously published studies.[106,107,109] A study assessing hepatic and renal impairment effects on the pharmacokinetics of olanzapine and samidorphan, reported that patients with moderate hepatic impairment experienced higher absorption and systemic exposure to olanzapine than healthy participants, and those with renal impairment had a 33% and 56% decrease in total body clearance of olanzapine and samidorphan, respectively.[110]

Olanzapine binds with high affinity at dopamine $D_{1-4}$, $5HT_{2a/2c}$, $5HT_6$, histamine-1 ($H_1$), and adrenergic-1 ($\alpha1$) receptors.[100] Blocking dopamine receptors, increases the risk of side effects such as akathisia, extrapyramidal symptoms, tardive dyskinesia, and neuroleptic malignant syndrome.[101] Samidorphan binds with high affinity to μ-, κ-, and δ-opioid receptors, primarily functioning as a μ-opioid antagonist and κ- and δ-opioid partial agonists.[98,103,104] In a phase II study, significantly lower weight gain of about 37% was observed in patients taking OLZ/SAM compared to those treated with olanzapine monotherapy.[104]

## CLINICAL STUDIES: SAFETY AND EFFICACY

OLZ/SAM has shown statistical and clinical efficacy and safety in several studies.[111] In the OLZ/SAM development program, 18 studies were used to evaluate the safety and the antipsychotic and weight-mitigating efficacy. The studies concluded the efficacy and safety of OLZ/SAM were similar to olanzapine, with reduced weight gain overall.[111]

In a recent study from 2015-2017, 401 adults with clinically diagnosed schizophrenia who were experiencing an acute episode of psychosis were administered ≥1 dose of OLZ/SAM. Of the 401 patients, 352 patients completed the treatment. Results showed significant improvement in the Positive and Negative Syndrome Score (PANSS) and Clinical Global Impression-Severity (CGI-S) score within 4 weeks of patients receiving OLZ/SAM versus placebo. Although OLZ/SAM showed the most efficacy, it also had the highest percentage of adverse effects (54.5% vs. 44.8% in placebo) of weight gain, somnolence, dry mouth, anxiety, and headache. Overall, OLZ/SAM was well tolerated and had efficacy and safety similar to that of olanzapine.[112]

In an open-label extension study, the long-term tolerability, safety, and efficacy were evaluated in patients with schizophrenia. Semi-structured one hour-long interviews were conducted in which all 41 patients indicated their di-

agnosis of schizophrenia had impacted personal, social, and financial aspects of their lives. Of the 41 patients that were administered OLZ/SAM, 39 patients had reported improvements in both positive and negative symptoms of psychosis. Overall, most of the patients were satisfied with their treatment.[113]

In a 52-week open-label extension study, OLZ/SAM was concluded to improve schizophrenia symptoms, while mitigating weight-gain in patients. Of the 281 patients that enrolled, 183 patients completed the 52-week trial. PANSS total and CGI-S scores declined in all patients that completed the trial. Increases in weight gain were stabilized by week 6, with an average 2.79% increase in weight gain. Overall, OLZ/SAM was well tolerated.[114]

In a randomized, double-blind, placebo-controlled study of 106 healthy, male normal weight volunteers, OLZ/SAM was shown to have similar safety and tolerability as olanzapine. However, OLZ/SAM had less side effects such as nausea, weight gain and metabolic risk. Further studies are needed to explore the side effects and efficacy of additional doses over a longer duration of time in schizophrenic patients.[98]

In randomized, controlled trials, OLZ/SAM and olanzapine-monotherapy were compared in healthy volunteers to determine short-term weight and cardiometabolic changes in these patients. In the OLZ/SAM group, weight changes were not statistically different than the olanzapine groups. However, OLZ/SAM was found to help prevent olanzapine-induced weight gain in healthy males with a lower initial BMI. This study concludes there is not sufficient evidence that OLZ/SAM prevents olanzapine-induced weight gain and olanzapine-induced cardiometabolic abnormalities.[115]

In a 24-week phase 3 double-blind trial, OLZ/SAM was assigned to 280 patients while olanzapine-monotherapy was assigned to 281 patients. Of these patients, 538 had post-baseline weight assessments. Of these 538 patients, the least-squares mean percent weight change from baseline of OLZ/SAM patients was approximately 4.21%; the olanzapine-monotherapy group was 6.59%. In addition, schizophrenia symptom improvement was similar to the olanzapine-monotherapy treatment. This study concluded that OLZ/SAM treatment was associated with similar schizophrenia symptom improvement, but with significantly less weight gain and smaller increases in waist circumference.[116]

In a multicenter, randomized phase 2 study of OLZ/SAM, the efficacy and weight gain side effects of OLZ/SAM were observed. Seventy-five patients received olanzapine plus placebo, and the rest received OLZ/SAM in different dosages (N=80; 5 mg, N=86; 10 mg, N=68; 20 mg). Results showed that OLZ/SAM resulted in statistically significant lower weight gain compared to olanzapine plus placebo patients, with OLZ/SAM showing a 37% lower weight gain compared to olanzapine plus placebo. In addition, the safety and efficacy of OLZ/SAM had a similar profile to olanzapine plus placebo, making OLZ/SAM a better option for mitigating weight gain while simultaneously treating schizophrenia.[99]

In phase 3, a 52-week open-label extension study of OLZ/SAM in patients with schizophrenia, the safety, efficacy, tolerability, and side effects were studied. Patients were di-

vided randomly into a 24-week, double-blind phase 3 study to compare weight gain in patients administered OLZ/SAM versus olanzapine-monotherapy. Two hundred sixty-five patients were administered OLZ/SAM, with 167 completing the extension of the remaining study. Fasting lipid, glycemic parameters, and PANSS scores remained stable throughout the study in patients receiving OLZ/SAM. CGI-S scores remained 3 or less in 81.3% of the patients, indicating mild illness severity. Results indicated patients that who were administered OLZ/SAM tolerated the medication well with significant results including smaller waist circumferences, smaller weight gain, and efficacy of the medication combination.[117,118]

In an open-label, randomized study, 48 healthy, non-smoking participants were randomly assigned to either generic olanzapine-monotherapy, OLZ/SAM, or Zyprexa, brand olanzapine (B-OLZ), in a 1:1:1:1:1:1 randomization. The pharmacokinetics of the drug-drug interactions between olanzapine and samidorphan were studied. Results indicated that OLZ/SAM was not shown to have any safety concerns nor affect the pharmacokinetics and bioavailability of olanzapine. In general, OLZ/SAM was well-tolerated by patients.[119]

Because OLZ/SAM is used in both schizophrenia and B1D, medications such as lithium or valproate are commonly prescribed along with OLZ/SAM. In an open-label, single-sequence two-cohort study, 34 healthy adults were administered lithium carbonate or divalproex sodium, once every 12 hours on days 1-7. On days 8-18, participants were administered olanzapine. The safety profiles of lithium and valproate while administered with OLZ/SAM were similar to the safety profile of what was previously reported for lithium and valproate. Administration of OLZ/SAM did not have a clinically significant effect on the pharmacokinetics of lithium or valproate and was generally well-tolerated.[120]

Because OLZ/SAM has an antipsychotic component, QTc intervals should be monitored for patients on this drug. In a randomized double-blind, placebo-controlled study, 100 patients with stable schizophrenia were randomized to receive OLZ/SAM or a placebo. Electrocardiograms (ECGs) and plasma drug concentrations were observed before and after dose administration. No clinically significant QTc effects were observed between OLZ/SAM doses.[121]

Although several studies have indicated OLZ/SAM has similar improvement rates to olanzapine-monotherapy, it has not had the same results in patients with a comorbidity of alcohol use disorder (AUD). In phase 2 double-blind study, patients with schizophrenia and AUD were enrolled in a 1:1 randomized trial of OLZ/SAM and placebo. After 30-60 weeks of treatment, no significant difference was observed between schizophrenics with comorbidity of AUD treated with OLZ/SAM vs olanzapine-monotherapy.[122]

## CONCLUSION

Schizophrenia and B1D are severe psychiatric illnesses with a significant economic burden of disease, high comorbidity rates, and poor prognoses despite relatively low prevalence rates.[3–5,9,10,32] Current pharmacological treatments of schizophrenia include FGAs, AAPs, and third-generation antipsychotics.[70–74] The current pharmacological treatment of B1D includes AAPs and lithium.[81,87] The use of combination drugs to treat psychiatric conditions is an emerging field with the primary goal of increasing therapeutic efficacy and decreasing undesirable side effects through targeting neurotransmission pathways.[74]

OLZ/SAM is approved by the FDA to treat schizophrenia and B1D. Olanzapine has proven effective for the treatment of schizophrenia and B1D through dopamine and serotonin receptor antagonism.[96,101] Samidorphan mitigates the weight gain side effects of olanzapine by antagonizing μ-, κ-, and δ-opioid receptors.[98,103,104] In clinical trials, OLZ/SAM showed similar efficacy in treating schizophrenia and B1D and exhibited less side effects (weight gain, somnolence, dry mouth, anxiety, headache) when compared to olanzapine-monotherapy.[112] No concerns regarding safety, pharmacokinetics, or bioavailability were identified during clinical trials.[119] Most patients reported improvements in symptoms of psychosis, reduced weight gain, and overall satisfaction with the combination treatment. OLZ/SAM has shown to be an effective and safe pharmaceutical option for the clinical management of schizophrenia and B1D.[113,116]

**Table 1. Lybalvi Studies and Findings**

| Author and Year | Groups Studied and Intervention | Results and Findings | Conclusions |
|---|---|---|---|
| Potkin et al[112] (2020) | 401 adults with clinically diagnosed schizophrenia who were experiencing an acute episode of psychosis were administered ≥1 dose of OLZ/SAM | Results indicated a significant improvement in PANSS and CGI-S total scores within 4 weeks in patients receiving OLZ/SAM versus placebo. | OLZ/SAM was well tolerated and had efficacy and safety similar to that of olanzapine-monotherapy |
| Simmons et al[113] (2021) | 41 patients with schizophrenia whose diagnosis of schizophrenia had impacted personal, social, and financial aspects of their lives were administered OLZ/SAM | Results indicated improvements in both positive and negative symptoms of psychosis in 39 of these patients | Most of the patients were satisfied with their treatment of OLZ/SAM |
| Citrome et al[111] (2021) | 18 studies were used to evaluate the antipsychotic and weight-mitigating efficacy and safety of OLZ/SAM in >1600 patients | Results indicated that the efficacy and safety of OLZ/SAM were similar to olanzapine, with reduced weight-gain overall | The efficacy and safety of OLZ/SAM were similar to olanzapine-monotherapy, with reduced weight-gain overall |
| Yagoda et al[114] (2021) | Patients with clinically diagnosed schizophrenia who completed the first phase of the ENLIGHTEN-1 study program were administered OLZ/SAM (N=277 administered ≥1 dose OLZ/SAM; N=183 completed 52 weeks of program) | Results indicated PANSS total and CGI-S scores declined in all patients that completed the trial. Increases in weight gain were stabilized by week 6, with an average 2.79% increase in weight gain | OLZ/SAM was concluded to improve schizophrenia symptoms, while mitigating weight-gain in patients |
| Brunette et al[122] (2020) | 234 patients with schizophrenia and AUD were enrolled in a 1:1 randomized trial of OLZ/SAM and placebo | Results indicated that no significant difference was observed between schizophrenics with comorbidity of AUD treated with OLZ/SAM vs olanzapine | OLZ/SAM can be used in schizophrenics with comorbidity of AUD. However, it is not superior to olanzapine and further studies are needed |
| Silverman et al[98] (2018) | 106 healthy, male normal weight volunteers were administered either OLZ/SAM, SAM, or placebo in a 2:2:1:1 ratio | Results indicated that OLZ/SAM was shown to have similar safety and tolerability as metabolic risk | Although OLZ/SAM had lesser side effects than olanzapine, further studies are needed in order to explore the side effects and efficacy of additional doses over a longer duration of time in schizophrenic patients |
| Sun et al[121] (2020) | 100 patients aged 18 to 60 years with stable schizophrenia were administered either OLZ/SAM or OLZ/SAM-matched placebo in a 3:2 ratio | Results indicated there were no clinically significant QTc effects, including QT prolongation, across the OLZ/SAM doses, ranging from 110 to 160 ng/mL | OLZ/SAM has no significant effect on QT intervals |
| Sun et al[120] (2020) | 34 healthy adults were administered lithium carbonate or divalproex sodium in a 1:1 ratio. On days 8-18, participants were administered olanzapine. | Results indicated that the safety profiles of lithium and valproate while administered with OLZ/SAM was similar to the safety profile of what was previously reported for lithium and valproate. | Administration of OLZ/SAM did not have a clinically significant effect on the pharmacokinetics of lithium or valproate and was generally well-tolerated. |
| Sun et al[119] (2018) | 48 healthy, nonsmoking participants were randomly assigned to either olanzapine monotherapy, OLZ/SAM, or B-OLZ in a 1:1:1:1:1:1 randomization where pharmacokinetics of the drug-drug interactions between olanzapine and samidorphan were studied. | Results indicated that OLZ/SAM was shown to not have any safety concerns nor affect the pharmacokinetics and bioavailability of olanzapine monotherapy | Simultaneous administration of olanzapine and samidorphan does not affect the bioavailability of olanzapine. In general, OLZ/SAM is well-tolerated by patients |
| Srisurapanont et al[115] (2021) | OLZ/SAM and olanzapine administration were compared in 1195 volunteers | Results indicated that the OLZ/SAM group's weight changes were not statistically different than the olanzapine group | There is not sufficient evidence that samidorphan prevents olanzapine-induced weight gain and olanzapine-induced cardiometabolic abnormalities. Samidorphan was well-tolerated by the patients |

| | | | treated with olanzapine in this study. |
|---|---|---|---|
| Correll et al[116] (2020) | OLZ/SAM was administred to 280 patients while olanzapine was assigned to 281 patients to compare the effects of OLZ/SAM on weight gain | Results indicated that schizophrenia symptom improvement was similar to the olanzapine treatment with statistically significant weight differences | This study concluded that OLZ/SAM treatment was associated with similar schizophrenia symptom improvement, but with significantly less weight gain and smaller increases in waist circumference |
| Martin et al[99] (2019) | 75 patients received olanzapine plus placebo, and the rest received OLZ/SAM in different dosages (N=80; 5 mg, N=86; 10 mg, N=68; 20 mg) to test OLZ/SAM weight gain mitigation | Results indicated that OLZ/SAM resulted in statistically significant lower weight gain compared to olanzapine plus placebo patients, with OLZ/SAM showing a 37% lower weight gain compared to olanzapine plus placebo. | Safety and efficacy of OLZ/SAM had a similar profile to olanzapine plus placebo, making OLZ/SAM a better option for mitigating weight gain while simultaneously treating schizophrenia |
| Kahn et al[117] (2021) | 265 patients with schizophrenia were administered either OLZ/SAM or olanzapine to compare the efficacy, safety, tolerability, and side effects of OLZ/SAM to olanzapine | Results indicated that fasting lipid, glycemic parameters, and PANSS scores remained stable throughout the study in patients receiving OLZ/SAM. CGI-S scores remained 3 or less in 81.3% of the patients, indicating mild illness severity. | Patients that were administered OLZ/SAM tolerated the medication well with significant results including smaller waist circumferences, smaller weight gain and efficacy of the medication combination |
| Kahn et al[118] (2021) | 167 patients with schizophrenia were administered either OLZ/SAM or olanzapine to compare the efficacy, safety, tolerability and side effects of OLZ/SAM to olanzapine | Results indicated that fasting lipid, glycemic parameters and PANSS scores remained stable throughout the study in patients receiving OLZ/SAM. CGI-S scores remained 3 or less in 81.3% of the patients, indicating mild illness severity. | Patients that were administered OLZ/SAM tolerated the medication well with significant results including smaller waist circumferences, smaller weight gain and efficacy of the medication combination |

Combination olanzapine and samidorphan (OLZ/SAM); Positive and Negative Syndrome Score (PANSS); Clinical Global Impression-Severity (CGI-S); alcohol use disorder (AUD); brand- olanzapine (B-OLZ)

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