

# Asenapine: A Synthesis of Efficacy Data in Bipolar Mania and Schizophrenia

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## Abstract

**Introduction:** This article briefly reviews the efficacy, as well as safety and tolerability, data pertaining to asenapine in bipolar mania and schizophrenia. Postulated mechanism of action is also reviewed. **Methods:** A PubMed search was conducted using the search term asenapine. All displayed articles were reviewed; we selected for review studies that were part of the regulatory registration package to the FDA as part of the bipolar disorder and schizophrenia indication. We also included a review of articles reporting on asenapine's preclinical profile. **Results:** Asenapine is a recently introduced atypical antipsychotic approved by the FDA for bipolar mania and mixed states with or without psychotic features, as well as for the treatment and prevention of psychotic relapses in schizophrenia. Preliminary evidence suggests that asenapine mitigates depressive symptoms in bipolar mania and offers superior efficacy to olanzapine or risperidone in the negative symptoms of schizophrenia. The pharmacodynamic profile of asenapine provides a rationale for hypothesizing efficacy in the treatment of cognitive deficits in mood and psychotic disorders. Asenapine is associated with sedation and/or somnolence; it has a lower propensity to weight gain and metabolic disruption than olanzapine. Extrapyramidal side effects (EPS) are associated with asenapine and may be dose-dependent. Asenapine is not associated with sustained hyperprolactinemia or cardiovascular toxicity. Dysgeusia and oral hypoesthesia/paresthesia is associated with asenapine, but is rarely a cause for treatment discontinuation. **Conclusions:** Asenapine is the only atypical antipsychotic available exclusively as a sublingual, fast-dissolved formulation. Electrophysiological, behavioral, pharmacological, and radioligand studies are predictive of antidepressant, mood-stabilizing, as well as antipsychotic, effects.

**Key Words:** Asenapine, Mania, Schizophrenia

## Introduction

Asenapine is an atypical antipsychotic approved by the U.S. Food and Drug Administration (FDA) in August 2009 for the treatment of adults with schizophrenia and for manic/mixed episodes with or without psychotic features associated with bipolar I disorder (1). Asenapine can be characterized by the following features: 1) it is a dibenzoxepino-pyrrole derivative; 2) it is the only psychotro-

pic agent available exclusively in a fast-dissolved, rapidly absorbed formulation; and, 3) it is the only atypical antipsychotic derived from a currently available conventional antidepressant. The fact that it has been derived from the tetracyclic antidepressant mianserin suggests that this antipsychotic agent would be in possession of antidepressant properties. Moreover, its dopamine blocking properties would be hypothesized to decrease propensity to engendering and/or intensifying hypomania in bipolar patients (3). Animal, pharmacological, electrophysiological, as well as pharmacoligand studies have provided evidence that asenapine has several points of pharmacodynamic similarity (e.g., differential affinity for 5-HT versus D2 receptors) and differences with other atypical agents (e.g., relative affinity for cell-surface receptors).

Herein, we provide synthesis of efficacy results of asenapine and briefly review its postulated mechanism of action. As our group and others have previously reported on asenapine in the form of original articles and reviews, this review will take a synthetic approach (1-4).

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Submitted: July 13, 2011; Revised: August 24, 2011;  
Accepted: October 27, 2011

### Methods

A PubMed search was conducted using the search term asenapine. All displayed articles were reviewed; we selected for review studies that were part of the regulatory registration package to the FDA as part of the bipolar disorder and schizophrenia indications. We also included a review of articles reporting on asenapine's preclinical profile.

### Results

#### *Bipolar Mania*

The efficacy of asenapine in adults with bipolar mania or mixed episodes has been established on the basis of two identically designed, randomized, placebo-controlled trials. The methods and results of these studies have been published and reviewed previously. Briefly, adults presenting with manic or mixed episodes with or without psychotic features were randomly assigned to a flexible dose sublingual asenapine beginning at 10 mg BID with the option of titrating to 5 mg BID between days 2–21 if clinically indicated. Olanzapine was an active control in both studies; treatment began at 15 mg on day 1 with the opportunity to titrate to 5–20 mg, if necessary. The primary efficacy parameter was change from baseline to endpoint in the total Young Mania Rating Scale Score (YMRS) (2, 3).

In both studies, the mean daily dose of asenapine was approximately 18 mg; a significantly greater least squares (LS), mean $\pm$ SE changes in YMRS scores were observed at endpoint (i.e., day 21) and at day 2. The presence of psychosis did not affect outcome on primary or secondary measures. Olanzapine also resulted in significant placebo separation at day 2 and day 21; comparative efficacy with asenapine was not planned a priori. The most commonly reported adverse events (AE) with asenapine were somnolence, dizziness, extrapyramidal side effects (other than akathisia), as well as weight increase. The overall weight increase with asenapine (i.e.,  $\geq 7\%$  increase from baseline) was approximately 4 to 6% (placebo subtracted). Weight increase with olanzapine using the clinical significance criterion was approximately 12 to 14% (placebo subtracted).

A recently published post hoc analysis indicated that asenapine treatment significantly reduces depressive symptoms as measured by the total score on the Montgomery-Asberg Depression Rating Scale (MADRS), as well as remission rates (i.e., total MADRS score  $\leq 12$ ) (5). This post hoc analysis defined three sub-populations from the two acute mania trials: 1) total MADRS score  $\geq 20$  (n=132); 2) Clinical Global Impression for Bipolar Disorder-Depression (CGI-BP-D) scale severity score  $\geq 4$  (n=170); and, 3) diagnosis of mixed episodes (n=302). Decreases in MADRS total score were statistically greater with asenapine versus placebo at

days 7 and 21 in the first group. In the second and third groups, improvements with MADRS reached significance at day 7. Remission rates were significant in groups 2 and 3 on day 7 and day 21.

Subjects enrolled in the acute monotherapy mania trials were eligible for a separate 9- and 40-week extension (4). The blind was not broken until week 12 of the study. Individuals assigned to placebo in the acute phase were switched to asenapine during the extension phases and were included for tolerability and safety only. Results from the 9-week extension indicated that the mean change from baseline in YMRS total score was -24.4 ( $\pm 8.7$ ) for asenapine and -23.9 ( $\pm 7.9$ ) for olanzapine. There were no significant differences in overall YMRS reduction between the asenapine and olanzapine groups. Incidence of EPS of any type was reported in 10% with placebo/asenapine, 15% with asenapine, and 13% with olanzapine. The percentage of patients with clinically significant weight gain was greater with olanzapine (31%) than asenapine (19%).

During the 40-week extension, noninferiority with asenapine and olanzapine was noted. The most commonly reported EPS was akathisia, occurring in 11.4% of asenapine and 10.3% of olanzapine patients. There were, however, no significant changes from baseline to endpoint on the Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Scale (BARS), or the Simpson-Angus Scale (SAS). Moreover, no significant changes were seen during the acute phase with asenapine; shifts from low or normal fasting blood glucose levels to high levels were observed in 10% of placebo/asenapine, 26% of asenapine, and 22.2% of olanzapine patients. No significant changes were noted in hepatic aminotransferase levels or prolactin levels. Moreover, no significant changes were noted on electrocardiographic parameters.

#### *Schizophrenia*

The efficacy of asenapine in acute schizophrenia has been demonstrated in two placebo-controlled studies (6, 7). Asenapine was also noted to have a failed and negative trial in schizophrenia. (The failed and negative trial included olanzapine as an active control.) It is not known if any single factor can sufficiently explain why two trials with this agent failed to beat placebo in the acute treatment of schizophrenia. Failed and negative studies affect approximately 50% of psychiatric medication submissions to the FDA. Herein, we briefly review the positive acute and recurrence prevention studies. The acute trials were six weeks in duration; the positive trials included risperidone (3 mg BID) and haloperidol (4 mg BID) as active controls. In contradistinction to the bipolar trials, wherein the starting dose was 10 mg BID, in the schizophrenia trials the effective dose was 5 mg BID with no evidence of a dose response curve on efficacy (there was,

however, a dose response curve on tolerability). At study endpoint, mean change from baseline was significantly greater with asenapine versus placebo on the primary efficacy parameter, the Positive and Negative Syndrome Scale (PANSS). Risperidone did not significantly separate from placebo on change from baseline on the total PANSS score.

Asenapine treatment was also associated with a significant improvement versus placebo on the PANSS negative subscale score while risperidone did not separate from placebo. The advantage in favor of asenapine on negative symptoms was not due to a higher rate of EPS in the risperidone treatment arm. Extrapyramidal side effects were recorded in the case report form; it is not known why there were no differences between groups. Based on these results, as well as preclinical findings and asenapine's derivation, the sponsor (Merck/Lundbeck) is evaluating asenapine's efficacy in schizophrenia with an emphasis on negative symptom efficacy. In the replication positive acute trial of schizophrenia, both asenapine-treated and haloperidol-treated subjects exhibited a significant change from baseline to endpoint in the total PANSS score.

Asenapine was also assessed in a double-blind, placebo-controlled trial that followed a 26-week open-label treatment (7). Time to relapse/impending relapse during double-blind treatment according to rating-scale criteria or investigators' judgment was the primary efficacy parameter. Relapse/impending relapse was operationalized as a CGI-S score  $\geq 4$  for  $\geq 2$  days within 1 week and accompanied by: a PANSS total score increase  $\geq 20\%$  from double-blind baseline (a  $\geq 10$ -point increase if baseline total score was  $\leq 50$ ), a PANSS item score  $\geq 5$  on "hostility" or "uncooperativeness", or a PANSS item score  $\geq 5$  on 2 items of "unusual thought content", "conceptual disorganization", or "hallucinatory behavior". Moreover, suicide risk, the need for concomitant medication, and other interventions, including hospitalization, were also considered an event. Time to relapse/impending relapse and discontinuation for any reason were significantly longer with asenapine than placebo. Moreover, the incidence of relapse/impending relapse was significantly lower with asenapine. Adverse events profiles in schizophrenia were similar to what was reported above in bipolar disorder.

## Asenapine: Neurobiological Targets

Asenapine's profile has been characterized in pharmacological, electrophysiological, animal behavioral, and pharmacoligand studies. Results from in-vitro human receptor studies indicate that asenapine exhibits a high affinity for an antagonistic action 5-HT<sub>2A</sub>, 5-HT<sub>2B</sub>, 5-HT<sub>2C</sub>, 5-HT<sub>5A</sub>, 5-HT<sub>6</sub>, 5-HT<sub>7</sub> receptors, and potent antagonism at dopaminergic (D<sub>2</sub> and D<sub>3</sub>), alpha-adrenergic ( $\alpha$ 1A,  $\alpha$ 2A,  $\alpha$ 2B,

$\alpha$ 2C), and histaminergic (H<sub>1</sub>, H<sub>2</sub>) receptors, with no appreciable activity at muscarinic cholinergic receptors. Moreover, asenapine is an agonist at the 5-HT<sub>1A</sub> receptor. A pharmacoligand study with asenapine indicates that asenapine exhibits high D<sub>2</sub> occupancy ( $>80\%$ ) at 5 and 10 mg BID (8-10). Taken together, this in-vitro receptor binding profile is predictive of minimal cholinergic side effects (e.g., dry mouth, constipation, as well as modest propensity for sedation/somnolence, and appetite stimulation). The higher affinity for 5-HT<sub>2A</sub>, when compared to D<sub>2</sub>, is a point of pharmacodynamic similarity with all other atypical agents and may be associated with lower propensity to EPS. It should be noted, however, that the role in blockade of 5-HT<sub>2A</sub> receptors has not been accepted as a factor in alleviating EPS (11, 12). Moreover, this in-vitro profile has been proposed to be predictive of antidepressant, mood-stabilizing, and antipsychotic effects.

Asenapine has also been demonstrated to produce a dose-dependent increase in dopamine efflux in the medial pre-frontal cortex (mPFC) and hippocampus (HIP). Asenapine also dose dependently increases acetylcholine (ACh) efflux in the mPFC and HIP but not in the nucleus accumbens (NAc). Asenapine's effect on dopamine efflux is blocked by pre-treatment with the 5-HT<sub>1A</sub> antagonist/D<sub>4</sub> agonist, WAY100635 (13, 14). Taken together, it could be conjectured that this profile may mediate the cognition in enhancing effects, antidepressant effects, as well as efficacy in negative symptoms. More specifically, agents that have been shown to modulate dopamine, for example, have been reported to mitigate attentional disturbances and mood symptoms across disparate psychiatric populations.

Asenapine's effect on its [3H]MK-801 to NMDA receptors has been documented. Subacute asenapine treatment decreases binding to the NMDA/MK-801 modulatory sites in nucleus accumbens (NAc), medial caudate/putamen (CPU) by approximately 25 to 30%. Asenapine did not alter binding of [3H]glycine to NMDA/glycine modulatory sites. Asenapine dose dependently altered [3H]AMPA binding to AMPA receptors in hippocampal CA1 and CA3 regions (Tarazi et al.) (9). Asenapine has also been shown to attenuate cognitive deficits (e.g., novel object recognition) in the subchronic phencyclidine PCP-induced model. The reversal effect of asenapine on PCP-induced deficit was antagonized by D<sub>1</sub> antagonism (9). It could be hypothesized that this pre-clinical profile is predictive of a cognitive-enhancing effect in human subjects.

Asenapine antidepressant effects are also suggested by results from the chronic mild stress-induced "anhedonia" model. Asenapine reverses the effect of anhedonia induced by chronic mild stress. This behavioral finding is also reported with conventional antidepressant therapies (15).

### Conclusions

Asenapine's efficacy in acute mania/mixed states with or without psychotic features, as well as in the treatment of psychotic episodes in schizophrenia, has been reported. Moreover, maintenance of acute antimanic efficacy and recurrence prevention in schizophrenia with asenapine is empirically supported. A post hoc analysis suggests that asenapine is highly efficacious in mitigating depressive symptoms in acutely manic patients. Moreover, early evidence also suggests that asenapine may offer improved efficacy (versus olanzapine or risperidone) in the treatment of negative symptoms. The pharmacodynamic profile of asenapine provides a rationale for hypothesizing a salutary effect on cognitive deficits.

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Asenapine has less weight gain propensity than olanzapine, but does in fact associate with clinically significant weight gain in some individuals. Asenapine does not disrupt metabolic parameters in most treated individuals, but may hazardously affect metabolic outcomes in some individuals. As such, it may not be accurate to refer to this agent as "weight and metabolically neutral."

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*Moreover, early evidence also suggests that asenapine may offer improved efficacy (versus olanzapine or risperidone) in the treatment of negative symptoms.*

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Asenapine is also associated with sedation and EPS in some individuals, but is not known to be associated with sustained hyperprolactinemia or cardiovascular toxicity. The availability in sublingual, rapid-absorbed formulation will be an advantage and preference for some patients. For others, the need to coordinate the administration of the medication with the avoidance of food or drink consumption for at least ten minutes will be a limitation. Asenapine can result in dysgeusia (i.e., unpleasant taste) and/or oral hypoesthesia/paresthesia in approximately 1 to 5% of treated subjects. Studies in healthy controls indicate that the rate of dysgeusia and/or oral hypoesthesia/paresthesia may be higher. In the United States, a black cherry formulation has been made available as an alternative to the conventional formulation. As with all atypical antipsychotics, insufficient evidence is

available regarding efficacy and safety in combination with other atypicals. Future studies are aiming to characterize asenapine's effect in the treatment of bipolar depression, major depressive episodes as part of major depressive disorder, and in the treatment of negative symptoms associated with schizophrenia. Although many agents are available to treat various phases of bipolar disorder and schizophrenia, most individuals do not achieve and/or sustain symptomatic remission or sufficiently tolerate existing therapy, inviting the need for alternatives.

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