Saphris: Does a unique delivery system equal a unique drug?

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ABSTRACT

Asenapine was approved by the Food and Drug Administration (FDA) in 2009. This article reviews clinically significant aspects of this new drug including: the FDA-approved indications, mechanism of action, administration, drug interactions, adverse effects, clinical trial evidence, innovative properties and place in therapy.

KEYWORDS

Asenapine, Saphris, antipsychotic, schizophrenia, acute mania, bipolar disorder

You are a clinical pharmacist at a local state hospital. A component of your clinical services includes providing routine medication education and discharge medication counseling. You are preparing to provide education to a patient with bipolar disorder who is being discharged on asenapine and lithium. Are there specific counseling points that must be addressed when a patient is prescribed asenapine?

WHAT ARE THE FDA-APPROVED INDICATIONS FOR ASENAPINE?

Asenapine (Saphris®) is a newer atypical antipsychotic, released to the US market in 2009. It is currently indicated for the treatment of schizophrenia as well as the treatment of acute mania or mixed episodes associated with bipolar disorder, type I in adults.[5]

WHAT IS THE RECEPTOR BINDING PROFILE OF ASENAPINE?

Asenapine is a second-generation antipsychotic that acts as a serotonin 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, 5-HT_5, 5-HT_6, 5-HT_7 and dopamine D_1, D_2, D_3, D_4 antagonist.[1,5] It also has antagonist activity at alpha$_1$, alpha$_2$, and histamine (H_1) receptors. It has no affinity for the muscarinic (M_1) receptors.

HOW IS ASENAPINE DOSED AND HOW SHOULD IT BE ADMINISTERED?

Patients with schizophrenia should be initiated on 5 mg sublingually twice daily. The dose may be increased to a maximum of 10 mg twice daily for adequate symptom control. For the treatment of acute mania, the dose may be initiated at 10 mg twice daily, when used as monotherapy.[5] The half-life of asenapine is 24 hours and steady-state is obtained in 3 days. Patients should be advised that the tablets should be placed under the tongue and left to dissolve for the best absorption. Eating, drinking, and smoking should be avoided for up to 10 minutes after taking asenapine. The bioavailability of asenapine is ~35% when dosed sublingually and <2% when taken orally. No dosage adjustments are necessary for patients with mild to moderate hepatic impairment; however asenapine should not be used in patients with severe hepatic impairment (Child-Pugh C). Dosage adjustments are not required based on age or renal impairment. Like most atypical antipsychotics, asenapine is pregnancy category C with no current studies in pregnant women.[5]

ARE THERE ANY CLINICALLY SIGNIFICANT DRUG INTERACTIONS WITH ASENAPINE?

Asenapine is metabolized hepatically via the CYP1A2 system, as well as through direct glucuronidation. It is a weak inhibitor of CYP2D6.[5] Asenapine should be used with caution with potent CYP1A2 inhibitors such as fluvoxamine and ciprofloxacin. It has no effect on lithium or valproate serum concentrations when used concomitantly. Smokers may need higher dosages due to CYP1A2 induction.

WHAT ADVERSE EFFECTS SHOULD I DISCUSS WITH MY PATIENT?

Clinically, orthostasis and some sedation due to alpha$_1$ and H_1 antagonism are expected. The most common adverse effects reported in clinical trials (≥5%) were somnolence, akathisia (dose-related increase from 4% at 10 mg/day to 11% at 20 mg/day) and other forms of extrapyramidal adverse effects (e.g., dystonia, muscle rigidity, parkinsonism, tardive dyskinesia), dizziness, and

oral hypoesthesia.[2,3,4,6] Decreased oral sensitivity usually occurs directly after administration and may last up to one hour. Oral mucosal lesions have been reported by patients clinically. The black box warning for increased mortality in elderly patients with dementia-related psychosis is the same for this antipsychotic as with all other antipsychotics. The asenapine package insert highlights the risk of metabolic changes associated with antipsychotic treatment. In a 52-week asenapine trial, the average weight gain was 0.9 kg, with a mean increase in fasting glucose of 2.4 mg/dL.[1,5] Monitoring of waist circumference, weight, blood pressure, BMI, fasting lipid panel, and glucose is recommended, similar to other atypical antipsychotics.

More recently, hypersensitivity reactions leading to the development of anaphylaxis, angioedema, hypotension, tachycardia, dyspnea, and swollen tongue have been reported. The FDA's Adverse Event Reporting System (AERS) database has identified 52 cases of Type I hypersensitivity reactions (allergic reactions) with asenapine use.[7]

HOW DID ASENAPINE PERFORM IN CLINICAL TRIALS?

Efficacy for the treatment of schizophrenia was established in three 6-week fixed-dose trials (5 mg BID and 10 mg BID). All were randomized, placebo-controlled, double-blind trials with active control groups including haloperidol, risperidone, and olanzapine. Two of these studies demonstrated superior efficacy to placebo, the third could not be distinguished from placebo. One 26-week maintenance trial demonstrated the sustained efficacy and tolerability of asenapine.[2,5,6] Efficacy for the treatment of acute mania was established in three 3-week trials (two monotherapy, one adjunctive to lithium or valproate). Asenapine was statistically superior to placebo on the Young Mania Rating Scale score for all three studies.[3,4,5]

WHAT IS INNOVATIVE ABOUT THIS NEWER ANTIPSYCHOTIC?

This is the first and only antipsychotic available as a sublingual tablet; however it is not presently available in any other delivery system. A sublingual delivery system may be clinical advantageous in a hospital setting when "cheeking" is suspected. It does come in a black cherry-flavored sublingual tablet, presumably to enhance treatment adherence. Its pharmacologic profile does not differ significantly from already available atypical antipsychotics. Efficacy data for asenapine does not appear to be superior to other antipsychotic agents available.

WHAT PLACE DOES ASENAPINE HAVE IN THE TREATMENT OF SCHIZOPHRENIA AND BIPOLAR DISORDER?

Asenapine provides clinicians with another atypical antipsychotic treatment option with a more favorable metabolic profile (less weight gain and hyperglycemia associated with its use). It appears to be a viable adjunctive treatment option for manic patients that have had a partial response to mood stabilizers such as lithium or valproate. As indicated in the case initially presented in this review, asenapine does have a unique delivery system requiring more extensive patient counseling for proper sublingual usage. It is supplied in a plastic case that holds ten sublingual tablets. While this delivery system is unique for antipsychotic medications, it may actually hinder treatment adherence in patients being treated for schizophrenia and bipolar disorder. Sedation is a much more common adverse effect associated with its use, and given the necessity of twice daily dosing, this may also negatively affect treatment adherence. Clinically, asenapine appears to be a less favorable treatment option for both schizophrenia and bipolar disorder due to its more complex delivery system and similar efficacy to other marketed antipsychotics.

REFERENCES

1. Citrome L. Asenapine for schizophrenia and bipolar disorder: a review of the efficacy and safety profile for this newly approved sublingually absorbed second-generation antipsychotic. Int J Clin Pract. 2009;63(12):1762-84. DOI: 10.1111/j.1742-1241.2009.02228.x. PubMed PMID: 19840150.
2. Kane JM, Cohen M, Zhao J, Alphs L, Panagides J. Efficacy and safety of asenapine in a placebo- and haloperidol-controlled trial in patients with acute exacerbation of schizophrenia. J Clin Psychopharmacol. 2010;30(2):106-15. DOI: 10.1097/JCP.0b013e3181d35d6b. PubMed PMID: 20520283.
3. McIntyre RS, Cohen M, Zhao J, Alphs L, Macek TA, Panagides J. A 3-week, randomized, placebo-controlled trial of asenapine in the treatment of acute mania in bipolar mania and mixed states. Bipolar Disord. 2009;11(7):673-86. DOI: 10.1111/j.1399-5618.2009.00748.x. PubMed PMID: 19839993.
4. McIntyre RS, Cohen M, Zhao J, Alphs L, Macek TA, Panagides J. Asenapine in the treatment of acute mania in bipolar I disorder: a randomized, double-blind, placebo-controlled trial. J Affect Disord. 2010;122(1-2):27-38. DOI: 10.1016/j.jad.2009.12.028. PubMed PMID: 20096936.
5. Merck. Saphris (asenapine) Sublingual Tablets Prescribing Information. Available from: http://www.spfiles.com/pisaphrisv1.pdf. Accessed November, 2011.
6. Potkin SG, Cohen M, Panagides J. Efficacy and tolerability of asenapine in acute schizophrenia: a placebo- and risperidone-controlled trial. J Clin Psychiatry. 2007;68(10):1492-500. PubMed PMID: 17960962.
7. SDI, Vector One®: National (VONA). August 2009-June 2011. Data extracted August 2011.

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