AN OVERVIEW ON ASENAPINE MALEATE: PK-PD, PRECLINICAL AND CLINICAL UPDATE

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Abstract: Schizophrenia and bipolar disorder are both prevalent types of psychiatric illness in World. The second-generation antipsychotics have become more viable first-line treatment options. Asenapine is a second-generation (atypical) antipsychotic currently marketed for the treatment of schizophrenia and bipolar mania/mixed episodes. The preclinical and clinical data suggest that asenapine shown antipsychotic activity with very low extra pyramidal side effect. Asenapine is available in 5 mg and 10 mg sublingual tablets and administered twice daily with a maximum daily dose allowed up to 20 mg. Patient is advised not eat or drink for 10 minutes after drug administration. The sublingual and oral absolute bioavailability of Asenapine at 5 mg is 35% and < 2%, respectively. Asenapine is highly bound to plasma protein (95%) with large volume of distribution (~20-25 l/kg). Higher variability in plasma concentration of asenapine may be observed if co-administered with CYP1A2 inducers or inhibitor. The other limitations associated with asenapine include non-adherence patient compliance with dosage form. Apart from these limitations, It may be a suitable treatment option in patients with increased risk of metabolic disturbances, diabetes or obese. Furthermore, it may, also be a safer alternative in patients with impaired renal function due to no dose adjustments are required in these individuals (as is the case with risperidone and paliperidone).

Keywords: Asenapine, Schizophrenia, Bipolar disorder, Second generation antipsychotic.

1. INTRODUCTION

Schizophrenia is severe chronic debilitating brain disease affecting approximately 1-2% of the world population, more affecting the urban population than rural population and affecting man and women equally [1]. In India, the number of patient affected by the schizophrenia is around 8.3 to 10.7 million. Age of onset is generally between 20 year to 35 year and it is characterized by positive symptoms (e.g., hallucinations, delusions and thought disorder), negative symptoms (e.g., deficits in social interaction, emotional expression and motivation) and cognitive dysfunction (e.g., impairments of attention and working memory). Schizophrenia has devastating effects on several aspects of the patient's life. It is among the top ten causes of disability world-wide and reduces the life span of those afflicted by an average of ten years. Suicide is the single greatest cause of premature death among patients with this disorder. In schizophrenia treatment, patient non-adherence is a major problem occurred as side effect associated with drug and long term therapy regimen. More than 34% of patient demonstrate adherence problems during the first 4-6 weeks of treatment and within 2 years its reached upto 74% [2-4]. The most common outcomes of non-adherence are usually a remitting course with one or multiple relapses in 50-92% of cases. Patients on medication have a relapse rate of 40%, while those who discontinue their treatment have a 1-year relapse rate of 65% and in 2-year rate more than 80% [5].

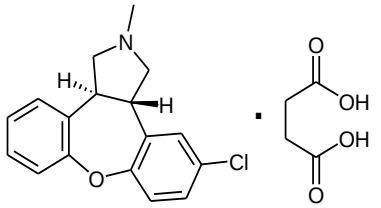
Asenapine (ASN) is claimed to be a novel psychopharmacologic agent with high affinity and potency for blocking dopamine, serotonin, α-adrenergic and histamine receptors, and no appreciable activity at muscarinic cholinergic receptors. The mechanism of action of asenapine, like other atypical antipsychotics is believed to be mediated through a combination of antagonist activity at 5-HT2A and D2 receptors. It is approved for the treatment of adults with schizophrenia and as an adjunctive therapy with lithium or valproate for the acute treatment of manic or mixed episodes associated with bipolar I disorder [6]. Asenapine has been developed as a structural modification of the atypical antidepressant mianserin [7]. It is the first antipsychotic drug to be administered through a sublingual route of administration. It is available in 5 and 10 mg sublingual tablet dosage form and administered twice daily with a maximum daily dose allowed up to 20 mg. Each tablet can be placed sublingual or buccal as long as it is not swallowed, should be allowed to dissolve completely, and the patient should not eat or drink for 10 minutes after drug administration [8].

The objective of this article was to provide a short overview on asenapine. Here, the pharmacokinetic, pharmacodynamic, preclinical and clinical profiles are presented and discussed.

2. PHYSICO-CHEMICAL PROPERTIES

Asenapine maleate is chemically (3aR*,12bR*)-5-Chloro-2,3,3a,12b-tetrahydro-2-methyl-1H-dibenz [2,3:6,7] oxepino[4,5-c] pyrrole maleate. It is a white to off-white non hygroscopic powder which is slightly soluble in water and sparingly soluble in 0.1 M HCl. It was developed by Organon laboratories (Org 5222) having CAS registry number 85650-56-2. The molecular formula of asenapine maleate is C17H16CINO.C4H4O4 with a molecular weight of 401.84 (285.8 as the free base). Asenapine is quite stable in crystalline form, although excessive light can induce degradation [7]. The pKa of the protonated free base is 8.51. Log P for neutral species and cationic species is 4.9, 1.4, respectively. The melting point of Asenapine maleate is 139.9 ºC (mp 141-145 ºC) [9, 10].

Table 1: Drug Summary [9].

Chemical Structure	
Molecular weight of free base (salt)	285.8 (401.8) g/ moles
Melting point	141-145 °C
Solubility (water)	Slightly soluble
Solubility (methano, ethanol and acetone)	Freely soluble
Intrinsic dissolution rate in water	123 mg/m^{2}s
pKa of free base	8.51
pKa of maleic acid	pK^1= 3 pK^2=7.52
Log P of free base	6.33
Caco-2 cell permeability	0.9-2.3 x 10

3. PHARMACOKINETICS

3.1 Absorption

Asenapine is absorbed rapidly on oral or gastric mucosa. The apparent permeability of asenapine through the Caco-2 cell monolayer was found to be 1x10-5cm/sec. After sublingual administration; the peak plasma concentration was obtained within 0.5 to 1.5 hours. The absorption is non linear with dose, increasing the dose two fold (5 to 10 mg twice daily) results in a less than linear (1.7 times) increase in both the extent of exposure and maximum concentration. The sublingual and oral absolute bioavailability of Asenapine at 5 mg is 35% and < 2% respectively [11]. Low oral bioavability was due to high hepatogastrointestinal first-pass metabolism. However, the oral bioavailability was also low in animals, i.e. between 20-65% in rats and up to 10% in dogs. The presence of water and food markedly affect the sublingual and oral bioavailability [12].

3.2 Distribution

Asenapine is rapidly distributed and has a large volume of distribution (~20-- 25 l/kg), indicating extensive extra vascular distribution. Asenapine is highly bound (95%) to plasma proteins, including albumin and α1-acid glycoprotein. Asenapine and its metabolite N-desmethyl asenapine are weak substrates of the human P-gp, resulting very less impact on *in-vivo* disposition of asenapine and N-desmethyl asenapine. The autoradiography of radioactive asenapine revealed that both asenapine and its N-

desmethyl metabolite penetrate the blood-brain-barrier and accumulate in brain up to 3 h post dosing. Asenapine accumulated to a greater extent, with a brain-to-tissue ratio of 19 at 3 hr post dosing [11, 12].

3.3 Metabolism and Excretion

Direct glucuronidation by UGT1A4 and oxidative metabolism by cytochrome P450 isoenzymes (predominantly CYP1A2) are the primary metabolic pathways for asenapine. The caution should be taken when using CYP1A2 inducers (carbamazepine or rifampin) or CYP1A2 inhibitors (fluvoxamine, ciprofloxacin, ketoconazole). Asenapine is metabolized into two inactive compounds: N-glucuronide-asenapine and N-desmethyl-asenapine [13]. After administration of a single dose of [^{14}C] labeled asenapine, about 90% of the dose was recovered; approximately 50% was recovered in urine, and 40% recovered in feces. Following an initial rapid-distribution phase, the mean $t_{½}$ was reported to be 24 h. Asenapine is an active moiety, however other metabolites have negligible effects due to their lower affinity towards dopamininergic and serotonergic receptors [12, 14]).

3.4 Population Pharmacokinetic

In population pharmacokinetic studies, the higher C_{max} and AUC were observed in elderly as compared to adult patient might be credited to slow drug clearance. In older population the asenapine C_{max} values were 12% higher with 5 mg BID and 21% higher with 10 mg BID. AUC (0-12 h) values were 21% higher with 5 mg BID and 30% higher with 10 mg BID. As per label information, no dose adjustment is required in elderly patient although slow drug clearance. The safety and efficacy of asenapine have not been established in pediatric population.

Potential gender differences in asenapine pharmacokinetics have not been studied in a dedicated trial; however in a population analysis, no significant differences between men and women on asenapine pharmacokinetics were observed. Although in a population pharmacokinetic analysis a 14% decrease in clearance was observed in Black subjects compared with subjects from other ethnic origins, the magnitude of this effect is small in relation to the overall variability in pharmacokinetics observed for asenapine. The product label concludes that no effect of race on asenapine concentrations was observed. In a dedicated study, the pharmacokinetics of asenapine was similar in Caucasian and Japanese subjects [11, 14].

Article Highlight:

- Asenapine is first approved sublingual tablet for treatment of Schizophrenia and Bipolar disorder.
- Human sublingual bioavailability is 35% for 5 mg tablet. However oral bioavailability is < 2% in human, 20-65% in rats and up to 10% in dogs.
- Asenapine is active moiety for antipsychotic activity due to its property to cross blood brain barriers as compared to metabolite.
- The caution should be taken when using CYP1A2 inducers (carbamazepine or rifampin) or CYP1A2 inhibitors.
- Due to its well tolerated in nature, no dose adjustment is required in elderly or renal impairment patient.
- Caution should be taken when using CYP1A2 inducer or CYP1A2 inhibitors with Asenapine.

4. PHARMACODYNAMIC

The precise mechanism of action of asenapine in the treatment of schizophrenia is not clearly known. Asenapine has similar receptor binding profile of other second-generation antipsychotic drugs, exhibit potent antagonism at serotonin, dopamine, noradrenaline and histamine receptors. Asenapine appears to have relatively higher potency at serotonin receptors than at dopamine receptors. It is hypothesized that the efficacy of asenapine is mediated through a combination of antagonist activity at the dopamine D_2 and serotonin 5-HT_{2A} receptors. This unique receptor signature and functional activity of asenapine supports its distinct psychopharmacological profile for the improved treatment of schizophrenia and bipolar mania [15, 16] .

Further study of the receptor activity of asenapine suggested that it has an upregulating effect on D1-like receptors, most likely secondary to direct blockade of these receptors. This finding is important because some evidence suggests that the upregulation of D1and D2 receptors is associated with a decreased likelihood of producing extrapyramidal symptom (EPS)–related adverse events. This finding is different from those of other antipsychotics, such as fluphenazine, olanzapine, and risperidone, which do not significantly cause a variation in D1-receptor levels [17, 18].

5. SAFETY AND TOLERABILITY

The majority of efficacy studies indicate that asenapine is generally well tolerated. The most common adverse effects that associated with asenapine are somnolence, dizziness, weight gain and extrapyramidal symptoms (EPS) dose relationship. Rates of EPS with asenapine treatment reported lower than with haloperidol and lower or equivalent to risperidone [19]. The lesser affinity for D2 receptors offers a benefit by decreasing the risk of EPS and hyper prolactinemia as seen with potent drugs such as haloperidol. Whereas, the risk of EPS was higher in asenapine compared with olanzapine, with a 35.4% increased incidence with asenapine versus 19% with olanzapine [20]. Although there is a risk of weight gain with asenapine but it is lesser than that associated with olanzapine. This has been attributed to the lower binding affinity of asenapine for the histamine receptor (H1) as compared to olanzapine and quetiapine which have strong H1 binding affinity and thereby carry a greater risk of weight gain. Elevated fasting glucose and cholesterol elevation may occur in some patients as with other atypical antipsychotics [13]. It may induce orthostatic hypotension and syncope because of its α1-adrenergic antagonist activity, though these adverse events were limited in both schizophrenia (0.2%) and bipolar mania (0.3%) patients [21].

6. PRECLINICAL EFFICACY

Asenapine were assessed in different animal model to evaluate antipsychotic activity for Schizophrenia and Bipolar disorder [22].

Conditioned avoidance response (CAR):

Asenapine (0.05, 0.1, and 0.2 mg/kg) was active in this model as it showed dose-dependent suppression of CAR, with the highest doses producing profound and sustained suppression of CAR for 90 min after administration. The median effective dose (ED50) for 80% CAR suppression was 0.12 mg/kg, which supports asenapine's ability to block D2 receptors [23].

Amphetamine-induced locomotor activity:

Administration of asenapine (0.1-- 1.0 mg/kg) prior to the injection of amphetamine (1.0 mg/kg) dose-dependently blocked D2 receptors and reversed amphetamine-induced locomotor activity in adult rats when assessed in activity monitors, which further supports the antipsychotic activity of this novel agent [24].

Apomorphine-induced disruption of prepulse inhibition of the startle reflex (PPI):

Administration of asenapine (0.1-- 1.0 mg/kg), significantly and dose-dependently increased startle response in apomorphine-pretreated compared to vehicle-pretreated rats. The potency of asenapine in reversing apomorphine-induced disruption of PPI was higher than that of olanzapine and risperidone, which probably reflects its higher affinity for D2 receptors [24, 25].

Catalepsy:

This animal test predicts the ability of a drug to induce EPS, and in particular Parkinsonism. In this test, animals are placed on an inclined grid and the amount of time the animal remains immobile after drug or vehicle treatment is calculated. Lower doses of asenapine (0.1 and 0.2 mg/kg) did not induce cataleptic behaviors. A higher dose of asenapine (0.5 mg/kg), which is 2.5 times the effective antipsychotic dose of asenapine in CAR, produced catalepsy 60-120 min after administration. These findings suggest that asenapine exhibits a fairly benign EPS profile, but it may induce EPS in patients at doses higher than optimal therapeutic doses [23, 26].

Chronic mild stress (CMS):

Repeated treatment with asenapine reversed the CMS induced reduction in sucrose consumption in a dose-dependent manner. This reversal was similar to that observed after treatment with the standard antidepressant imipramine. The mechanism behind asenapine's potential antidepressant activity is remains unclear. However, recent evidence suggesting that serotonin 5-HT_{2C} and 5-HT_7 receptors play a role in mediating the actions of antidepressant drugs, and the high affinity and selectivity of asenapine for both receptor subtypes, suggests that these novel targets may mediate, at least in part, the antidepressant actions of asenapine [27, 28] .

7. CLINICAL EFFICACY IN SCHIZOPHRENIA AND BIPOLAR DISORDER

Asenapine may be useful alternative treatment option in the management of schizophrenia and bipolar I disorder. It has shown efficacy in the treatment of schizophrenia and mixed or manic episodes associated with bipolar I disorder in

short- and long-term trials. Asenapine appears to be well tolerated. It has a low propensity for causing antimuscarinic adverse effects because of its lack of appreciable binding to muscarinic receptors. Its 'atypical' pharmacological profile (high $5HT_{2A}$:D_2 affinity ratio) also suggests a low risk of EPS-related adverse effects. Asenapine effects on prolactin and metabolic parameters are modest and it has a more favourable weight gain profile than olanzapine. It may therefore be a suitable treatment option in patients who are at increased risk of metabolic disturbances or diabetes or obese. Furthermore, it may also be a safer alternative in patients with impaired renal function because no dosage adjustments are required in these individuals (as is the case with risperidone and paliperidone). Asenapine's sublingual formulation may be an advantage in people with swallowing difficulties [7, 16, 17, 20, 29].

8. REGULATORY AFFAIRS

USA:

Asenapine is available in the name of "Saphris" in USA. It was approved by USFDA on Aug 13, 2009 for the acute treatment of schizophrenia as well as for the acute treatment of manic or mixed episodes associated with bipolar 1 disorder with or without psychotic features.

European Union:

It was approved by European Medicines Agency on Sep 01, 2010 and sold in the brand name "Sycrest". In contrary to other indication, it is only approved for the indicated for treatment of moderate to severe manic episodes associated with bipolar I disorder in adults.

9. CONCLUSION

Asenapine sublingual administration twice a day has shown clinical efficacy in reducing the symptoms of acute schizophrenia with the most robust effect on positive symptoms. Side effects and adverse reactions include somnolence, akathesia and oral hypoesthesia, but the drug is generally well tolerated and, importantly, seems to result in less clinically relevant weight gain than some other atypical antipsychotics. The disadvantage of sublingual route of administration is that patients cannot eat or drink for 10 min after ingestion. Given that asenapine is reported to have a bitter taste, strict compliance with the administration instructions may prove challenging for patients, especially as the drug has to be taken twice daily versus once-a-day dosing for most other antipsychotic. The twice-daily dosing requirement confers its own disadvantage independent of the sublingual administration, as increases in dosing frequencies seem to have a significant negative effect on schizophrenia patients' adherence to antipsychotic medication regimens. Apart from above issues, Asenapine sublingual tablets are a new option for the treatment of acute episodes of schizophrenia and for the treatment of acute manic or mixed episodes of bipolar I disorder.

10. REFERENCES

[1] W. Rossler, H.J. Salize, J. van Os, A. Riecher-Rossler, *Size of burden of schizophrenia and psychotic disorders*, Eur Neuropsychopharmacol, 15 (2005) 399-409.

[2] T.P. Gilmer, C.R. Dolder, J.P. Lacro, D.P. Folsom, L. Lindamer, P. Garcia, D.V. Jeste, *Adherence to treatment with antipsychotic medication and health care costs among Medicaid beneficiaries with schizophrenia*, Am J Psychiatry, 161 (2004) 692-699.

[3] J.A. Lieberman, T.S. Stroup, J.P. McEvoy, M.S. Swartz, R.A. Rosenheck, D.O. Perkins, R.S. Keefe, S.M. Davis, C.E. Davis, B.D. Lebowitz, J. Severe, J.K. Hsiao, *Effectiveness of antipsychotic drugs in patients with chronic schizophrenia*, N Engl J Med, 353 (2005) 1209-1223.

[4] M. Valenstein, F.C. Blow, L.A. Copeland, J.F. McCarthy, J.E. Zeber, L. Gillon, C.R. Bingham, T. Stavenger, *Poor antipsychotic adherence among patients with schizophrenia: medication and patient factors*, Schizophr Bull, 30 (2004) 255-264.

[5] G.D. Tollefson, T.M. Sanger, Y. Lu, M.E. Thieme, *Depressive signs and symptoms in schizophrenia: a prospective blinded trial of olanzapine and haloperidol*, Arch Gen Psychiatry, 55 (1998) 250-258.

[6] F.I. Tarazi, M. Shahid, *Asenapine maleate: a new drug for the treatment of schizophrenia and bipolar mania*, Drugs of today, 45 (2009) 865-876.

[7] A. Minassian, J.W. Young, *Evaluation of the clinical efficacy of asenapine in schizophrenia*, Expert opinion on pharmacotherapy, 11 (2010) 2107-2115.

[8] S. Label, SAPHRIS ®(asenapine) Sublingual tablets Initial U.S. Approval: 2009.

[9] J.A. Bartlett, K. van der Voort Maarschalk, *Understanding the oral mucosal absorption and*

resulting clinical pharmacokinetics of asenapine, AAPS PharmSciTech, 13 (2012) 1110-1115.

[10] EMA Asinapine assessment report (EMA/CHMP/583011/2010) [Accessed 20 January 2015].

[11] L. Citrome, *Asenapine review, part I: chemistry, receptor affinity profile, pharmacokinetics and metabolism*, Expert opinion on drug metabolism & toxicology, 10 (2014) 893-903.

[12] US Food and Drug Administration. Asenapine Drug Approval Package. (Pharmacology review) October 2, 2009, updated December 18, 2009. Available from: http://www. accessdata.fda.gov /drugsatfda_docs/nda/2009/022117s000TOC.cfm [Accessed 20 January 2015].

[13] M. George, R. Amrutheshwar, R.P. Rajkumar, S. Kattimani, S.A. Dkhar, *Newer antipsychotics and upcoming molecules for schizophrenia*, European journal of clinical pharmacology, 69 (2013) 1497-1509.

[14] Merck & Co., Inc. Sahphris (asenapine) sublingual tablets. Prescribing information, Available from: http://www.merck.com/product/usa/pi_circulars/s/saphris/saphris_pi.pdf [Accessed 19 January 2015].

[15] L. Citrome, *Asenapine review, part II: clinical efficacy, safety and tolerability*, Expert opinion on drug safety, 13 (2014) 803-830.

[16] L. Citrome, *Asenapine for schizophrenia and bipolar disorder: a review of the efficacy and safety profile for this newly approved sublingually absorbed second-generation antipsychotic*, International journal of clinical practice, 63 (2009) 1762-1784.

[17] S.C. Stoner, H.A. Pace, *Asenapine: a clinical review of a second-generation antipsychotic*, Clinical therapeutics, 34 (2012) 1023-1040.

[18] F.I. Tarazi, T. Moran-Gates, E.H. Wong, B. Henry, M. Shahid, *Differential regional and dose-related effects of asenapine on dopamine receptor subtypes*, Psychopharmacology, 198 (2008) 103-111.

[19] K. Fleming, S.G. Potkin, B. Binneman, D. Keller, L. Alphs, J. Panagides, P.3.c.073 *Effects of asenapine on cognitive function in acute schizophrenia: a placebo- and risperidone-controlled trial*, European Neuropsychopharmacology, 17, Supplement 4 (2007) S466-S467.

[20] D. Bishara, E. Whiskey, D. Taylor, *Asenapine: novel antipsychotic for treatment of bipolar I disorder*, Future Prescriber, 12 (2011) 5-9.

[21] F.I. Tarazi, S.M. Stahl, *Iloperidone, asenapine and lurasidone: a primer on their current status*, Expert opinion on pharmacotherapy, 13 (2012) 1911-1922.

[22] F.I. Tarazi, J.C. Neill, *The preclinical profile of asenapine: clinical relevance for the treatment of schizophrenia and bipolar mania*, Expert opinion on drug discovery, 8 (2013) 93-103.

[23] O. Franberg, C. Wiker, M.M. Marcus, A. Konradsson, K. Jardemark, B. Schilstrom, M. Shahid, E.H. Wong, T.H. Svensson, *Asenapine, a novel psychopharmacologic agent: preclinical evidence for clinical effects in schizophrenia*, Psychopharmacology, 196 (2008) 417-429.

[24] H.M. Marston, J.W. Young, F.D. Martin, K.A. Serpa, C.L. Moore, E.H. Wong, L. Gold, L.T. Meltzer, M.R. Azar, M.A. Geyer, M. Shahid, *Asenapine effects in animal models of psychosis and cognitive function*, Psychopharmacology, 206 (2009) 699-714.

[25] A.L. Auclair, M.S. Kleven, J. Besnard, R. Depoortere, A. Newman-Tancredi, *Actions of novel antipsychotic agents on apomorphine-induced PPI disruption: influence of combined serotonin 5-HT1A receptor activation and dopamine D2 receptor blockade*, Neuropsychopharmacology, 31 (2006) 1900-1909.

[26] S. Ahlenius, V. Hillegaart, *Involvement of extrapyramidal motor mechanisms in the suppression of locomotor activity by antipsychotic drugs: a comparison between the effects produced by pre- and post-synaptic inhibition of dopaminergic neurotransmission*, Pharmacology, biochemistry, and behavior, 24 (1986) 1409-1415.

[27] M. Papp, E. Moryl, P. Willner, *Pharmacological validation of the chronic mild stress model of depression*, European journal of pharmacology, 296 (1996) 129-136.

[28] M.J. Millan, *Serotonin 5-HT2C receptors as a target for the treatment of depressive and anxious states: focus on novel therapeutic strategies*, Therapie, 60 (2005) 441-460.

[29] R.S. McIntyre, R. Wong, *Asenapine: a synthesis of efficacy data in bipolar mania and schizophrenia*, Clinical schizophrenia & related psychoses, 5 (2012) 217-220.