

Asenapine, a new sublingual atypical antipsychotic

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INTRODUCTION

The common psychiatric disorders such as schizophrenia, bipolar disorder are very devastating, and antipsychotic drugs form the first line of treatment while psychotherapy plays an adjunctive role in promoting drug compliance, improving family relationships, etc.^[1] Chlorpromazine and haloperidol are classical antipsychotics (neuroleptics) that are efficacious against positive symptoms of schizophrenia. They have little effect on negative symptoms and produce elevation in serum prolactin which hinder their long-term use. Clozapine made a resurgence in 1989 which lead to a new group called 'atypical antipsychotics'. This group rapidly replaced the older antipsychotics as it had comparable efficacy and lesser incidence of extrapyramidal symptoms. But clozapine causes potentially fatal adverse effects such as agranulocytosis. This further led to the discovery of olanzapine, risperidone, quetiabine, etc. The last addition to this armamentarium was aripiprazole in 2004. Aripiprazole is proposed to have a novel mechanism of action as it alters the high and low affinity forms of dopamine D₂ receptors.^[2] Asenapine is the latest in this group that has received US FDA approval in August 2009.

MECHANISM OF ACTION

Asenapine is an antagonist at various dopaminergic (D₂, D₃ and D₄), serotonergic (5HT_{2A}, 5HT_{2B}, 5HT_{2C}, 5HT₆ and 5HT₇) and alpha adrenergic receptors (α_{1A} and α_2). It has an appreciably high affinity for 5HT_{2A} receptors than D₂ receptors. The inhibition constant (K_i) ratio for 5HT_{2A}/D₂ receptors is approximately 20.^[3] Antagonism of α_2 adrenoceptors is said to improve the negative symptoms and cognitive function in schizophrenia. As asenapine blocks α_2 receptors, it has the potential to offer these benefits. The antagonistic activity at α_1 adrenoceptor accounts for the orthostatic hypotension caused by the drug.^[4]

Asenapine has no activity at muscarinic receptors in the therapeutic dose range. So asenapine does not cause any anticholinergic adverse effects and metabolic syndrome, which is seen with other atypical antipsychotics such as olanzapine and clozapine. It is also an antagonist at histamine H₁ receptors and hence causes sedation. By its activity at H₁ receptors, it was predicted to cause weight gain and has also done so in clinical trials.^[4]

PHARMACOKINETICS

Asenapine has a high hepatic first pass metabolism and its oral bioavailability is <2%. So it was initially investigated for intravenous route, but later it was successfully formulated as a sublingual fast dissolving tablet. Food and water intake immediately after a sublingual dose can affect the bioavailability, since food intake can increase the hepatic blood flow leading to increased clearance of asenapine by liver. Hence eating and drinking should be avoided for 10 minutes after its sublingual administration.^[5]

Asenapine is primarily metabolized by CYP1A2 and to a lesser extent by CYP3A4 and CYP2D6. Asenapine itself is active and its metabolism in liver yields nearly 38 metabolites. These do not have any significant effect (both beneficial and adverse) as they have very low affinity for receptors and do not cross blood brain barrier.^[4] Asenapine has a high plasma protein binding (95%).

CLINICAL TRIALS

The efficacy and safety of asenapine in schizophrenia and bipolar disorders is evaluated by many clinical trials. Among these only a very few are published in peer reviewed journals.

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The details of the other clinical trials can be obtained from <http://www.clinicaltrials.gov>. To date, all the clinical trials done with asenapine are conducted by the manufacturer and there are no independent clinical trials.^[4]

The approval by US FDA is based on four pivotal clinical trials for efficacy. Asenapine 5 mg, sublingually twice daily was compared with placebo and risperidone (3 mg bd) in a six week double blind randomized trial involving 174 schizophrenia patients. The total score by the positive and negative syndrome scale (PANSS) was the primary efficacy parameter. Asenapine showed a statistically significant efficacy from second week onwards when compared to placebo.^[6] Short term clinical trials conducted in bipolar disorder patients have also shown that the efficacy of asenapine is statistically significant compared to placebo. Clinical trials designed for a head-to-head comparison with other atypical antipsychotics in schizophrenia and bipolar disorders are lacking.

ADVERSE EFFECTS

The most common adverse effect associated with asenapine is somnolence.^[4] The other common adverse effect is orthostatic hypotension and the patient should be instructed to follow non-pharmacological measures like sitting on the bed for sometime before getting up and getting up slowly from chair to avoid this adverse effect. Asenapine has a more favorable weight gain profile than the other atypical antipsychotics such as olanzepine. It has less propensity to cause metabolic syndrome.^[6] Asenapine has a mild effect on QT_c prolongation which is comparable with quetiapine. The long term safety is not yet established for this drug. Effects at toxic doses are also not yet known. Oral hypoesthesia is a peculiar adverse effect of asenapine.^[4]

CURRENT STATUS

Asenapine was approved in August 2009 by US FDA for the acute treatment of schizophrenia and manic episodes of bipolar disorders. It is formulated as sublingual tablets in two strengths (5 and 10 mg). It is not yet available in India.

ADVANTAGES AND DISADVANTAGES

The incidence of extrapyramidal symptoms is comparable with other atypical antipsychotics. It has a favourable weight gain profile and less propensity to cause metabolic disturbance. It is predicted from animal studies to be effective in treatment resistant cases^[7] but clinical trials are lacking. It is formulated as a sublingual tablet and it is difficult to administer drugs by this route in a patient with schizophrenia or mania.

CONCLUSION

Asenapine is an atypical antipsychotic with antagonistic activity at dopaminergic, serotonergic and adrenergic receptors. It is recently approved by US FDA for acute treatment of schizophrenia and manic episodes of bipolar disorders. It has a lesser propensity to cause metabolic disturbances and weight gain. At this point of time, as there are no independent trials for a head-to-head comparison with other atypical antipsychotics, asenapine appears like a “me-too” atypical antipsychotic. It is predicted from animal studies to be effective in treatment resistant cases and if this is proved in trials, then this drug anchor its own place in the treatment of schizophrenia. Presently, as long term safety is not yet established, clinicians are advised to use this drug cautiously.

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