Asenapine: A Clinical Overview

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Asenapine is a new, second-generation (atypical) antipsychotic medication with demonstrated efficacy for the acute and maintenance treatment of schizophrenia. It is administered as sublingual tablets in doses of 5 or 10 mg bid. It is well tolerated, with a dropout rate for adverse events similar to that of placebo. Asenapine is associated with a mean weight gain of less than 1 kg over a year and a relatively neutral effect on lipid and glucose levels. It can cause sedation and mild extrapyramidal side effects. Asenapine has a broad receptor affinity profile for most serotonergic, dopaminergic, and adrenergic receptors, with no appreciable affinity for muscarinic receptors. Asenapine may be a helpful treatment option for patients with schizophrenia when weight gain, dyslipidemia, and endocrine abnormalities are a concern.

(J Clin Psychiatry 2011;72[suppl 1]:14–18)

OVERVIEW OF DEVELOPMENT

Asenapine is a second-generation (atypical) antipsychotic indicated for acute and maintenance treatment of schizophrenia and acute treatment of bipolar disorder in adults.[1] It is administered as a sublingual formulation. Asenapine was first developed, through phase 3 trials, by Organon International. Its New Drug Application was submitted to the US Food and Drug Administration (FDA) by Schering-Plough in November 2007 after Schering-Plough merged with Organon, and it was approved for marketing in August 2009. Asenapine is marketed in the United States by Merck & Co, Inc, as Saphris.

PHARMACOLOGIC PROFILE

Asenapine is a tetracyclic of the dibenzo[2,3:6,7] oxepino[4,5-*c*]pyrrole class with many similarities to the tetracyclic antidepressant mirtazapine. Although its mechanism of action is unknown, it is hypothesized that its efficacy in schizophrenia is primarily mediated through a combination of antagonist activity at D_2 and 5-HT_{2A} receptors.[1]

Pharmacokinetics

Following sublingual administration, peak plasma concentrations occur in 0.5–1.5 hours, with a mean terminal half-life of approximately 24 hours.[1] The absolute bioavailability of 5 mg of sublingual asenapine is 35%, but < 2% when an oral tablet is swallowed. Intake of water 2 minutes after sublingual administration decreases absorption from 35% to 28%; intake of water 5 minutes after sublingual administration decreases absorption from 35% to 31%. The labeling recommends patients avoid eating and drinking for 10 minutes after tablet administration to maximize absorption.[1]

Asenapine is cleared primarily through direct glucuronidation by UGT1A4 and oxidative metabolism by cytochrome P450 isoenzymes (predominantly CYP1A2). Dose adjustments may be needed when fluvoxamine, a CYP1A2 inhibitor, is coadministered, because rather low doses of fluvoxamine may greatly increase asenapine exposure. However, no dosage adjustment is required for smoking. No dose adjustments are required for coadministration of CYP2D6 inhibitors (eg, paroxetine) or inhibitors or inducers of CYP3A4 (eg, imipramine, cimetidine, carbamazepine). Asenapine may enhance the inhibitory effects of paroxetine (a CYP2D6 substrate and inhibitor) on its own metabolism so that caution should be exercised in coadministering asenapine with drugs that are both substrates and inhibitors for CYP2D6. Surprisingly, although valproate is a UGT1A4 inhibitor, a study found no asenapine dose adjustment was needed when these agents are coadministered.[1]

Pharmacodynamics

Asenapine has high affinity for many receptors, with greater affinity for serotonin 5-HT_{2A}, 5-HT_{2C}, 5-HT_6, and 5-HT_7; dopamine D_3 and D_4; and α_1- and α_2-adrenergic receptors than for dopamine D_2 receptors. It has approximately the same affinity for D_1 and 5-HT_{1A} receptors. It has the highest affinity for 5-HT_{2C} receptors of all currently available antipsychotic medications. It has moderate affinity for histamine H_2 receptors and somewhat higher affinity for histamine H_1 receptors but no appreciable affinity for muscarinic cholinergic M_1 receptors.[1] Therefore, asenapine would be expected to have strong serotonergic, dopaminergic, and adrenergic effects but no anticholinergic effects.

The serotonin receptor 5-HT_{2A} has been associated with antipsychotic effects, while the 5-HT_6 and 5-HT_7 receptors as well as the α-adrenergic receptors have putative effects on neurocognition. Given asenapine's affinity for H_1, some sedation may be expected. On the basis of asenapine's substantial affinity for H_1 and 5-HT_{2C} receptors, considerable weight gain would also be expected, but data on clinical outcomes (reviewed in the Safety and Tolerability section) do not support this receptor-based prediction.

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Figure 1. Asenapine vs Risperidone vs Placebo Change From Baseline to Day 42 in Total Score on the Positive and Negative Syndrome Scale[a,b]
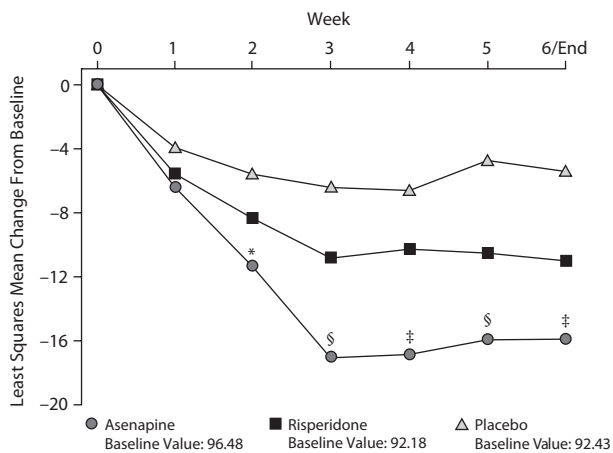
[a]Adapted with permission from Potkin et al.[2]

[b]The change from baseline in the total score on the Positive and Negative Syndrome Scale (PANSS) was determined at study end (6 weeks) or at the end of treatment with last observed data carried forward, using least squares mean (LSM) and 2-factor analysis of variance.

*$P < .05$, asenapine versus placebo.

‡$P \le .005$, asenapine versus placebo.

§$P = .001$, asenapine versus placebo.

EFFICACY

Short-Term Trials

Asenapine was approved by the FDA for treatment of schizophrenia in adults based on three 6-week, randomized, double-blind, placebo- and active-controlled trials in patients with acute exacerbations of schizophrenia. The primary outcome measure was improvement from baseline on the Positive and Negative Syndrome Scale (PANSS) total score. Secondary outcomes included changes in Clinical Global Impressions-Severity of Illness (CGI-S) scores and PANSS positive, negative, and general psychopathology subscale scores. Inclusion criteria specified patients with an acute exacerbation of schizophrenia, a PANSS score ≥ 60, and moderate levels of symptomatology on at least 2 of the positive subscale items (eg, hallucinations, delusions). Patients with substance abuse were excluded. The mean PANSS score in participants was greater than 90, indicating a moderately severe to severe level of symptomatology.

The first study compared asenapine 5 mg bid with placebo and risperidone 3 mg bid in 174 patients.[2] Dropout rates for lack of efficacy were 29% for placebo, 15% for asenapine, and 27% for risperidone. Asenapine separated from placebo on PANSS total score ($P < .005$) and on the positive ($P = .01$), negative ($P = .01$), and general psychopathology ($P < .005$) subscales (Figure 1). Risperidone did not separate from placebo on total PANSS or on the negative subscale score, but did separate on the PANSS positive subscale ($P < .05$).

The second study compared asenapine 5 mg and 10 mg bid with placebo and haloperidol 4 mg bid in 448 patients.[3] Dropout rates for lack of efficacy were 18% for placebo, 11% for asenapine 5 mg bid, 8% for asenapine 10 mg bid,

Figure 2. Asenapine vs Haloperidol vs Placebo Change in Total Score on the Positive and Negative Syndrome Scale (PANSS) at Day 42 (Mean ± SE; last observation carried forward)[a]
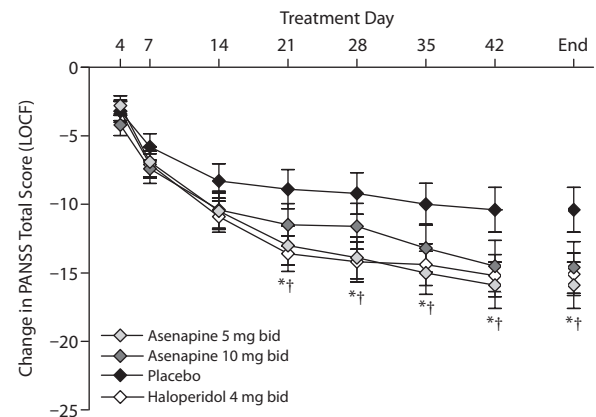
[a]Adapted with permission from Kane et al.[3]

*$P < .05$, asenapine at 5 mg bid vs placebo.

†$P < .05$, haloperidol at 4 mg bid vs placebo.

and 4% for haloperidol. Asenapine 5 mg bid showed consistent positive effects on all outcome measures compared with placebo (Figure 2). The 10-mg bid dose failed to reach statistical significance on a number of outcomes, although it did separate statistically from placebo on the positive symptom subscale. Haloperidol separated from placebo on total PANSS score and on the positive and general psychopathology subscales.

In the third study, asenapine 5 and 10 mg bid both failed to separate from placebo, while the comparator drug, olanzapine 15 mg/d, did separate.[4] The placebo response rate (30% decrease in PANSS total score) was 5.3% in the first study and more than twice that in the second (10.7%) and third (11.1%) studies. In contrast, mean decreases in PANSS scores with asenapine 5 mg bid were similar across the studies: 15.9 in the first study,[2] 16.2 in the second study,[3] and 14.5 in the third study.[4]

Longer-Term Trials

Maintenance treatment. The long-term efficacy of asenapine in preventing relapse in schizophrenia was assessed in a 26-week double-blind, placebo-controlled trial that followed 26 weeks of open-label treatment.[5] Approximately 700 stable patients with schizophrenia were cross-titrated from previous medication to open-label treatment with asenapine 5 or 10 mg bid based on tolerability. After 26 weeks, slightly more than half (n = 386) met predefined criteria for stability and were randomized to 26 weeks of double-blind treatment either continuing with asenapine or switching to placebo. The primary outcome measure was time to relapse or impending relapse during double-blind treatment based on prespecified rating-scale criteria or investigator's judgment. Times to relapse/impending relapse and discontinuation for any reason were significantly longer with asenapine than placebo ($P < .0001$ for both) and incidence of relapse/

impending relapse was lower with asenapine than placebo (12.1% vs 47.4%, $P < .0001$).

Negative symptoms. Although the first acute study provided some evidence that asenapine was effective in reducing negative symptoms,[2] further studies were needed because of the difficulty of studying negative symptoms in acute trials given their short length and challenges in determining whether improvements in social functioning, for example, are due to reductions in positive or negative symptoms (eg, social withdrawal can be a negative symptom or can be due to paranoia). Two double-blind, flexible-dose sister studies, which were designed to evaluate effects on negative symptoms, compared asenapine (5–10 mg bid) with olanzapine (5–20 mg/d) over a 26-week core study with a 26-week extension. Patients were required to have a diagnosis of schizophrenia with predominant negative symptoms present for at least 5 months before the study and prospectively established for at least 1 month between screening and baseline.[6] Patients could have positive symptoms if less severe than the negative symptoms. Patients with extrapyramidal symptoms (EPS) or depression were excluded because these symptoms can be confused with negative symptoms.

The primary outcome was change on the Negative Symptom Assessment (NSA-16), a scale specifically designed to measure negative symptoms, from baseline to week 26 and from week 26 to 52.[7] Although no differences between groups were found at week 26 for combined data, asenapine separated from olanzapine during the extension phase, showing greater efficacy for negative symptoms at the end of the 52-week study. More patients, however, dropped out of treatment in the asenapine group than the olanzapine group.[8] Patients receiving asenapine tended to lose weight, while those taking olanzapine gained a mean of just under 10 pounds over 52 weeks.

SAFETY AND TOLERABILITY

Overview of Adverse Effect Profile

Changes in weight. Given concern about weight gain with atypical antipsychotics and the high affinity of asenapine for H_1 histamine and 5-HT_{2C} receptors, changes in weight were carefully monitored in the clinical trials, with results showing a favorable profile. In the short-term studies, 4.9% of patients receiving asenapine showed an increase in body weight of 7% or more compared with 2% of patients taking placebo, with a mean weight gain of 1.1 kg with asenapine compared with 0.1 kg with placebo.[1–3] A long-term safety/tolerability study found low mean weight gain of 0.9 kg with asenapine (observed case analysis), with 14.7% of patients showing an increase in body weight of 7% or more over the 52 weeks of the study.[9] During the second 6-month phase of the relapse prevention study, only 3.7% of those taking asenapine and 0.5% of those taking placebo showed an increase in body weight of 7% or more.[5] These studies suggest that weight gain with asenapine is modest and that, when it occurs, it is relatively early in treatment and is not progressive. The favorable weight gain profile seen in both short- and long-term

trials contrasts with the predictions based on asenapine's high 5-HT_{2C} and H_1 receptor affinity.

Extrapyramidal symptoms. In short-term trials, scores on 3 extrapyramidal rating scales[10–12] showed mean changes from baseline comparable to placebo with asenapine 5 mg and 10 mg bid. The percentage of patients reporting EPS-related events, excluding akathisia, was 7% for placebo, 9% for asenapine 5 mg bid, and 12% for asenapine 10 mg bid; rates of akathisia reported were 3% with placebo and 4% and 11% with asenapine 5 and 10 mg bid, respectively.[1] Parkinsonism and akathisia were dose related with the 5-mg bid rate similar to the placebo rate.[1]

Glucose and lipid levels. No clinically relevant mean changes in glucose and lipid levels were found in the short- and long-term trials. In the short-term trials, rates of elevated fasting glucose (≥ 126 mg/dL) were 7.4% with asenapine and 6% with placebo, rates of elevated total fasting cholesterol (≥ 240 mg/dL) were 8.3% with asenapine and 7.0% with placebo, and rates of elevated triglycerides (≥ 200 mg/dL) were 13.2% with asenapine and 10.5% with placebo.[1–3] In the 52-week safety/tolerability trial, patients receiving asenapine showed a mean increase from baseline in fasting glucose levels of 2.4 mg/dL, a medically nonsignificant change, and a mean decrease from baseline in total fasting cholesterol of 6 mg/dL and in fasting triglycerides of 9.8 mg/dL.[1,9] The lipid decreases were most likely due in part to reductions from elevations caused by previous medications.

Orthostatic hypotension. Despite asenapine's relatively high affinity for α_1-adrenergic receptors, it does not appear to be associated with syncope. Orthostatic hypotension occurred at less than 2%, and dizziness was not dose related (4% for placebo, 7% for asenapine 5 mg bid, 3% for asenapine 10 mg bid).[1] No titration is generally required even to the 10-mg bid dose.

QTc interval. There was no evidence of significantly prolonged QTc intervals (mean increase was 2–5 milliseconds, with no patient experiencing an increase ≥ 60 milliseconds from baseline QTc or a QTc ≥ 500 milliseconds).[1]

Prolactin levels. Short-term trials showed no clinically relevant changes in mean prolactin levels from baseline (mean decrease was 6.5 ng/mL with asenapine and 10.7 ng/mL with placebo).[1] In the 52-week safety/tolerability trial, patients receiving asenapine showed a mean decrease from baseline in prolactin of 26.9 ng/mL.[9] These changes may reflect previous treatment with prolactin-elevating medications.

Tolerability. Short-term studies[1] had discontinuation rates due to adverse effects of 9% with asenapine and 10% with placebo, reflecting good tolerability.[1] Hypersensitivity reactions, some serious, including anaphylaxis, angioedema, swollen tongue, wheezing, and rash, noted in the development program, have also been observed postmarketing, leading to a drug safety communication.[13] Patients developing such symptoms should not be reexposed to asenapine.

Adverse Events in Short-Term Clinical Trials

The most commonly reported adverse events in the short-term trials[1] were somnolence (13% for asenapine, 7% for

Table 1. Spontaneously Reported Adverse Events in Short-Term Trials of Asenapine for the Acute Treatment of Schizophrenia With Incidence ≥ 5% and 2-Fold Greater Than Placebo[a]

Adverse Event	Placebo Rate[b]	Asenapine 5 mg bid		Asenapine 10 mg bid	
		Rate[b]	NNH[c]	Rate[b]	NNH[c]
Oral hypoesthesia	1%	6%	20	7%	17
Akathisia	3%	4%	100	11%	13
Somnolence	7%	15%	13	13%	17

[a]Adverse event rates from Saphris prescribing information.[1]
[b]Percentage of patients reporting reaction.
[c]Number needed to harm (NNH) for asenapine versus placebo. NNH is used to denote how many patients one would need to treat with 1 intervention versus another in order to encounter 1 additional adverse outcome.[14] The higher the NNH, the less likely that the event will be encountered with asenapine versus the comparator, in this case placebo.

placebo), akathisia (6% for asenapine, 3% for placebo), and oral hypoesthesia (numbing of the tongue, 5% for asenapine, 1% for placebo), a side effect related to the drug's sublingual administration (Table 1). There does not appear to be a dose-response relationship for somnolence or oral hypoesthesia, but there appears to be a clear dose-response relationship for akathisia, with some suggestion of a dose effect for EPS excluding akathisia (7% for placebo, 9% for asenapine 5 mg bid, 12% for asenapine 10 mg bid[1]). Weight gain as a reported adverse event does not appear to be dose related (< 1% for placebo, 2% for 5 and 10 mg bid asenapine[1]). Seizure rates with asenapine were extremely low.[1]

Long-Term Health Effects

The availability of effective antipsychotics with low weight gain liability and favorable metabolic profiles is very important, since cardiovascular disease is the leading cause of death in patients with schizophrenia. The lifespan of patients with schizophrenia is on average 20%–25% shorter than that of those without schizophrenia.[15] Substantial evidence indicates that the very large majority of patients with schizophrenia require long-term continued antipsychotic treatment; therefore, the axiom of "doing no harm" is relevant.

CLINICAL GUIDANCE

In acute-phase schizophrenia studies, asenapine 5 mg bid was at least as effective as 10 mg bid and had fewer side effects. Doses higher than 10 mg bid have not been evaluated clinically. No dosage adjustment appears to be required for age, gender, or race or for patients with renal impairment or mild or moderate hepatic impairment. Asenapine is not recommended for patients with severe hepatic impairment. Patients in the maintenance study[5] continued treatment with both 5 and 10 mg bid. The kinetics of asenapine are not linear so that 10 mg bid produces blood concentrations approximately 1.7 times that of a 5-mg bid dose. Individual patients may do well on either 5 or 10 mg bid or perhaps an intermediate dose of 15 mg/d (eg, 5 mg in the morning and 10 mg at night when more sedation may be an advantage).

Sedation tends to occur early in the course of treatment and most but not all patients develop tolerance to it.

Asenapine is administered as a sublingual tablet that dissolves in the saliva within seconds of being placed under the tongue. It is absorbed through the oral mucosa with a T_{max} of approximately an hour, so that it is not completely absorbed immediately from the saliva. Sublingual administration is used to avoid first-pass hepatic metabolism, leading to predictable and stable plasma concentrations. When asenapine tablets are swallowed, bioavailability is less than 2% compared with approximately 35% for sublingual administration.[1] Thus, "overdose" by swallowing asenapine tablets is unlikely to have medical consequences. The tablets should not be chewed or swallowed or handled with wet fingers.

The prescribing information notes that "eating and drinking should be avoided for 10 minutes after administration."[1] This caution is based on studies showing bioavailability without water or food of 34% at 10 minutes and 30 minutes with no advantage in waiting more than 10 minutes.[1] However, bioavailability was 31% at 5 minutes and 28% at 2 minutes, so there is only a 6% difference in bioavailability when the patient drinks or eats after 2 minutes compared with 10 minutes.[1]

Oral hypoesthesia, related to the sublingual administration of asenapine, was reported in 5% of patients in short-term trials,[1] although this effect appears more frequent in postmarketing experience. Patients also mention a sort of bitterness or dysgeusia, although discontinuation rates for oral hypoesthesia or dysgeusia were just a fraction of 1%.[1] Oral hypoesthesia and dysgeusia can be an issue for some patients, and tolerance to these side effects typically does not develop. The area of hypoesthesia appears to be about the size of a dime or quarter and usually lasts about 10 minutes but can persist for up to half an hour. A black cherry formulation of asenapine is available, which is a preferred option for many patients. It is very helpful if the patient takes the first dose in the physician's presence so that he or she can give instructions (eg, how to open the packaging, not to handle the tablet with wet fingers or crush or chew it), describe potential taste and hypoesthesia effects, and observe if they occur. Preempting possible unusual side effects helps build the patient alliance and increases compliance.

CONCLUSION

Asenapine is a new antipsychotic with demonstrated efficacy for acute exacerbation of schizophrenia and maintenance treatment of schizophrenia in adults. It is well tolerated, with a dropout rate for adverse events similar to that for placebo. Some data suggest that asenapine may also be efficacious for negative symptoms in patients with schizophrenia, including patients with predominant negative symptoms. Asenapine has a favorable profile in terms of weight gain (mean increase < 1 kg in a year-long study,[9] although some patients did gain more), a generally neutral effect on lipids, and only very mild elevation of prolactin levels. However, it is associated with some sedation, mild parkinsonism, and akathisia. Given its

indication for maintenance therapy, asenapine could be a treatment option for continued treatment of responding patients, especially when weight gain, dyslipidemia, and endocrine abnormalities are a concern.

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