

Asenapine: an atypical antipsychotic with atypical formulations

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Abstract: Asenapine is a second-generation (atypical) antipsychotic medication not available in a pill that can be swallowed; rather, it is commercialized in sublingual and transdermal formulations. This is a consequence of extensive first-pass metabolism if ingested. The sublingual formulation is approved in many jurisdictions for the treatment of schizophrenia and manic or mixed episodes associated with bipolar I disorder and is available generically. The efficacy profile is well characterized in a number of clinical trials, including an off-label use for the management of agitation. Obstacles to its use include food and drink restrictions, twice-daily dosing and adverse effects such as dysgeusia (distorted, altered, or unpleasant taste) and oral hypoesthesia (numbness). Transdermal asenapine was approved by the US Food and Drug Administration in 2019 for the treatment of schizophrenia in adults. Efficacy was established in a registrational study examining acutely ill inpatients with schizophrenia. The patch needs to be changed once daily. Obstacles to its use include the potential for skin reactions such as erythema and pruritis, and being a branded product, it is more costly than other options. This is a narrative review of the chemistry and pharmacokinetics/pharmacodynamics of asenapine, as well as summarizing the efficacy and tolerability of both sublingual and transdermal asenapine, and its possible place in treatment.

Keywords: antipsychotic, asenapine, bipolar, psychopharmacology, schizophrenia, sublingual, transdermal

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Introduction

Asenapine is a second-generation (atypical) antipsychotic (SGA) medication with two formulations that differ from other available antipsychotics, a sublingual tablet and a transdermal ‘patch.’ Asenapine, under the name ORG 5222, was first introduced into the scientific literature in 1990 as a potential antipsychotic and anxiolytic agent.¹ High first-pass metabolism limited the use of ORG 5222 as an oral agent, leading to the subsequent development and research of ORG 5222 in a sublingual form.² Asenapine, as a sublingual tablet, first gained US Food and Drug Administration (FDA) approval in 2009 in the treatment of acute schizophrenia and acute mixed and manic episodes of bipolar I disorder. It was subsequently approved for the maintenance treatment of schizophrenia, as adjunctive therapy with lithium or valproate in the treatment of acute mixed or manic

episodes of bipolar I disorder, and as monotherapy in the treatment of bipolar I disorder in the pediatric population.³ In 2019, the FDA approved a second formulation of asenapine, the transdermal patch, for the treatment of schizophrenia.⁴

This article will summarize the pharmacokinetics, safety and efficacy of both sublingual and transdermal asenapine and will provide information about the potential uses and limitations in treatment for these ‘atypical’ formulations.

Methods

A literature search was conducted on 14 December 2020 using the US National Library of Medicine’s PubMed.gov database (<https://www.ncbi.nlm.nih.gov/pubmed/>) using the word ‘asenapine’. Only full-text articles written in the English language

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with available abstracts were considered, and there were no other filters. The search yielded a total of 386 results. The results were reviewed by the authors for information regarding asenapine's efficacy or tolerability profile. Additional citations were identified by examining reference lists and supplemented by an archive of additional papers, book chapters, posters, and publicly available regulatory documents maintained by one of the authors (LC). Anecdotal case reports or case series were excluded from further consideration, as were *post hoc* analyses or clinical trials where the number of subjects were less than 10. No other databases (Embase, Web of Science, etc.) were queried for the purposes of this narrative review.

Chemistry

Asenapine belongs to the chemical class of dibenzoxepino pyrroles and acts antagonistically at a number of receptors, and this combination of receptor-binding affinities differs from other available antipsychotics.⁵ Asenapine has high affinity (K_i , expressed in nmol/l) for several 5-hydroxytryptamine (5-HT)-receptor subtypes, including 5-HT_{2C} (0.03), 5-HT_{2A} (0.07), 5-HT₇ (0.11), 5-HT_{2B} (0.18), and 5-HT₆ (0.25). Asenapine also has high affinity for several dopamine receptor subtypes, including D₄ (1.1) D_{2L} (1.3), D_{2S} (1.4), D₁ (1.4), and D₃ (0.42); norepinephrine α_{1A} (1.2), α_{2A} (1.2), α_{2C} (1.2) and α_{2B} (0.33) receptors, and histaminic H₁ (1.0) receptors.⁶

Asenapine exhibits dose-dependent D₂-receptor occupancy, with correlation between asenapine plasma concentration and D₂-receptor occupancy. A sublingual dose of 4.8 mg twice-daily results in a mean D₂ receptor occupancy of 79% 3–6 h after dosing.²

Formulations

Sublingual

Sublingual asenapine is currently available in two forms: the original unflavored formulation, and a black-cherry-flavored formulation. The instructions for sublingual asenapine advise that the medication should be placed under the tongue, and allowed to dissolve. Once placed in the mouth, the tablet dissolves within 10 s, and anecdotally, almost immediately.⁷

The recommended dosage of asenapine for acute schizophrenia in adults is 5 mg twice daily (BID),

based on the outcomes of the pivotal clinical trials that led to regulatory approval. However, 10 mg BID is commonly used, and was the modal dose in the double-blind maintenance trial. For monotherapy in bipolar manic or mixed episodes, the recommended dose is 10 mg BID, and when used adjunctively with lithium or valproate, the recommended dose is 5 mg BID. In the pediatric population with bipolar mania, the recommended dosage of asenapine is 2.5 mg BID, and can be increased up to 10 mg BID.³ Sublingual asenapine is now available generically.

Transdermal

In 2019, transdermal asenapine was approved by the FDA for treatment of schizophrenia and is the first antipsychotic patch to be approved in the US. The asenapine transdermal system is applied every 24 h. The recommended starting dose is 3.8 mg/24 h but can be increased to doses of 5.7 mg/24 h or 7.6 mg/24 h, as needed, after 1 week. Application sites include the upper arm, upper back, abdomen, or hip. The patch needs to be placed at a different application site every day.⁸

Pharmacokinetics and metabolism

Asenapine is metabolized hepatically by direct glucuronidation by the enzyme UGT1A4 and through oxidative metabolism by cytochrome P450 isoenzymes, particularly CYP1A2.³ First-pass metabolism of asenapine is >95%, requiring the availability of non-traditional routes of administration, as described below.⁷

Sublingual

The sublingual formulation of asenapine allows the drug to bypass first-pass metabolism and demonstrates a bioavailability of approximately 35%. If swallowed, the bioavailability of asenapine is reduced to <2%, rendering that route of administration unfeasible.^{7,8} Peak plasma levels occur 30–90 min following administration of sublingual asenapine, and the half-life is approximately 24 h.³

Although it is recommended that sublingual asenapine be placed under the tongue, one study found that asenapine exposure with buccal administration was 25% higher when compared with sublingual exposure, and that supralingual exposure was comparable with sublingual exposure.⁹

In a study examining the impact of meal timing on sublingual asenapine exposure, there was a transient 2.5-fold increase in asenapine clearance after eating a high-fat meal, thought to be caused by a transient increase in liver bloodflow after eating. The net effects on asenapine exposure, however, were noted to be small and not clinically relevant.¹⁰ However, because drinking water close in time after sublingual asenapine administration has been shown to reduce bioavailability, patients are instructed to not eat or drink 10 min following asenapine administration.⁸

Transdermal

Pharmacokinetics of transdermal asenapine have been studied by applying the transdermal patch on subjects and examining serial blood samples for asenapine concentration. After administration of a single 1.9 mg/24 h patch, asenapine concentration increases gradually and achieves a sustained maximum concentration between 12 h and 24 h. This is in contrast to the rapid absorption of sublingual asenapine, which demonstrates a t_{max} of 1.25 h. Slower, sustained absorption, along with lower peak-to-trough fluctuations in concentration, as compared with equivalent doses of sublingual asenapine has also been shown for the asenapine transdermal patch at higher doses (Table 1). By examining area under the curve (AUC) values, a transdermal dose of 3.8 mg/24 h is equivalent to a sublingual asenapine dose of 5 mg BID. Transdermal asenapine at a dose of 7.6 mg/24 h is equivalent to a sublingual asenapine dose of 10 mg BID (Table 1).¹¹

For transdermal asenapine, application-site location did not impact pharmacokinetic parameters. Special considerations for the patch include that it should not be placed over broken skin, and direct application of heat, such as from a heating pad, increases plasma concentrations of asenapine. Environmental heat is not known to affect absorption rate.¹¹

Special populations

Asenapine is not recommended in patients with severe hepatic impairment (Child-Pugh class C) because asenapine concentrations are seven times higher in this population than in patients with normal hepatic function. Individuals with mild and moderate hepatic impairment can use asenapine without dose adjustment. No dose adjustment is necessary for individuals with renal impairment.³

No known studies have been conducted evaluating the use of asenapine in pregnancy or breastfeeding.¹³

Because asenapine is metabolized by CYP1A2, caution should be used when using asenapine with CYP1A2 inducers and inhibitors. Although the polyaromatic compounds found in cigarette smoke can induce CYP1A2, in a study of healthy male subjects, smoking was not shown to significantly impact asenapine pharmacokinetics. However, the antidepressant medication fluvoxamine is a potent CYP1A2 inhibitor and can increase asenapine levels by 29% and therefore this combination should be used cautiously.³

Efficacy

Schizophrenia

Acute short-term studies (Table 2). Four 6-week, randomized, double-blind, placebo- and active comparator-controlled multicenter studies were conducted to assess asenapine's efficacy in treating acute exacerbations of schizophrenia using the approved dosing range of 5–10 mg BID.^{2,14,15} Two of these trials demonstrated asenapine's efficacy.^{14,15} In the first positive trial, 182 patients with acute schizophrenia were randomly assigned to receive asenapine, risperidone, or placebo. At the endpoint of 6 weeks, the mean change in Positive and Negative Syndrome Scale (PANSS) total score was significantly greater in the asenapine (5 mg BID)-treated group compared with the placebo group, whereas the mean change in PANSS total score in the risperidone-treated group was not significantly different compared with the placebo group, which is unusual for an active control used to assure assay sensitivity.^{14,16}

In the second positive study, 458 patients with acute schizophrenia were randomly assigned to one of two fixed doses of asenapine, placebo or haloperidol. Asenapine 5 mg BID and haloperidol were both superior to placebo in showing a greater change from baseline (CFB) PANSS total score. Asenapine 10 mg BID did not demonstrate a statistically significant advantage over placebo, which the authors hypothesized may have been due to the high placebo response rate in that trial.¹⁵

Of the two remaining trials, one was considered a negative study and the other a failed study. In the negative study, 417 patients with acute schizophrenia were randomized to receive asenapine at

Table 1. Pharmacokinetics of asenapine: a comparison of sublingual and transdermal formulations.

	Sublingual asenapine	Transdermal asenapine
AUC ₀₋₂₄ (ng h/ml) ¹¹	5 mg BID–53.2*	3.8 mg/24 h–45.8
	10 mg BID–86.8*	5.7 mg/24 h–69.3
		7.6 mg/24 h–96.2
C _{max} (in ng/ml) ¹¹	5 mg BID–4.23	3.8 mg/24 h–2.26
	10 mg BID–6.56	5.7 mg/24 h–3.4
		7.6 mg/24 h–4.68
T _{max} (in h) ¹¹	5 mg BID–1.75	3.8 mg/24 h–16
	10 mg BID–1.96	5.7 mg/24 h–14
		7.6 mg/24 h–12
T _{1/2} ¹¹	17.7 h (after single 5 mg dose)	33.9 h (asenapine 1.9 mg/24 h patch)
Peak-to-trough ratio of asenapine concentration at steady state	~3 ¹²	1.5 ¹¹
Impact of location of medication placement on asenapine pharmacokinetics	Swallowing asenapine reduces bioavailability to <2%; ⁸ asenapine exposure with buccal administration is 25% higher when compared with sublingual administration; supralingual administration results in similar asenapine exposure as sublingual administration ⁹	Application-site location does not impact pharmacokinetic parameters ¹¹
Impact of eating or drinking at the time of medication administration	Drinking close in time to asenapine administration can reduce bioavailability. ⁸	NA
Impact of direct heat (i.e. heating pad) on asenapine pharmacokinetics	NA	Direct heat (i.e. heating pad) can increase the absorption rate from the patch. ¹¹
*Mean AUC ₀₋₂₄ for sublingual asenapine calculated as double the reported mean AUC ₀₋₁₂ for comparison purposes. AUC, area under the receiver operating curve; BID, twice daily; C _{max} , maximum concentration observed; NA, not applicable; T _{1/2} , half-life; T _{max} , time of maximum time observed.		

doses of 5 mg BID or 10 mg BID, placebo or olanzapine at 15 mg daily. At the study endpoint, the olanzapine group demonstrated a change in the mean PANSS score that was statistically significant when compared with the placebo group, whereas the treatment effects were not statistically significant for either asenapine group when compared with placebo. In the failed study, patients were randomized to receive flexibly dosed asenapine 5–10 mg BID, olanzapine 10–20 mg daily, or placebo. At the study endpoint, neither the asenapine group nor olanzapine group demonstrated a significant change in mean

PANSS score from baseline compared with the placebo group.²

Data from the four aforementioned studies were pooled in a meta-analysis conducted by the manufacturer. When using both last observation carried forward (LOCF) and mixed model for repeated measures analyses, asenapine was superior to placebo in demonstrating a CFB PANSS total score. The magnitude of asenapine's pooled effect was similar to the pooled effect of the active controls as compared with placebo. Using network meta-analysis to compare the efficacy of asenapine with other SGAs, the authors found that the relative efficacy

Table 2. Asenapine's efficacy in treating schizophrenia: acute studies.

Study	Study design	Duration (weeks)	Disease state(s)	Randomized (n)	Asenapine dose (n)	Active control dose (n)	Placebo (n)	Comments regarding efficacy outcomes
Potkin et al. ¹⁴	Randomized, double-blind, placebo- and active comparator-controlled study	6	Schizophrenia, acute exacerbation	182	5 mg BID (60)	Risperidone 3 mg BID (60)	62	Incidence of withdrawal due to lack of efficacy was lower for asenapine (15% of treated patients) than for risperidone (29% of treated patients) and placebo (27% of treated patients); asenapine-treated group demonstrated significantly significant reduction in PANSS total score (-15.9) compared with placebo group (-5.3, $p < 0.005$); mean change in PANSS total score of risperidone-treated group (-10.9) was not significantly different from placebo-treated group; both risperidone- and asenapine-treated groups demonstrated significant changes on CGI-S scale compared with placebo group [-0.74 for the asenapine-treated group versus 0.28 for placebo ($p < 0.01$); -0.75 for the risperidone-treated group ($p < 0.005$)]; asenapine and risperidone treatment conferred greater decrease in PANSS-positive subscale scores at endpoint [-5.5 for asenapine versus -2.5 for placebo ($p = 0.01$); -5.1 for risperidone ($p < 0.05$)]; asenapine demonstrated a significantly greater change in PANSS-negative subscale score (-3.2) compared with placebo (-0.6, $p = 0.01$); change in risperidone group was not significantly different from placebo; change in mean PANSS general psychopathology subscale score in asenapine group (-7.2) was significantly different from placebo group (-2.2, $p < 0.005$); change in risperidone group (-4.8) was not significantly different from placebo
Citrome ²	Randomized, double-blind, placebo- and active comparator-controlled study	6	Schizophrenia, acute exacerbation	417	5 mg BID (106); 10 mg BID (102)	Olanzapine 15 mg daily (103)	106	Change in PANSS total score from baseline to endpoint was not statistically significant for the asenapine group [-14.5 for asenapine 5 mg BID, -13.4 for asenapine 10 mg BID] compared with placebo (-11.1); change in PANSS total score was significant for olanzapine group [-16.5] compared with placebo group
Citrome ²	Randomized, double-blind, placebo- and active comparator-controlled study	6	Schizophrenia, acute exacerbation	277	5-10 mg BID (91)	Olanzapine 10-20 mg/day (93)	93	Change in PANSS total score from baseline to endpoint was not statistically significant for the asenapine group [-9.4] or olanzapine group [-11.2] as compared with the placebo group [-9.9]
Kane et al. ¹⁵	Randomized, double-blind, placebo- and active comparator-controlled study	6	Schizophrenia, acute exacerbation	458	5 mg BID (114); 10 mg BID (106)	Haloperidol 4 mg BID (115)	123	Asenapine 5 mg BID and haloperidol groups demonstrated greater change from baseline PANSS total score compared with placebo group; asenapine 10 mg BID did not demonstrate a statistically significant advantage over placebo
Findling et al. ¹⁷	Randomized, double-blind placebo-controlled study	8	Schizophrenia (adolescent population, ages 12-17)	306	2.5 mg BID (98); 5 mg BID (106)	None	102	Differences between groups in the PANSS score at day 56 were not significantly different; significant improvement was however observed in the asenapine 5 mg BID group in the CGI-S score in comparison with the placebo group (least squares mean -0.3, $p = 0.024$) on day 56; completers were given the option to continue in a 26-week flexible-dose asenapine-only extension trial (see below)
Findling et al. ¹⁷	Flexible-dose asenapine-only extension trial	25	Schizophrenia (adolescent population, ages 12-17)	196	Flexible dose (mean dose 8.7 mg/day)	None	None	PANSS total scores changed by -16.1 points in the group previously treated with placebo ($n = 62$) and by -11.2 points in the group that had received asenapine in the 8-week total ($n = 131$) from the extension trial baseline to week 56

(Continued)

Table 2. (Continued)

Study	Study design	Duration (weeks)	Disease state(s)	Randomized (n)	Asenapine dose (n)	Active control dose (n)	Placebo (n)	Comments regarding efficacy outcomes
Kinoshita <i>et al.</i> ¹⁸	Randomized, double-blind, placebo-controlled study	6	Schizophrenia, acute exacerbation	532	5 mg BID (175); 10 mg BID (181)	None	174	Asenapine 5 mg BID and 10 mg BID showed a statistically significant difference in the total PANSS score compared with placebo, beginning at days 14 and 7 respectively, the least squares mean change in the PANSS total score at the end of treatment was -12.4 [95% CI: -15.28, -9.20] for the asenapine 5 mg BID group, -14.7 [95% CI -17.2, -11.22] in the asenapine 10 mg BID group, and -0.95 [95% CI -3.95, 2.06] in the placebo group. Both asenapine groups were statistically superior compared with placebo in changes in PANSS-positive and -negative subscale scores and in changes in CGI-S scores (both $p < 0.0001$)
Landbloom <i>et al.</i> ¹⁹	Randomized, double-blind, placebo- and active comparator-controlled study	6	Schizophrenia, acute exacerbation	357	2.5 mg BID (97); 5 mg BID (113)	Olanzapine 15 mg daily (46)	101	Asenapine 5 mg BID was superior to placebo with a mean change in total PANSS total score between asenapine 5 mg BID and placebo being -5.5 points (unadjusted 95% CI: -10.1, -1.0) at study endpoint; asenapine 2.5 mg BID was not superior to placebo. Mean change in PANSS score between olanzapine and placebo was -5.4 points, but this change was not statistically significant; neither olanzapine nor asenapine demonstrated statistically significant superiority to placebo in the secondary endpoints of change in CGI-S score or rate of PANSS responders
Maitra <i>et al.</i> ²⁰	Randomized, single-blind, active comparator-controlled study	12	Schizophrenia	80	10 mg total daily dose (39)	Olanzapine 10 mg total daily dose (38)	None	Asenapine demonstrated a decrease in BPRS score that was statistically significant; similarly, the asenapine group demonstrated a decrease in CGI-S and CGI-I scores that was statistically significant
Citrome <i>et al.</i> ²¹	Randomized, double-blind, placebo-controlled, study	6	Schizophrenia, acute exacerbation	614	3.8 mg/24h (204); 7.6 mg/24h (204)	None	206	Both doses of transdermal asenapine demonstrated statistically significant improvement compared with placebo [7.6 mg/24h: change from baseline (CFB) in PANSS total score versus placebo -4.8 [95% CI: -8.06 to -1.63, adjusted $p = 0.003$]; 3.8 mg/24h: CFB in PANSS total score -6.6 [95% CI: -9.81 to -3.4, adjusted $p < 0.001$]; both doses of transdermal asenapine demonstrated statistically significant improvements in week 6 CGI-S change from baseline scores and week 6 CGI-I scores

BID, twice daily; BPRS, Brief Psychiatric Rating Scale; CGI-I, clinical global impression-improvement; CGI-S, clinical global impression-severity; CI, confidence interval; PANSS, positive and negative syndrome scale.

of asenapine was fourth among eight examined antipsychotic medications.²²

Subsequent studies have demonstrated asenapine's efficacy in treating acute schizophrenia. A 2016 study examined the efficacy of asenapine in treating schizophrenia in Asian patients. A total of 532 participants were randomized to receive asenapine 5 mg BID, asenapine 10 mg BID, or placebo for 6 weeks. Both asenapine-treated groups showed a statistically significant difference in the total PANSS score, PANSS-positive and -negative subscale scores and Clinical Global Impression–Severity of Illness (CGI-S) scores compared with placebo.^{18,23} In a 2017 study, the efficacy of asenapine in treating acute schizophrenia was compared with olanzapine and placebo. Patients were randomized to receive asenapine 2.5 mg BID, 5 mg BID, placebo, or olanzapine 15 mg daily. Asenapine at 5 mg BID, but not 2.5 mg BID, was superior to placebo in demonstrating a change in PANSS total score from baseline to day 42.¹⁹

In a single blind, randomized, controlled, parallel-group, single-center trial, asenapine's efficacy was again examined in comparison with olanzapine. A total of 80 individuals with schizophrenia were randomized to receive asenapine or olanzapine for 12 weeks. Subjects were seen for a baseline visit and three follow-up visits. Asenapine demonstrated decreases in Brief Psychiatric Rating Scale (BPRS), CGI-S and Clinical Global Impression–Improvement (CGI-I) scores at the second and final follow-up visits that were statistically significant.^{20,23,24}

Transdermal asenapine's efficacy in treating acute schizophrenia was demonstrated in a 6-week multicenter, placebo-controlled, randomized, double-blind study in which subjects were randomized to receive transdermal asenapine at doses of 3.8 mg/24 h, 7.6 mg/24 h, or placebo. Both transdermal asenapine groups demonstrated statistically significant improvement compared with placebo in CFB in PANSS total score and in week 6 CGI-S CFB scores and week 6 CGI-I scores.²¹

Sublingual asenapine's efficacy in treating schizophrenia in adolescents was evaluated in an 8-week double-blind placebo-controlled trial in which subjects aged 12–17 meeting diagnostic criteria for schizophrenia were randomized to receive placebo, asenapine 2.5 mg BID, or asenapine 5 mg

BID. Subjects who completed the 8-week trial were given the option to continue in a 26-week flexible-dose asenapine-only extension trial. Differences between groups in the PANSS score at day 56 were not significant. However, significant improvement was observed in the asenapine 5 mg BID group in the CGI-S score in comparison with the placebo group on day 56. In the extension trial, PANSS total scores decreased further in both groups.¹⁷

Relapse prevention and other long-term studies (Table 3). Asenapine's efficacy in preventing schizophrenia relapse was assessed in a 26-week double-blind, placebo-controlled trial. Individuals who had been stable on asenapine for 26 weeks were randomized to either continue on asenapine at 10 mg BID or switch to placebo. Time to relapse or impending relapse was significantly longer in the asenapine-treated group, and the incidence of relapse or impending relapse was significantly lower in the asenapine-treated group.²⁵

Asenapine's long-term efficacy in treating schizophrenia was also studied in a double-blind trial in which 1225 subjects with diagnoses of schizophrenia or schizoaffective disorder were randomized to receive asenapine at 5 or 10 mg BID or olanzapine at 10 or 20 mg daily for 1 year. While both asenapine-treated and olanzapine-treated groups demonstrated differences in PANSS total scores at the endpoint, the olanzapine-treated group demonstrated a statistically significant improvement in PANSS total scores compared with the asenapine-treated group using LOCR.²⁶ Subjects were given the option to then continue treatment until the study blind was broken, and 290 asenapine and 150 olanzapine patients continued in the extension trial. During this extension trial, clinical stability on both asenapine and olanzapine was maintained.²⁷

The efficacy of asenapine compared with olanzapine in treating persistent negative symptoms of schizophrenia was examined in two 26-week core studies. Next, 26-week extension studies were completed to assess the long-term safety and efficacy of the antipsychotic medications. In the core studies, subjects were randomized to receive asenapine or olanzapine. Asenapine was not superior to olanzapine in change in the 16-item Negative Symptom Assessment Scale (NSA-16) in either core study.³⁰ In one of the extension studies, asenapine was superior to olanzapine in

Table 3. Asenapine's efficacy in treating schizophrenia: longer-term studies.

Study	Study design	Duration (weeks)	Disease state(s)	Randomized (n)	Asenapine dose (n)	Active control dose (n)	Placebo (n)	Comments regarding efficacy
Kane <i>et al.</i> ²⁵	Randomized, double-blind, placebo-controlled study	26	Schizophrenia	386	10–20 mg BID (194)	None	192	Time to relapse or impending relapse was significantly longer in the asenapine-treated group ($p < 0.0001$), and the incidence of relapse or impending relapse was significantly lower in the asenapine-treated group [12.1% versus 47.4% in the placebo group, $p < 0.0001$]
Schoemaker <i>et al.</i> ²⁶	Randomized, double-blind, active comparator-controlled study	52	Schizophrenia or schizoaffective disorder	1225	5–10 mg BID (913)	Olanzapine 10–20 mg daily (312)	None	While both treatment groups demonstrated a change in PANSS total scores at the study endpoint, there was a statistically significant difference in PANSS total scores in favor of olanzapine (-21.0 ± 22.8 for the asenapine group and -27.5 ± 22.0 for the olanzapine group; $p < 0.0001$) using last observations carried forward. Subjects were then given the option to continue in treatment until the study blind was broken. ²⁷
Schoemaker <i>et al.</i> ²⁷	Extension study	Variable	Schizophrenia or schizoaffective disorder	440	5–10 mg BID (290)	Olanzapine 10–20 mg daily (150)	None	Clinical stability on both asenapine and olanzapine was maintained, with asenapine demonstrating a -1.6 further decrease in total PANSS score and olanzapine demonstrating a -0.8 change at the extension study endpoint; no changes in other efficacy measures [PANSS subscales, PANSS Marder factors, CGI-S, CGI-I, and Calgary Depression Scale for Schizophrenia (CDSS) ²⁸] were found
Buchanan <i>et al.</i> (Study 1: Eastern Hemisphere) ²⁹	Randomized, double-blind, active comparator-controlled study	26	Schizophrenia with persistent negative symptoms	481	10–20 mg/day (241)	Olanzapine 10–20 mg/day (240)	None	Completers were eligible for 26-week extension study; asenapine was not superior to olanzapine in change in the NSA-16 in the core or extension study. Compared with asenapine, olanzapine demonstrated modestly greater but statistically significant changes in the PANSS-positive subscale at several assessment points in the core study
Buchanan <i>et al.</i> (Study 2: Western Hemisphere) ²⁹	Randomized, double-blind, active comparator-controlled study	26	Schizophrenia with persistent negative symptoms	468	10–20 mg/day (244)	Olanzapine 10–20 mg/day (224)	None	Completers were eligible for 26-week extension study; asenapine was not superior to olanzapine in change in the NSA-16 in the core study, but in the extension study, asenapine was superior to olanzapine in change in the NSA-16 (15.8 ± 1.48 versus -11 ± 1.27 ; $p = 0.03$). Compared with asenapine, olanzapine demonstrated modestly greater but statistically significant changes in the PANSS-positive subscale at several assessment points in both the core and extension study

BID, twice daily; CGI-I, clinical global impression–improvement; CGI-S, clinical global impression–severity; NSA-16, 16-item negative symptom assessment scale; PANSS, positive and negative syndrome scale.

change in the NSA-16. Compared with asenapine, olanzapine demonstrated modestly greater but statistically significant changes in the PANSS-positive subscale at several assessment points in both core studies, as well as in one of the extension studies.²⁹

Bipolar disorder

Acute short-term studies (Table 4). The efficacy of asenapine for the treatment of manic or mixed episodes of bipolar I disorder was established in a clinical trial program consisting of two phase III randomized, placebo, and active comparator-controlled clinical trials where asenapine was flexibly dosed.^{31,32} These two trials were acute 3-week studies with identical methods, followed by an optional 9-week extension study.³³ Individuals that completed the 9-week extension study were eligible to participate in an additional 40-week extension study.³⁴ In the short-term trials, adults experiencing manic or mixed bipolar episodes were randomized to flexible-dose asenapine (5 or 10 mg BID), placebo, or olanzapine (5–20 mg daily). Efficacy was established by measuring the change in Young Mania Rating Scale (YMRS) total score from baseline to day 21.³⁵

In both phase III studies, the primary efficacy endpoint for asenapine was met, with a reduction in YMRS scores being significantly greater in the asenapine group relative to placebo.^{31,32}

The efficacy of asenapine was further assessed in a fixed-dose study. In a multicenter, double-blind, fixed-dose, parallel-group, 3-week placebo-controlled trial, the efficacy of asenapine 5 mg and 10 mg BID was assessed in patients with bipolar I disorder experiencing an acute manic or mixed episode. Asenapine 5 mg and 10 mg BID were both superior to placebo.³⁷

Longer-term studies (Table 5). The longer-term efficacy of asenapine for patients with manic or mixed episodes of bipolar was first evaluated in a 9-week extension trial of the initial two pivotal trials, followed by a 40-week extension trial.^{33,34} For the 9-week extension, the primary efficacy outcome was CFB to day 84 on the YMRS total score. A total of 504 patients that completed the initial trials enrolled and were continued on the study medication that they received during the initial trial. Those that received placebo were blindly switched to asenapine. Asenapine was

efficacious and non-inferior to olanzapine. Using LOCF in the intention-to-treat population, the rates of response and remission for asenapine and olanzapine were similar on day 84. Individuals that completed the 9-week extension trial were then eligible to continue in a 40-week extension trial (218 enrolled out of 308 possible patients).³⁴ Participants remained blinded and continued with their existing study medication. The long-term efficacy of asenapine was supported, with nearly identical reductions in YMRS total score from baseline to study endpoint for asenapine and olanzapine. Additionally, rates of response and remission were nearly identical for each study drug.

An extension study was also carried out for the fixed-dose asenapine trial completed by Landbloom *et al.* After completing the initial 3-week trial, participants were eligible to enroll in a 26-week, fixed-dose (5 or 10 mg BID), double-blind, extension study.^{37,38} Individuals that received placebo in the acute trial received asenapine 5 mg BID in the extension study (placebo/asenapine group), otherwise, patients continued the dosage of asenapine that they previously received. Mean change in YMRS total score from acute trial baseline to extension trial endpoint was similar across treatment groups. Response and remission rates increased in each group from extension trial baseline to study endpoint.

Maintenance phase. In a phase IIIb, randomized, placebo-controlled, double-blind, parallel-group trial, the effectiveness of asenapine in preventing the recurrence of a bipolar episode was assessed.⁴⁴ Individuals with bipolar I experiencing an acute manic or mixed episode were treated with asenapine 5 mg or 10 mg BID during a 12–16-week open-label period. Patients meeting treatment response criteria for 8 weeks were randomized to 26 weeks of double-blind treatment with asenapine (5 mg or 10 mg BID) or placebo. The primary efficacy outcome was time to recurrence of any mood event. The risk of recurrence and the time to recurrence of any mood episode was significantly longer in asenapine-treated individuals than placebo-treated individuals.

Adjunctive trials. In a 12-week, double-blind, placebo-controlled study, followed by a double-blind, placebo-controlled 40-week extension study to assess safety and tolerability (52 weeks total), adjunctive asenapine (5 or 10 mg BID) was compared with placebo in patients with an

Table 4. Acute studies of asenapine for bipolar disorder.

Study	Study design	Duration (weeks)	Disease state	Randomized (n)	Asenapine dose (n)	Active control dose (n)	Placebo (n)	Comments regarding efficacy outcomes
McIntyre <i>et al.</i> ³¹	Double-blind, flexible-dose, randomized control trial	3	Manic or mixed episode, bipolar I disorder	489	Initiated at 20 mg/day, then 10 mg or 20 mg/day (194); mean dose 18.2 mg/day	Olanzapine initiated at 15 mg/day, then 5–20 mg/day (191); mean dose 15.8 mg/day	104	Asenapine separated from placebo as early as day 2 ($p < 0.008$). There was a YMRS change of -10.8 ± 0.8 from baseline until day 21 in the asenapine group compared with -5.5 ± 1.0 in the placebo group ($p < 0.0001$). Asenapine and olanzapine rates of response and remission were comparable and significantly greater than placebo; the NNT for response and remission for asenapine <i>versus</i> placebo was 6, whereas the NNT for olanzapine <i>versus</i> placebo was 5; study completers were eligible to enroll in a 9-week extension trial ³³
McIntyre <i>et al.</i> ³²	Double blind, flexible dose, randomized control trial	3	Manic or mixed episode, bipolar I disorder	488	Initiated at 20 mg/day, then 10 or 20 mg/day (185); mean dose 18.4 mg/day	Olanzapine initiated at 15 mg/day, then 5–20 mg/day (205); mean dose 15.9 mg/day	98	Asenapine separated from placebo as early as day 2 ($p = 0.022$), and YMRS change from baseline at day 21, was -11.5 ± 0.8 with asenapine ($p < 0.007$ <i>versus</i> placebo) and -7.8 ± 1.1 with placebo; asenapine rates of response and remission were not significantly different from placebo, whereas olanzapine rates were significantly superior to placebo. The NNT for asenapine <i>versus</i> placebo was 12 for response and 22 for remission, whereas the NNT for olanzapine <i>versus</i> placebo was 5 and 7 for response and remission, respectively, and 9 and 10 for olanzapine <i>versus</i> asenapine, respectively ³⁴ . Study completers were eligible to enroll in a 9-week extension trial ³²
Landbloom <i>et al.</i> ³⁷	Double blind, fixed dose, randomized control trial	3	Manic or mixed episode, bipolar I disorder	367	Asenapine 5 mg BID ($n = 122$) or asenapine 5 mg BID for one day and then 10 mg BID ($n = 119$)	None	126	Asenapine was superior to placebo as measured by YMRS total score change from baseline at day 21. YMRS was -10.9 , -14.4 ($p = 0.0136$ <i>versus</i> placebo), and -14.9 ($p = 0.01$ <i>versus</i> placebo) for placebo, asenapine 5 mg and 10 mg BID, respectively. However, neither asenapine dose had significantly more YMRS responders than placebo, 39.7%, 45%, 46.9% of patients receiving placebo, asenapine 5 mg and 10 mg BID, respectively; study completers were eligible to enroll in a 26-week extension trial ³⁸
Findling <i>et al.</i> ³⁹	Randomized, double-blind, placebo-controlled trial	3	Adolescents aged 10–17 years with manic or mixed episode, bipolar I disorder	403	Asenapine 2.5 mg (104), 5 mg (99), or 10 mg BID (99).	None	101	Each dose of asenapine was statistically superior to placebo in improving YMRS total score from baseline to day 21, -3.2 , -5.3 , and -6.2 ($p < 0.001$ for each asenapine 2.5 mg, 5 mg, and 10 mg BID <i>versus</i> placebo, respectively); each dose separated by day 4; the YMRS responder rates were significantly greater for asenapine (42%; NNT = 8, 54%; NNT = 4, 52%; NNT = 5, for asenapine 2.5 mg, 5 mg, and 10 mg BID, respectively) than placebo (28%) ³³ . Patients that completed the trial were eligible to be enrolled in a 50-week extension trial ⁴⁰

(Continued)

Table 4. (Continued)

Study	Study design	Duration (weeks)	Disease state	Randomized (n)	Asenapine dose (n)	Active control dose (n)	Placebo (n)	Comments regarding efficacy outcomes
Baruch <i>et al.</i> ⁴¹	Open label	4	Older-adult (mean age 67.7 ± 6.1 years) inpatients with manic episodes of bipolar I	11 consecutively admitted inpatients meeting study criteria	Asenapine was started at 5 mg BID for 3 days and then titrated to 10 mg BID	None	None	YMRS change from baseline was -21.4 ± 12.9, $p < 0.001$; the YMRS response rate was 81.8% (9/11) and the remission rate was 63.6% (7/11); CGI-BP mania severity scores changed by -2.6 ± 0.5 ($p < 0.002$) ⁴²
Barak <i>et al.</i> ⁴³	Open label	3	Older-adult (mean age 67.2 years) inpatients with manic episodes of bipolar I	34 consecutive inpatients meeting study criteria	Asenapine was started at 5 mg BID for 3 days and then titrated to 10 mg BID	None	None	YMRS total score decreased from a mean of 27.0 ± 8.8 to 13.3 ± 12.2 at the study endpoint ($p < 0.001$), and 14 (56%) patients achieved YMRS remission; CGI-BP was observed from a mean of 5.5 ± 1.7 at baseline to a mean of 3.1 ± 1.3 at completion ($p < 0.01$)
Szegedi <i>et al.</i> ⁴⁴	Randomized, flexible-dose, double-blind, placebo-controlled trial	26	Manic or mixed episode of bipolar I	253 patients that achieved treatment response during an initial open-label period	Asenapine 5 mg or 10 mg BID	None	127	Time to recurrence of any mood episode was longer in asenapine-treated patients than placebo-treated patients ($p < 0.0001$; hazard ratio = 0.22, 95% CI = 0.11–0.43; NNT = 5) Recurrence defined as any of the following: requiring non-study medication to treat mood symptoms, hospitalization or study discontinuation due to a mood event, or total YMRS or MADRS score ≥ 16 ; ⁴⁵ the most common predictor of recurrence was a YMRS and/or MADRS score ≥ 16 The calculated hazard ratio (0.22) correlates to an approximate fourfold higher risk of recurrence for placebo-treated versus asenapine-treated patients

BID, twice daily; CGI-BP, Clinical Global Impression for Bipolar Disorder Scale; MADRS, Montgomery-Åsberg Depression Rating Scale; NNT, number needed to treat; YMRS, Young Mania Rating Scale.

Table 5. Longer-term studies of asenapine for bipolar disorder.

Study	Study design	Duration (weeks)	Disease state	Randomized (n)	Asenapine dose (n)	Active control dose (n)	Placebo (n)	Comments regarding efficacy outcomes
McIntyre <i>et al.</i> ³³	Double-blind, extension trial of two double-blind, flexible-dose, randomized control trials ^{31,32}	9	Manic or mixed episode, bipolar I disorder	504	Patients randomized to placebo in either of two 3-week acute trials were blindly randomized to asenapine 5 mg or 10 mg BID (94). Patients that received asenapine in the acute trials continued the same regimen (181)	Olanzapine 5–20 mg/day (229)	None	At study endpoint, mean YMRS change from baseline was -24.4 (8.7) and -23.9 (7.9) for asenapine and olanzapine respectively, and there was no statistical difference. Rates of response and remission were similar between groups; study completers were eligible to enroll in a 40-week extension trial ³⁴ .
McIntyre <i>et al.</i> ³⁴	Double-blind, flexible-dose, extension trial of a prior 9-week extension trial ³³	40	Manic or mixed episode, bipolar I disorder	218	Patients were continued on pre-established treatment from a prior 9-week extension trial: placebo/asenapine 5 or 10 mg BID (32) or asenapine 5 mg or 10 mg BID (79)	Olanzapine 5–20 mg/day (107)	None	Mean change in YMRS were comparable between asenapine and olanzapine; the mean \pm SD change in YMRS total score from baseline in the ITT population at week 52 was -28.6 ± 8.1 for asenapine versus -28.2 ± 6.8 for olanzapine; rates of response and remission were also nearly identical.
Ketter <i>et al.</i> ³⁸	Double-blind, fixed-dose, extension trial of a prior 3-week trial ³⁷	26	Manic or mixed episode, bipolar I disorder	164	Asenapine 5 mg BID (53) or asenapine 10 mg BID (51). Patients that received placebo in the acute trial received asenapine 5 mg BID (placebo/ asenapine group; 60)	None	None	Mean change in YMRS total score from acute trial baseline to extension trial endpoint was similar across treatment groups (-22.3 , -22.9 , -22.0 , in placebo/asenapine, asenapine 5 mg and asenapine 10 mg BID, respectively); response rates increased in each group from extension trial baseline ($+43.6\%$ in the placebo/asenapine 5 mg group, 87.7% overall) responding, $+38.0\%$ in the asenapine 5 mg group, 88% overall, and $+26.0\%$ in the asenapine 10 mg group, 84% overall).
Szegedi <i>et al.</i> ⁴⁶	Double-blind, randomized, placebo-controlled, augmentation trial	12	Manic or mixed episode, bipolar I disorder. Patients had to be continuously treated with lithium or valproate for 2 weeks or longer before screening	326	Adjunctive, flexible-dose, asenapine 5 mg or 10 mg BID with concurrent open-label lithium or valproate treatment	None	166	Adjunctive asenapine was superior to placebo at week 3 with a greater YMRS total score improvement [-10.3 (SD 0.8) versus -7.9 (0.8), $p = 0.026$). Asenapine had a significantly greater reduction in YMRS total score compared with placebo at weeks 2, 6, 9, and 12 ($p < 0.05$ at each time point); the rates of asenapine and placebo YMRS response did not significantly differ at week 3 (34.2% versus 27%), but did at week 12 (47.7% versus 34.4% , $p = 0.0152$); rates of YMRS remission were significantly greater for asenapine versus placebo-treated patients, with an NNT for asenapine versus placebo of 9 (95% CI, 4.5–43) and 8 (95% CI, 4.2–37.7) at weeks 3 and 12, respectively.

(Continued)

Table 5. (Continued)

Study	Study design	Duration (weeks)	Disease state	Randomized (n)	Asenapine dose (n)	Active control dose (n)	Placebo (n)	Comments regarding efficacy outcomes
Szegedi <i>et al.</i> ⁴⁶	Double-blind, placebo-control extension trial of an acute augmentation trial	40	Manic or mixed episode, bipolar I disorder, continuing to receive lithium or valproate	77	Adjunctive, flexible-dose, asenapine 5 mg or 10 mg BID with concurrent open-label lithium or valproate treatment	None	36	Mean YMRS total score changes at the extension trial end point were not significantly different between asenapine and placebo groups. Rates of YMRS response [asenapine, 68.4%; placebo, 78.8%] and remission [asenapine, 65.8%; placebo, 78.8%] at week 52 were not statistically different
Findling <i>et al.</i> ⁴⁰	Flexible-dose, open-label extension study of an acute trial ⁴⁶	50	Adolescents aged 10–17 years with manic or mixed episode, bipolar I disorder	321	Patients treated with placebo (80) in the antecedent acute phase trial were transitioned to treatment with flexible-dose asenapine; the remaining patients (241) were also treated with flexible-dose asenapine (5–20 mg/day); overall, 31 (9.7%) patients received a modal dose of asenapine 2.5 mg BID, 105 (32.7%) patients received 5 mg BID, and 170 (53.0%) patients received 10 mg BID 15 patients (4.7%) received treatment for <8 days for which no modal dose was determined	None	None	Mean change in YMRS total score from open-label extension baseline at week 50 was –15.2 in the placebo/asenapine group and –6.5 in the asenapine/asenapine group; of 141 patients who were YMRS responders at the end of the acute trial, 46 patients (32.6%) failed to maintain this response; at the end of 26 weeks of treatment, 118 (79.2%) of patients remaining in the trial achieved YMRS response, whereas 102 (68.5%) of remaining patients had achieved YMRS remission
Sajatovic <i>et al.</i> ⁴⁷	Open-label, adjunct asenapine	12	Older-adult (mean age 68.6 years) outpatients with bipolar I or 2 disorder having a suboptimal response to current psychotropic treatment	15	Patients were started on asenapine 5 mg/day and titrated to a mean dose of 11.2 mg/day (SD 6.2) as an augmentation to their existing pharmacologic treatment	None	None	Based on baseline YMRS, HAM-D, and MADRS, the majority of participants had moderate-to-severe depression at baseline, while a smaller proportion had manic symptoms; among patients with manic symptoms, there was an improvement in YMRS scores ($p < 0.01$). Among individuals with depressive symptoms, there was a trend for significant improvement on MADRS ($p = 0.06$) and HAM-D ($p = 0.01$) scores

BID, twice-daily; CI, confidence interval; HAM-D, Hamilton Depression Rating Scale⁴⁸; ITT, intention to treat; MADRS, Montgomery-Åsberg Depression Rating Scale; SD, standard deviation; YMRS, Young Mania Rating Scale.

inadequate response to lithium or valproate monotherapy.⁴⁶ In the initial 12-week trial, the primary outcome measure was CFBYMRS total score at week 3. Adjunctive asenapine was found to be superior to placebo and no significant difference was observed between patients receiving lithium and those receiving valproate. Due to the limited number of participants recruited into the 40-week extension study, efficacy outcomes at week 52 were limited, and there was no statistically significant difference between adjunctive asenapine and placebo.

Special populations

Child and adolescent populations. The efficacy of asenapine in treating adolescent patients aged 10–17-years old with an acute manic or mixed episode of bipolar I disorder was established in a 3-week, double-blind, placebo-controlled trial, followed by a 50-week open-label, flexible-dose, extension study (Tables 4 and 5).^{39,40} In the acute trial, the primary efficacy measure was CFB in YMRS total score at day 21. On day 21, asenapine was superior to placebo. YMRS responder rates were also significantly greater for asenapine than placebo. In the 50-week extension trial, there was no placebo group, and each patient received flexible-dose asenapine (see Table 5).

Older adults. The efficacy of asenapine in older adults with bipolar I disorder was evaluated in two inpatient open-label studies and one outpatient open-label study.^{41–47} For both inpatient studies, asenapine was titrated to 10 mg BID (Table 4). The first trial was a 4-week study of older-adult inpatients with manic episodes of bipolar I disorder, and mean YMRS changes from baseline to day 28 were statistically significant.⁴¹ In a second 3-week study of older-adult inpatients with a manic episode of bipolar, asenapine-treated patients showed a significant decrease in YMRS at study endpoint.⁴³ In a 12-week study of older outpatients with bipolar I or II disorder, currently having a suboptimal response to current psychotropic treatment, participants were started on adjunctive asenapine (Table 5).⁴⁷ Augmentation with asenapine resulted in an improvement of both manic and depressive symptoms.

Observational studies. A naturalistic, real-world, observational study evaluating the short-term efficacy of asenapine for the treatment of manic episodes secondary to bipolar disorder or schizoaffective disorder was conducted in Italy.⁴⁹

Twenty hospitalized patients treated with asenapine, and a comparison group of patients not treated with asenapine were selected and followed over 6 months. The mean length-of-stay was 17.9 [standard deviation (SD) \pm 9] days in the asenapine group and 14.7 (SD \pm 12.7) days in the comparator group ($p=0.138$). The rehospitalization rate during the 6-month follow up was 17.7% ($n=3$) in the asenapine group and 41.2% ($n=7$) in the comparator group, though at 6 months, only two patients remained on asenapine.

Other uses

Asenapine has also been utilized for the off-label treatment of post-traumatic stress disorder, delusional disorder, catatonia, cocaine-induced psychotic disorder, and borderline personality disorder.^{50–56} Three open-label trials have evaluated asenapine for the treatment of borderline personality disorder. In the first identified outpatient study ($n=12$), asenapine resulted in statistically significant improvements on the CGI scale modified for borderline personality disorder (CGI-BPD) global scores ($p<0.001$) and affect instability, emptiness, and impulsivity subscales (each had $p\leq 0.01$), as well as a symptom reduction on the Borderline Symptom List-23 (BLS-23) ($p=0.048$).^{55,57,58} In another study of 51 adult outpatients with a diagnosis of borderline personality disorder, patients were randomized to receive asenapine (5–10 mg/day) or olanzapine (5–10 mg/day) and were assessed at baseline and after 12 weeks.⁵⁴ Asenapine and olanzapine were found to have similar efficacy with few differences in global symptoms, though neither led to a decrease in depressive or aggressive symptoms. In the third and final trial, adjunctive asenapine was added to existing treatment in patients with bipolar I disorder with and without borderline personality disorder.⁵⁶ In the 12-week study, 50 consecutive outpatients with bipolar I disorder were evaluated for borderline personality disorder and divided into two groups, those with and without borderline personality disorder. Asenapine was found to reduce both aggression and impulsiveness in each group ($p<0.001$); however, no significant difference was found between the two groups.

Aggression and agitation

Sublingual asenapine provides a less invasive option to traditionally used short-acting intramuscular antipsychotic agents in the treatment of

agitation. The effectiveness of sublingual asenapine in the treatment of acute agitation was investigated in a randomized, double-blind, placebo-controlled study in which agitated adults were randomized to receive either sublingual asenapine at 10 mg ($n=60$) or placebo ($n=60$). The authors measured the change in the patients' PANSS-Excited Component (PANSS-EC) at 2 h.^{15,59,60} The change in PANSS-EC scores for the asenapine-treated group was significantly greater than the change in PANSS-EC scores for the placebo-treated group. The effect of sublingual asenapine was rapid, with changes in the PANSS-EC score occurring as early as 15 min after asenapine administration.⁶¹

The use of asenapine to treat aggression in the inpatient psychiatric setting was assessed in a prospective, naturalistic, pilot, proof-of-concept study. Patients were administered the Refined Aggression Questionnaire and Modified Overt Aggression Scale (MOAS) on both hospital admission and discharge.^{62,63} Based on admissions ratings on these scales, patients were categorized as aggressive and non-aggressive. Those patients deemed aggressive were divided further into those receiving asenapine ($n=5$) and those not receiving asenapine ($n=42$). Those patients who received asenapine were noted to have a significant reduction in total aggression measured by the MOAS compared with those patients that did not receive asenapine (-14.7 ± 11.59 versus -5.4 ± 10.12 , $p < 0.0001$).⁶⁴

Tolerability

Sublingual asenapine

Asenapine has unique adverse effects attributed to its sublingual method of administration and can precipitate dysgeusia (distorted, altered, or unpleasant taste) and oral hypoesthesia (numbness). A black-cherry formulation is available to possibly lessen the unpleasant taste.⁶⁵ The etiology of the oral hypoesthesia is likely attributable to local anesthetic activity; however, the effects are typically transient and resolve within 1 h.^{66,67}

The most common adverse effects (incidence $\geq 5\%$ and at least twice that for placebo) of asenapine are akathisia, oral hypoesthesia, and somnolence in adult patients with schizophrenia, and somnolence, oral hypoesthesia, dizziness, extrapyramidal symptoms (EPS; excluding akathisia), and akathisia in adults with bipolar I disorder.⁷

In the short-term clinical trials program for bipolar disorder, the percentage of patients reporting adverse events of interest (asenapine versus placebo) were: (a) somnolence, 24% versus 6% [number needed to harm (NNH) = 6; 95% confidence interval (95% CI) 5–9]; (b) dizziness, 11% versus 3% (NNH = 13, 95% CI 9–25); (c) EPS other than akathisia, 7% versus 2% (NNH = 20, 95% CI 9–25); (d) increased body weight, 24% versus $<1\%$ (NNH = 6, 95% CI 5–9).⁶⁵ There was an increase in body weight ($\geq 7\%$) in 5.8% of patients receiving asenapine versus 0.5% receiving placebo. In comparison with olanzapine, there was a significant weight increase in 39.2% of asenapine-treated patients compared with 55.1% in olanzapine-treated patients.⁶⁸ The percentage of patients discontinuing treatment due to adverse effects was 10% for asenapine and 6% for placebo [NNH = 25, non-significant (NS)].⁶⁵ Additionally, fixed-dose short-term studies showed that there is a dose-dependent increase in adverse effects, with treatment-emergent adverse events occurring at a rate of 59.8% with asenapine 5 mg, and 74.8% with asenapine 10 mg BID.¹⁹ Incorporating fixed-dose and flexible-dosed short-term studies for bipolar disorder, the rate of oral hypoesthesia was 10% versus 1%, and the rate of dysgeusia was 4% versus $<1\%$ in the asenapine and placebo groups, respectively.⁸

The long-term tolerability of asenapine has been evaluated in three long-term extensions to acute bipolar trials.^{34,38,44} In a 40-week, double-blind, flexible-dose extension trial, three groups of patients with bipolar disorder were assessed for safety and tolerability outcomes. The groups consisted of: (a) a placebo/asenapine group for patients that received placebo during the initial 3-week acute trial and were then converted to asenapine; (b) an asenapine group; (c) an olanzapine group.³⁴ The overall incidence of treatment-emergent adverse effects was 71.9%, 86.1%, and 79.4% in the placebo/asenapine, asenapine, and olanzapine groups, respectively. Adverse events occurring $\geq 10\%$ in each group were as follows: (a) placebo/asenapine: headache, somnolence, insomnia, nausea, parkinsonism, tremor, and constipation; (b) asenapine: insomnia, sedation, depression, headache, somnolence, increased weight, dizziness, nausea, and akathisia; (c) olanzapine: increased weight, somnolence, sedation, headache, insomnia, and akathisia. Clinically significant weight gain ($\geq 7\%$ increase from baseline) occurred in 21.9%, 39.2%, and 55.1% of patients in the placebo/asenapine,

asenapine, and olanzapine groups, respectively, with an NNH for olanzapine *versus* asenapine of seven. However, the rate of discontinuation attributed to adverse events was relatively low, 10.8% among all patients who received asenapine and 8.4% among the olanzapine group. In a 26-week, fixed-dose, double-blind, extension trial of a 3-week acute efficacy trial, the long-term tolerability of asenapine at difference dosages was evaluated.³⁸ A dose-dependent effect (5 mg *versus* 10 mg BID) among treatment-emergent adverse events was not evident.³⁷ Moreover, in a more recent 26-week extension trial of treatment responders, the study authors reported, ‘the known safety and tolerability profile for asenapine was confirmed in this trial, with no detection of new safety or tolerability signals.’⁴⁴

The safety and tolerability of asenapine that was observed in the bipolar I disorder trials was maintained and confirmed in trials evaluating asenapine for adult patients with schizophrenia. In the short-term clinical trials program for schizophrenia, two 6-week trials established the efficacy and safety profile of asenapine for the treatment of schizophrenia.^{14,15} Cumulatively, 9% of asenapine- and 10% of placebo-treated patients discontinued treatment due to adverse events. From the short-term registrational studies, the estimates of NNH *versus* placebo were 35 for the outcome of weight gain $\geq 7\%$, 17 for adverse events of somnolence, and 35 for adverse events of akathisia; these NNH values are comparable with other well-tolerated first-line SGAs in the treatment of schizophrenia.⁶⁹

Across the short-term schizophrenia and bipolar trials and the 52-week schizophrenia trial, the rate of discontinuation due to oral hypoesthesia was 0.27%.⁶⁶

Asenapine has a minimal effect on the QT/QTc interval, with an increase in QTc ranging from 2 ms to 5 ms compared with placebo. In a dedicated QTc interval study ($n=151$), no patient treated with asenapine experienced QTc increase ≥ 60 ms from baseline, or QTc of ≥ 500 ms.⁷⁰

All antipsychotics carry warnings regarding orthostatic hypotension and syncope. As per product labeling, the rates of syncope with sublingual asenapine were low and mostly similar to that for placebo among the populations tested.⁸ There were no reports of syncope for both doses of transdermal asenapine in the placebo-controlled

trial (orthostatic hypotension, considered a prelude to potential syncope, occurred at rates of 1.5% of patients treated with 3.8 mg/24 h and 0% of patients treated with 7.6 mg/24 h, compared with $<1\%$ of patients treated with placebo).⁷¹

Asenapine functions, in part, as a dopamine D₂ receptor antagonist, and as such, was expected to be associated with an increased serum prolactin level. However, short-term trials of asenapine for the treatment of schizophrenia and bipolar disorder did not result in clinically relevant changes attributable to prolactin levels (0.4% for asenapine *versus* 0% for placebo), and in a 26-week study of patients with bipolar disorder, there were no treatment-emergent adverse effects related to prolactin abnormalities.^{8,38}

In the largest identified network meta-analysis to date, the comparative tolerability of 32 oral antipsychotics for the treatment of schizophrenia was evaluated. In terms of tolerability, asenapine ranked toward the middle in most areas. For all-cause discontinuation, asenapine ranked 21st out of 32 antipsychotics. It ranked 15th out of 27 for weight gain, 14th out of 21 for increase in prolactin, 21st out of 33 (includes placebo) for sedation, and 14th out of 31 for akathisia.⁷²

Pediatric tolerability

Although asenapine is approved by the FDA for the treatment of manic and mixed episodes of bipolar I disorder in children and adolescents aged 10–17, it has also been studied for the treatment of schizophrenia in this patient population. In the acute trials of children and adolescents with bipolar I disorder and schizophrenia, adverse effects were comparable between conditions. In the bipolar trial, there was no difference between placebo and treatment groups in the discontinuation rate due to adverse effects.³⁹ In the schizophrenia trial, the rates were 2.9%, 6.1%, and 7.5% for placebo, asenapine 2.5 mg and 5 mg BID, respectively.¹⁷ Treatment-emergent adverse events with an incidence of $\geq 5\%$ and at least twice that of placebo for each asenapine group in the bipolar and schizophrenia trials include somnolence, sedation, and oral hypoesthesia/dysgeusia.

In general, the incidence of weight gain from SGAs is higher in children and adolescents than it is in adults.⁷³ In each asenapine adolescent study, the incidence of weight gain $\geq 7\%$ from baseline was significantly higher in patients treated with

asenapine when compared with placebo. In the bipolar trial, the incidence of weight gain $\geq 7\%$ for asenapine 2.5 mg, 5 mg, and 10 mg twice daily *versus* placebo was 12.0%, 8.9%, and 8.0% *versus* 1.1%.

Following the short-term trial of asenapine in a pediatric bipolar I population, patients were eligible to enroll in a 50-week, flexible-dose (2.5–10 mg BID), extension trial.⁴⁰ Long-term treatment with asenapine was generally well tolerated, and discontinuation due to treatment-emergent adverse events was 15%. The most common adverse event was combined somnolence/sedation/hypersomnia, occurring in 42.4% of patients treated with asenapine, followed by oral hypoesthesia/dysgeusia (7.5%), EPS (6.2%), and akathisia (4.7%). Weight gain in patients receiving asenapine exceeded what would be expected as part of normal growth and development, and 34.8% of patients experienced clinically significant weight gain $\geq 7\%$ of their body weight. In a systematic meta-review of the safety of 80 antidepressants, antipsychotics, anti-attention-deficit/hyperactivity medications and mood stabilizers in children and adolescents with psychiatric disorders, among the identified antipsychotic medications, asenapine was favorably ranked.⁷⁴

Transdermal asenapine

The tolerability of transdermal asenapine was evaluated in a phase III, randomized, double-blind, fixed-dose, placebo-controlled trial that evaluated the efficacy and tolerability of transdermal asenapine in patients with schizophrenia.²¹ Transdermal asenapine was well tolerated, with adverse events comparable with placebo [55.4%, 53.9%, and 51.5% in the high-dose asenapine (HP-3070 7.6 mg/24 h), low-dose asenapine (HP-3070 3.8 mg/24 h), and placebo groups respectively]. Most side effects were mild, and serious adverse events were similar across groups ($< 2\%$ of patients in each group). The discontinuation rate due to adverse events was 7.8%, 4.9%, and 6.8% in high-dose, low-dose, and placebo groups, respectively.²¹

Adverse effects that are not dependent on the method of medication administration were comparable between sublingual and transdermal asenapine. Non-dermatologic adverse events (occurring in $\geq 5\%$ of asenapine-treated patients and at least double that of placebo) include: EPS (13% *versus* 8% *versus* 2% in asenapine high-dose, low-dose, placebo groups, respectively) and

weight gain (6% *versus* 2%, high-dose asenapine *versus* placebo). EPS and weight gain appear dose related for transdermal asenapine. Somnolence does not seem to be associated with the transdermal formulation.^{21,75}

The application site for transdermal asenapine is adjusted daily to minimize skin irritation. Transdermal asenapine can result in dermatologic side effects, including erythema (9.8%, 9.3%, 3%) and pruritis (3.9%, 4.9%, 1.9%) in the 7.6 mg/24 h, 3.8 mg/24 h, and placebo groups, respectively. There was one serious adverse event, in which one patient receiving HP-3070 7.6 mg/24 h experienced severe application-site erythema which resolved without intervention, and the patient remained in the study. Overall, the rates of discontinuation due to dermatologic conditions or reactions were $\leq 0.5\%$ across all groups.

Limitations to use

The largest barrier to more widespread use of asenapine at this time appears to be cost, and in turn, limited availability. At this time, 60 tablets of generic 10 mg asenapine costs between \$219 and \$326. The transdermal patch formulation of asenapine is only available as a branded product, and 30 7.6/24 h patches currently cost between \$1189 and \$1259.⁷⁶ When considering cost, the potentially favorable impact of asenapine on healthcare utilization should also be considered. In a retrospective cohort study conducted by the company marketing sublingual asenapine, patients were less likely to be hospitalized in the 6 months following initiation of asenapine treatment as compared with the 6 months prior to the initiation of asenapine treatment (41.8% *versus* 26.2%, $p < 0.001$) or be seen in the emergency room (24.9% *versus* 18.9%, $p = 0.03$). Healthcare costs decreased by \$4776 in the post-asenapine treatment period despite mean pharmacy costs increasing by \$828.⁷⁷

As with any oral (or transdermal) medication, a certain degree of patient co-operation is required, precluding its use in patients requiring parenteral administration of an antipsychotic on an emergent basis. Patients who have difficulty avoiding food or drink may not be ideal candidates for sublingual asenapine because patients are advised not to eat or drink in the 10 min following asenapine administration. However, waiting the full 10 min may not be necessary; the tablet itself disintegrates within 10 s (dissolution is rapid because

the tablet is highly porous with high aqueous solubility) and the mean asenapine exposure for subjects given water at 2 min was only ~20% lower, and at 5 min was only ~10% lower.⁷ Still, this may be challenging for patients taking other medications that require juice or water to aid in swallowing. Additionally, patients may find adhering to the twice-daily dosing of sublingual asenapine difficult. In contrast, while transdermal asenapine provides an opportunity for improved medication adherence, limitations include the potential for application-site and environmental factors to influence adhesion and absorption.⁷⁸

Place in treatment

Based on a recent network meta-analysis, asenapine ranks as a moderate metabolic offender and is comparable with brexpiprazole and risperidone in terms of weight gain, and causes minimal change in blood glucose, similar to lurasidone and ziprasidone.⁷⁹ In terms of comparative efficacy, the rate of all-cause discontinuation for asenapine places it in a tier alongside aripiprazole, quetiapine, and lurasidone.⁷² Although asenapine ranked 5th and 8th out of 21 antipsychotics for alleviating negative and positive symptoms of schizophrenia, respectively, there is considerable overlap in terms of the 95% credible intervals for the standardized mean differences for these outcomes among almost all of the tested antipsychotics.

What truly distinguishes asenapine is its atypical method of administration. Sublingual and transdermal asenapine have the potential to enhance treatment adherence by minimizing covert non-adherence ('cheeking'). Unrecognized cheeking of pills can lead to complex and unnecessary treatment regimens.⁸⁰ In considering the heterogeneous landscape of antipsychotic medications, asenapine has a unique profile and could likely be utilized in patients that prioritize metabolically favorable medications, or prefer a sublingual or transdermal preparation. Further work on characterizing potentially different clinical outcomes based on the formulation used would be of interest.

Conclusion

Asenapine is an atypical antipsychotic medication available in two different atypical formulations: a sublingually absorbed tablet and a transdermal 'patch.' This is a consequence of asenapine having almost no bioavailability if directly swallowed. The clinical trial development program for the

sublingual preparation has led to FDA approval for the treatment of schizophrenia in adults, acute monotherapy treatment of manic or mixed episodes in bipolar I disorder in adults and pediatric patients 10–17 years of age, adjunctive treatment to lithium or valproate in bipolar I disorder in adults, and for maintenance monotherapy treatment in bipolar I disorder in adults. The transdermal formulation has received FDA approval solely for the treatment of adults with schizophrenia, as studies of this preparation were not conducted in bipolar disorder nor in pediatric patients. The efficacy and tolerability of asenapine has been established in acute and long-term trials, with its tolerability being similar to the more metabolically favorable SGAs. Adverse events unique to the formulations include oral hypoesthesia and dysgeusia for the sublingual format, and application-site erythema and pruritus for the transdermal system.

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Leslie Citrome MD, MPH: Consultant for AbbVie, Acadia, Alkermes, Allergan, Angelini, Astellas, Avanir, Axsome, BioXcel, Boehringer Ingelheim, Cadent Therapeutics, Eisai, Impel, Intra-Cellular Therapies, Janssen, Karuna, Lundbeck, Lyndra, Medavante-ProPhase, Merck, Neurocrine, Noven, Otsuka, Ovid, Relmada, Sage, Sunovion, Teva, University of Arizona, and one-off *ad hoc* consulting for individuals/entities conducting marketing, commercial, or scientific scoping research. Speaker for AbbVie, Acadia, Alkermes, Allergan, Angelini, Eisai, Intra-Cellular Therapies, Janssen, Lundbeck, Neurocrine, Noven, Otsuka, Sunovion, Takeda, Teva, and CME activities organized by medical education companies such as Medscape, NACCME, NEI, Vindico, and universities and professional organizations/societies. Stocks (small number of shares of common stock) with Bristol-Myers Squibb, Eli Lilly, J & J, Merck, Pfizer purchased >10 years ago. Royalties from Wiley (Editor-in-Chief, International Journal of Clinical Practice, through end 2019), UpToDate (reviewer), Springer Healthcare (book), Elsevier (Topic Editor, psychiatry, clinical therapeutics).

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