Efficacy and Tolerability of Asenapine in Acute Schizophrenia: A Placebo- and Risperidone-Controlled Trial

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Objective: This 6-week trial assessed the efficacy, tolerability, and safety of the investigational psychopharmacologic agent asenapine versus placebo and risperidone in patients with acute schizophrenia (DSM-IV criteria).

Method: In a study conducted from August 2001 to May 2002, patients were randomly assigned to receive sublingual asenapine 5 mg b.i.d., placebo b.i.d., or oral risperidone 3 mg b.i.d. The primary outcome measure was improvement from baseline in Positive and Negative Syndrome Scale (PANSS) total score. Secondary outcomes included changes in Clinical Global Impressions-Severity of Illness (CGI-S) score and scores on PANSS positive, negative, and general psychopathology subscales.

Results: The intent-to-treat population comprised 174 patients who received ≥ 1 dose of study drug and ≥ 1 postbaseline assessment. At study end or last observation, mean improvements on PANSS total, negative subscale, and general psychopathology subscale scores were all significantly greater with asenapine than with placebo ($p < .005$, $p = .01$, and $p < .005$, respectively). Compared with placebo, improvements on CGI-S and PANSS positive subscale scores were significantly greater with both asenapine ($p < .01$ and $p = .01$) and risperidone ($p < .005$ and $p < .05$). Overall incidence rates of adverse events were comparable for asenapine and placebo, whereas risperidone was associated with substantial weight gain and prolactin elevation.

Conclusion: Asenapine was effective and well tolerated in patients with acute schizophrenia and may provide a new option for control of negative symptoms.

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The atypical antipsychotics represented an important advance in the treatment of schizophrenia, offering effectiveness comparable to that of conventional antipsychotics but with a lower propensity to cause extrapyramidal symptoms (EPS).[1,2] However, various atypical antipsychotics have been associated with weight gain, diabetes, and dyslipidemia (raising the risk of metabolic syndrome and associated cardiovascular disease), as well as sexual dysfunction and sedation.[3–6] Anticholinergic and hematologic effects, QTc prolongation, stroke, and increased mortality in elderly patients have also been reported with some atypical antipsychotic drugs.[3,7–9]

The effectiveness of pharmacotherapy for schizophrenia is most often assessed in terms of efficacy in controlling positive symptoms during an acute psychotic episode. Antipsychotic effectiveness is also measured by prevention or delay of relapse during maintenance after stabilization of positive symptoms. Underpinning this objective is the premise that patients will remain on prescribed therapy. However, patient discontinuations from both conventional and atypical antipsychotics are frequent,[10] raising the risk of relapse[11,12] and the need for costly rehospitalization.

Moreover, manifestations of schizophrenia other than the positive symptoms seen in acute psychotic episodes (i.e., negative, cognitive, and affective symptoms) account for much suffering, disability, morbidity, and mortality.[13,14] Although all antipsychotics ameliorate such symptoms to varying degrees, none are completely

effective in all symptom domains.[15,16] Thus, there is a need for newer, more effective agents to treat the full range of symptoms expressed in schizophrenia.

Asenapine is a novel psychopharmacologic agent in clinical development for the treatment of schizophrenia and bipolar disorder. Like all effective antipsychotic agents, asenapine modulates activity at dopamine D_2 receptors to control the positive symptoms of schizophrenia; positron emission tomography studies showed > 65% occupancy of D_2 receptors in schizophrenia patients given asenapine 6 mg/day.[17]

Atypical antipsychotics are characterized by a high ratio of 5-HT_{2A} to D_2 activity; however, relative to its D_2 affinity, asenapine also shows higher binding affinity at serotonin 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, 5-HT_6, and 5-HT_7 receptors as well as at dopamine D_1, D_3, and D_4 receptors and α-adrenergic and histaminic receptor subtypes (including H_2 receptors).[18] In contrast to olanzapine and clozapine, asenapine shows almost no affinity for muscarinic receptors, and thus incurs minimal risk of anticholinergic side effects. In comparison with the atypical antipsychotics, asenapine shows generally greater potency as an antagonist at all serotonin receptor subtypes except for 5-HT_{1A} and 5-HT_{1B}.[18]

Current pharmacotherapy for schizophrenia is limited by inconsistent or inadequate control of negative, affective, and cognitive symptoms, as well as by distressing side effects. Consequently, there is a high incidence of poor adherence and discontinuation, often resulting in relapse requiring costly rehospitalization. Antipsychotic pharmacotherapy offering improved effectiveness in treating the full range of positive, negative, affective, and cognitive symptoms associated with schizophrenia, plus improved tolerability, therefore remains an important unmet clinical need.

The unusual pharmacologic characteristics of asenapine may contribute to a favorable clinical profile in controlling schizophrenic and bipolar symptoms with a high degree of safety and tolerability. We therefore designed the present study to evaluate the efficacy and tolerability of asenapine versus placebo in patients with acute exacerbation of schizophrenia; risperidone was also compared against placebo as a means of verifying the general validity of the trial design but was not compared directly against asenapine.

METHOD

Trial Design

This double-blind, double-dummy, 3-arm, fixed-dose, 6-week, placebo- and risperidone-controlled trial was conducted from August 2001 to May 2002 at 21 sites in the United States. The study received approval from the institutional review board or ethics committee at each trial site prior to enrollment of the first patient, and was conducted according to Declaration of Helsinki and International Committee on Harmonization Guidelines for Good Clinical Practice criteria.

Eligible patients entered a single-blind placebo washout of 3 to 7 days in a hospital. Those who were > 75% adherent during this phase were randomized to treatment with asenapine, placebo, or risperidone. For weeks 1 to 3, the study was conducted on an inpatient basis; for weeks 4 to 6, patients who had improved sufficiently from baseline were treated on an outpatient basis.

Patients

Eligibility requirements included age ≥ 18 years, a *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition (DSM-IV) diagnosis of schizophrenia with symptoms of the disorganized (295.10), paranoid (295.30), catatonic (295.20), or undifferentiated (295.90) subtypes. Acute exacerbation was defined by a baseline Clinical Global Impressions-Severity of Illness (CGI-S)[19] score ≥ 4 (at least moderately ill) and a Positive and Negative Syndrome Scale (PANSS)[20] total score ≥ 60. In addition, baseline scores ≥ 4 were required on ≥ 2 items of the PANSS positive subscale (delusions, conceptual disorganization, hallucinatory behavior, grandiosity, and suspiciousness/persecution), and the baseline PANSS total score had to be ≥ 80% of that at prior visits.

Patients who had taken previous antipsychotic medication (other than clozapine) were required to have had a clinically meaningful response to the antipsychotic. Current antipsychotic medication was discontinued ≥ 3 days before baseline assessment; mood stabilizers (e.g., valproic acid, divalproex, and carbamazepine) were discontinued ≥ 5 days before baseline. In patients who had received depot neuroleptics, ≥ 1 month had to elapse between the last injection and the first dose of trial medication.

Reasons for ineligibility included actively suicidal state; DSM-IV diagnosis of residual-type schizophrenia (295.60), schizophreniform disorder (295.40), or schizoaffective disorder (295.70); or a primary psychiatric diagnosis other than schizophrenia. Women who were pregnant or breastfeeding were excluded, as were women of child-bearing age who did not use an acceptable method of contraception. Patients were also excluded if they had taken any experimental medication within 30 days before baseline or had untreated or clinically significant renal, endocrine, hepatic, respiratory, cardiovascular, hematologic, immunologic, malignant, or cerebrovascular disease. Patients with a history of neurologic illness (including seizures, previous use of anticonvulsants, > 1 childhood febrile convulsion) or previous exposure to asenapine were also excluded. Clinically significant abnormalities on physical examination, in vital signs, laboratory parameters, or 12-lead

electrocardiogram (ECG); a score > 2 (mild) on any item of the Abnormal Involuntary Movement Scale (AIMS)[21] at screening; or a diagnosis of drug and/or alcohol abuse (DSM-IV criterion, 305.00) within 30 days before screening were all criteria for exclusion.

All patients were required to have a caregiver and be able to understand the trial procedures. Patients were enrolled after providing written informed consent following full disclosure of the nature, procedures, and risks of the trial.

Table 1. Demographics and Baseline Clinical Characteristics (treated population, N = 180)

Characteristic	Asenapine	Placebo	Risperidone
Randomly assigned population, N	60	62	60
Treated population, N	59	62	59
Intent-to-treat population, N	58	60	56
Treated population			
Men, N (%)	46 (78)	49 (79)	36 (61)
Mean (range) age, y	38 (21–70)	42 (22–68)	43 (22–61)
Mean (range) weight, kg	89 (59–155)	90 (55–150)	85 (57–162)
Ethnicity, N (%)			
White	25 (42)	20 (32)	25 (42)
Black	28 (47)	32 (52)	26 (44)
Other	6 (10)	10 (16)	8 (14)
Schizophrenia diagnosis, N (%)			
Paranoid	50 (85)	60 (97)	50 (85)
Disorganized	1 (2)	0	3 (5)
Undifferentiated	7 (12)	1 (2)	4 (7)
Not specified or not obtained	1 (2)	1 (2)	2 (3)
Duration of present episode, N (%)			
< 1 month	34 (58)	39 (63)	44 (75)
1–6 months	21 (36)	16 (26)	11 (19)
> 6 months	3 (5)	6 (10)	3 (5)
Not specified or not obtained	1 (2)	1 (2)	1 (2)
Negative symptoms, N (%)			
Episodic with prominent negative symptoms	23 (39)	20 (32)	22 (37)
Continuous episodic with prominent negative symptoms	11 (19)	9 (15)	10 (17)
Absent, other pattern, or not specified or not obtained	25 (42)	33 (53)	27 (46)

Study Treatments

All study regimens called for b.i.d. dosing (morning and evening). Sublingual asenapine was titrated as 1 mg b.i.d. on day 1, 2 mg b.i.d. on day 2, 3 mg b.i.d. on day 3, 4 mg b.i.d. on day 4, and 5 mg b.i.d. on days 5 to 42. Oral risperidone was titrated as 1 mg b.i.d. on day 1, 2 mg b.i.d. on day 2, and 3 mg b.i.d. on days 3 to 42. In this double-dummy design, asenapine-treated patients also received oral placebo b.i.d., risperidone-treated patients also received sublingual placebo b.i.d., and patients in the placebo-control group received oral and sublingual placebo b.i.d.

Concomitant medication was permitted for sleep induction (with zolpidem tartrate ≤ 10 mg/day, zaleplon ≤ 20 mg/day, or chloral hydrate ≤ 3000 mg/day) or agitation (with benzodiazepines at daily doses equivalent to lorazepam ≤ 10 mg/day). Other psychotropic medications were prohibited. Anticholinergic agents could be given for newly emergent EPS, but other medication regimens had to be stable at trial entry.

Clinical Assessments

Efficacy evaluations. The primary efficacy outcome measure was change from baseline in PANSS total score at end point. Secondary efficacy outcome measures included changes in CGI-S score and PANSS positive, negative, and general psychopathology subscale scores. Postbaseline assessments were obtained weekly (on days 7, 14, 21, 28, 35, and 42).

Prerequisites for raters conducting efficacy evaluations were ≥ 2 years experience in performing clinical evaluations of patients with schizophrenia and participation in a study-specific rater-education program.

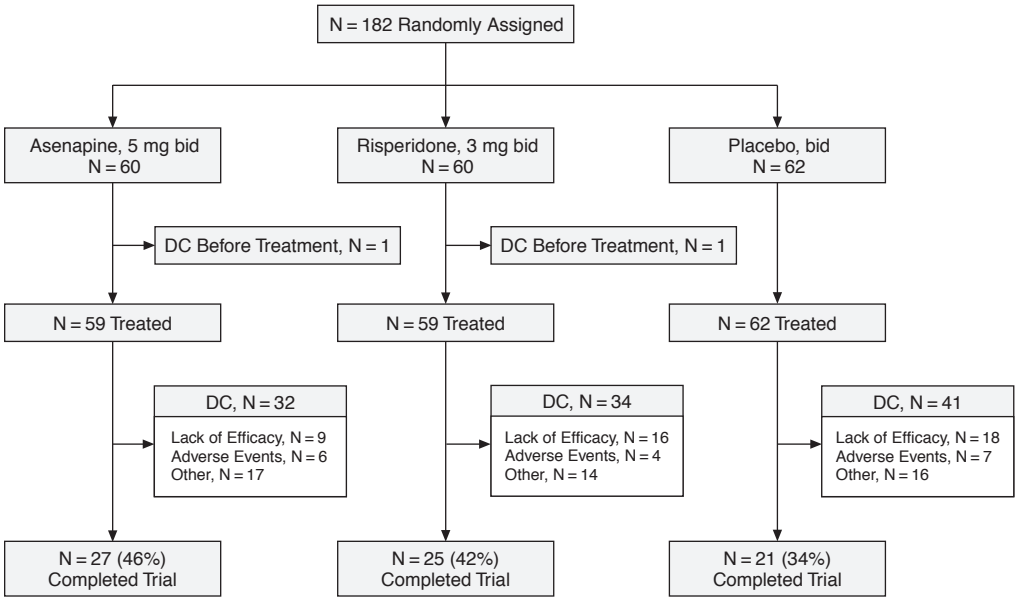
Safety evaluations. Laboratory and ECG assessments were conducted at screening and weekly intervals postbaseline. Laboratory measures (fasting) were obtained per protocol. Full physical examinations were conducted at screening and end point. In the washout and inpatient phases, blood pressure and heart rate were measured twice daily, temperature and respiratory rate once daily; in the outpatient phase, vital signs were measured weekly.

Adverse events were recorded weekly postbaseline. Extrapyramidal symptom assessments were performed weekly using the Barnes Akathisia Scale (BAS),[22] the Simpson-Angus Scale (SAS),[23] and the AIMS. Adverse events were monitored and treated as appropriate until symptoms resolved. A telephone interview was conducted approximately 30 days after the last dose of trial medication to evaluate any sequelae.

Adherence. Adherence with study medication during inpatient treatment was recorded by hospital staff. During outpatient treatment, adherence was monitored by counts of returned tablets and patients' reports of nonadherence. Adequate adherence was defined as taking ≥ 75% of assigned medication.

Statistical analysis. It was estimated that 60 patients per treatment arm would provide adequate power to detect a difference of 15 points on PANSS total score between active treatment and placebo with 95% confidence. For the intent-to-treat (ITT) population (treated patients with ≥ 1 postbaseline efficacy evaluation), the primary outcome measure (change from baseline in PANSS total score with asenapine vs. placebo at end point or last observation carried forward [LOCF]) was analyzed using least-squares means based on 2-way analysis of variance, with treatment and center as factors. For secondary outcome measures, similar comparisons were made for asenapine versus placebo and risperidone versus placebo. Between-group comparisons for body weight and laboratory values were analyzed using χ^2 tests or Fisher exact test.

Figure 1. Patient Disposition[a]



[a]Numbers of patients who were randomly assigned, were treated, and completed treatment, with reasons for discontinuation (DC) shown.

RESULTS

Patient Demographics and Disposition

From 182 randomly assigned patients, 180 formed the treated population (patients who received ≥ 1 dose of study medication; N = 59, N = 62, and N = 59 in the asenapine, placebo, and risperidone groups, respectively). Within the treated population, 165 patients (92%) had received previous antipsychotic drug treatment. The ITT population (treated patients with ≥ 1 postbaseline assessment) comprised 174 patients (N = 58, N = 60, and N = 56 in the asenapine, placebo, and risperidone groups). The treatment groups were generally well matched with regard to demographic and baseline clinical characteristics (Table 1).

Patient disposition is shown in Figure 1. The proportions of treated patients who completed the trial were greater in the asenapine and risperidone groups (46% and 42%, respectively) than in the placebo group (34%). For asenapine, the gender ratio among dropouts matched the gender ratio in the treated population (each, 78% men and 22% women). The male/female ratio among dropouts was similar to the ratio in the treated population for both risperidone (65%:35% vs. 61%:39%) and placebo (83%:17% vs. 79%:21%). The incidence of withdrawal due to lack of efficacy was lower for asenapine (15% of treated patients in the asenapine group, 28% of withdrawals from the asenapine group) than for placebo (29%, 44%) or risperidone (27%, 47%). The incidence of withdrawal due to adverse events was comparable for asenapine (10% of treated patients, 19% of withdrawals), placebo (11%, 17%), and risperidone (7%, 12%).

Adherence and Concomitant Medication

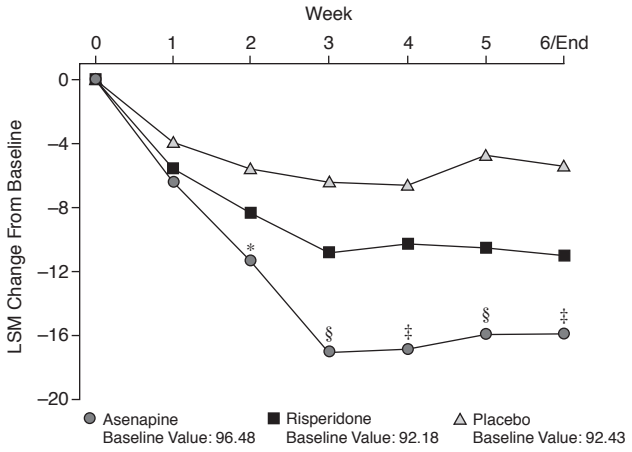
Although the overall rate of discontinuation before the end of the study was close to 60%, adherence among those patients still participating in the study at any time was good (96% [173/180] during inpatient treatment, 97% [89/92] in the outpatient phase). There were no significant between-group differences in adherence rates.

The proportion of treated patients taking concomitant medication was similar for the 3 treatment groups. The most frequently prescribed concomitant medications were lorazepam (59%, 69%, and 68% for the asenapine, placebo, and risperidone groups, respectively) and zolpidem (31%, 27%, and 27%). Antiparkinsonian drugs were more frequently prescribed for risperidone-treated patients (31%) than for asenapine- or placebo-treated patients (17% and 21%, respectively).

Primary Efficacy Measure: PANSS Total Score

For the ITT population, mean baseline PANSS total scores were similar across the treatment groups: 96.5, 92.4, and 92.2 for the asenapine, placebo, and risperidone groups, respectively. At end point, mean changes from baseline were –15.9 with asenapine versus –5.3 with placebo ($p < .005$); the change with risperidone (–10.9) was nonsignificant versus placebo. Compared with placebo, asenapine produced significantly greater decreases in PANSS total scores from week 2 onward (Figure 2).

Figure 2. Primary Measure of Efficacy in the Intent-to-Treat Population: Change From Baseline in PANSS Total Score[a]



[a]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 ≤ .005, asenapine versus placebo.
§p = .001, asenapine versus placebo.

Secondary Efficacy Measures

CGI-S score. Mean baseline scores were 4.7, 4.6, and 4.6 for the asenapine, placebo, and risperidone groups, respectively. At end point, mean changes from baseline were –0.74 for asenapine versus –0.28 for placebo ($p < .01$); change with risperidone (–0.75) was also significant versus placebo ($p < .005$). Compared with placebo, both active treatments were associated with significantly greater decreases in CGI-S scores from week 4 onward (Figure 3A).

PANSS positive subscale score. Mean baseline scores were 25.2, 24.1, and 24.7 for the asenapine, placebo, and risperidone groups, respectively. At end point, mean changes from baseline were –5.5 for asenapine versus –2.5 for placebo ($p = .01$); change with risperidone (–5.1) was also significant versus placebo ($p < .05$). Compared with placebo, there were significantly greater decreases in PANSS positive subscale scores with asenapine from week 3 onward, and with risperidone at weeks 1, 3, 5, and 6 (Figure 3B).

PANSS negative subscale score. Mean baseline scores were 24.1, 23.1, and 21.9 for the asenapine, placebo, and risperidone groups, respectively. At end point, mean changes from baseline were –3.2 for asenapine versus –0.6 for placebo ($p = .01$); change with risperidone (–1.05) was nonsignificant versus placebo. Compared with placebo, asenapine produced significantly greater decreases in PANSS negative subscale scores from week 3 onward (Figure 3C).

PANSS general psychopathology subscale score. Mean baseline scores were 47.2, 45.2, and 45.6 for the asenapine, placebo, and risperidone groups, respectively. At end point, mean changes from baseline were –7.2 for asenapine versus –2.2 for placebo ($p < .005$); change with risperidone (–4.8) was nonsignificant versus placebo. Compared with placebo, asenapine produced significantly greater decreases in PANSS general psychopathology subscale scores from week 2 onward (Figure 3D).

Tolerability and Safety

Adverse events. Of 180 treated patients, 151 (84%) experienced ≥ 1 adverse event at some time during the study (83%, 79%, and 90% of patients in the asenapine, placebo, and risperidone groups, respectively). Incidence rates for adverse events considered to be severe or serious were 12% and 8%, respectively, in the asenapine group; 6% and 10%, respectively, in the placebo group; and 7% and 7% in the risperidone group. All patients with adverse events recovered without sequelae.

Adverse events occurring in ≥ 10% of patients in any treatment group are shown in Table 2. The most frequently reported adverse events were insomnia, somnolence, nausea, anxiety, and agitation in the asenapine group; agitation, headache, anxiety, and dizziness in the placebo group; and insomnia, somnolence, anxiety, agitation, and headache in the risperidone group.

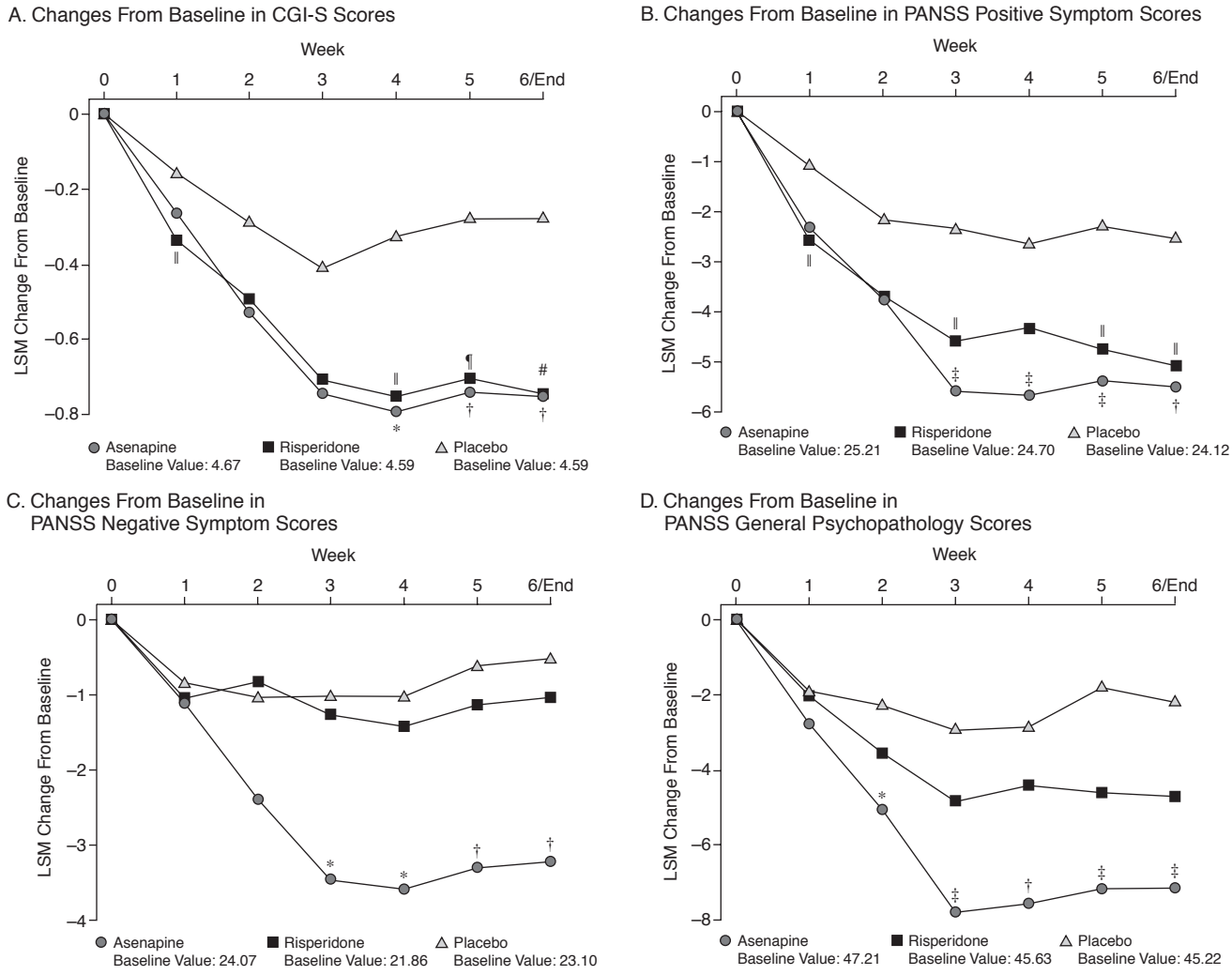
Extrapyramidal symptoms. As shown in Table 3, there were no significant between-group differences on the SAS, BAS, and AIMS. However, compared with the other treatment groups, risperidone-treated patients were more likely to report symptoms resembling hypertonia (12% vs. 0% for asenapine and 3% for placebo) and hyperkinesia (7% vs. 0% for asenapine and placebo) as adverse events; also, as stated, risperidone-treated patients were more likely to use antiparkinsonian drugs.

Body weight. The incidence of clinically significant weight gain (≥ 7% increase from baseline) was 17.0% with risperidone versus 4.3% with asenapine and 1.9% with placebo (Figure 4A). The incidence of clinically significant weight gain parallels the actual mean weight gain by treatment group: 1.6 kg with risperidone versus 0.47 kg with asenapine and 0.15 kg with placebo (Figure 4B). The greatest mean weight gain (3.4 kg) occurred in risperidone-treated patients with baseline body mass index > 25 kg/m^2.

Clinical laboratory values. The proportion of patients with normal baseline prolactin levels but postbaseline levels ≥ 2 times the laboratory upper limit of normal (ULN) was higher in the risperidone group (79%) than in the asenapine or placebo groups (9% and 2%, respectively). Figure 5 shows prolactin levels week by week.

Post-baseline fasting glucose levels ≥ 20% above ULN occurred in 14%, 12%, and 20% of patients treated with asenapine, placebo, and risperidone, respectively. Mean

Figure 3. Secondary Measures of Efficacy in the Intent-to-Treat Population[a]



[a]Changes from baseline in scores on (A) the Clinical Global Impressions-Severity of Illness (CGI-S) scale and on the Positive and Negative Syndrome Scale (PANSS) subscales for (B) positive symptoms, (C) negative symptoms, and (D) general psychopathology were determined at study end or at the end of treatment using least squares mean (LSM) and 2-factor analysis of variance.
*$p < .05$, asenapine versus placebo.
†$p \leq .01$, asenapine versus placebo.
‡$p \leq .005$, asenapine versus placebo.
‖$p < .05$, risperidone versus placebo.
¶$p < .01$, risperidone versus placebo.
#$p < .005$, risperidone versus placebo.

changes from baseline in total cholesterol were –0.4, –1.7, and +2.3 mmol/L for the asenapine, placebo, and risperidone groups, respectively; mean changes in fasting triglycerides were 0, –0.1, and 0 mmol/L.

Cardiovascular assessments. There were no clinically important between-group differences with respect to treatment effects on blood pressure or heart rate during the study. Among all treated patients with normal ECG at baseline, the incidence of sinus tachycardia (≥ 100 bpm or rate increase ≥ 15 bpm) was 12% with asenapine, 12% with placebo, and 18% with risperidone. At least 1 postbaseline QTc interval ≥ 450 ms was observed in 9%, 10%, and 18% of patients treated with asenapine, placebo, and risperidone, respectively, but there were no reports of QT interval prolongation > 500 ms in any treatment group. Mean changes in QTc from baseline were +4.6 ms with asenapine, –1.6 ms with placebo, and +4.4 ms with risperidone.

DISCUSSION

In this randomized, double-blind clinical trial of adult patients with acute schizophrenia, the investigational psychopharmacologic agent asenapine was compared with placebo; a third treatment group received the atypical anti-

Table 2. Incidence of Adverse Events in ≥10% of Patients in Any Treatment Group (treated population)

World Health Organization Preferred Term	Patients, N (%)[a]		
	Asenapine (N = 59)	Placebo (N = 62)	Risperidone (N = 59)
Insomnia	11 (19)	8 (13)	13 (22)
Somnolence	11 (19)	8 (13)	9 (15)
Nausea	11 (19)	8 (13)	7 (12)
Anxiety	10 (17)	9 (15)	9 (15)
Agitation	9 (15)	15 (24)	11 (19)
Headache	8 (14)	17 (27)	13 (22)
Vomiting	8 (14)	7 (11)	3 (5)
Constipation	6 (10)	6 (10)	4 (7)
Psychosis	6 (10)	4 (6)	4 (7)
Dizziness	5 (8)	9 (15)	4 (7)
Dyspepsia	4 (7)	5 (8)	7 (12)
Upper respiratory tract infection	4 (7)	3 (5)	6 (10)
Pain	3 (5)	4 (6)	6 (10)
Fatigue	2 (3)	4 (6)	6 (10)
Hypertonia	0 (0)	2 (3)	7 (12)

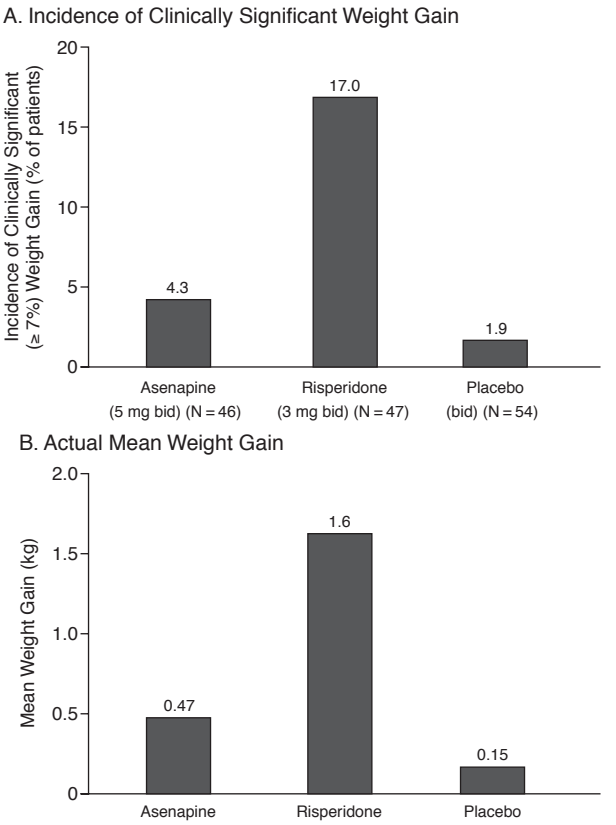
[a]Adverse events are not mutually exclusive within groups.

Table 3. Change[a] From Baseline to End Point in Mean Scores on Extrapyramidal Symptom Rating Instruments

Rating Scale	Asenapine (N = 56–57)		Placebo (N = 59–60)		Risperidone (N = 56)	
	Baseline	Change	Baseline	Change	Baseline	Change
BAS	1.00	–0.21	0.53	0.25	0.68	0.14
SAS	1.11	–0.32	0.64	–0.24	0.75	0.05
AIMS	1.05	0.04	0.93	0.46	1.36	–0.02

[a]Negative change indicates improvement; positive change indicates worsening.
Abbreviations: AIMS = Abnormal Involuntary Movement Scale, BAS = Barnes Akathisia Scale, SAS = Simpson-Angus Scale.

Figure 4. Treatment Effects on Body Weight[a]



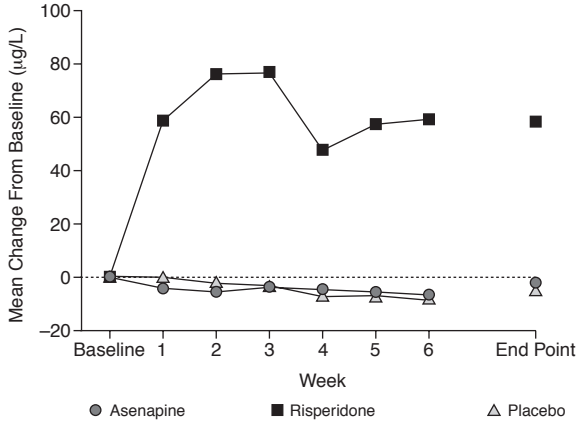
[a]Effects on weight were assessed at study end or at the end of treatment in terms of (A) the incidence of clinically significant weight gain (≥ 7% increase from baseline) and (B) actual mean weight gain.

psychotic drug risperidone. Like most of the atypical antipsychotics, asenapine acts as an antagonist at dopamine D_2 receptors but shows greater binding affinity at serotonin 5-HT_{2A} receptors. Asenapine also shows a high degree of affinity at several other serotonin receptor subtypes (5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, 5-HT_6, and 5-HT_7) as well as at dopamine D_1, D_3, and D_4 receptors, and α-adrenergic and histaminic receptor subtypes, but almost no affinity for muscarinic receptors. This pharmacologic profile may explain, at least in part, the effectiveness and tolerability of asenapine in controlling a wide range of schizophrenia symptoms.

The main finding from the present study is that asenapine 5 mg b.i.d. was superior to placebo in treating the positive and negative symptoms of schizophrenia. Risperidone 3 mg b.i.d. also was superior to placebo in reducing positive symptoms, but its effect on negative symptoms was nonsignificant versus placebo, in contrast to early trials showing significantly greater improvement on the PANSS negative subscale score with risperidone 6 mg/day than with placebo.[24,25] Although there were no direct statistical comparisons between asenapine and risperidone, it may be worth noting that discontinuations due to treatment ineffectiveness were more common with risperidone than with asenapine.

The performance of risperidone versus placebo in this trial was not as good as might have been expected, and it may be questioned whether the dosage (6 mg per day) was excessive. A review of schizophrenia trial data correlated clinical responses with risperidone at different dosages, and concluded that a dosage of 4 mg per day would be optimal, that 6 mg per day offered no further advantage, and that 10 mg per day and higher would lead to decreased efficacy.[26] Thus, the dosage used in this trial may have exceeded the optimal dosage but is not likely to have compromised the efficacy results for risperidone. Another possible factor is that the proportion of women was higher in the risperidone group (39%) than in the asenapine and placebo groups (22%, 21%), and it has been reported that risperidone in the dosages used in this trial is associated with higher dropout rates in women than in men.[27] In the present trial, however, dropout rates by gender approximated the gender ratio in each treated population, and dropout rates among women were no higher for risperidone (12 of 23 women in the risperidone-treated population [52%]) than for asenapine or placebo (each, 7 of 13 [54%]).

Figure 5. Treatment Effects on Serum Prolactin[a]



[a]Prolactin levels were assessed at weekly intervals to study end (6 weeks) or the end of treatment (last observation carried forward).

The findings from this study may be clinically important, because current antipsychotics have an uneven record of efficacy against persistent negative symptoms (PNS; negative symptoms that are not secondary to positive or affective symptoms, adverse effects of medication, or environmental deprivation and do not resolve with correction of these problems),[28] and because PNS can contribute to impaired social and occupational functioning, reduced quality of life, increased time in hospital, increased burden on caregivers and family members, and poor long-term outcome.[13,29–31] However, the short-term effects of drug treatment on negative symptoms in the acutely ill patients in this study are not necessarily predictive of long-term effects on PNS. Thus, to obtain a realistic appraisal of the effects of asenapine on PNS, the present 6-week study should be followed by studies of long-term use in patients with predominant persistent negative symptoms.

In terms of safety and tolerability, the incidence of clinically significant weight gain was similar for asenapine and placebo in this trial, while the higher incidence of significant weight gain with risperidone is consistent with previous reports,[32–34] reflecting the fact that weight gain varies widely among antipsychotic drugs. Laboratory findings in this study suggest that asenapine does not produce the metabolic disturbances observed with some antipsychotic drugs[3–5] or clinically relevant cardiovascular effects (changes in blood pressure and heart rate, QTc prolongation).

Limitations in this study include the high rate of discontinuance (54%, 66%, and 58% from the asenapine, placebo, and risperidone groups, respectively), which may be due in part to the use of fixed doses instead of flexible dose adjustment based on clinical effects, and may also reflect the high rates of discontinuance that are characteristic of drug trials in patients with schizophrenia. In a post hoc analysis of pooled data from 4 randomized, double-blind clinical trials involving 1627 patients treated with atypical antipsychotics for schizophrenia or related disorders, 53% dropped out at an early stage; poor therapeutic response was the most frequently cited reason for discontinuance.[35]

Many clinical trials in this population, in which dropout rates are often high, use LOCF methodology to account for the missing data, as was done in this study. LOCF is generally considered a conservative method, in that bias is more likely to underestimate than overestimate drug effectiveness (as low scores from patients who drop out because of treatment ineffectiveness are retained with no decrease in the size of N). An analysis of 8 studies (total N = 3725) comparing atypical to conventional antipsychotic pharmacotherapy showed no bias in favor of the atypicals when data were analyzed by LOCF versus other models (although some of the individual trials, when considered separately, did show larger effect sizes with LOCF).[36] More sophisticated techniques, such as mixed model repeated measures, offer the prospect of reduced bias of any kind and may therefore be utilized more routinely in future trials.[37] We performed a post hoc mixed model repeated measures analysis, which confirmed the overall efficacy of asenapine in the primary outcome measure, change from baseline in PANSS total score (mean change: –19.8 ± 3.3 with asenapine, –16.2 ± 3.3 with risperidone, –8.5 ± 3.4 with placebo; difference vs. placebo: –11.33 ± 4.68 [p = .018] with asenapine, –7.72 ± 4.69 [p = .104] with risperidone).

Another limitation was reliance on pill counts and patients' self-reports to monitor adherence, rather than more reliable measures, such as measurement of drug levels in blood. Adherence was similarly and surprisingly high in all 3 treatment groups in this study, but there is no reason to assume that there were significant between-group differences in actual adherence.

Another potential concern is between-group differences in rating scale scores at baseline. Although these differences did not appear to be large, it was the asenapine group that showed the poorest baseline ratings on every scale (baseline differences between risperidone and placebo were very small). Therefore, to assess the possibility that changes from baseline were larger for asenapine than for placebo because the asenapine patients had the most room for improvement, we performed a post hoc analysis of covariance to ascertain whether these differences could be affecting the efficacy data for asenapine. For the primary outcome measure (PANSS total score), the improvement with asenapine became nonsignificant versus placebo at week 2 but remained significant at all other time points.

In conclusion, this double-blind, placebo- and risperidone-controlled 6-week study showed that asenapine 5 mg b.i.d. was effective and well tolerated in the treatment of acute schizophrenia and may be a useful option in patients with negative symptoms.

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Drug names: carbamazepine (Carbatrol, Equetro, and others), clozapine (Clozaril, FazaClo, and others), divalproex (Depakote), lorazepam (Ativan and others), olanzapine (Zyprexa), risperidone (Risperdal), valproic acid (Depakene and others), zaleplon (Sonata), zolpidem tartrate (Ambien, Tovalt, and others).

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