Meta-Analyses of the Efficacy of Asenapine for Acute Schizophrenia: Comparisons With Placebo and Other Antipsychotics

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ABSTRACT

Context: Asenapine is an approved treatment for schizophrenia in the United States.

Objective: Meta-analyses were conducted to evaluate the efficacy of asenapine in acute schizophrenia compared with placebo and other antipsychotics.

Data Sources: Four asenapine trials from the asenapine development program were pooled for the meta-analysis. To compare asenapine versus placebo treatment effect with other antipsychotics, we added integrated asenapine data to a previously published meta-analysis. For comparative efficacy of asenapine versus other second-generation antipsychotics (SGAs), data from a second published meta-analysis were combined with the 4 asenapine trials.

Data Analyses: To evaluate efficacy, mean change in Positive and Negative Syndrome Scale (PANSS) total score was examined in asenapine and other antipsychotics. To assess clinical relevance, PANSS response rates and associated odds ratios (ORs) for treatment response were assessed. To assess the relative efficacy of SGAs, a network meta-analysis with PANSS total score change was conducted by using data from the 2 published meta-analyses together with asenapine data.

Results: Asenapine was superior to placebo with regard to mean change in PANSS total score (last observation carried forward [LOCF]: −3.6, *P* = .002; mixed model for repeated measures [MMRM]: −4.1, *P* = .001), an effect comparable to active controls from the same trials (LOCF: −4.0, *P* = .002; MMRM: −4.8, *P* = .001). PANSS responder rates were significantly better with asenapine versus placebo (OR, 1.9; *P* < .001) and comparable to active controls (OR, 1.7; *P* = .002). Effect sizes for asenapine were somewhat lower than those reported in the literature for other SGAs. Network meta-analysis also demonstrated that the efficacy of asenapine was comparable to that of other SGAs; estimated differences between asenapine and other SGAs ranged from 3.9 points (95% CI, 0.3 to 7.4) greater than ziprasidone to 2.9 points (95% CI, −0.1 to 5.9) less than olanzapine.

Conclusions: These meta-analyses indicate that the efficacy of asenapine for acute schizophrenia is superior to placebo and comparable to several other SGAs.

In the last 2 decades, a variety of second-generation antipsychotics (SGAs) have been developed for schizophrenia. Asenapine has recently been added as a treatment option for schizophrenia for adults by the US Food and Drug Administration and as monotherapy or adjunctive therapy with lithium or valproate in the treatment of manic or mixed episodes associated with bipolar I disorder. Asenapine is also indicated in the European Union for the treatment of moderate to severe manic episodes associated with bipolar I disorder.[1] Evaluating treatment options among SGAs is a complex task for a variety of reasons. Second-generation antipsychotics are not a pharmacologically homogeneous drug class,[2] presumably resulting in different safety and tolerability profiles.[3] Moreover, only a subset of schizophrenia patients will respond to any given SGA.[4] Risk-benefit assessments across agents must be made on an individual patient basis, and response to an SGA will remain uncertain. Thus, it is valuable to have a new treatment option available.

Evaluating SGAs on the basis of risk-benefit is complex because even comparing "average" efficacy is not straightforward. First, even in large randomized clinical trials, observed treatment effects do not necessarily provide a homogeneous pattern. Asenapine data also illustrate this variability. Four active- and placebo-controlled short-term trials were conducted with asenapine in the effective dose range of 5 or 10 mg twice daily: 2 trials were robustly positive,[5,6] 1 was negative,[7] and 1 failed.[8] Second, placebo-controlled trials have shown efficacy for SGAs versus placebo, although this effect has been reduced over time,[9,10] even when including compounds that traditionally showed substantial effect sizes. This reduction in efficacy increases the problem of comparing efficacy across SGAs.

Therefore, we used meta-analytic techniques to comprehensively evaluate efficacy data from all applicable randomized asenapine clinical trials. Specifically, we performed meta-analytic comparisons (vs placebo) of mean change in Positive and Negative Syndrome Scale (PANSS)[11] total score for asenapine and other antipsychotics used as active controls in the same trials. To more clearly assess the clinical relevance of these treatment effects, PANSS response rates and associated odds ratios (ORs) for treatment response were assessed. Relative risk for treatment nonresponse with asenapine and other antipsychotics was examined by using data published by Leucht et al[12] into which asenapine data were integrated. Consistent with previous reports,[9,10] these efficacy analyses suggested that treatment effect might be influenced by publication year. Therefore, we further explored this finding by using a meta-regression to assess the impact of publication year on antipsychotic treatment effect versus placebo. Finally, to assess the relative efficacy of SGAs, a

head-to-head network meta-analysis of PANSS total score change was conducted by using data from published head-to-head SGA trials,[13] into which asenapine data were also integrated. These analyses comprehensively characterize the relative efficacy of asenapine within the SGA class, regardless of whether direct comparisons are available, and provide an update of the relative efficacy of the entire SGA class.

DATA SOURCES

Meta-Analyses of Asenapine Clinical Trial Program

Data for the meta-analysis included all randomized, placebo-controlled, 6-week studies of asenapine for acute schizophrenia that administered asenapine in the effective dosage range of 5 or 10 mg twice daily (041004[6] [asenapine 5 mg, n = 58; placebo, n = 60; risperidone, n = 56], 041021[7] [asenapine 5 mg, n = 102; asenapine 10 mg, n = 96; placebo, n = 93; olanzapine, n = 95], 041022[8] [asenapine 5 or 10 mg, n = 85; placebo, n = 89; olanzapine, n = 85], 041023[5] [asenapine 5 mg, n = 109; asenapine 10 mg, n = 105; placebo, n = 122; haloperidol, n = 112]). Each trial had similar inclusion and exclusion criteria and was designed to meet regulatory standards. The primary outcome measure in each trial was change from baseline PANSS total score to study end point in the intent-to-treat (ITT) population, with last observation carried forward (LOCF) as the primary method of imputing missing data; a mixed model for repeated measures (MMRM) was a prespecified secondary analysis in phase 3 trials.[5,7,8]

Meta-analyses were performed by using individual patient data, with asenapine (fixed-dose 5 mg twice daily, fixed-dose 10 mg twice daily, flexible-dose 5 or 10 mg twice daily) and active comparator data pooled across treatment regimens. For all analyses, data from small centers were pooled, as specified in the original statistical analysis plan for each protocol.

For LOCF analysis, meta-analyses were performed using analysis of covariance, with fixed factors for protocol, center (nested in protocol), and randomized treatment group; baseline PANSS total score was a covariate. This method was an extension of the primary analysis specified in each study protocol. The MMRM analysis included fixed factors for protocol, center (nested in protocol), randomized treatment group, visit (repeated measure), and visit-by-treatment interaction; the baseline PANSS total score was a fixed covariate. An unstructured variance-covariance structure was used to model within-patient errors. Denominator degrees of freedom were approximated using the Satterthwaite method[14]; estimates were derived by using the appropriate contrast at week 6.

In asenapine trials, PANSS responders were defined as patients with ≥ 30% decrease from baseline PANSS total score at end point. A meta-analysis on individual patient data was performed by using logistic regression for PANSS responders, with fixed factors for protocol, treatment, and center (nested in protocol); baseline PANSS total score was a covariate. This analysis provided ORs and 95% Wald-type

Clinical Points

- Asenapine is an approved treatment for schizophrenia in the United States.

- The reported meta-analyses indicate that the efficacy of asenapine for acute schizophrenia is superior to placebo and comparable to several other second-generation antipsychotics.

confidence intervals (CIs) for asenapine and active controls versus placebo. The number needed to treat (NNT [the number of patients who must be treated with active drug to achieve 1 additional responder relative to placebo]) was derived from the inverse of the estimated difference in response rates from placebo established using PANSS total score meta-analyses, with binomial regression and the identity link function.

Meta-Analyses of Published Studies With Integrated Asenapine Data

To compare the asenapine treatment effect versus placebo with that of other antipsychotics, all placebo-controlled asenapine clinical trial results were added to a meta-analysis published by Leucht et al[12]; an additional asenapine trial (041002 [Merck; unpublished data on file; 2000]) supplied data for risperidone but not asenapine (the asenapine dose in this study was below the effective range). For each drug, meta-analysis on the standardized effect size using Hedges' g was performed by method of DerSimonian and Laird,[15] allowing for studies using scales other than the PANSS (eg, the Brief Psychiatric Rating Scale) to be included.

To compare PANSS responder results for asenapine with other antipsychotics, asenapine clinical data were combined with data from Leucht et al.[12] However, Leucht et al[12] expressed treatment differences as risk ratios for treatment nonresponse with 95% CIs rather than ORs for treatment response. For consistency, risk ratios for treatment nonresponse were calculated for asenapine.

Effect of Publication Year on Treatment Effect

Meta-regression was performed to assess the impact of publication year on antipsychotic treatment effect versus placebo by using a weighted regression analysis with the inverse of the squared standard error of each placebo comparison as a weight and publication year as a predictor of the standardized treatment effect. Although the years of the study period are more likely to impact treatment effect than the study publication year, publication years were used in these analyses because they simplify study sorting and because the publication year roughly correlates with the study periods.

Head-To-Head Network Meta-Analysis: Asenapine Versus Other SGAs

To assess the comparative efficacy of asenapine and other SGAs, a network meta-analysis combined data published

by Leucht et al[13] with all asenapine trials that included SGA active controls (studies 041004, 041021, 041022).[6–8] In addition, data from the first 6 weeks of a 52-week asenapine safety trial (25517 [NCT00212784]: asenapine 5 or 10 mg, n = 869; olanzapine, n = 297)[16] that used olanzapine as the active control were included. In total, data from 49 head-to-head SGA comparison studies were updated with data from 4 asenapine clinical trials (117 treatment groups; 14,861 patients). As in Leucht et al,[13] we used change from baseline PANSS total score as the primary end point; LOCF accounted for imputed missing data.

The network meta-analysis proceeded in 2 steps. First, for each pair of SGAs for which data were available, a meta-analysis using the DerSimonian and Laird[15] random effects model was performed to estimate relative efficacy and associated variances, taking into account possible heterogeneity. Second, these meta-analytic results were entered into a single linear regression.[17] The design matrix was specified with indicators for each separate comparison (by study), and fixed variance components were used that included the DerSimonian and Laird[15] random effects contribution. By designating 1 SGA as a reference, relative efficacy and associated 95% CIs versus all other SGAs were estimated with maximum likelihood techniques by using the relative efficacy of all available trials.
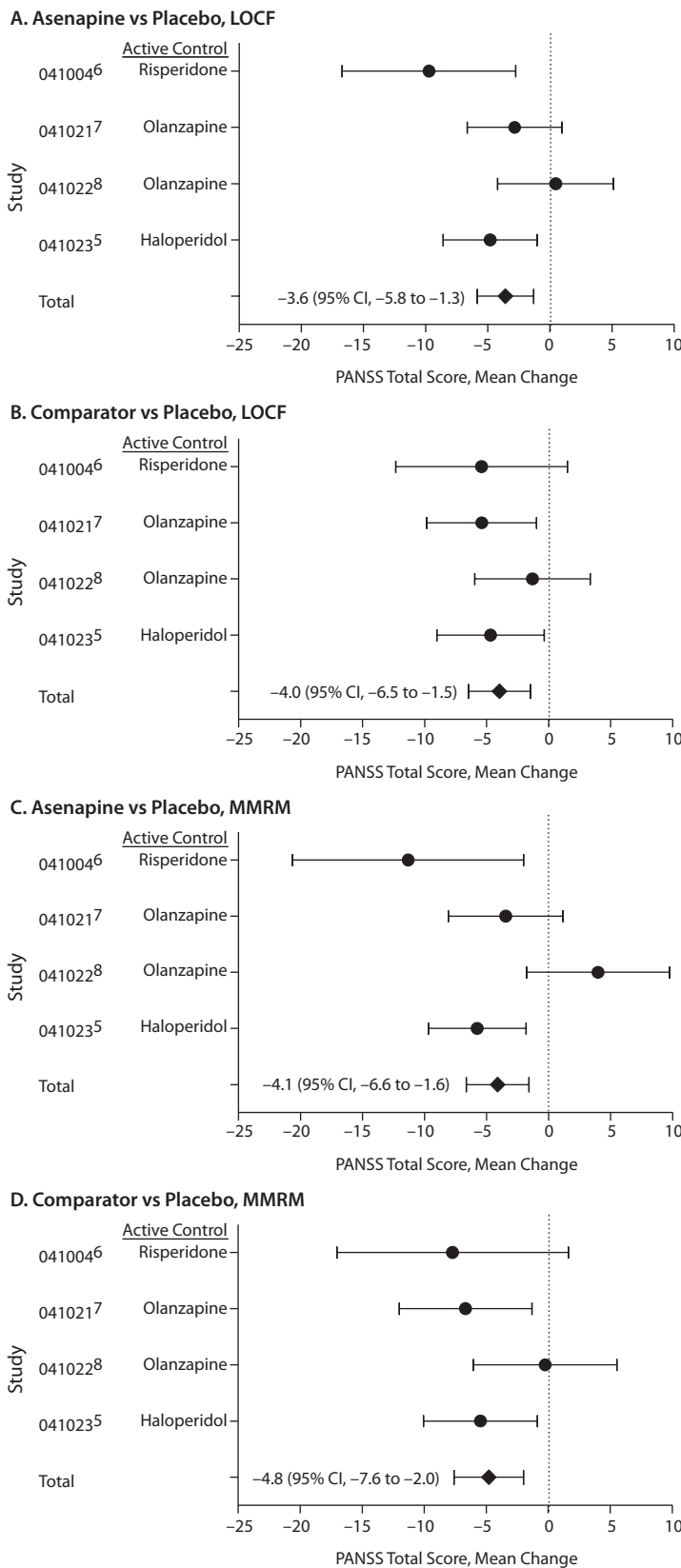
RESULTS

Data from the ITT populations of each study, as defined in the study protocols, were included in the meta-analyses.

Meta-Analyses of the Asenapine Clinical Trial Program

Mean change in PANSS total score: asenapine and active controls versus placebo. Meta-analysis of change from baseline PANSS total score indicated that asenapine was superior to placebo when using LOCF (−3.6; $P = .002$) and MMRM (−4.1; $P = .001$; Figure 1).[5–8] The magnitude of the pooled asenapine effect was comparable to the pooled effect versus placebo for active controls used in the same trials (LOCF, −4.0, $P = .002$; MMRM, −4.8, $P = .001$; Figure 1).

PANSS response rates: asenapine and active controls versus placebo. The PANSS response rates with asenapine and active controls numerically exceeded placebo in 3 of 4 trials (see Supplementary eTable 1 at PSYCHIATRIST.COM). Asenapine was statistically superior to placebo in 2 trials (study 041004[6]: 5 mg twice a day, $P = .029$; study 041023[5]: 5 mg twice a day, $P < .01$, and 10 mg twice a day, $P = .016$); active controls were statistically superior

Figure 1. Mean Change in PANSS Total Score for Asenapine (A and C) and Active Controls (B and D) Versus Placebo[a]

A. Asenapine vs Placebo, LOCF

B. Comparator vs Placebo, LOCF

C. Asenapine vs Placebo, MMRM

D. Comparator vs Placebo, MMRM

[a]Error bars represent 95% CIs.
Abbreviations: LOCF = last observation carried forward, MMRM = mixed model for repeated measures, PANSS = Positive and Negative Syndrome Scale.

Figure 2. Odds Ratios (ORs) and 95% CIs for PANSS Response for Asenapine (A) and Active Controls Versus Placebo (B)

A. PANSS Responder, Asenapine vs Placebo
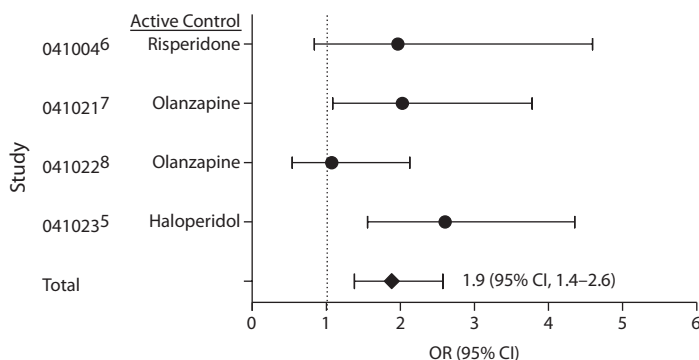
B. PANSS Responder, Comparator vs Placebo
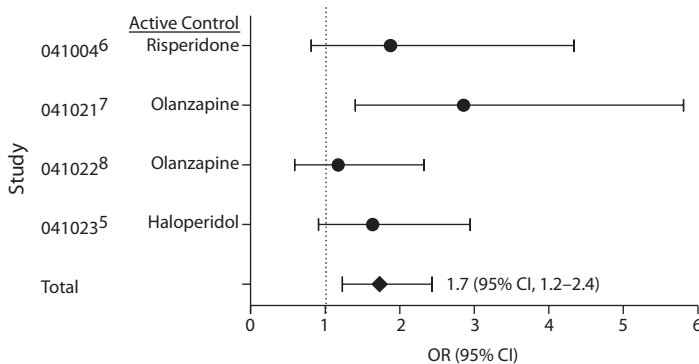
Abbreviation: PANSS = Positive and Negative Syndrome Scale.

to placebo in 1 trial (study 041004[6]: olanzapine 15 mg every day, $P = .011$). When study noncompleters (ie, those who did not complete a study for any reason) were categorized as PANSS nonresponders, PANSS response rates for asenapine were statistically superior to placebo in 1 study (study 041023[5]: 5 mg twice a day, $P = .001$, and 10 mg twice a day, $P = .012$), and none of the active controls were superior to placebo (see Supplementary eTable 1).

Treatment response ORs: asenapine and active controls versus placebo. Odds ratios for treatment response with asenapine and active controls generally exceeded 1.0 across individual trials (see Supplementary eTable 1), with 95% CIs above 1.0 in those cases in which PANSS response rates were statistically higher than those for placebo.

Meta-analysis of the ORs for treatment response reported statistical superiority of asenapine over placebo ($P < .001$; Figure 2)[5–8,18]; the corresponding NNT was 10.2. Comparable findings were obtained for pooled active controls ($P = .002$; Figure 2); the NNT was 12.0. When study noncompleters (ie, those who did not complete a study for any reason) were considered nonresponders, similar ORs were reported for asenapine (1.6 [95% CI, 1.2–2.3]; $P = .003$; NNT = 14.1) and active controls (1.5 [95% CI, 1.1–2.2]; $P = .019$; NNT = 17.3).

Meta-Analyses of Published Studies With Integrated Asenapine Data

Mean change in PANSS total score: asenapine and SGAs versus placebo and the effects of publication year. To illustrate the effect size of publication year, asenapine data were added to the findings that were based on Leucht et al.[12] Figure 3[5–8,18–50] summarizes the standardized effect sizes (Hedges' g) versus placebo. Asenapine and active-control effect sizes versus placebo in asenapine clinical trials were somewhat lower than what has been historically observed for other SGAs. The meta-regression confirmed that effect size versus placebo has decreased over time ($P = .01$; see Supplementary eFigure 1).

Treatment nonresponse risk ratio: asenapine and SGAs versus placebo. Individual trial risk ratios for treatment nonresponse for asenapine and other SGAs did not significantly differ from placebo. When study results were pooled, risk ratios tended to favor active drug over placebo (Figure 4).

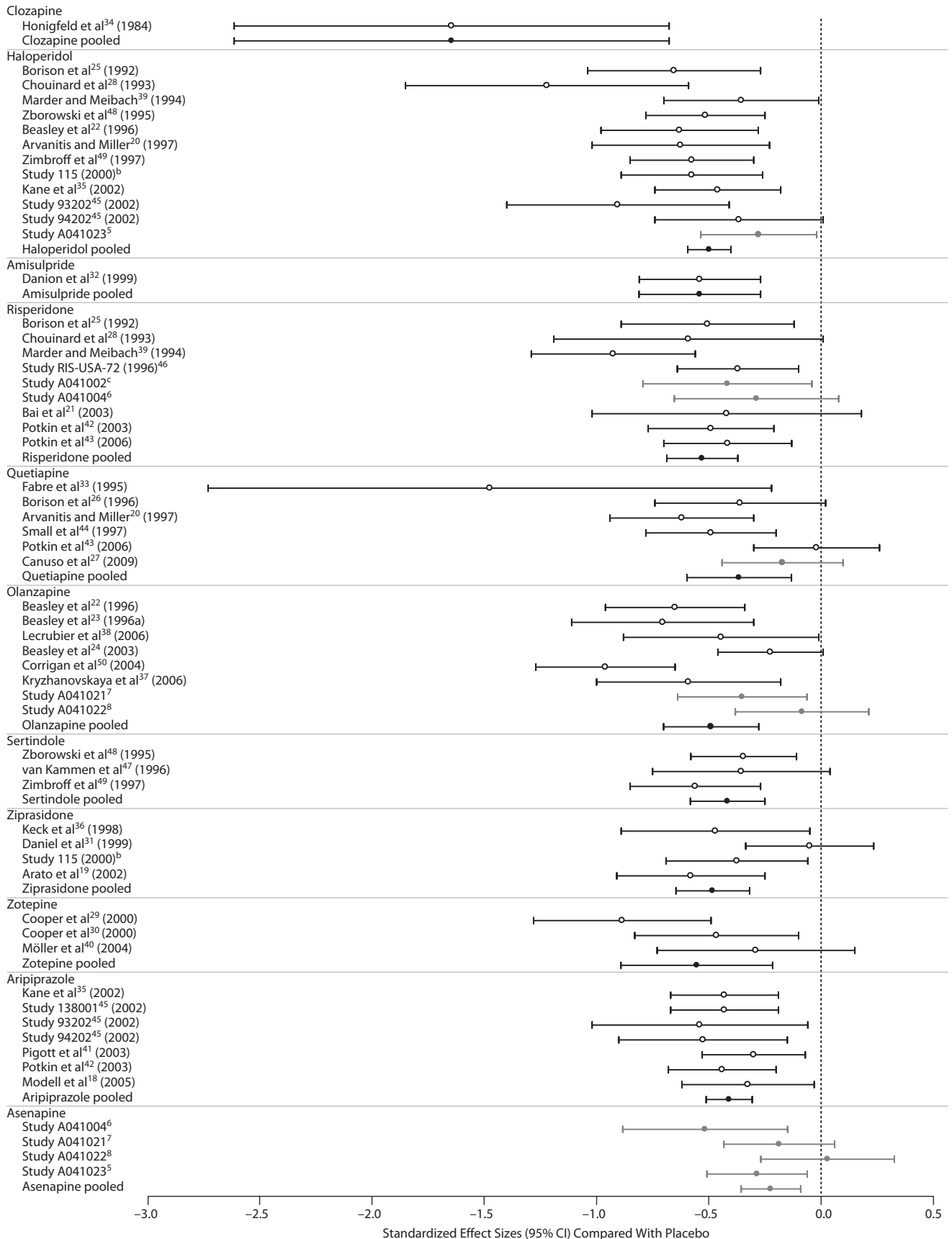### Head-To-Head Network Meta-Analysis: Asenapine Versus Other SGAs

The network of head-to-head SGA comparisons can be schematically depicted by a line diagram, with the width of each line reflecting the size of the database available for direct comparison between 2 drugs (see Supplementary eFigure 2; thicker lines indicate larger numbers of patients). Estimates are based on all connections and reveal that relative PANSS total score reductions were highest with olanzapine and lowest with ziprasidone (see Supplementary eTable 2). Relative efficacy was more favorable for asenapine compared with clozapine, sertindole, quetiapine, aripiprazole, and ziprasidone; effect size with asenapine was less favorable compared with olanzapine, risperidone, and amisulpride, with estimated differences versus asenapine ranging from 3.9 points more than ziprasidone to 2.9 points less than olanzapine (Figure 5). Asenapine ranked fourth among the 8 agents in this analysis, while olanzapine ranked first and ziprasidone ranked last. The differences between asenapine and other drugs, with the exception of ziprasidone, were not statistically significant.

DISCUSSION

These meta-analytic results support the efficacy of asenapine in the treatment of acute schizophrenia, showing superiority over placebo in the change from baseline PANSS total score (the primary end point for asenapine schizophrenia trials). The effect size of asenapine was comparable to that of active controls.

The average effect sizes versus placebo for asenapine and active control were lower than what has been historically observed for SGAs and also illustrated by a "failed" study[8] in which neither asenapine nor olanzapine were significantly different from placebo. However, the finding of

Figure 3. Comparison of Studies That Show the Magnitude of Effect of Asenapine and Other Antipsychotics Versus Placebo[a]

Clozapine
Honigfeld et al[34] (1984)
Clozapine pooled

Haloperidol
Borison et al[25] (1992)
Chouinard et al[28] (1993)
Marder and Meibach[39] (1994)
Zborowski et al[48] (1995)
Beasley et al[22] (1996)
Arvanitis and Miller[20] (1997)
Zimbroff et al[49] (1997)
Study 115 (2000)[b]
Kane et al[35] (2002)
Study 93202[45] (2002)
Study 94202[45] (2002)
Study A041023[5]
Haloperidol pooled

Amisulpride
Danion et al[32] (1999)
Amisulpride pooled

Risperidone
Borison et al[25] (1992)
Chouinard et al[28] (1993)
Marder and Meibach[39] (1994)
Study RIS-USA-72 (1996)[46]
Study A041002[c]
Study A041004[6]
Bai et al[21] (2003)
Potkin et al[42] (2003)
Potkin et al[43] (2006)
Risperidone pooled

Quetiapine
Fabre et al[33] (1995)
Borison et al[26] (1996)
Arvanitis and Miller[20] (1997)
Small et al[44] (1997)
Potkin et al[43] (2006)
Canuso et al[27] (2009)
Quetiapine pooled

Olanzapine
Beasley et al[22] (1996)
Beasley et al[23] (1996a)
Lecrubier et al[38] (2006)
Beasley et al[24] (2003)
Corrigan et al[50] (2004)
Kryzhanovskaya et al[37] (2006)
Study A041021[7]
Study A041022[8]
Olanzapine pooled

Sertindole
Zborowski et al[48] (1995)
van Kammen et al[47] (1996)
Zimbroff et al[49] (1997)
Sertindole pooled

Ziprasidone
Keck et al[36] (1998)
Daniel et al[31] (1999)
Study 115 (2000)[b]
Arato et al[19] (2002)
Ziprasidone pooled

Zotepine
Cooper et al[29] (2000)
Cooper et al[30] (2000)
Möller et al[40] (2004)
Zotepine pooled

Aripiprazole
Kane et al[35] (2002)
Study 138001[45] (2002)
Study 93202[45] (2002)
Study 94202[45] (2002)
Pigott et al[41] (2003)
Potkin et al[42] (2003)
Modell et al[18] (2005)
Aripiprazole pooled

Asenapine
Study A041004[6]
Study A041021[7]
Study A041022[8]
Study A041023[5]
Asenapine pooled

Standardized Effect Sizes (95% CI) Compared With Placebo

[a]Data added to the work of Leucht et al[12] (2009) are shown in light gray. Black closed circles represent data from pooled analyses.   [b]Study 115: data on file, Merck.   [c]Study A041002: phase 2b study on asenapine, risperidone, placebo (Merck; unpublished data on file; 1998–2000).

Figure 4. Risk Ratios for Treatment Nonresponse of Asenapine and Other Second-Generation Antipsychotics Versus Placebo Based on Pooled Data
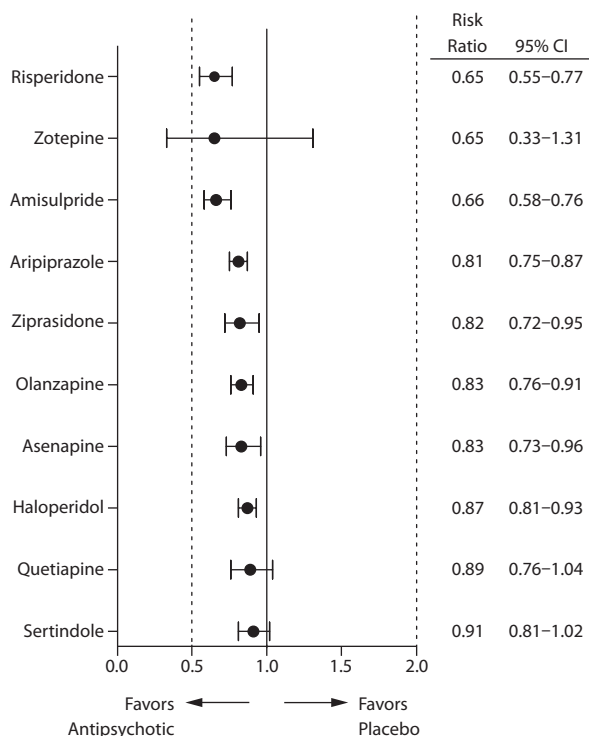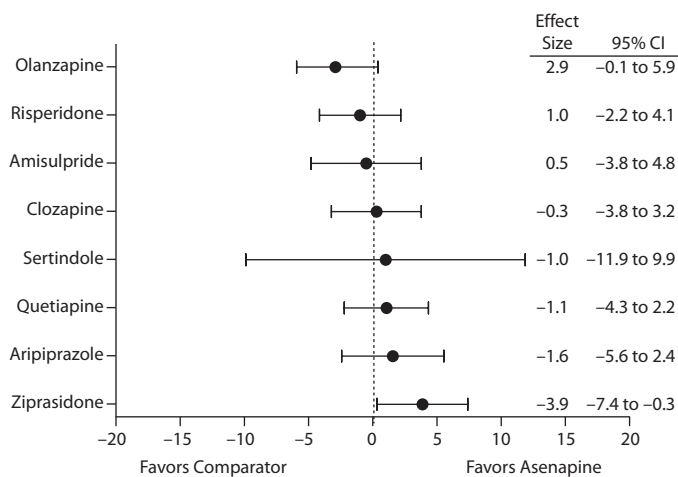

	Risk Ratio	95% CI
Risperidone	0.65	0.55–0.77
Zotepine	0.65	0.33–1.31
Amisulpride	0.66	0.58–0.76
Aripiprazole	0.81	0.75–0.87
Ziprasidone	0.82	0.72–0.95
Olanzapine	0.83	0.76–0.91
Asenapine	0.83	0.73–0.96
Haloperidol	0.87	0.81–0.93
Quetiapine	0.89	0.76–1.04
Sertindole	0.91	0.81–1.02

Favors Antipsychotic ← → Favors Placebo

Figure 5. Results of Network Meta-Analysis of Change in PANSS Total Score for Second-Generation Antipsychotics Versus Asenapine

	Effect Size	95% CI
Olanzapine	2.9	−0.1 to 5.9
Risperidone	1.0	−2.2 to 4.1
Amisulpride	0.5	−3.8 to 4.8
Clozapine	−0.3	−3.8 to 3.2
Sertindole	−1.0	−11.9 to 9.9
Quetiapine	−1.1	−4.3 to 2.2
Aripiprazole	−1.6	−5.6 to 2.4
Ziprasidone	−3.9	−7.4 to −0.3

Favors Comparator ← → Favors Asenapine

reduced efficacy is not unexpected; as demonstrated by the meta-regression of publication year on effect size, treatment effects versus placebo in clinical trials have decreased over time.[9,10] Placebo response also tended to be larger than historically expected, a finding consistent with previous reports of increased placebo response in recently conducted clinical trials.[10]

Given the issues surrounding decreased effect size and increased placebo response over time, direct head-to-head comparisons of agents used in the same trial are likely to be the best means of judging the relative efficacy of different agents. The primary disadvantage of relying on head-to-head comparisons among antipsychotics is the inability to perform comparisons among all agents owing to a lack of sufficient data. However, this disadvantage can be overcome to a large extent with network meta-analysis.

By using network meta-analysis to establish relative efficacy for all agents for which data are available, and the precision of that relative efficacy, comparisons for which direct head-to-head data are not available can be made. For example, comparisons with olanzapine are available for many drugs. By comparing those relative efficacies, conclusions can also be drawn regarding the relative efficacy of drugs that were not directly compared. As a result, fair conclusions can be made from the relative abundance of some head-to-head comparisons. Therefore, what this publication adds, in addition to the assessment of the efficacy of asenapine, is a method for estimating relative efficacy across a complete SGA network.

Similar analyses have been conducted for major depressive disorder[51]; however, our approach is preferable because maximum-likelihood–based estimates are used instead of Markov chain Monte Carlo simulations.[51] Because the maximum-likelihood–based estimates technique is relatively new, it is important to note the key assumption that is required for interpretation of the analyses. That is, it is assumed that differences in mean change from baseline in PANSS total score across studies are comparable, despite differences in patient population, treatment duration, time the study was conducted, and other factors. In essence, this assumption exists in any meta-analysis, and, ultimately, meta-analyses are only as good as the underlying studies on which they are based. No additional assumptions are required for a network meta-analysis, which can therefore be considered as the appropriate method for quantitatively integrating individual study results across drugs.

Although mean change from baseline PANSS total score is widely accepted as the primary efficacy end point in clinical trials and has been used in the current analysis, additional efficacy measures can be made with Brief Psychiatric Rating Scale or Clinical Global Impressions scales. However, the clinical relevance of an average treatment effect remains difficult to interpret. Analysis of individual treatment response rates may be more easily understood from a clinical perspective. Within the asenapine program, PANSS responder rates with asenapine were superior to placebo and comparable to active controls. When expressed as NNT, 10.2 patients need to be treated with asenapine (12.0 for pooled comparators) to achieve 1 additional responder compared with placebo. To compare the effect of asenapine versus placebo with that of other antipsychotics, we used data from Leucht et al,[12]

in which responder rates were expressed as risk ratios for nonresponse. This analysis revealed that antipsychotics were not superior to placebo in many individual trials, possibly due to variations in the response to treatment across trials, but all were superior to placebo when pooled with meta-analytic techniques. When we used comparison with placebo as the reference for relative efficacy, the treatment nonresponse risk ratio for asenapine was comparable to that for olanzapine, ziprasidone, and aripiprazole and numerically higher than that for risperidone, zotepine, and amisulpride.

Although these analyses focus on the "average" efficacy response, individual responses can vary considerably across patients. The clinician is continually challenged to select the appropriate antipsychotic even though an individual patient's response cannot be reliably predicted before treatment. The same is true for safety and tolerability responses, with some patients having markedly better tolerance for one drug than another. Although we have included only efficacy measures in the present analysis, it should be noted that efficacy together with safety and tolerability predicts treatment outcome of SGAs. In essence, drug selection occurs by trial and error, with clinicians switching among agents based on the patient's response to and tolerance of treatment. In that sense, we show that asenapine offers clinicians another alternative, with efficacy comparable to that of most other SGAs.

Limitation

As with all meta-analyses, our findings are indirect comparisons, as the data for other SGAs were extrapolated from different studies with all the inherent limitations specific to those individual studies. Some of these limitations include differences in patient population, treatment duration, and time the study was conducted.

In conclusion, these meta-analyses provide additional support for the superiority of asenapine over placebo for acute schizophrenia. Further, the network meta-analysis suggests that the efficacy of asenapine is comparable to or nonsignificantly better than that of several other SGAs in treating acute schizophrenia.

Drug names: aripiprazole (Abilify), asenapine (Saphris), clozapine (FazaClo, Clozaril, and others), haloperidol (Haldol and others), lithium (Lithobid and others), olanzapine (Zyprexa and others), quetiapine (Seroquel and others), risperidone (Risperdal and others), ziprasidone (Geodon and others).

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Supplementary Material

List of Supplementary Material for the article

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Supplementary eTable 1. Summary of Difference in PANSS Response[a] Rate and Odds Ratios Versus Placebo in Asenapine Clinical Trials

	Treatment	PANSS Response Rate Difference From Placebo			Odds Ratios	
ITT Population			95% CI	*P* Value	Ratio	95% CI
Study 041004	Asenapine 5 mg b.i.d.	12.9	−3.9 to 29.2	.13	2.0	0.9 to 4.7
	Risperidone 3 mg b.i.d.	14.3	−2.8 to 30.8	.10	2.0	0.8 to 4.5
Study 041021	Asenapine 5 mg b.i.d.	14.6	1.5 to 27.1	*.029*	2.2	1.1 to 4.4
	Asenapine 10 mg b.i.d.	10.7	−2.3 to 23.4	.11	1.9	0.9 to 3.8
	Olanzapine 15 mg q.d.	17.4	4.0 to 30.2	*.011*	2.9	1.4 to 5.8
Study 041022	Asenapine 5 or 10 mg b.i.d.	−1.7	−16.0 to 12.8	.82	1.1	0.5 to 2.1
	Olanzapine 10–20 mg q.d.	−0.5	−14.9 to 13.9	.95	1.2	0.6 to 2.3
Study 041023	Asenapine 5 mg b.i.d.	22.3	9.5 to 34.4	*<.01*	3.0	1.7 to 5.5
	Asenapine 10 mg b.i.d.	15.8	3.0 to 28.2	*.016*	2.2	1.2 to 4.0
	Haloperidol 4 mg b.i.d.	10.1	−2.4 to 22.3	.11	1.6	0.9 to 3.0
Study Noncompleters[b] = Nonresponders						
Study 041004	Asenapine 5 mg b.i.d.	12.6	−2.6 to 27.8	.104	2.4	0.9 to 6.2
	Risperidone 3 mg b.i.d.	8.3	−6.6 to 23.4	.270	1.6	0.6 to 4.2
Study 041021	Asenapine 5 mg b.i.d.	4.9	−7.5 to 16.9	.435	1.2	0.6 to 2.5
	Asenapine 10 mg b.i.d.	4.5	−7.9 to 16.8	.475	1.3	0.6 to 2.7
	Olanzapine 15 mg q.d.	9.0	−3.8 to 21.6	.166	1.8	0.9 to 3.7
Study 041022	Asenapine 5 or 10 mg b.i.d.	−5.6	−18.8 to 7.8	.407	0.8	0.4 to 1.7
	Olanzapine 10–20 mg q.d.	1.4	−12.3 to 15.2	.839	1.3	0.6 to 2.6
Study 041023	Asenapine 5 mg b.i.d.	20.9	8.3 to 32.9	*.001*	2.8	1.5 to 5.1
	Asenapine 10 mg b.i.d.	16.1	3.5 to 28.3	*.012*	2.2	1.2 to 4.0
	Haloperidol 4 mg b.i.d.	8.8	−3.3 to 20.8	.153	1.5	0.9 to 2.8

[a]PANSS response was designated as a decrease from baseline of ≥30% at study end point.

[b]Noncompleter are those who did not complete a study for any reason.

b.i.d.=twice daily; ITT=intent to treat; PANSS=Positive and Negative Syndrome Scale; q.d.=once daily.

Supplementary eTable 2. Network Meta-analysis of Change From Baseline in PANSS Total Score and Associated 95% CIs for Asenapine Versus Other Second-Generation Antipsychotics

|	Olanzapine	Risperidone	Amisulpride	Asenapine	Clozapine	Sertindole	Quetiapine	Aripiprazole	Ziprasidone
Olanzapine	—	−1.9 (−3.0 to −0.8)	−2.4 (−5.4 to 0.7)	−2.9 (−5.9 to 0.1)	−3.2 (−5.0 to −1.4)	−3.9 (−14.3 to 6.6)	−4.0 (−5.3 to −2.6)	−4.5 (−7.1 to −1.8)	−6.8 (−8.6 to −4.9)
Risperidone	1.9 (0.8 to 3.0)	—	−0.5 (−3.6 to 2.6)	−1.0 (−4.1 to 2.2)	−1.3 (−3.2 to 0.7)	−2.0 (−12.4 to 8.4)	−2.0 (−3.5 to −0.6)	−2.5 (−5.2 to 0.2)	−4.9 (−6.8 to −2.9)
Amisulpride	2.4 (−0.7 to 5.4)	0.5 (−2.6 to 3.6)	—	−0.5 (−4.8 to 3.8)	−0.8 (−4.3 to 2.7)	−1.5 (−12.3 to 9.3)	−1.6 (−4.8 to 1.7)	−2.1 (−6.0 to 1.9)	−4.4 (−7.7 to −1.1)
Asenapine	2.9 (−0.1 to 5.9)	1.0 (−2.2 to 4.1)	0.5 (−3.8 to 4.8)	—	−0.3 (−3.8 to 3.2)	−1.0 (−11.9 to 9.9)	−1.1 (−4.3 to 2.2)	−1.6 (−5.6 to 2.4)	−3.9 (−7.4 to −0.3)
Clozapine	3.2 (1.4 to 5.0)	1.3 (−0.7 to 3.2)	0.8 (−2.7 to 4.3)	0.3 (−3.2 to 3.8)	—	−0.7 (−11.3 to 9.9)	−0.8 (−2.5 to 1.0)	−1.3 (−4.4 to 1.9)	−3.6 (−6.0 to −1.1)
Sertindole	3.9 (−6.6 to 14.3)	2.0 (−8.4 to 12.4)	1.5 (−9.3 to 12.3)	1.0 (−9.9 to 11.9)	0.7 (−9.9 to 11.3)	—	−0.1 (−10.6 to 10.4)	−0.6 (−11.3 to 10.2)	−2.9 (−13.5 to 7.7)
Quetiapine	4.0 (2.6 to 5.3)	2.0 (0.6 to 3.5)	1.6 (−1.7 to 4.8)	1.1 (−2.2 to 4.3)	0.8 (−1.0 to 2.5)	0.1 (−10.4 to 10.6)	—	−0.5 (−3.4 to 2.4)	−2.8 (−4.9 to −0.7)
Aripiprazole	4.5 (1.8 to 7.1)	2.5 (−0.2 to 5.2)	2.1 (−1.9 to 6.0)	1.6 (−2.4 to 5.6)	1.3 (−1.9 to 4.4)	0.6 (−10.2 to 11.3)	0.5 (−2.4 to 3.4)	—	−2.3 (−5.5 to 0.9)
Ziprasidone	6.8 (4.9 to 8.6)	4.9 (2.9 to 6.8)	4.4 (1.1 to 7.7)	3.9 (0.3 to 7.4)	3.6 (1.1 to 6.0)	2.9 (−7.7 to 13.5)	2.8 (0.7 to 4.9)	2.3 (−0.9 to 5.5)	—

Based on data from Leucht et al.[12] and last-observation-carried-forward results from 6-week asenapine trials with second-generation antipsychotic controls (041004, 041021 and 041022)[6–8] and a 52-week asenapine trial with olanzapine as an active control (25517).[15]

Data are placebo-corrected relative efficacy differences (based on PANSS total score changes from baseline) and associated 95% CIs between second-generation antipsychotics as estimated over the entire network.

A positive number indicates a more favorable outcome with the agent in top row relative to the agent in far left column; a negative number indicates a less favorable outcome with the agent in top row relative to the agent in far left column.

CI=confidence interval; PANSS=Positive and Negative Syndrome Scale.

Supplementary eFigure 1. Meta-regression of the Effects of Publication Year on the Effect Size of Antipsychotics Versus Placebo
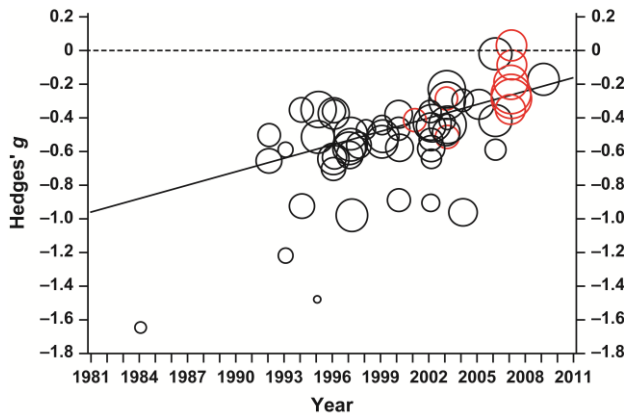
Circles represent each comparison of active treatment versus placebo. The radius of each circle represents the precision within the study, which determines the impact of the comparison in the analysis (i.e., larger studies tend to have larger circles). Red circles represent comparisons to placebo derived from the asenapine program. The line represents the regression of effect size over time based on these data. The dotted line represents a Hedges' g of 0 (i.e., no difference vs placebo). Data for comparators other than asenapine were obtained from Leucht et al (2009a).

Supplementary eFigure 2. Schematic Overview of the Network of Head-to-Head Comparisons of Second-Generation Antipsychotics Available in the Treatment of Schizophrenia
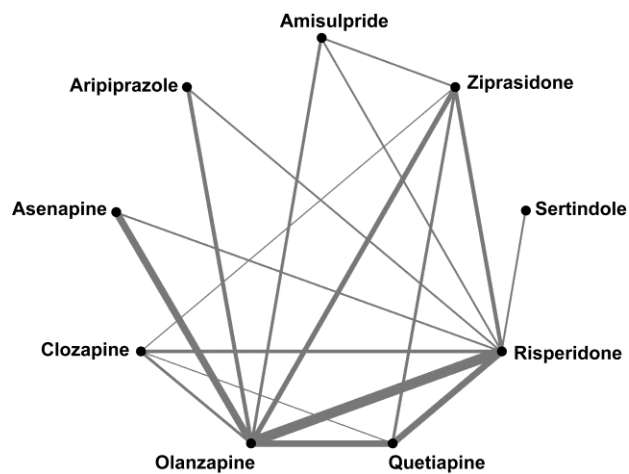
The width of each line reflects the size of the database available for direct comparison of each drug, with thicker lines indicating larger numbers of patients. Comparisons for risperidone and in particular olanzapine form an important bridge between many of the other antipsychotics.