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Supplementary Material

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

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

ITT Population	Treatment	PANSS Response Rate Difference From Placebo			Odds Ratios	
			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
Study 041022	Olanzapine 15 mg q.d.	17.4	4.0 to 30.2	.011	2.9	1.4 to 5.8
	Asenapine 5 or 10 mg b.i.d.	-1.7	-16.0 to 12.8	.82	1.1	0.5 to 2.1
Study 041023	Olanzapine 10–20 mg q.d.	-0.5	-14.9 to 13.9	.95	1.2	0.6 to 2.3
	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
Study 041022	Olanzapine 15 mg q.d.	9.0	-3.8 to 21.6	.166	1.8	0.9 to 3.7
	Asenapine 5 or 10 mg b.i.d.	-5.6	-18.8 to 7.8	.407	0.8	0.4 to 1.7
Study 041023	Olanzapine 10–20 mg q.d.	1.4	-12.3 to 15.2	.839	1.3	0.6 to 2.6
	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

^aPANSS response was designated as a decrease from baseline of $\geq 30\%$ at study end point.

^bNoncompleter 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)	—

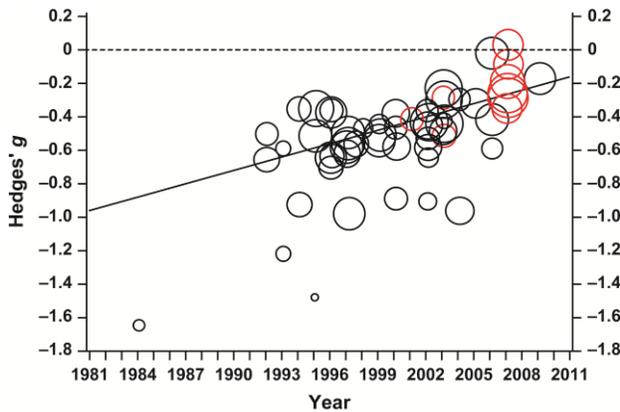
Based on data from Leucht et al.¹² and last-observation-carried-forward results from 6-week asenapine trials with second-generation antipsychotic controls (041004, 041021 and 041022)⁶⁻⁸ and a 52-week asenapine trial with olanzapine as an active control (25517).¹⁵

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.

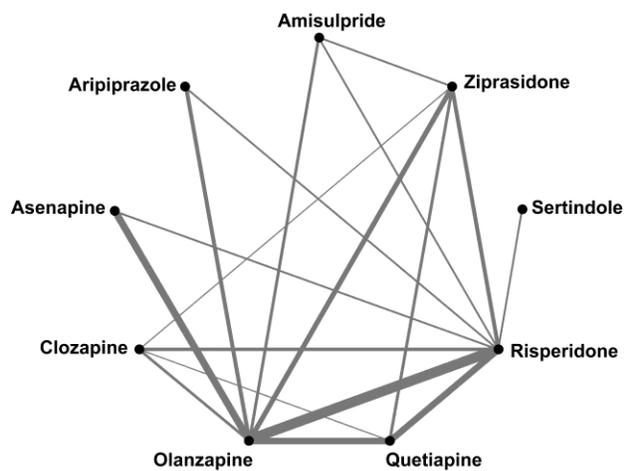
CI=confidence interval; PANSS=Positive and Negative Syndrome Scale.

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.