THE JOURNAL OF CLINICAL PSYCHIATRY
THE OFFICIAL JOURNAL OF THE AMERICAN SOCIETY OF CLINICAL PSYCHOPHARMACOLOGY

Supplementary Material

Article Title: Lumateperone for the Treatment of Schizophrenia: Number Needed to Treat, Number Needed to Harm, and Likelihood to Be Helped or Harmed

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DOI Number: https://doi.org/10.4088/JCP.22r14631

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SUPPLEMENTARY APPENDIX FOR

Lumateperone for the Treatment of Schizophrenia: Number Needed to Treat, Number Needed to Harm, and Likelihood to be Helped or Harmed

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SUPPLEMENTARY TABLES

Supplementary Table 1. Lumateperone efficacy outcomes and NNT vs. placebo

Supplementary Table 1a. Lumateperone efficacy outcomes and NNT vs. placebo: Study 005

Percent reduction from baseline on the PANSS Total score at various timepoints	Placebo (N=80)		Lumateperone 42 mg/d (N=76)			Lumateperone 84 mg/d (N=80)			Risperidone 4 mg/d (N=75)		
	n	%	n	%	NNT (95% CI)	n	%	NNT (95% CI)[a]	n	%	NNT (95% CI)[a]
≥ 20% reduction at Week 1	14	17.5	17	22.4	21 (ns)	16	20.0	40 (ns)	27	36.0	6 (4–21)
≥ 20% reduction at Week 2	25	31.3	26	34.2	34 (ns)	20	25.0	−16 (ns)	30	40.0	12 (ns)
≥ 20% reduction at Week 3	28	35.0	34	44.7	11 (ns)	29	36.3	80 (ns)	35	46.7	9 (ns)
≥ 20% reduction at Week 4	28	35.0	37	48.7	8 (ns)	23	28.8	−16 (ns)	39	52.0	6 (4–63)
≥ 20% reduction at endpoint[b]	28	35.0	38	50.0	7 (ns)	25	31.3	−27 (ns)	41	54.7	6 (3–24)
≥ 30% reduction at Week 1	3	3.8	9	11.8	13 (ns)	9	11.3	14 (ns)	14	18.7	7 (5–20)
≥ 30% reduction at Week 2	15	18.8	23	30.3	9 (ns)	12	15.0	−27 (ns)	22	29.3	10 (ns)
≥ 30% reduction at Week 3	16	20.0	23	30.3	10 (ns)	17	21.3	80 (ns)	26	34.7	7 (4–129)
≥ 30% reduction at Week 4	18	22.5	31	40.8	6 (4–26)	20	25.0	40 (ns)	30	40.0	6 (4–32)
≥ 30% reduction at endpoint[b]	18	22.5	32	42.1	6 (3–20)	21	26.3	27 (ns)	31	41.3	6 (3–23)
≥ 40% reduction at Week 1	1	1.3	6	7.9	15 (8–897)	3	3.8	40 (ns)	2	2.7	71 (ns)
≥ 40% reduction at Week 2	9	11.3	9	11.8	169 (ns)	6	7.5	−27 (ns)	11	14.7	30 (ns)
≥ 40% reduction at Week 3	10	12.5	17	22.4	11 (ns)	5	6.3	−16 (ns)	16	21.3	12 (ns)
≥ 40% reduction at Week 4	11	13.8	19	25.0	9 (ns)	14	17.5	27 (ns)	17	22.7	12 (ns)
≥ 40% reduction at endpoint[b]	11	13.8	19	25.0	9 (ns)	14	17.5	27 (ns)	18	24.0	10 (ns)
≥ 50% reduction at Week 1	0	0.0	3	3.9	26 (ns)	2	2.5	40 (ns)	1	1.3	75 (ns)
≥ 50% reduction at Week 2	1	1.3	3	3.9	38 (ns)	1	1.3	ND	4	5.3	25 (ns)
≥ 50% reduction at Week 3	3	3.8	9	11.8	13 (ns)	2	2.5	−80 (ns)	7	9.3	18 (ns)
≥ 50% reduction at Week 4	8	10.0	11	14.5	23 (ns)	4	5.0	−20 (ns)	10	13.3	30 (ns)
≥ 50% reduction at endpoint[b]	8	10.0	11	14.5	23 (ns)	4	5.0	−20 (ns)	11	14.7	22 (ns)

[a]A "negative" NNT occurs when the rate for placebo is greater than the rate for the antipsychotic tested.
[b]Week 4 or early termination.
Abbreviations: CI: confidence interval; ND: no difference; NNT: number needed to treat; ns: not significant at the *P* <.05 threshold, thus the 95% CI is not shown; PANSS: Positive and Negative Syndrome Scale.

Supplementary Table 1b. Lumateperone efficacy outcomes and NNT vs. placebo: Study 301

Percent reduction from baseline on the PANSS Total score at various timepoints	Placebo (N=141)		Lumateperone 28 mg/d (N=146)			Lumateperone 42 mg/d (N=148)		
	n	%	n	%	NNT (95% CI)[a]	n	%	NNT (95% CI)
≥ 20% reduction at Week 1	38	27.0	46	31.5	22 (ns)	52	35.1	13 (ns)
≥ 20% reduction at Week 2	55	39.0	57	39.0	2941 (ns)	73	49.3	10 (ns)
≥ 20% reduction at Week 3	52	36.9	71	48.6	9 (5–259)	73	49.3	8 (5–90)
≥ 20% reduction at Week 4	54	38.3	71	48.6	10 (ns)	74	50.0	9 (5–301)
≥ 20% reduction at endpoint[b]	59	41.8	76	52.1	10 (ns)	77	52.0	10 (ns)
≥ 30% reduction at Week 1	13	9.2	21	14.4	20 (ns)	29	19.6	10 (6–42)
≥ 30% reduction at Week 2	31	22.0	31	21.2	−133 (ns)	40	27.0	20 (ns)
≥ 30% reduction at Week 3	37	26.2	52	35.6	11 (ns)	51	34.5	13 (ns)
≥ 30% reduction at Week 4	36	25.5	53	36.3	10 (5–641)	54	36.5	10 (5–268)
≥ 30% reduction at endpoint[b]	39	27.7	57	39.0	9 (5–179)	56	37.8	10 (ns)
≥ 40% reduction at Week 1	3	2.1	14	9.6	14 (8–48)	11	7.4	19 (10–221)
≥ 40% reduction at Week 2	10	7.1	15	10.3	32 (ns)	21	14.2	15 (8–1745)
≥ 40% reduction at Week 3	21	14.9	27	18.5	28 (ns)	31	20.9	17 (ns)
≥ 40% reduction at Week 4	23	16.3	30	20.5	24 (ns)	38	25.7	11 (6–1966)
≥ 40% reduction at endpoint[b]	23	16.3	31	21.2	21 (ns)	39	26.4	10 (6–147)
≥ 50% reduction at Week 1	2	1.4	4	2.7	76 (ns)	3	2.0	165 (ns)
≥ 50% reduction at Week 2	2	1.4	10	6.8	19 (10–113)	12	8.1	15 (9–54)
≥ 50% reduction at Week 3	7	5.0	16	11.0	17 (ns)	23	15.5	10 (6–27)
≥ 50% reduction at Week 4	12	8.5	17	11.6	32 (ns)	28	18.9	10 (6–39)
≥ 50% reduction at endpoint[b]	12	8.5	17	11.6	32 (ns)	28	18.9	10 (6–39)

[a]A "negative" NNT occurs when the rate for placebo is greater than the rate for the antipsychotic tested.
[b]Week 4 or early termination.
Abbreviations: CI: confidence interval; NNT: number needed to treat; ns: not significant at the $P < .05$ threshold, thus the 95% CI is not shown; PANSS: Positive and Negative Syndrome Scale.

Supplementary Table 1c. Lumateperone efficacy outcomes and NNT vs. placebo: studies 005 and 301, pooled placebo and lumateperone 42 mg/d

Percent reduction from baseline on the PANSS Total score at various timepoints	Placebo (N=221)		Lumateperone 42 mg/d (N=224)		
	n	%	n	%	NNT (95% CI)
≥ 20% reduction at Week 1	52	23.5	69	30.8	14 (ns)
≥ 20% reduction at Week 2	80	36.2	99	44.2	13 (ns)
≥ 20% reduction at Week 3	80	36.2	107	47.8	9 (5–41)
≥ 20% reduction at Week 4	82	37.1	111	49.6	8 (5–31)
≥ 20% reduction at endpoint[a]	87	39.4	115	51.3	9 (5–36)
≥ 30% reduction at Week 1	16	7.2	38	17.0	11 (7–27)
≥ 30% reduction at Week 2	46	20.8	63	28.1	14 (ns)
≥ 30% reduction at Week 3	53	24.0	74	33.0	11 (6–141)
≥ 30% reduction at Week 4	54	24.4	85	37.9	8 (5–20)
≥ 30% reduction at endpoint[a]	57	25.8	88	39.3	8 (5–21)
≥ 40% reduction at Week 1	4	1.8	17	7.6	18 (11–53)
≥ 40% reduction at Week 2	19	8.6	30	13.4	21 (ns)
≥ 40% reduction at Week 3	31	14.0	48	21.4	14 (7–293)
≥ 40% reduction at Week 4	34	15.4	57	25.4	10 (6–38)
≥ 40% reduction at endpoint[a]	34	15.4	58	25.9	10 (6–33)
≥ 50% reduction at Week 1	2	0.9	6	2.7	57 (ns)
≥ 50% reduction at Week 2	3	1.4	15	6.7	19 (12–58)
≥ 50% reduction at Week 3	10	4.5	32	14.3	11 (7–23)
≥ 50% reduction at Week 4	20	9.0	39	17.4	12 (7–48)
≥ 50% reduction at endpoint[a]	20	9.0	39	17.4	12 (7–48)

[a]Week 4 or early termination.
Abbreviations: CI: confidence interval; NNT: number needed to treat; ns: not significant at the $P < .05$ threshold, thus the 95% CI is not shown; PANSS: Positive and Negative Syndrome Scale.

Supplementary Table 1d. Sensitivity analyses for response

Studies 005, 301, and 302: pooled placebo and lumateperone 42 mg/d					
Percent reduction from baseline on the PANSS Total score at Week 4	**Placebo**		**Lumateperone 42 mg/d**		
	n/N	**%**	**n/N**	**%**	**NNT (95% CI)**
≥ 20% reduction at Week 4	156/390	40.0	193/386	50.0	10 (6–33)
≥ 30% reduction at Week 4	107/390	27.4	141/386	36.5	11 (7–40)
Studies 005 and 302: pooled placebo and risperidone 4 mg/d					
Percent reduction from baseline on the PANSS Total score at Week 4	**Placebo**		**Risperidone 4 mg/d**		
	n/N	**%**	**n/N**	**%**	**NNT (95% CI)**
≥ 20% reduction at Week 4	102/249	41.0	123/232	53.0	9 (5–32)
≥ 30% reduction at Week 4	71/249	28.5	97/232	41.8	8 (5–21)

Abbreviations: CI: confidence interval; NNT: number needed to treat; PANSS: Positive and Negative Syndrome Scale.

Supplementary Table 2. Lumateperone safety/tolerability outcomes and NNH vs. placebo

Supplementary Table 2a. Lumateperone safety/tolerability outcomes and NNH vs. placebo: Study 005

Outcome	Placebo (N=85)[a]		Lumateperone 42 mg/d (N=84)[b]			Lumateperone 84 mg/d (N=83)[c]			Risperidone 4 mg/d (N=82)[d]		
	n	%	n	%	NNH (95% CI)[e]	n	%	NNH (95% CI)[e]	n	%	NNH (95% CI)[e]
Discontinuation from the study because of an adverse event	1	1.2	2	2.4	83 (ns)	0	0.0	−85 (ns)	3	3.7	41 (ns)
AE of somnolence/ sedation	11	12.9	14	16.7	27 (ns)	27	32.5	6 (4–14)	16	19.5	16 (ns)
AE of dry mouth	2	2.4	4	4.8	42 (ns)	8	9.6	14 (7–605)	5	6.1	27 (ns)
AE of nausea	1	1.2	6	7.1	17 (9–120576)	8	9.6	12 (7–59)	4	4.9	27 (ns)
AE of dizziness or dizziness postural	1	1.2	5	6.0	21 (ns)	8	9.6	12 (7–59)	1	1.2	2324 (ns)
Shifts of total cholesterol at any time from < 240 mg/dL to ≥ 240 mg/dL	19	22.4	19	22.6	376 (ns)	12	14.5	−13 (ns)	9	11.0	−9 (−5 to −431)
Shifts of fasting glucose at any time from < 126 mg/dL to ≥ 126 mg/dL	10	11.8	7	8.3	−30 (ns)	9	10.8	−109 (ns)	10	12.2	233 (ns)
Shifts of LDL cholesterol at any time from < 160 mg/dL to ≥ 160 mg/dL	14	16.5	12	14.3	−46 (ns)	8	9.6	−15 (ns)	4	4.9	−9 (−5 to −42)
Shifts of fasting triglycerides at any time from < 200 mg/dL to ≥ 200 mg/dL	21	24.7	9	10.7	−8 (−4 to −38)	7	8.4	−7 (−4 to −19)	13	15.9	−12 (ns)
Shifts of ECG QTcB interval at any time from < 450 msec to ≥ 450 msec	7	8.2	9	10.7	41 (ns)	13	15.7	14 (ns)	13	15.9	14 (ns)
Shifts of ECG QTcF interval at any time from < 450 msec to ≥ 450 msec	0	0.0	0	0.0	ND	3	3.6	28 (ns)	0	0.0	ND
Weight gain of ≥ 7% from baseline at LOCF endpoint[f]	4	4.7	9	10.7	17 (ns)	12	14.5	11 (6–106)	13	15.9	9 (5–49)
Total cholesterol at LOCF endpoint[f] ≥ 240 mg/dL	14	16.5	14	16.7	510 (ns)	4	4.8	−9 (−5 to −40)	8	9.8	−15 (ns)
Fasting glucose at LOCF endpoint[f] ≥ 126 mg/dL	7	8.2	3	3.6	−22 (ns)	3	3.6	−22 (ns)	7	8.5	332 (ns)
LDL cholesterol at LOCF endpoint[f] ≥ 160 mg/dL	12	14.1	10	11.9	−46 (ns)	3	3.6	−10 (−6 to −48)	2	2.4	−9 (−6 to −29)
Fasting triglyceride value at LOCF endpoint[f] ≥ 200 mg/dL	14	16.5	6	7.1	−11 (ns)	5	6.0	−10 (−5 to −96)	11	13.4	−33 (ns)
Plasma prolactin value at LOCF endpoint at various concentrations[f]											
≥ 17 ng/mL (men)	9	13.8	11	16.7	36 (ns)	5	6.9	−15 (ns)	54	74.0	2 (2–3)
≥ 34 ng/mL (men)	0	0.0	0	0.0	ND	0	0.0	ND	0	0.0	ND
≥ 25 ng/mL (women)	5	25.0	3	16.7	−12 (ns)	0	0.0	−4 (−3 to −17)	7	77.8	2 (2–6)
≥ 50 ng/mL (women)	0	0.0	0	0.0	ND	0	0.0	ND	0	0.0	ND

The populations consisted of [a]65 men and 20 women; [b]66 men and 18 women; [c]72 men and 11 women; and [d]73 men and 9 women.

[e]A "negative" NNH occurs when the rate for placebo is greater than the rate for the antipsychotic tested.

[f]Week 4 or early termination.

Abbreviations: AE: adverse event; CI: confidence interval; ECG: electrocardiogram; LDL: low-density lipoprotein; LOCF: last observation carried forward; ND: no difference; NNH: number needed to harm; ns: not significant at the $P < .05$ threshold, thus the 95% CI is not shown.

Supplementary Table 2b. Lumateperone safety/tolerability outcomes and NNH vs. placebo: Study 301

Outcome	Placebo (N=149)[a]		Lumateperone 28 mg/d (N=150)[b]			Lumateperone 42 mg/d (N=150)[c]		
	n	%	n	%	NNH (95% CI)[d]	n	%	NNH (95% CI)[d]
Discontinuation from the study because of an adverse event	1	0.7	6	(4.0)	30 (ns)	2	1.3	151 (ns)
AE of somnolence/sedation	14	9.4	31	20.7	9 (6–31)	45	30.0	5 (4–9)
AE of dry mouth	7	4.7	9	6.0	77 (ns)	11	7.3	38 (ns)
AE of nausea	11	7.4	7	4.7	−37 (ns)	16	10.7	31 (ns)
AE of dizziness or dizziness postural	6	4.0	7	4.7	157 (ns)	10	6.7	38 (ns)
Shifts of total cholesterol at any time from < 240 mg/dL to ≥ 240 mg/dL	18	12.1	25	16.7	22 (ns)	29	19.3	14 (ns)
Shifts of fasting glucose at any time from < 126 mg/dL to ≥ 126 mg/dL	7	4.7	7	4.7	−3193 (ns)	6	4.0	−144 (ns)
Shifts of LDL cholesterol at any time from < 160 mg/dL to ≥ 160 mg/dL	16	10.7	17	11.3	168 (ns)	21	14.0	31 (ns)
Shifts of fasting triglycerides at any time from < 200 mg/dL to ≥ 200 mg/dL	21	14.1	25	16.7	39 (ns)	18	12.0	−48 (ns)
Shifts of ECG QTcB interval at any time from < 450 msec to ≥ 450 msec	7	4.7	12	8.0	31 (ns)	9	6.0	77 (ns)
Shifts of ECG QTcF interval at any time from < 450 msec to ≥ 450 msec	1	0.7	3	2.0	76 (ns)	0	0.0	−149 (ns)
Weight gain of ≥ 7% from baseline at LOCF endpoint[e]	5	3.4	6	4.0	156 (ns)	12	8.0	22 (ns)
Total cholesterol at LOCF endpoint[e] ≥ 240 mg/dL	14	9.4	15	10.0	166 (ns)	20	13.3	26 (ns)
Fasting glucose at LOCF endpoint[e] ≥ 126 mg/dL	6	4.0	5	3.3	−145 (ns)	4	2.7	−74 (ns)
LDL cholesterol at LOCF endpoint[e] ≥ 160 mg/dL	13	8.7	12	8.0	−138 (ns)	15	10.0	79 (ns)
Fasting triglyceride value at LOCF endpoint[e] ≥ 200 mg/dL	16	10.7	17	11.3	168 (ns)	8	5.3	−19 (ns)
Plasma prolactin value at LOCF endpoint at various concentrations[e]								
≥ 17 ng/mL (men)	14	11.4	11	9.7	−61 (ns)	13	11.8	230 (ns)
≥ 34 ng/mL (men)	0	0.0	0	0.0	ND	0	0.0	ND
≥ 25 ng/mL (women)	3	11.5	3	8.1	−30 (ns)	0	0.0	−9 (ns)
≥ 50 ng/mL (women)	0	0.0	0	0.0	ND	0	0.0	ND

The populations consisted of [a]123 men and 26 women; [b]113 men and 37 women; [c]110 men and 40 women.

[d]A "negative" NNH occurs when the rate for placebo is greater than the rate for the antipsychotic tested.

[e]Week 4 or early termination.

Abbreviations: AE: adverse event; CI: confidence interval; ECG: electrocardiogram; LDL: low-density lipoprotein; LOCF: last observation carried forward; ND: no difference; NNH: number needed to harm; ns: not significant at the *P* <.05 threshold, thus the 95% CI is not shown.

Supplementary Table 2c. Lumateperone safety/tolerability outcomes and NNH vs. placebo: Study 302, from start of study to end of Week 4

Outcome	Placebo (N=178)[a]		Lumateperone 14 mg/d (N=172)[b]			Lumateperone 42 mg/d (N=172)[c]			Risperidone 4 mg/d (N=173)[d]		
	n	%	n	%	NNH (95% CI)[e]	n	%	NNH (95% CI)[e]	n	%	NNH (95% CI)[e]
Discontinuation from the study because of an adverse event	1	0.6	5	2.9	43 (ns)	0	0.0	−178 (ns)	8	4.6	25 (14–135)
AE of somnolence/ sedation	16	9.0	29	16.9	13 (7–115)	38	22.1	8 (5–18)	43	24.9	7 (5–13)
AE of dry mouth	0	0.0	3	1.7	58 (ns)	8	4.7	22 (13–67)	7	4.0	25 (15–91)
AE of nausea	7	3.9	6	3.5	−226 (ns)	14	8.1	24 (ns)	12	6.9	34 (ns)
AE of dizziness or dizziness postural	4	2.2	6	3.5	81 (ns)	7	4.1	55 (ns)	8	4.6	43 (ns)
Shifts of total cholesterol at any time from < 240 mg/dL to ≥ 240 mg/dL	16	9.0	14	8.1	−118 (ns)	19	11.0	49 (ns)	14	8.1	−112 (ns)
Shifts of fasting glucose at any time from < 126 mg/dL to ≥ 126 mg/dL	7	3.9	5	2.9	−98 (ns)	5	2.9	−98 (ns)	12	6.9	34 (ns)
Shifts of LDL cholesterol at any time from < 160 mg/dL to ≥ 160 mg/dL	11	6.2	11	6.4	464 (ns)	18	10.5	24 (ns)	5	2.9	−31 (ns)
Shifts of fasting triglycerides at any time from < 200 mg/dL to ≥ 200 mg/dL	15	8.4	12	7.0	−69 (ns)	13	7.6	−116 (ns)	27	15.6	14 (8–247)
Shifts of ECG QTcB interval at any time from < 450 msec to ≥ 450 msec	9	5.1	7	4.1	−102 (ns)	14	8.1	33 (ns)	12	6.9	54 (ns)
Shifts of ECG QTcF interval at any time from < 450 msec to ≥ 450 msec	2	1.1	0	0.0	−89 (ns)	1	0.6	−185 (ns)	2	1.2	3080 (ns)
Weight gain of ≥ 7% from baseline at LOCF endpoint[f]	14	7.9	9	5.2	−38 (ns)	5	2.9	−21 (−11 to −366)	23	13.3	19 (ns)
Total cholesterol at LOCF endpoint[f] ≥ 240 mg/dL	22	12.4	20	11.6	−137 (ns)	22	12.8	232 (ns)	21	12.1	−453 (ns)
Fasting glucose at LOCF endpoint[f] ≥ 126 mg/dL	9	5.1	4	2.3	−37 (ns)	6	3.5	−64 (ns)	14	8.1	33 (ns)
LDL cholesterol at LOCF endpoint[f] ≥ 160 mg/dL	15	8.4	13	7.6	−116 (ns)	22	12.8	23 (ns)	11	6.4	−49 (ns)
Fasting triglyceride value at LOCF endpoint[f] ≥ 200 mg/dL	18	10.1	15	8.7	−72 (ns)	15	8.7	−72 (ns)	24	13.9	27 (ns)
Plasma prolactin value at LOCF endpoint at various concentrations[f]											
≥ 17 ng/mL (men)	13	9.8	10	8.0	−55 (ns)	11	8.9	−111 (ns)	110	83.3	2 (2–2)
≥ 34 ng/mL (men)	0	0.0	0	0.0	ND	0	0.0	ND	0	0.0	ND

≥ 25 ng/mL (women)	4	8.7	5	10.6	52 (ns)	4	8.2	−188 (ns)	35	85.4	2 (2–2)
≥ 50 ng/mL (women)	0	0.0	0	0.0	ND	0	0.0	ND	0	0.0	ND

The populations consisted of [a]132 men and 46 women; [b]125 men and 47 women; [c]123 men and 49 women; [d]132 men and 41 women.

[e]A "negative" NNH occurs when the rate for placebo is greater than the rate for the antipsychotic tested.

[f]Week 4 or early termination.

Abbreviations: AE: adverse event; CI: confidence interval; ECG: electrocardiogram; LDL: low-density lipoprotein; LOCF: last observation carried forward; ND: no difference; NNH: number needed to harm; ns: not significant at the $P < .05$ threshold, thus the 95% CI is not shown.

Supplementary Table 2d. Lumateperone safety/tolerability outcomes and NNH vs. placebo: Study 302, from start of study to end of Week 6

Outcome	Placebo (N=178)[a]		Lumateperone 14 mg/d (N=172)[b]			Lumateperone 42 mg/d (N=172)[c]			Risperidone 4 mg/d (N=173)[d]		
	n	%	n	%	NNH (95% CI)[e]	n	%	NNH (95% CI)[e]	n	%	NNH (95% CI)[e]
Discontinuation from the study because of an adverse event	1	0.6	6	3.5	35 (ns)	0	0.0	−178 (ns)	10	5.8	20 (12–64)
AE of somnolence/sedation	16	9.0	30	17.4	12 (7–72)	38	22.1	8 (5–18)	44	25.4	7 (5–12)
AE of dry mouth	0	0.0	4	2.3	43 (22–1367)	9	5.2	20 (12–53)	7	4.0	25 (15–91)
AE of nausea	8	4.5	7	4.1	−236 (ns)	16	9.3	21 (ns)	15	8.7	24 (ns)
AE of dizziness or dizziness postural	4	2.2	6	3.5	81 (ns)	7	4.1	55 (ns)	8	4.6	43 (ns)
Shifts of total cholesterol at any time from < 240 mg/dL to ≥ 240 mg/dL	23	12.9	18	10.5	−41 (ns)	19	11.0	−54 (ns)	19	11.0	−52 (ns)
Shifts of fasting glucose at any time from < 126 mg/dL to ≥ 126 mg/dL	15	8.4	8	4.7	−27 (ns)	9	5.2	−32 (ns)	14	8.1	−299 (ns)
Shifts of LDL cholesterol at any time from < 160 mg/dL to ≥ 160 mg/dL	18	10.1	12	7.0	−32 (ns)	19	11.0	107 (ns)	8	4.6	−19 (−10 to −1542)
Shifts of fasting triglycerides at any time from < 200 mg/dL to ≥ 200 mg/dL	24	13.5	17	9.9	−28 (ns)	18	10.5	−34 (ns)	33	19.1	18 (ns)
Shifts of ECG QTcB interval at any time from < 450 msec to ≥ 450 msec	12	6.7	14	8.1	72 (ns)	15	8.7	51 (ns)	16	9.2	40 (ns)
Shifts of ECG QTcF interval at any time from < 450 msec to ≥ 450 msec	3	1.7	0	0.0	−60 (ns)	1	0.6	−91 (ns)	3	1.7	2053 (ns)
Weight gain of ≥ 7% from baseline at LOCF endpoint[f]	18	10.1	21	12.2	48 (ns)	8	4.7	−19 (−10 to −3608)	31	17.9	13 (7–174)
Total cholesterol at LOCF endpoint[f] ≥ 240 mg/dL	19	10.7	19	11.0	269 (ns)	19	11.0	269 (ns)	16	9.2	−71 (ns)
Fasting glucose at LOCF endpoint[f] ≥ 126 mg/dL	15	8.4	6	3.5	−21 (−11 to −4568)	8	4.7	−27 (ns)	16	9.2	122 (ns)
LDL cholesterol at LOCF endpoint[f] ≥ 160 mg/dL	16	9.0	14	8.1	−118 (ns)	19	11.0	49 (ns)	10	5.8	−32 (ns)
Fasting triglyceride value at LOCF endpoint[f] ≥ 200 mg/dL	20	11.2	18	10.5	−130 (ns)	16	9.3	−52 (ns)	24	13.9	38 (ns)
Plasma prolactin value at LOCF endpoint at various concentrations[f]											
≥ 17 ng/mL (men)	10	7.6	10	8.0	236 (ns)	13	10.6	34 (ns)	99	75.0	2 (2–2)
≥ 34 ng/mL (men)	0	0.0	0	0.0	ND	0	0.0	ND	0	0.0	ND
≥ 25 ng/mL (women)	5	10.9	6	12.8	53 (ns)	3	6.1	−22 (ns)	35	85.4	2 (2–2)
≥ 50 ng/mL (women)	0	0.0	0	0.0	ND	0	0.0	ND	0	0.0	ND

The populations consisted of [a]132 men and 46 women; [b]125 men and 47 women; [c]123 men and 49 women; [d]132 men and 41 women.

[e]A "negative" NNH occurs when the rate for placebo is greater than the rate for the antipsychotic tested.
[f]Week 4 or early termination.
Abbreviations: AE: adverse event; CI: confidence interval; ECG: electrocardiogram; LDL: low-density lipoprotein; LOCF: last observation carried forward; ND: no difference; NNH: number needed to harm; ns: not significant at the $P < .05$ threshold, thus the 95% CI is not shown.

Supplementary Table 3. Antipsychotic-associated somnolence and/or sedation AEs for first-line, oral, second-generation antipsychotics approved for the treatment of schizophrenia, as observed in short-term, acute, placebo-controlled clinical trials[a]

Antipsychotic, dose, length of studies	Available AE Categories	Antipsychotic n/N (%)	Placebo n/N (%)	ARI (%) [95% CI]
Lumateperone 42 mg/d, 4 weeks	Somnolence or sedation combined terms	97/406 (23.9)	41/412 (10.0)	13.9 [8.9, 19.0]
	Somnolence	66/406 (16.3)	22/412 (5.3)	10.9 [6.7, 15.1]
	Sedation	32/406 (7.9)	19/412 (4.6)	3.3 [−0.04, 6.6]
Aripiprazole 2–30 mg/d, 4–6 weeks	Somnolence	102/926 (11.0)	33/413 (8.0)	3.0 [−0.3, 6.3]
Asenapine 10–20 mg/d, 6 weeks	Somnolence or sedation combined terms (also includes hypersomnia, numerator for asenapine is an estimate)	74.36/572 (13)	26/378 (6.9)	6.1 [2.4, 9.9]
	Somnolence	41/572 (7.2)	11/503 (2.2)	5.0 [2.5, 7.5]
	Sedation	35/572 (6.1)	23/503 (4.6)	1.5 [−1.1, 4.2]
Brexpiprazole 1–4 mg/d, 6 weeks	Somnolence or sedation combined terms (also includes hypersomnia, numerators are estimates)	42.6/852 (5)	11.04/368 (3)	2 [−0.3, 4.3]
	Somnolence	20/852 (2.3)	10/368 (2.7)	−0.4 [−2.3, 1.6]
	Sedation	18/852 (2.1)	3/368 (0.8)	1.3 [-0.04, 2.6]
Cariprazine 1.5–6 mg/d, 6 weeks	Somnolence or sedation combined terms (also includes hypersomnia, numerators are estimates)	72.95/1114 (6.5)	29.2/584 (5)	1.5 [−0.7, 3.8]
Iloperidone 10–24 mg/d, 4–6 weeks	Somnolence and sedation	104/874 (11.9)	31/587 (5.3)	6.6 [3.8, 9.4]
	Somnolence	48/874 (5.5)	14/587 (2.4)	3.1 [1.2, 5.1]
	Sedation	59/874 (6.8)	18/587 (3.1)	3.7 [1.5, 5.9]
Lurasidone 20–160 mg/d, 6 weeks	Somnolence or sedation combined terms (also includes hypersomnia, hypersomnolence)	194.53/1508 (12.9)	21.24/708 (3.0)	9.9 [7.8, 12.0]
	Somnolence	119/1508 (7.9)	19/708 (2.7)	5.2 [3.4, 7.0]
	Sedation	113/1508 (7.5)	24/708 (3.4)	4.1 [2.2, 6.0]
Olanzapine 2.5–17.5 mg/d, 6 weeks	Somnolence	65/248 (26.2)	18/118 (15.3)	11.0 [2.5, 19.4]
Paliperidone 3–12 mg/d, 6 weeks	Somnolence or sedation (from product label, numerators are estimates)	80/850 (9.4)	24.85/355 (7.0)	2.4 [−0.9, 5.7]
	Somnolence	36/850 (4.2)	12/355 (3.4)	0.9 [−1.5, 3.2]
	Sedation	42/850 (4.9)	13/355 (3.7)	1.3 [−1.2, 3.7]
Quetiapine IR 75–750 mg/d,	Somnolence	89/510 (17.5)	22/206 (10.7)	6.8 [1.4, 12.1]

3–6 weeks				
Quetiapine XR 300–800 mg/d, 6 weeks	Sedation and somnolence	235/951 (24.7)	33/319 (10.3)	14.4 [10.0, 18.7]
	Somnolence	115/951 (12.1)	12/319 (3.8)	8.3 [5.4, 11.3]
	Sedation	121/951 (12.7)	21/319 (6.6)	6.1 [2.7, 9.6]
Risperidone 2–8 mg/d, 4–8 weeks	Sedation (numerators are estimates)	36.6/366 (10)	4.5/225 (2)	8 [4.4, 11.6]
Ziprasidone 10–200 mg/d, 4–6 weeks	Somnolence (numerators are estimates)	101.09/702 (14.4)	18.02/273 (6.6)	7.8 [3.9, 11.7]

[a]Data are reported in Table 2, Integrated Summary of Safety (data on file, Intra-Cellular Therapies, Inc.), and Citrome (34); the table shows ARI vs. placebo. Abbreviations: AE: adverse event; ARI: absolute risk increase; CI; confidence interval; IR: immediate release; XR: extended release.

Supplementary Table 4. Overall tolerability/acceptability as measured by NNH for discontinuation because of an AE vs. placebo for lumateperone and for other oral second-generation antipsychotics, from the acute pivotal placebo-controlled trials in adults, as noted in product labeling[a]

Antipsychotic	Antipsychotic n/N (%)	Placebo n/N (%)	NNH (95% CI)[b]
Lumateperone 42 mg/d, 4 weeks	4/406 (1.0)	3/412 (0.7)	389 (ns)
Aripiprazole 2–30 mg/d, 4–6 weeks	65/926 (7.0)	41/413 (9.9)	−35 (ns)
Asenapine 10–20 mg/d, 6 weeks	51/572 (8.9)	51/503 (10.1)[c]	-82 (ns)
Brexpiprazole 1–4 mg/d, 6 weeks	67/852 (7.9)	54/368 (14.7)	−15 (−10 to −37)
Cariprazine 1.5–6 mg/d, 6 weeks	95/1031 (9.2)	71/581 (12.2)	−34 (ns)
Iloperidone 10–24 mg/d, 4–6 weeks	43/874 (4.9)	32/587 (5.5)	−189 (ns)
Lurasidone 20–160 mg/d, 6 weeks	143/1508 (9.5)	66/708 (9.3)	623 (ns)
Olanzapine 2.5–17.5 mg/d, 6 weeks	12/248 (4.8)	7/118 (5.9)	−92 (ns)
Paliperidone 3–12 mg/d, 6 weeks	41/850 (4.8)	18/355 (5.1)	−405 (ns)
Quetiapine IR 75–750 mg/d, 3–6 weeks	19/510 (3.7)	7/206 (3.4)	306 (ns)
Quetiapine XR 300–800 mg/d, 6 weeks	61/951 (6.4)	24/319 (7.5)	−91 (ns)
Risperidone 2–16 mg/d, 4–8 weeks	39/564 (6.9)	10/225 (4.4)	41 (ns)
Ziprasidone 10–200 mg/d, 4–6 weeks	29/702 (4.1)	6/273 (2.2)	52 (ns)

[a]Data are reported for lumateperone (Table 2) and lurasidone (35), risperidone (36), ziprasidone (37), or the Drug Approval Package (all others; 8, 38-46).

[b]A "negative" NNH occurs when the rate for placebo is greater than the rate for the antipsychotic tested.

[c]Includes placebo data from 2 additional controlled trials where doses of asenapine < 10 mg/d were tested.

Abbreviations: AE: adverse event; CI: confidence interval; IR: immediate release; NNH: number needed to harm; ns: not significant at the $P < .05$ threshold, thus the 95% CI is not shown; XR: extended release.

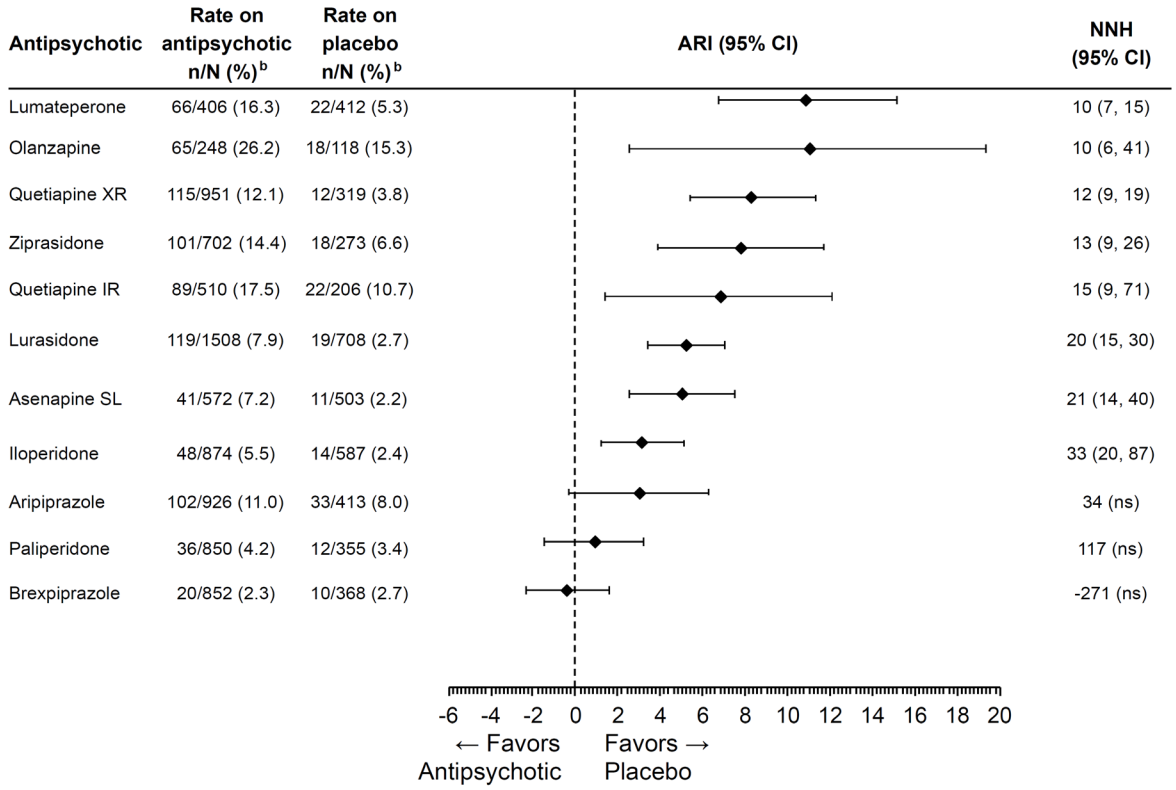
Supplementary Table 5. Benefit/risk as evaluated by LHH[a]

	Lumateperone 42 mg/d		Risperidone 4 mg/d	
	≥ 20% PANSS response (95% CI)[b]	**≥ 30% PANSS response (95% CI)[b]**	**≥ 20% PANSS response (95% CI)[b]**	**≥ 30% PANSS response (95% CI)[b]**
NNT for response	9 (5–36)	8 (5–21)	6 (3–24)	6 (3–23)
NNH for discontinuation because of an AE	389 (ns)	389 (ns)	29 (16–118)	29 (16–118)
LHH for response vs. discontinuation because of an AE	43.2	48.6	4.8	4.8
NNH for weight gain ≥ 7%	122 (ns)	122 (ns)	14 (8–50)	14 (8–50)
LHH for response vs. weight gain ≥ 7%	13.6	15.2	2.3	2.3
NNH for somnolence or sedation AEs	8 (6–12)	8 (6–12)	8 (6–16)	8 (6–16)
LHH for response vs. somnolence or sedation AEs	0.9	1.0	1.3	1.3
NNH for akathisia AEs[c]	−107 (ns)	−107 (ns)	56 (ns)	56 (ns)
LHH for response vs. akathisia AEs	not assessable	not assessable	9.3	9.3

[a]NNT values from Table 1; NNH values from Table 2 (risperidone) and calculated from the Drug Approval Package (8) for akathisia.
[b]Definition of response: percentage threshold improvement in PANSS Total score from baseline
[c]A "negative" NNH occurs when the rate for placebo is greater than the rate for the antipsychotic tested.
Term is defined "not assessable" as the NNH is negative and an LHH cannot be determined.
Abbreviations: CI: confidence interval; LHH: likelihood to be helped or harmed; NNH: number needed to harm; NNT: number needed to treat; ns: not significant at the $P < .05$ threshold, thus the 95% CI is not shown; PANSS: Positive and Negative Syndrome Scale.

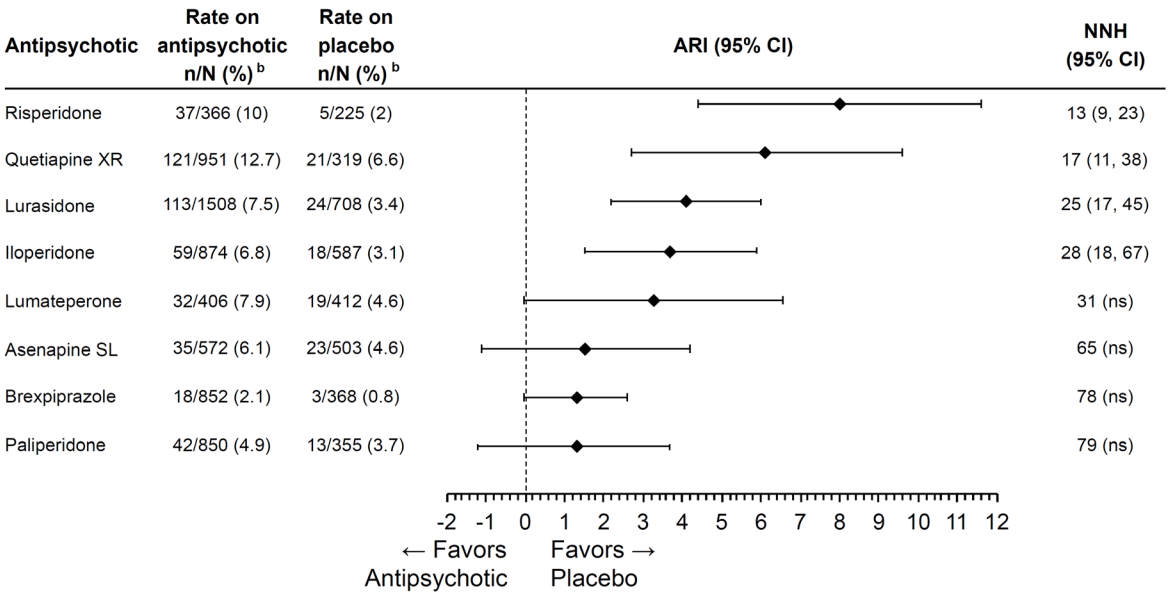
SUPPLEMENTARY FIGURES

Supplementary Figure 1. Antipsychotic-associated somnolence (single-term) AEs for first-line, oral, second-generation antipsychotics approved for the treatment of schizophrenia, as observed in short-term, acute, placebo-controlled clinical trials[a]



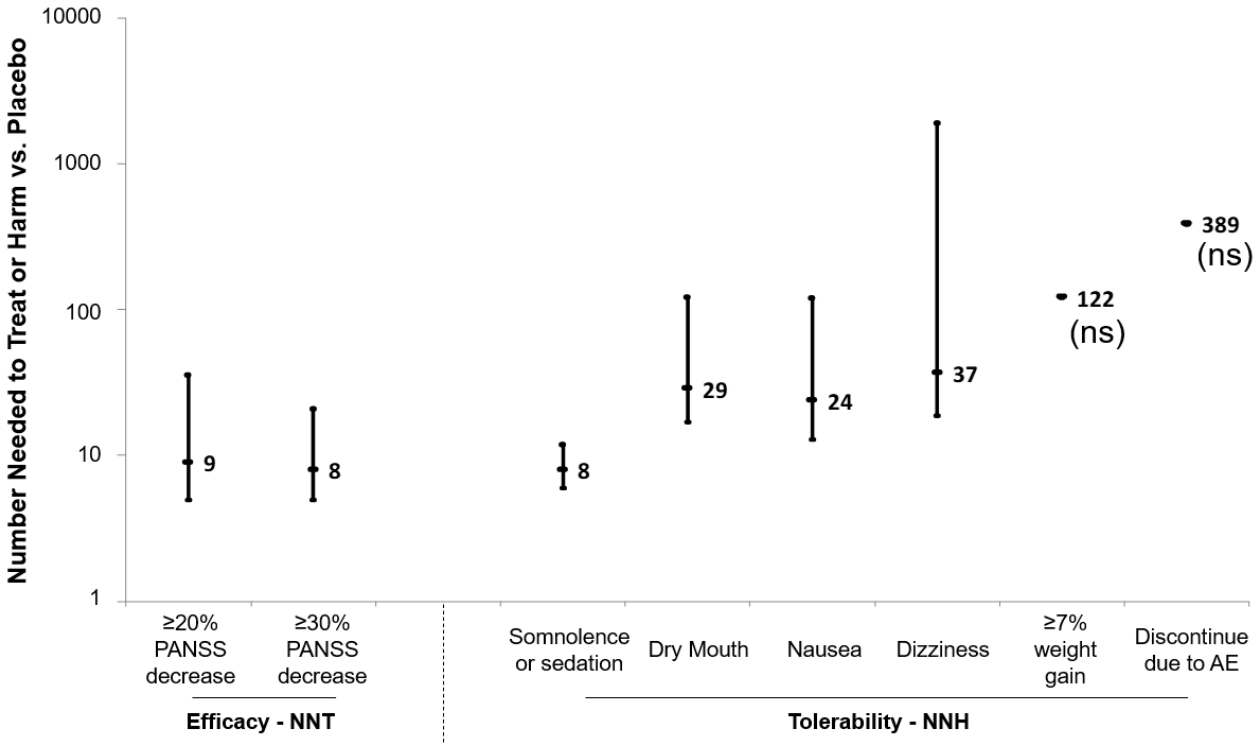
[a]Data are reported in Supplementary Table 3 and Citrome (34); the figure shows ARI and NNH vs. placebo.
[b]Numerators are estimates unless exact values are available.
Abbreviations: AE: adverse event; ARI: absolute risk increase; CI: confidence interval; IR: immediate release; NNH: number needed to harm; SL: sublingual; XR: extended release.

Supplementary Figure 2. Antipsychotic-associated sedation (single-term) AEs for first-line, oral, second-generation antipsychotics approved for the treatment of schizophrenia, as observed in short-term, acute, placebo-controlled clinical trials[a]



[a]Data are reported in Supplementary Table 3 and Citrome (34); the figure shows ARI and NNH vs. placebo.
[b]Numerators are estimates unless exact values are available.
Abbreviations: AE: adverse event; ARI: absolute risk increase; CI: confidence interval; NNH: number needed to harm; SL: sublingual; XR: extended release.

Supplementary Figure 3. Lumateperone 42 mg/d benefit harm through the lens of NNT and NNH vs. placebo with 95% CIs[a,b,c]



[a]Data are pooled from Tables 1 and 2.
[b]Akathisia not shown because the rate of akathisia was higher for placebo than for lumateperone.
[c]No confidence intervals are shown for the outcomes of weight gain ≥ 7% from baseline or discontinuation because of an AE because the 95% CI includes infinity and thus the estimate is not statistically significant.
Abbreviations: AE: adverse event; CI: confidence interval; NNH: number needed to harm; NNT: number needed to treat; ns: not significant at the P <.05 threshold, thus the 95% CI is not shown; PANSS: Positive and Negative Syndrome Scale.