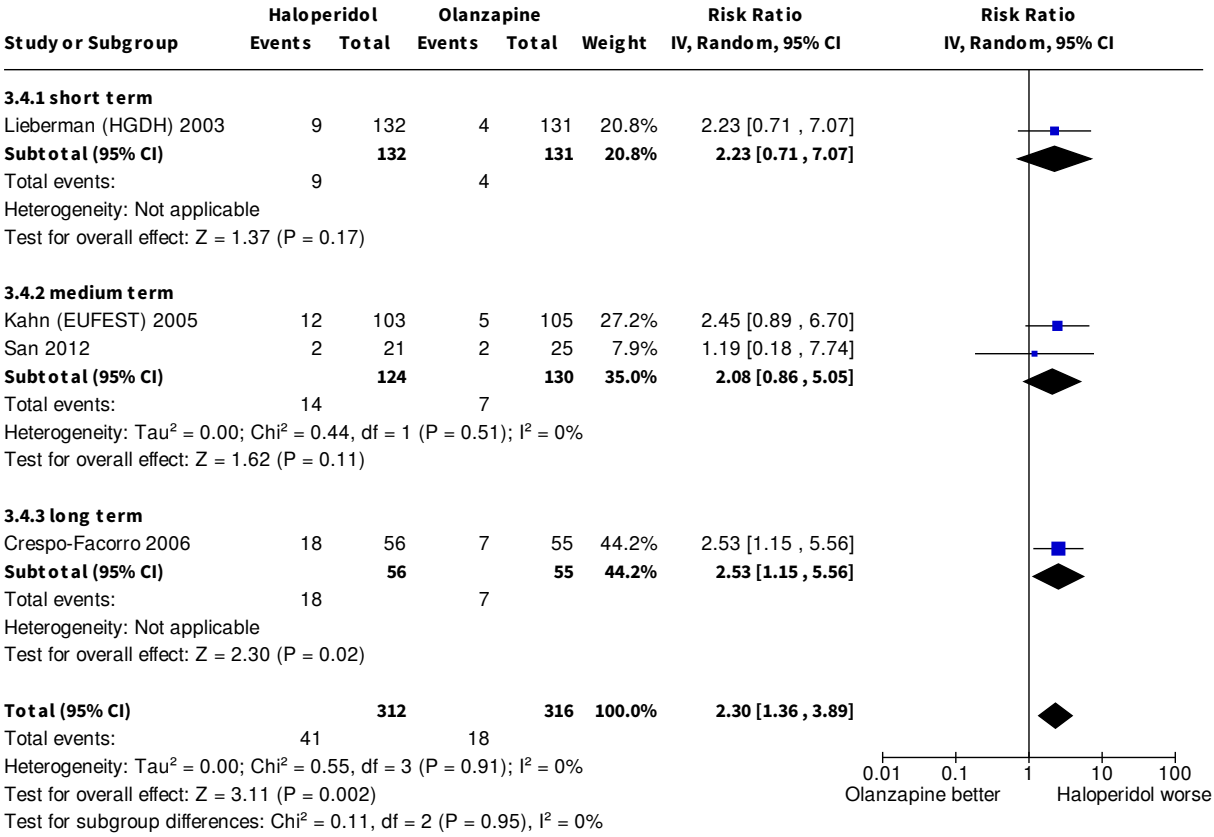
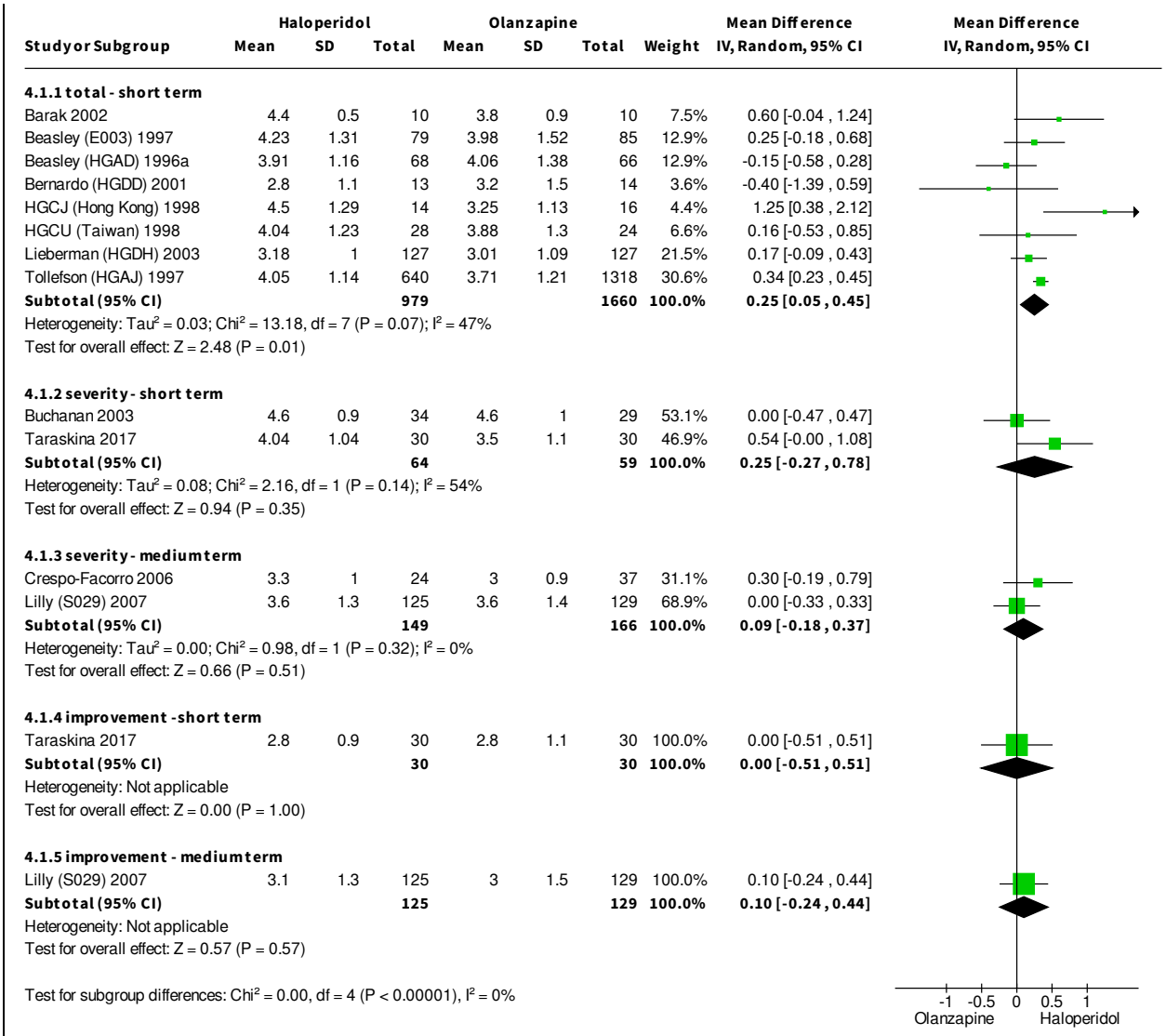


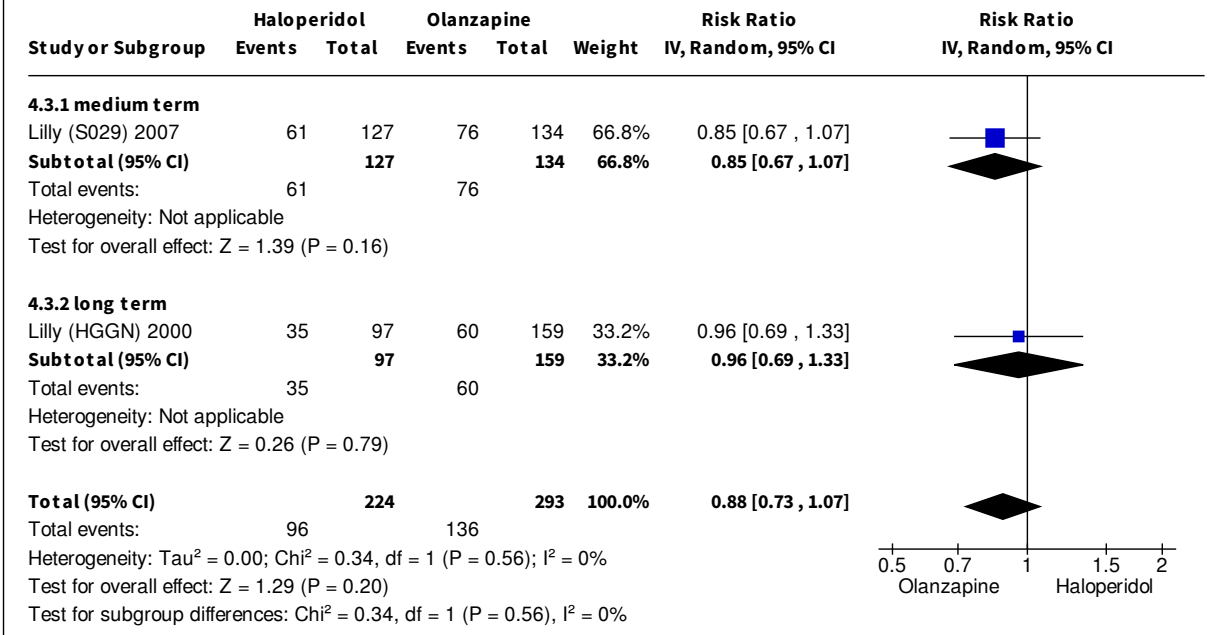
Comparison 3: COMPARISON HALOPERIDOL vs OLANZAPINE: SUBGROUP ANALYSES, Outcome 4: Leaving the study early: Adverse effects. Subgroup analyses: First episode schizophrenia

Analysis 4.1



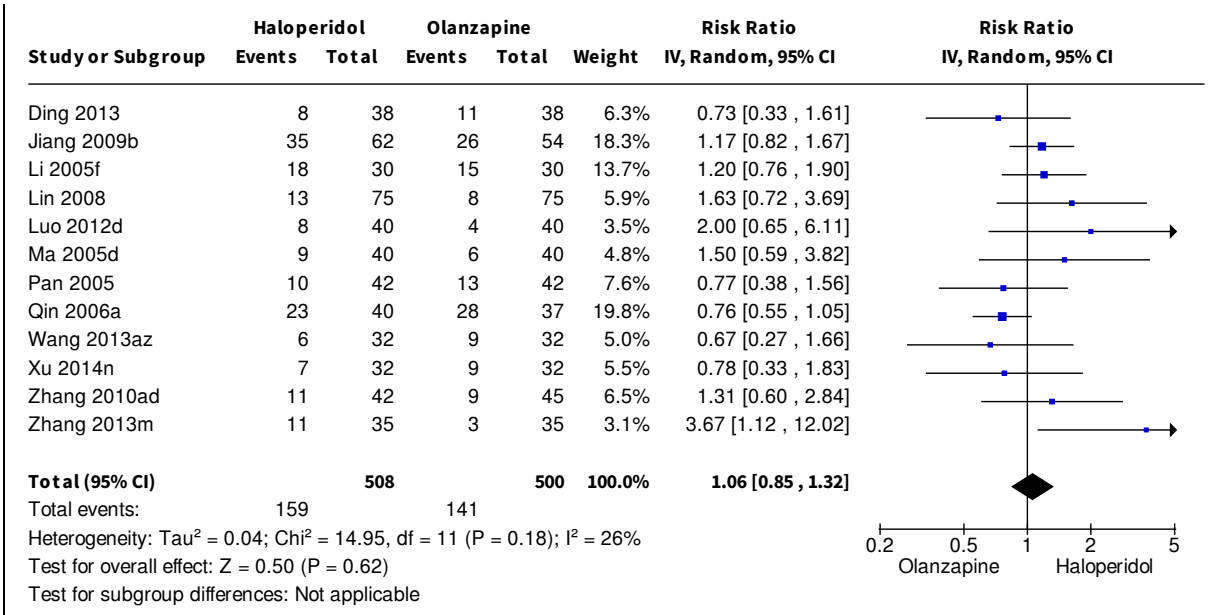
Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 1: Global state: 1a. Average endpoint score (CGI, high=poor)

Analysis 4.3



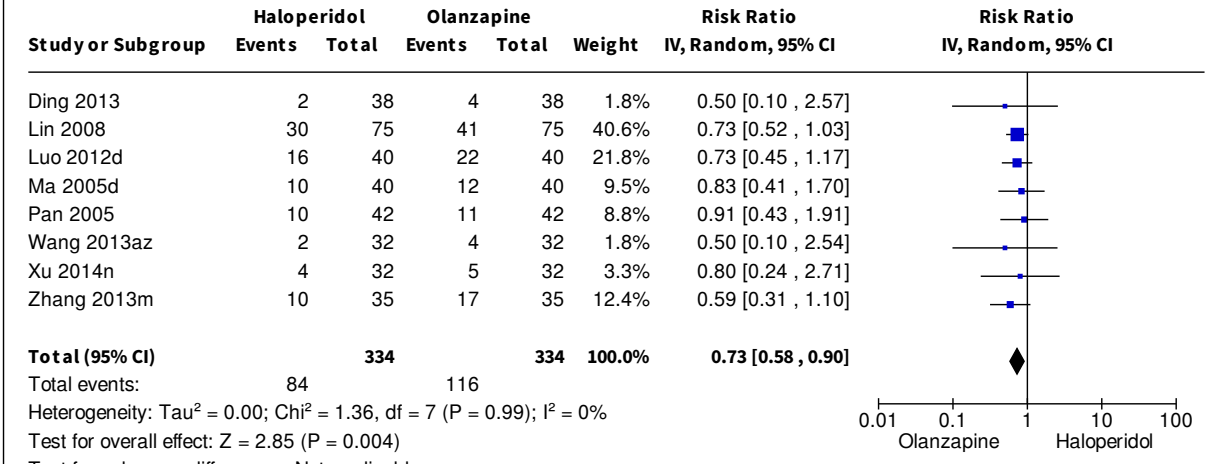
Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 3: Mental state: 1a. Overall - clinically important change in overall mental state (>/= 20% reduction in PANSS endpoint score)

Analysis 4.4



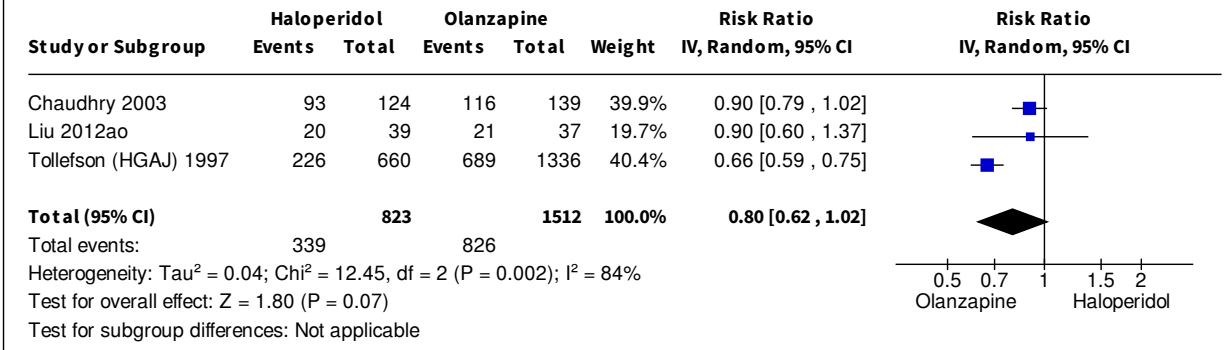
Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 4: Mental state: 1b. Overall - clinically important change in overall mental state - short term (>/= 25% reduction in PANSS endpoint score)

Analysis 4.5



Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 5: Mental state: 1c. Overall - clinically important change in overall mental state - short term (>/= 75% reduction in PANSS endpoint score)

Analysis 4.6

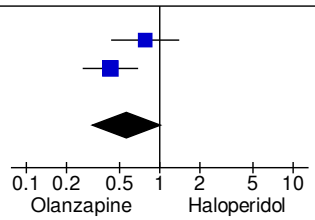


Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 6: Mental state: 1d. Overall - clinically important change in overall mental state - short term (>/=40% reduction in BPRS endpoint score)

Analysis 4.7

Study or Subgroup	Haloperisol Events	Haloperisol Total	Olanzapine Events	Olanzapine Total	Weight	Risk Ratio IV, Random, 95% CI
Crespo-Facorro 2006	14	54	18	54	45.8%	0.78 [0.43 , 1.40]
Kahn (EUFEST) 2005	18	103	43	105	54.2%	0.43 [0.26 , 0.69]
Total (95% CI)		**157**		**159**	**100.0%**	**0.56 [0.31 , 1.01]**
Total events:	32		61			

Heterogeneity: Tau² = 0.11; Chi² = 2.41, df = 1 (P = 0.12); I² = 59%
Test for overall effect: Z = 1.93 (P = 0.05)
Test for subgroup differences: Not applicable



Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 7: Mental state: 1e. Overall - clinically important change in overall mental state- remission-medium term (PANSS score <=3 per symptom at least for 6 months)

Analysis 4.8

Study or Subgroup	Haloperidol Mean	Haloperidol SD	Haloperidol Total	Olanzapine Mean	Olanzapine SD	Olanzapine Total	Weight	Mean Difference IV, Random, 95% CI	Risk of Bias A B C D E F G
4.8.1 short term									
Barak 2002	74.3	9.6	10	65.1	19.3	10	1.2%	9.20 [-4.16 , 22.56]	+ ? − − + + ?
Beasley (E003) 1997	85.22	25.6	79	78.93	28.62	85	2.2%	6.29 [-2.01 , 14.59]	+ + + + + + ?
Bernardo (HGDD) 2001	62.7	20.7	13	68	23.3	14	0.8%	-5.30 [-21.90 , 11.30]	+ ? + + + ? ?
Boulay 2002	56.1	12.97	13	62	12.84	14	1.8%	-5.90 [-15.64 , 3.84]	+ + + ? + ? ?
Cui 2016e	56.74	10.912	80	51.31	7.066	80	4.3%	5.43 [2.58 , 8.28]	+ ? ? ? + ? +
de Hann 2003	60.45	21.03	11	58.89	21.85	9	0.6%	1.56 [-17.37 , 20.49]	+ ? + + + ? +
HGCJ (Hong Kong) 1998	78.43	23.71	14	57.25	17.25	16	1.0%	21.18 [6.16 , 36.20]	+ + + + + ? +
HGCU (Taiwan) 1998	70.11	23.66	28	61.92	19.32	24	1.4%	8.19 [-3.50 , 19.88]	+ ? + + + ? +
Ishigooka 2001	75.69	22.69	78	77.46	24.56	80	2.5%	-1.77 [-9.14 , 5.60]	+ ? ? ? − ? ?
Jiang 2009b	51.37	18.7401	62	43.24	21.0901	54	2.5%	8.13 [0.82 , 15.44]	+ ? ? ? + ? +
Li 2005f	53.1	25.3048	30	50.15	22.5114	30	1.3%	2.95 [-9.17 , 15.07]	? ? ? ? + ? +
Lieberman (HGDH) 2003	59.35	16.63	125	55.85	16.52	126	3.8%	3.50 [-0.60 , 7.60]	+ ? + + + + ?
Lin 2008 (1)	52.3	8.5	75	50.2	8.4	75	4.4%	2.10 [-0.60 , 4.80]	? ? ? ? + ? +
Lindenmayer 2007	67.58	17.7	19	57.25	11.73	16	1.8%	10.33 [0.51 , 20.15]	+ ? + ? + + +
Liu 2010l	51.2	9.4	50	40.4	7.6	50	4.1%	10.80 [7.45 , 14.15]	+ ? ? ? + ? +
Luo 2012d	52.3	8.5	40	50.2	8.4	40	4.0%	2.10 [-1.60 , 5.80]	? ? ? ? + ? +
Ma 2005d	40.83	6.86	40	31.35	6.17	40	4.3%	9.48 [6.62 , 12.34]	? ? ? ? + ? +
Taraskina 2017	73.5	17.3	30	63.8	19.3	30	1.9%	9.70 [0.43 , 18.97]	+ ? ? ? + − +
Tollefson (HGAJ) 1997	78.73	22.92	636	72.41	23.5	1312	4.6%	6.32 [4.13 , 8.51]	? + + + + + ?
Zhang 2010ad	54.05	4.85	42	51.73	5.14	45	4.6%	2.32 [0.22 , 4.42]	? ? ? ? + ? +
Zhang 2016al	43.6	9.7	36	44	9.8	36	3.6%	-0.40 [-4.90 , 4.10]	? ? ? ? + ? +
Zheng 2003b	46.67	7.81	34	39.75	7.14	34	4.0%	6.92 [3.36 , 10.48]	? ? ? ? + ? +
Subtotal (95% CI)			**1545**			**2220**	**60.9%**	**5.02 [3.21 , 6.82]**	

Heterogeneity: Tau² = 8.93; Chi² = 60.42, df = 21 (P < 0.0001); I² = 65%
Test for overall effect: Z = 5.44 (P < 0.00001)

4.8.2 medium term									
Ding 2013	68.58	13.01	38	60.67	12.13	38	3.1%	7.91 [2.25 , 13.57]	? ? − ? + ? +
Kahn (EUFEST) 2005	53.3	17.2531	103	52.4	17.4198	105	3.5%	0.90 [-3.81 , 5.61]	+ ? − − + + ?
Lilly (S029) 2007	62.3	20.7	120	62.1	20.1	127	3.4%	0.20 [-4.89 , 5.29]	+ + + + + + ?
Lilly 2006a	72.77	19.26	40	48.07	10.79	31	2.6%	24.70 [17.63 , 31.77]	? ? − − ? + ?
Qin 2006a	60.2	20.1	40	54.8	16.9	40	2.2%	5.40 [-2.74 , 13.54]	? ? ? ? − ? +
San 2012	66.67	27.35	21	45.48	16.95	25	1.1%	21.19 [7.74 , 34.64]	+ ? − − + ? +
Song 2009c	42.93	7.67	50	38.26	9.37	50	4.1%	4.67 [1.31 , 8.03]	? ? ? ? + ? +
Wang 2013az	68.58	13.01	32	60.67	12.31	32	2.9%	7.91 [1.70 , 14.12]	? ? ? ? + ? +
Xianzhen 2004	63.9	9.6	60	51.5	9.3	60	4.1%	12.40 [9.02 , 15.78]	+ ? ? ? + ? +
Xu 2014n	68.5	13.01	34	61.6	12.31	34	3.0%	6.90 [0.88 , 12.92]	+ ? ? ? + ? +
Zhang 2013m	60.2	5.09	35	53.95	5.52	35	4.5%	6.25 [3.76 , 8.74]	? ? ? ? + ? +
Zhu 2014f	39.8	7.43	30	41.79	15.15	30	3.0%	-1.99 [-8.03 , 4.05]	? ? ? + + ? +
Subtotal (95% CI)			**603**			**607**	**37.6%**	**7.27 [3.86 , 10.67]**	

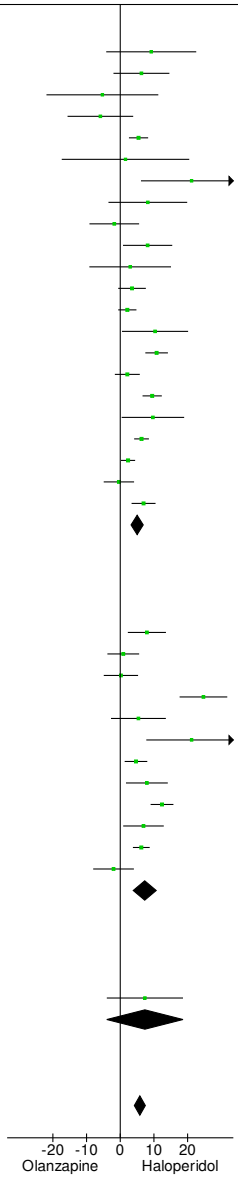
Heterogeneity: Tau² = 27.27; Chi² = 62.22, df = 11 (P < 0.00001); I² = 82%
Test for overall effect: Z = 4.18 (P < 0.0001)

4.8.3 long term									
Jones 1998 (P022)	65.43	18.45	23	58.11	19.7	21	1.5%	7.32 [-3.99 , 18.63]	+ ? + + + ? +
Subtotal (95% CI)			**23**			**21**	**1.5%**	**7.32 [-3.99 , 18.63]**	

Heterogeneity: Not applicable
Test for overall effect: Z = 1.27 (P = 0.20)

Total (95% CI)			**2171**			**2848**	**100.0%**	**5.82 [4.18 , 7.45]**	

Heterogeneity: Tau² = 13.88; Chi² = 127.14, df = 34 (P < 0.00001); I² = 73%
Test for overall effect: Z = 6.97 (P < 0.00001)
Test for subgroup differences: Chi² = 1.40, df = 2 (P = 0.50), I² = 0%



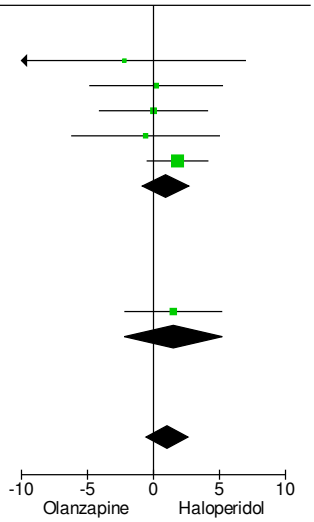
Footnotes
(1) Suspicious standard deviations

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 8: Mental state: 2a. Overall - average endpoint score (PANSS total, high=poor)

Analysis 4.9

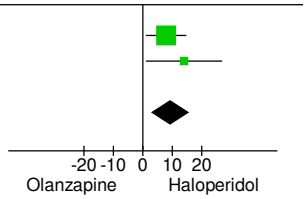
Study or Subgroup	Haloperidol Mean	SD	Total	Olanzapine Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
4.9.1 short term								
Bernardo (HGDD) 2001	34.4	11.9	13	36.6	12.5	14	3.0%	-2.20 [-11.40 , 7.00]
Buchanan 2003	33.6	10.6	34	33.4	9.9	29	9.8%	0.20 [-4.87 , 5.27]
Ishigooka 2001	40.41	13.11	80	40.41	13.67	81	14.8%	0.00 [-4.14 , 4.14]
Lahti 2007	33.2	8.1	12	33.8	6.9	17	8.0%	-0.60 [-6.24 , 5.04]
Liu 2012ao	24.35	4.45	39	22.53	5.83	37	46.1%	1.82 [-0.52 , 4.16]
Subtotal (95% CI)			**178**			**178**	**81.6%**	**0.91 [-0.85 , 2.67]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.56$, df = 4 (P = 0.82); $I^2 = 0\%$								
Test for overall effect: Z = 1.02 (P = 0.31)								
4.9.2 medium term								
Crespo-Facorro 2006	31.1	7.1	24	29.6	7.4	37	18.4%	1.50 [-2.21 , 5.21]
Subtotal (95% CI)			**24**			**37**	**18.4%**	**1.50 [-2.21 , 5.21]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.79 (P = 0.43)								
Total (95% CI)			**202**			**215**	**100.0%**	**1.02 [-0.57 , 2.61]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.63$, df = 5 (P = 0.90); $I^2 = 0\%$								
Test for overall effect: Z = 1.26 (P = 0.21)								
Test for subgroup differences: $Chi^2 = 0.08$, df = 1 (P = 0.78), $I^2 = 0\%$								



Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 9: Mental state: 2b. Overall - average endpoint score (BPRS total, high=poor)

Analysis 4.11

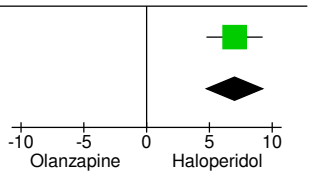
Study or Subgroup	Haloperidol Mean	SD	Total	Olanzapine Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Chaudhry 2003	-36.7	28.5723	123	-44.6	28.0241	139	78.0%	7.90 [1.03 , 14.77]
Dhar 2010	-46	15.1	20	-60	25.37	20	22.0%	14.00 [1.06 , 26.94]
Total (95% CI)			**143**			**159**	**100.0%**	**9.24 [3.17 , 15.31]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.67$, df = 1 (P = 0.41); $I^2 = 0\%$								
Test for overall effect: Z = 2.99 (P = 0.003)								
Test for subgroup differences: Not applicable								



Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 11: Mental state: 3a. Overall - average change score - short term (PANSS total, high=poor)

Analysis 4.13

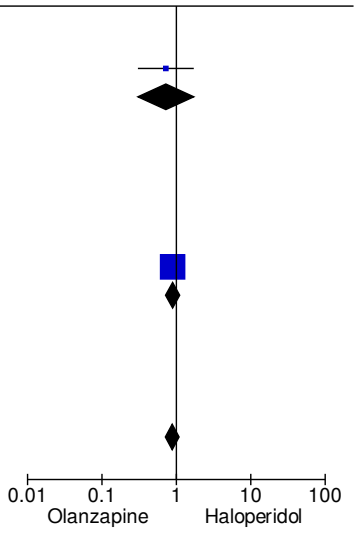
Study or Subgroup	Haloperidol Mean	SD	Total	Olanzapine Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Nag 2013	22.2	3.1939	10	15.2	1.676	10	100.0%	7.00 [4.76 , 9.24]
Total (95% CI)			**10**			**10**	**100.0%**	**7.00 [4.76 , 9.24]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 6.14 (P < 0.00001)								
Test for subgroup differences: Not applicable								



Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 13: Mental state: 4a. Specific - average endpoint score - depression - short term (MADRS , high=poor)

Analysis 4.17

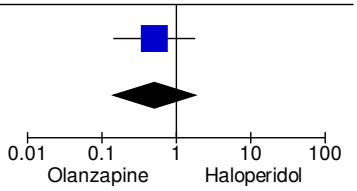
Study or Subgroup	Haloperidol Events	Total	Olanzapine Events	Total	Weight	Risk Ratio IV, Random, 95% CI
4.17.1 short term						
Lindenmayer 2007	6	19	7	16	6.0%	0.72 [0.30 , 1.71]
Subtotal (95% CI)		**19**		**16**	**6.0%**	**0.72 [0.30 , 1.71]**
Total events:	6		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.74 (P = 0.46)						
4.17.2 medium term						
Lilly (S029) 2007	68	133	81	141	94.0%	0.89 [0.72 , 1.11]
Subtotal (95% CI)		**133**		**141**	**94.0%**	**0.89 [0.72 , 1.11]**
Total events:	68		81			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.04 (P = 0.30)						
Total (95% CI)		**152**		**157**	**100.0%**	**0.88 [0.71 , 1.09]**
Total events:	74		88			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.21$, df = 1 (P = 0.65); $I^2 = 0\%$						
Test for overall effect: Z = 1.19 (P = 0.23)						
Test for subgroup differences: $Chi^2 = 0.21$, df = 1 (P = 0.65), $I^2 = 0\%$						



Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 17: Mental state: 5a. Specific - negative symptoms - clinically important change(>/=20% reduction in PANSS-N)

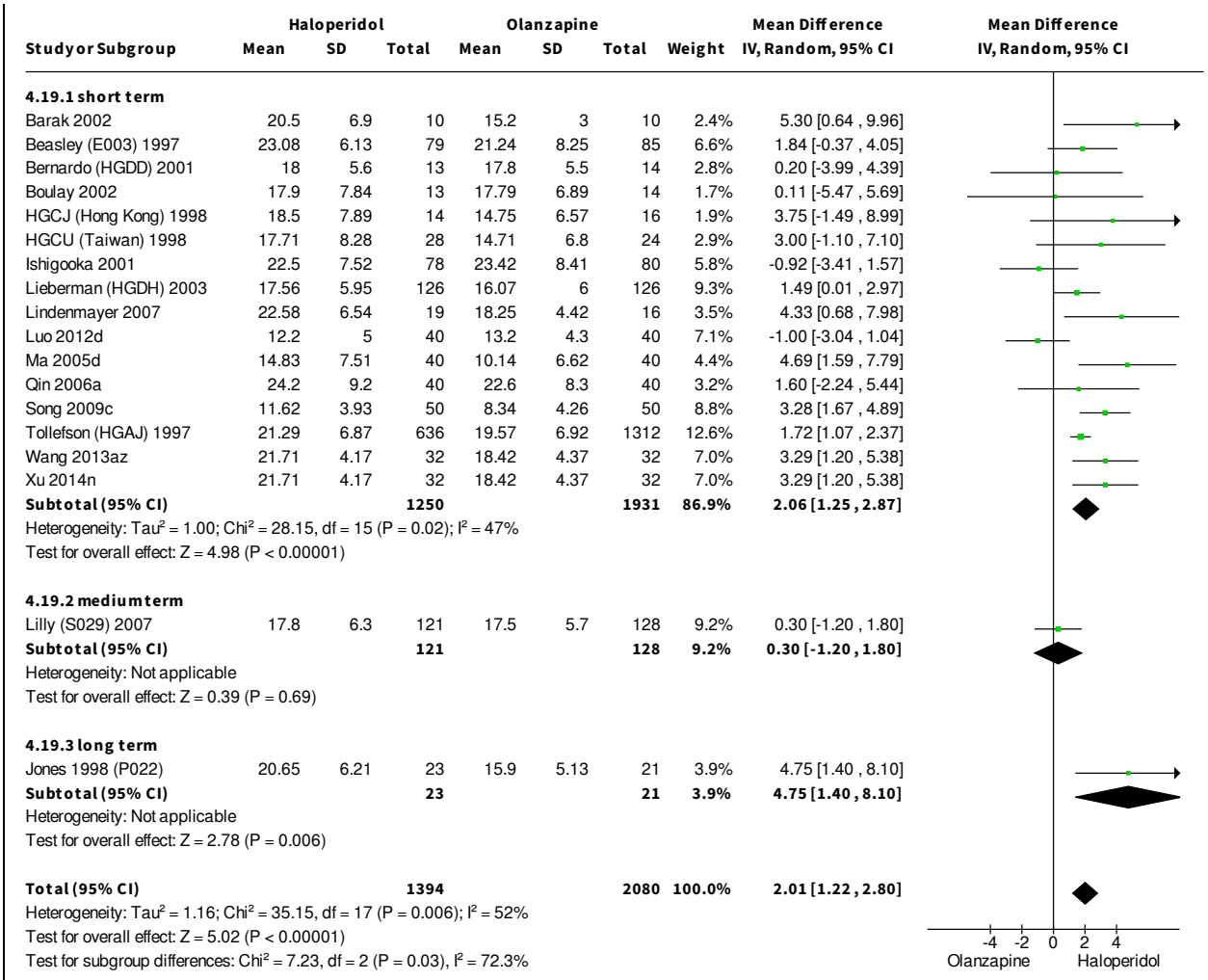
Analysis 4.18

Study or Subgroup	Haloperidol Events	Total	Olanzapine Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Lindenmayer 2007	3	19	5	16	100.0%	0.51 [0.14 , 1.79]
Total (95% CI)		**19**		**16**	**100.0%**	**0.51 [0.14 , 1.79]**
Total events:	3		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.06 (P = 0.29)						
Test for subgroup differences: Not applicable						



Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 18: Mental state: 5b. Specific - negative symptoms - clinically important change - short term (>/=40% reduction in PANSS-N)

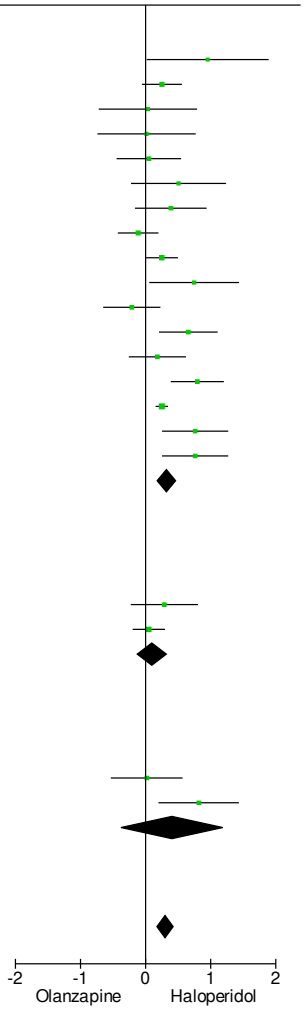
Analysis 4.19



Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 19: Mental state: 5c. Specific - negative symptoms - average endpoint score (PANSS-N, high=poor)

Analysis 4.20

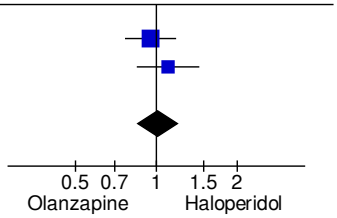
Study or Subgroup	Haloperidol Mean	SD	Total	Olanzapine Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
4.20.1 short term								
Barak 2002	20.5	6.9	10	15.2	3	10	1.6%	0.95 [0.02 , 1.89]
Beasley (E003) 1997	23.08	6.13	79	21.24	8.25	85	7.1%	0.25 [-0.06 , 0.56]
Bernardo (HGDD) 2001	18	5.6	13	17.8	5.5	14	2.2%	0.03 [-0.72 , 0.79]
Boulay 2002	17.9	7.84	13	17.79	6.89	14	2.2%	0.01 [-0.74 , 0.77]
Buchanan 2003	30.2	11.6	34	29.6	12.4	29	4.2%	0.05 [-0.45 , 0.54]
HGCJ (Hong Kong) 1998	18.5	7.89	14	14.75	6.57	16	2.4%	0.51 [-0.22 , 1.24]
HGCU (Taiwan) 1998	17.71	8.28	28	14.71	6.8	24	3.6%	0.39 [-0.16 , 0.94]
Ishigooka 2001	22.5	7.52	78	23.42	8.41	80	7.0%	-0.11 [-0.43 , 0.20]
Lieberman (HGDH) 2003	17.56	5.95	126	16.07	6	126	8.4%	0.25 [0.00 , 0.50]
Lindenmayer 2007	22.58	6.54	19	18.25	4.42	16	2.6%	0.75 [0.06 , 1.44]
Luo 2012d	12.2	5	40	13.2	4.3	40	4.9%	-0.21 [-0.65 , 0.23]
Ma 2005d	14.83	7.51	40	10.14	6.62	40	4.8%	0.66 [0.21 , 1.11]
Qin 2006a	24.2	9.2	40	22.6	8.3	40	4.9%	0.18 [-0.26 , 0.62]
Song 2009c	11.62	3.93	50	8.34	4.26	50	5.4%	0.79 [0.39 , 1.20]
Tollefson (HGAJ) 1997	21.29	6.87	636	19.57	6.92	1312	11.6%	0.25 [0.15 , 0.34]
Wang 2013az	21.71	4.17	32	18.42	4.37	32	4.1%	0.76 [0.25 , 1.27]
Xu 2014n	21.71	4.17	32	18.42	4.37	32	4.1%	0.76 [0.25 , 1.27]
Subtotal (95% CI)			**1284**			**1960**	**81.0%**	**0.32 [0.18 , 0.46]**
Heterogeneity: Tau² = 0.04; Chi² = 33.20, df = 16 (P = 0.007); I² = 52%								
Test for overall effect: Z = 4.41 (P < 0.0001)								
4.20.2 medium term								
Crespo-Facorro 2006	4.8	5.3	24	3.5	3.8	37	4.0%	0.29 [-0.23 , 0.81]
Lilly (S029) 2007	17.8	6.3	121	17.5	5.7	128	8.3%	0.05 [-0.20 , 0.30]
Subtotal (95% CI)			**145**			**165**	**12.3%**	**0.09 [-0.13 , 0.32]**
Heterogeneity: Tau² = 0.00; Chi² = 0.67, df = 1 (P = 0.41); I² = 0%								
Test for overall effect: Z = 0.83 (P = 0.41)								
4.20.3 long term								
Crespo-Facorro 2006	4.39	4.47	28	4.31	4.96	23	3.6%	0.02 [-0.53 , 0.57]
Jones 1998 (P022)	20.65	6.21	23	15.9	5.13	21	3.1%	0.82 [0.20 , 1.43]
Subtotal (95% CI)			**51**			**44**	**6.7%**	**0.40 [-0.38 , 1.19]**
Heterogeneity: Tau² = 0.23; Chi² = 3.57, df = 1 (P = 0.06); I² = 72%								
Test for overall effect: Z = 1.01 (P = 0.31)								
Total (95% CI)			**1480**			**2169**	**100.0%**	**0.30 [0.17 , 0.42]**
Heterogeneity: Tau² = 0.03; Chi² = 39.86, df = 20 (P = 0.005); I² = 50%								
Test for overall effect: Z = 4.68 (P < 0.00001)								
Test for subgroup differences: Chi² = 2.88, df = 2 (P = 0.24), I² = 30.7%								



Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 20: Mental state: 5d. Specific - negative symptoms - average endpoint score (PANSS-N, SANS scales, SMD, high=poor)

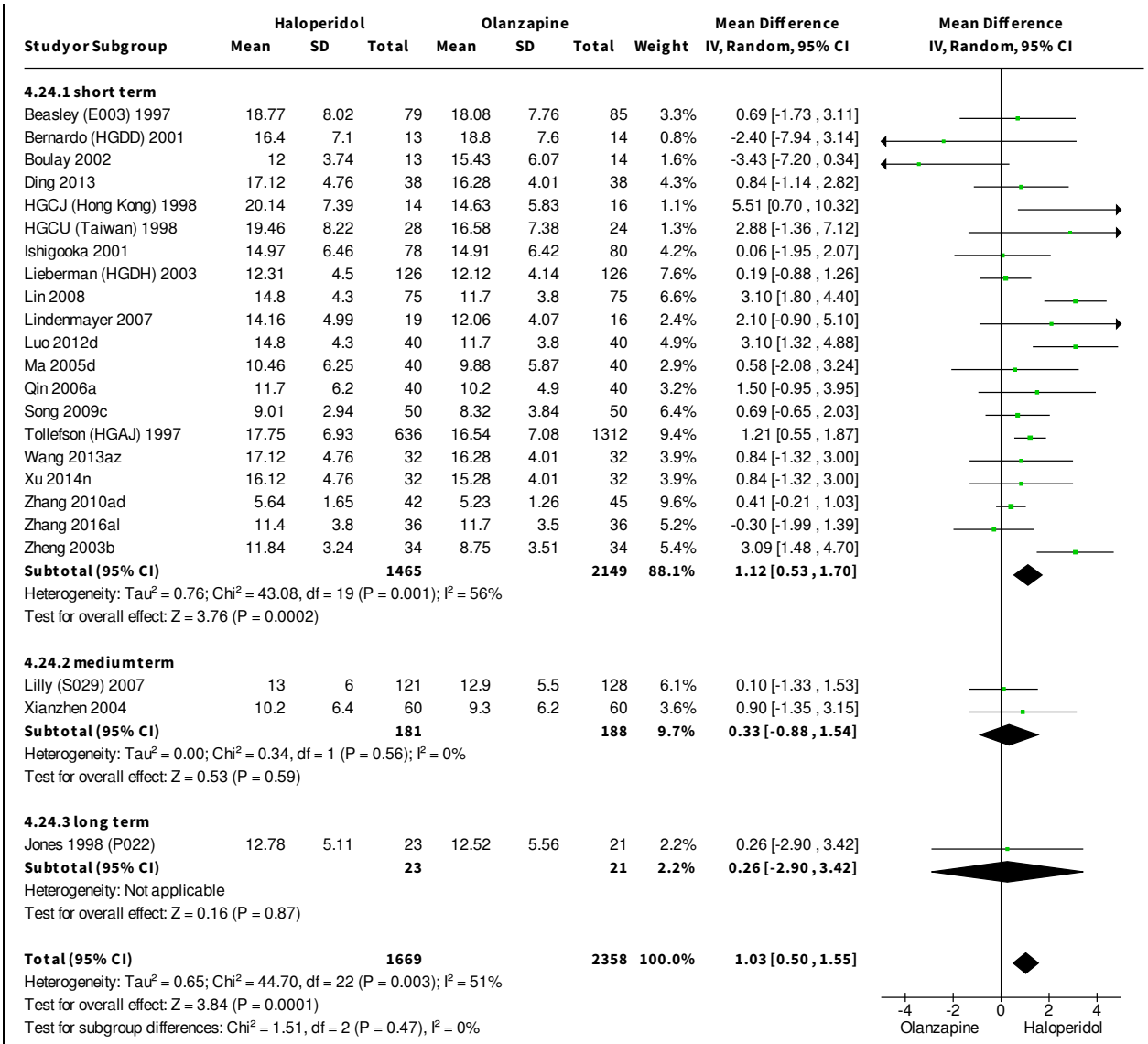
Analysis 4.23

Study or Subgroup	Haloperidol Events	Total	Olanzapine Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Lilly (S029) 2007	70	133	78	141	59.9%	0.95 [0.76 , 1.18]
Mousavi 2013	10	10	9	10	40.1%	1.11 [0.85 , 1.44]
Total (95% CI)		**143**		**151**	**100.0%**	**1.01 [0.85 , 1.20]**
Total events:	80		87			
Heterogeneity: Tau² = 0.00; Chi² = 0.72, df = 1 (P = 0.40); I² = 0%						
Test for overall effect: Z = 0.12 (P = 0.91)						
Test for subgroup differences: Not applicable						



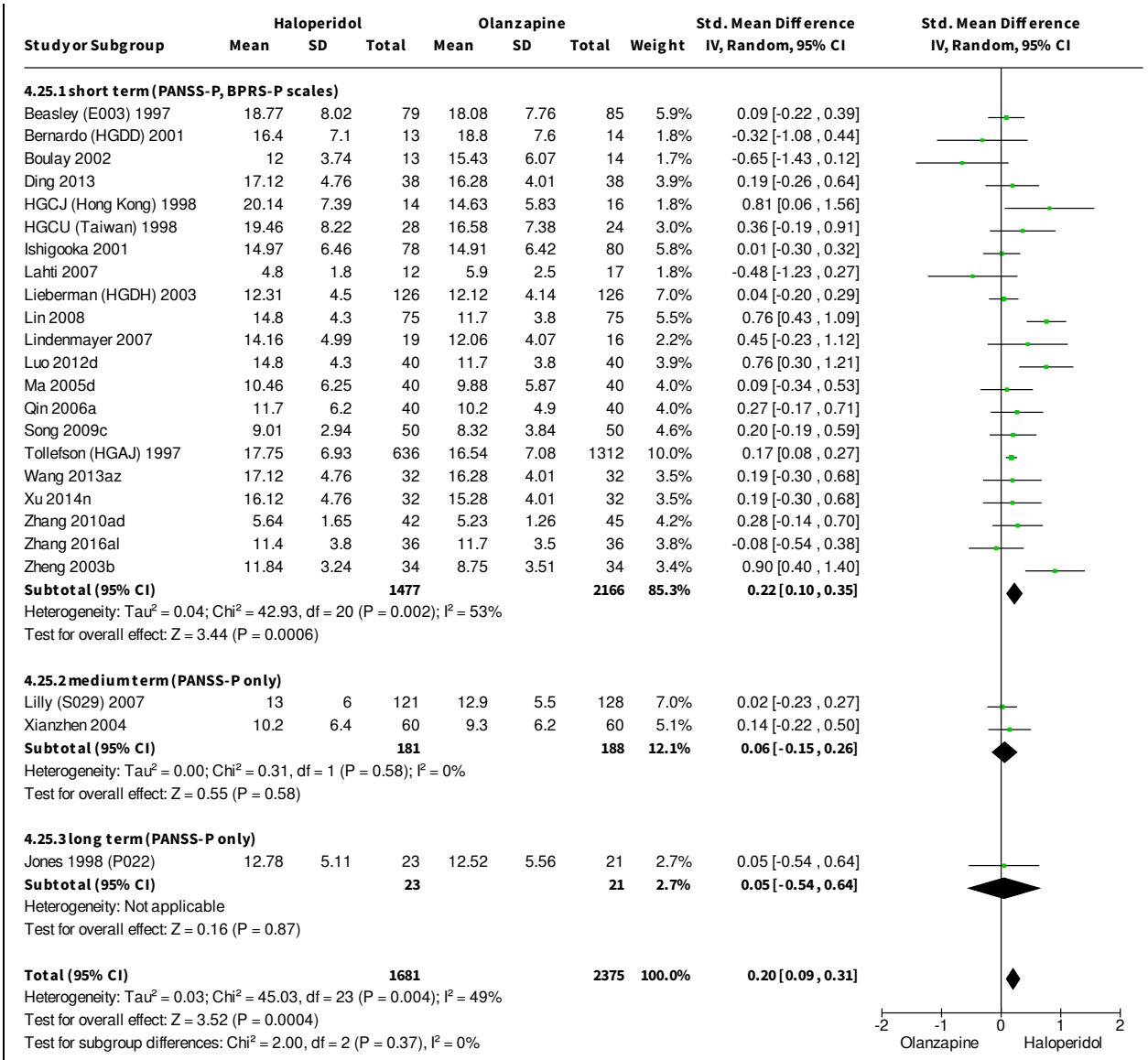
Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 23: Mental state: 6a. Specific - positive symptoms - clinically important change - medium term (>/= 20% reduction in PANSS-P)

Analysis 4.24



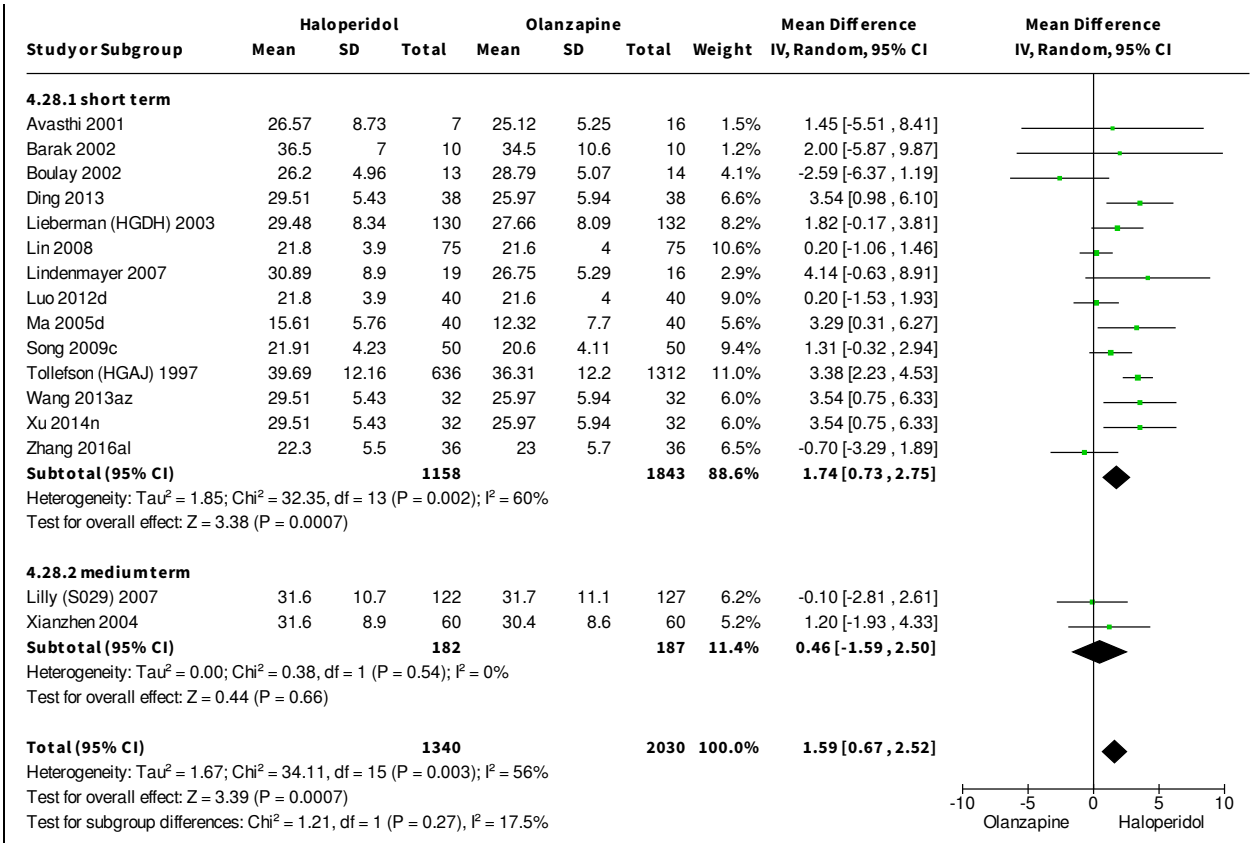
Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 24: Mental state: 6b. Specific - positive symptoms - average endpoint score (PANSS-P, high=poor)

Analysis 4.25



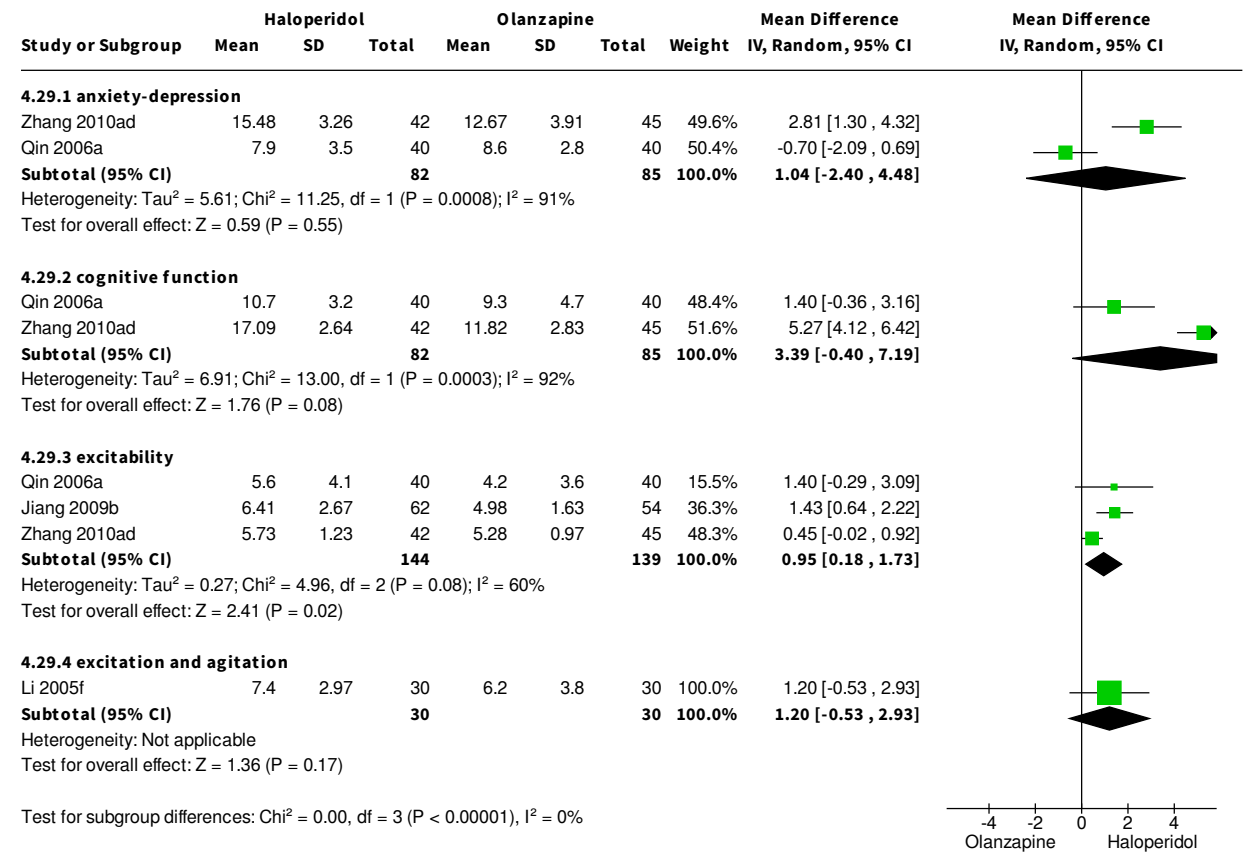
Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 25: Mental state: 6c. Specific - positive symptoms - average endpoint score (PANSS-P, BPRS-P, SMD, high=poor)

Analysis 4.28



Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 28: Mental state: 7. Specific - psychopathology, general - average endpoint score (PANSS psychopathology, high=poor)

Analysis 4.29

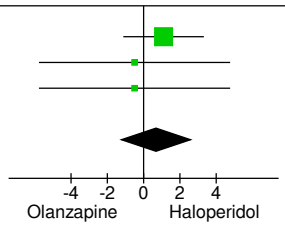


Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 29: Mental state: 8. Specific - various - average endpoint score - short term (PANSS subscales, high=poor)

Analysis 4.30

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Ma 2005d	16.5	5.4	40	15.4	4.7	40	73.8%	1.10 [-1.12 , 3.32]
Qin 2006a	20.2	13.6	40	20.7	10.2	40	13.1%	-0.50 [-5.77 , 4.77]
Zhang 2010ae	20.2	13.6	40	20.7	10.2	40	13.1%	-0.50 [-5.77 , 4.77]
Total (95% CI)			**120**			**120**	**100.0%**	**0.68 [-1.23 , 2.59]**

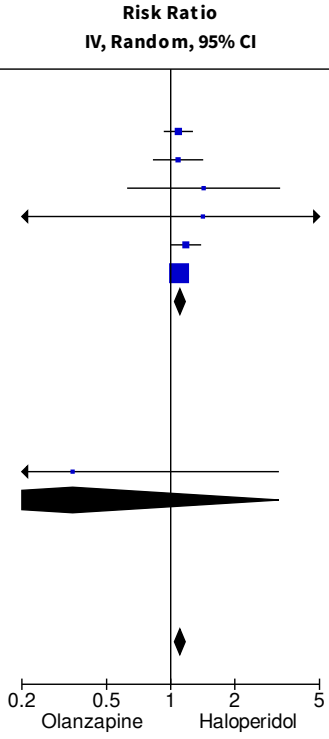
Heterogeneity: Tau² = 0.00; Chi² = 0.52, df = 2 (P = 0.77); I² = 0%
Test for overall effect: Z = 0.70 (P = 0.48)
Test for subgroup differences: Not applicable



Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 30: Mental state: 9. Specific - time to onset of effect - short term

Analysis 4.31

Study or Subgroup	Haloperidol Events	Total	Olanzapine Events	Total	Weight	Risk Ratio IV, Random, 95% CI
4.31.1 short term						
Beasley (HGAD) 1996a	53	69	140	198	13.5%	1.09 [0.93 , 1.27]
Chaudhry 2003	57	124	59	139	4.5%	1.08 [0.83 , 1.42]
Crespo-Facorro 2006	11	52	8	54	0.5%	1.43 [0.62 , 3.27]
Lahti 2007	1	12	1	17	0.0%	1.42 [0.10 , 20.49]
Lieberman (HGDH) 2003	97	131	83	132	12.2%	1.18 [1.00 , 1.39]
Tollefson (HGAJ) 1997	437	660	808	1336	69.1%	1.09 [1.02 , 1.17]
Subtotal (95% CI)		**1048**		**1876**	**99.9%**	**1.10 [1.04 , 1.17]**
Total events:	656		1099			
Heterogeneity: Tau² = 0.00; Chi² = 1.10, df = 5 (P = 0.95); I² = 0%						
Test for overall effect: Z = 3.36 (P = 0.0008)						
4.31.2 medium term						
Crespo-Facorro 2006	1	52	3	54	0.1%	0.35 [0.04 , 3.22]
Subtotal (95% CI)		**52**		**54**	**0.1%**	**0.35 [0.04 , 3.22]**
Total events:	1		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.93 (P = 0.35)						
Total (95% CI)		**1100**		**1930**	**100.0%**	**1.10 [1.04 , 1.17]**
Total events:	657		1102			
Heterogeneity: Tau² = 0.00; Chi² = 2.14, df = 6 (P = 0.91); I² = 0%						
Test for overall effect: Z = 3.34 (P = 0.0008)						
Test for subgroup differences: Chi² = 1.04, df = 1 (P = 0.31), I² = 3.7%						

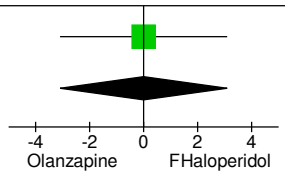


Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 31: Mental state: 10. Specific - Needing additional benzodiazepines

Analysis 4.32

Study or Subgroup	Haloperidol Mean	SD	Total	Olanzapine Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Buchanan 2003	18.1	5.9	28	18.1	5.7	26	100.0%	0.00 [-3.09 , 3.09]
Total (95% CI)			**28**			**26**	**100.0%**	**0.00 [-3.09 , 3.09]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)
Test for subgroup differences: Not applicable

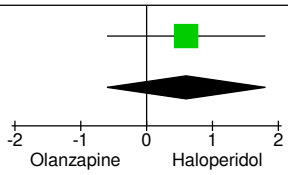


Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 32: Functioning: 1a. General - average endpoint score - short term (GAF, high=good)

Analysis 4.34

Study or Subgroup	Haloperidol Mean	SD	Total	Olanzapine Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Lilly (S029) 2007	6.9	4.7	118	6.3	4.8	122	100.0%	0.60 [-0.60 , 1.80]
Total (95% CI)			**118**			**122**	**100.0%**	**0.60 [-0.60 , 1.80]**

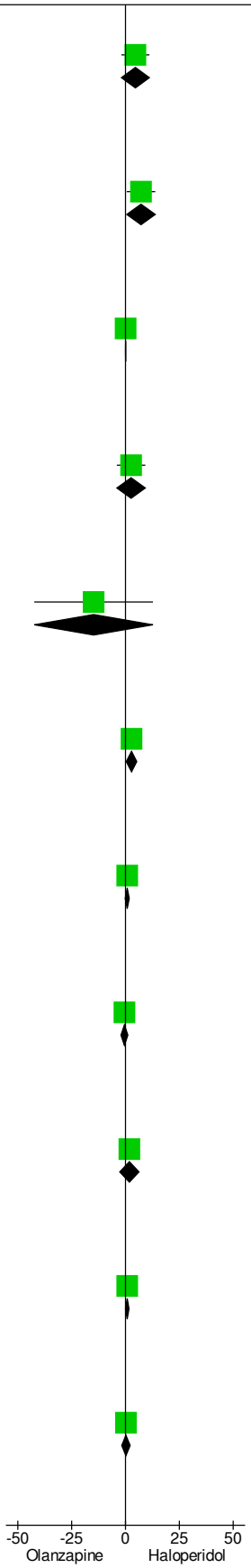
Heterogeneity: Not applicable
Test for overall effect: Z = 0.98 (P = 0.33)
Test for subgroup differences: Not applicable



Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 34: Functioning: 2a. Specific - cognition- average endpoint score - long term (SCD, high=poor)

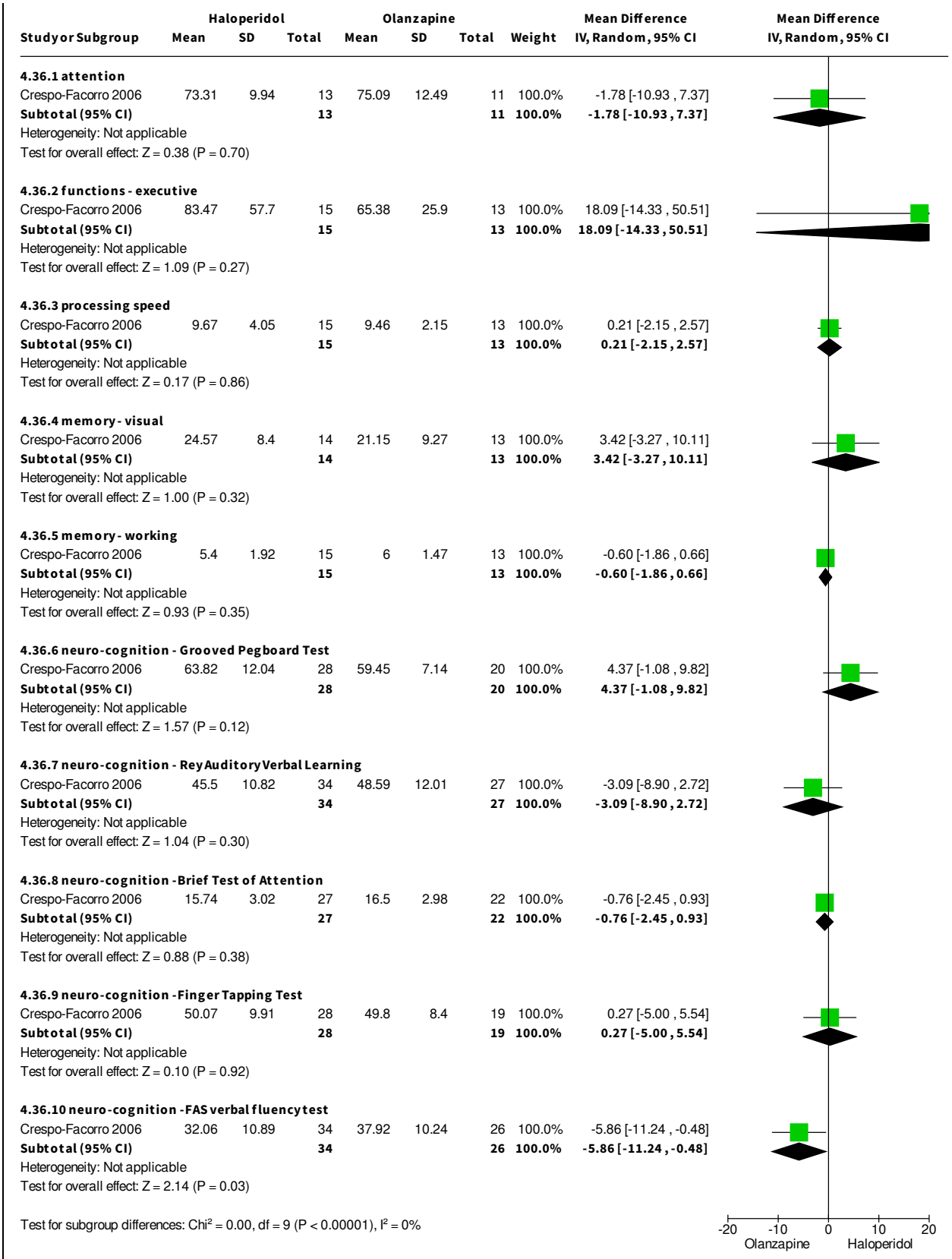
Analysis 4.35

Study or Subgroup	Haloperidol Mean	SD	Total	Olanzapine Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
4.35.1 neuro-cognition - California Verbal Learning Test								
Sergi 2007	51	12.6	20	46.4	11.1	40	100.0%	4.60 [-1.91 , 11.11]
Subtotal (95% CI)			**20**			**40**	**100.0%**	**4.60 [-1.91 , 11.11]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.39 (P = 0.17)								
4.35.2 neuro-cognition - Controlled Oral Word Association Test								
Sergi 2007	52.7	12.8	20	45.5	11.4	40	100.0%	7.20 [0.57 , 13.83]
Subtotal (95% CI)			**20**			**40**	**100.0%**	**7.20 [0.57 , 13.83]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.13 (P = 0.03)								
4.35.3 neuro-cognition - Degraded Stimulus Continuous Performance Test								
Sergi 2007	0.86	0.08	20	0.81	0.15	40	100.0%	0.05 [-0.01 , 0.11]
Subtotal (95% CI)			**20**			**40**	**100.0%**	**0.05 [-0.01 , 0.11]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.68 (P = 0.09)								
4.35.4 neuro-cognition - Digit Symbol coding								
Sergi 2007	51.3	11.8	20	48.7	13.3	40	100.0%	2.60 [-4.01 , 9.21]
Subtotal (95% CI)			**20**			**40**	**100.0%**	**2.60 [-4.01 , 9.21]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.77 (P = 0.44)								
4.35.5 neuro-cognition - Grooved Pegboard Test								
Sergi 2007	202.8	35.5	20	217.6	73.4	40	100.0%	-14.80 [-42.36 , 12.76]
Subtotal (95% CI)			**20**			**40**	**100.0%**	**-14.80 [-42.36 , 12.76]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.05 (P = 0.29)								
4.35.6 neuro-cognition - Letter Number Span								
Sergi 2007	20.7	5	20	17.9	3.5	40	100.0%	2.80 [0.35 , 5.25]
Subtotal (95% CI)			**20**			**40**	**100.0%**	**2.80 [0.35 , 5.25]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.24 (P = 0.02)								
4.35.7 neuro-cognition - Wisconsin Card Sorting Test								
Sergi 2007	2.4	1.7	20	1.6	1.9	40	100.0%	0.80 [-0.15 , 1.75]
Subtotal (95% CI)			**20**			**40**	**100.0%**	**0.80 [-0.15 , 1.75]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.65 (P = 0.10)								
4.35.8 social cognition - Facial Emotion Identification Test								
Sergi 2007	10.6	3.1	20	11.1	2.8	40	100.0%	-0.50 [-2.11 , 1.11]
Subtotal (95% CI)			**20**			**40**	**100.0%**	**-0.50 [-2.11 , 1.11]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.61 (P = 0.54)								
4.35.9 social cognition - Half Profile of Nonverbal Sensitivity								
Sergi 2007	79.8	8.5	20	78	8	40	100.0%	1.80 [-2.67 , 6.27]
Subtotal (95% CI)			**20**			**40**	**100.0%**	**1.80 [-2.67 , 6.27]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.79 (P = 0.43)								
4.35.10 social cognition - Interpersonal Perception Task								
Sergi 2007	9.2	1.4	20	8.4	1.8	40	100.0%	0.80 [-0.03 , 1.63]
Subtotal (95% CI)			**20**			**40**	**100.0%**	**0.80 [-0.03 , 1.63]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.89 (P = 0.06)								
4.35.11 social cognition - Voice Emotion Identification Test								
Sergi 2007	10.6	3.9	20	10.4	3.1	40	100.0%	0.20 [-1.76 , 2.16]
Subtotal (95% CI)			**20**			**40**	**100.0%**	**0.20 [-1.76 , 2.16]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.20 (P = 0.84)								
Test for subgroup differences: $Chi^2 = 0.00$, df = 10 (P < 0.00001), $I^2 = 0\%$								



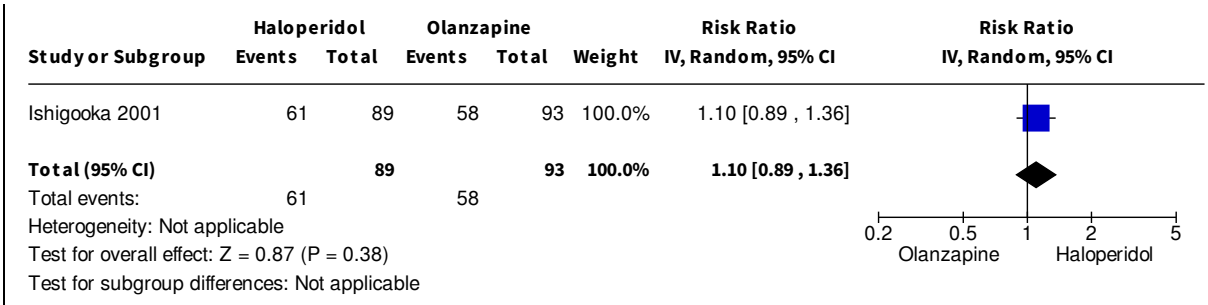
Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 35: Functioning: 2b. Specific - cognition - average endpoint scores - short term (various domains, high=good)

Analysis 4.36



Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 36: Functioning: 2c. Specific - cognition - average endpoint scores - medium term (various domains, high=good)

Analysis 4.38

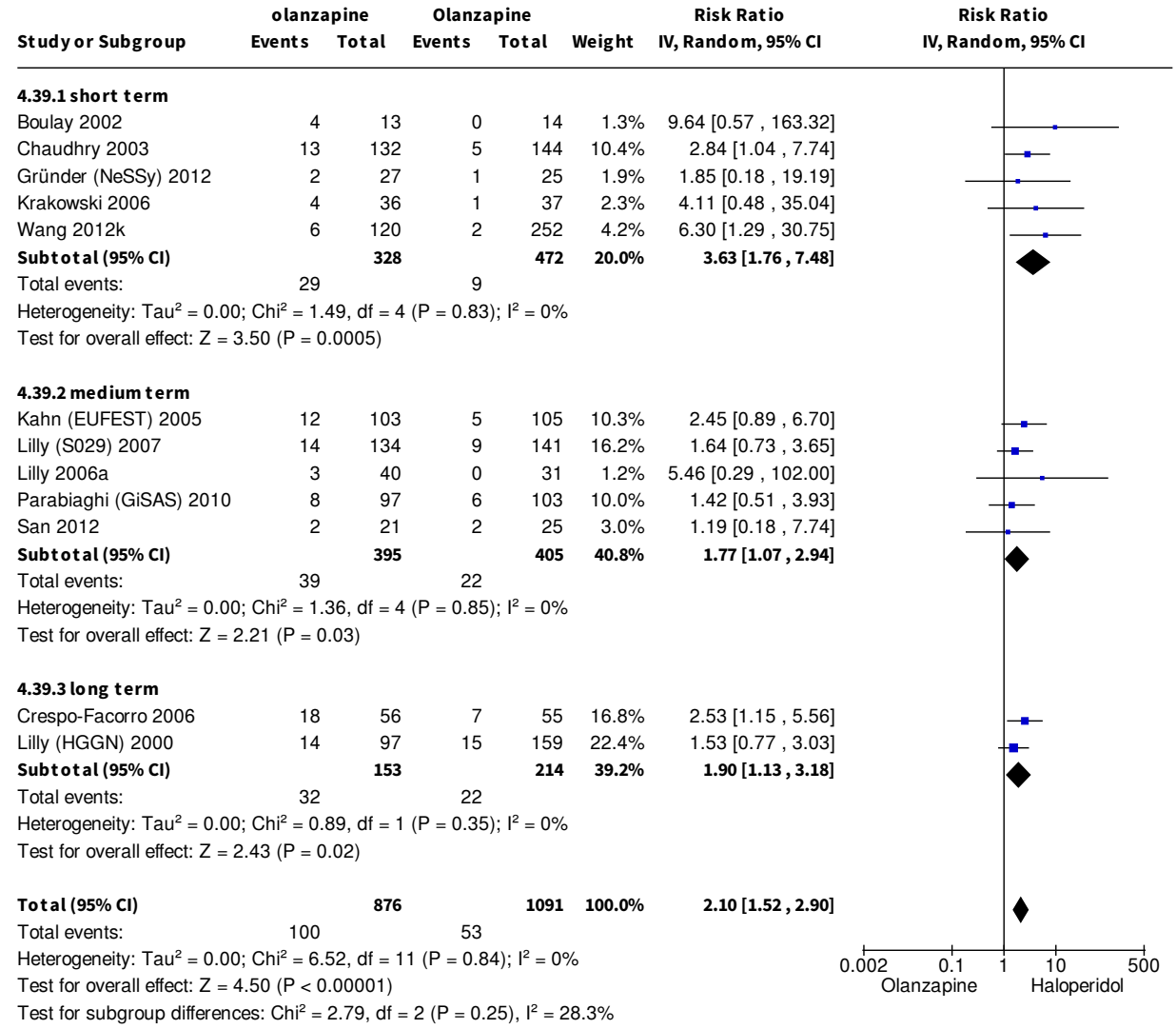


Study or Subgroup	Haloperidol Events	Total	Olanzapine Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Ishigooka 2001	61	89	58	93	100.0%	1.10 [0.89 , 1.36]
Total (95% CI)		**89**		**93**	**100.0%**	**1.10 [0.89 , 1.36]**
Total events:	61		58			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.87 (P = 0.38)
Test for subgroup differences: Not applicable

Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 38: Adverse effects/events: 1a. General - at least one event or effect - short term (various scales)

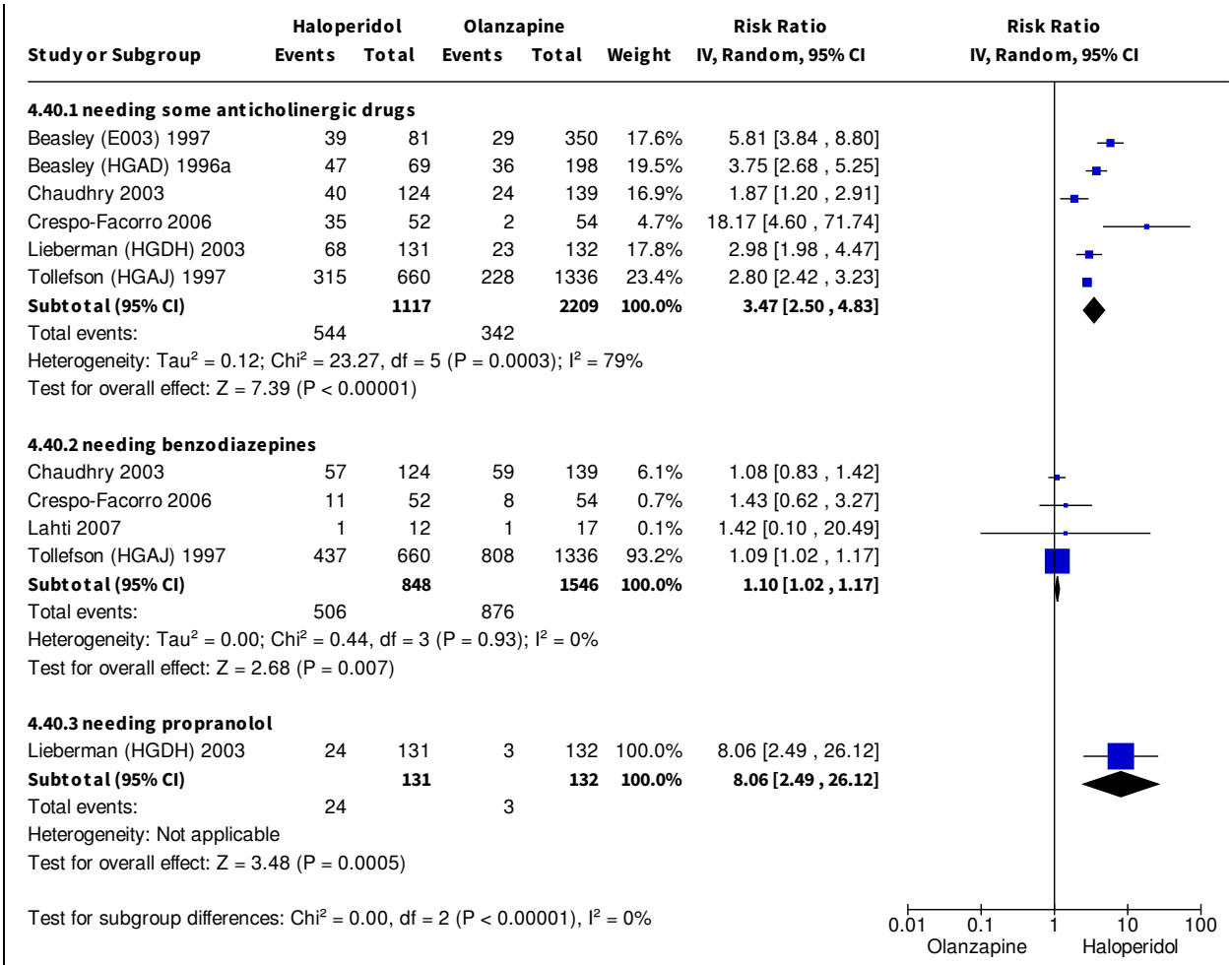
Analysis 4.39



Study or Subgroup	olanzapine Events	Total	Olanzapine Events	Total	Weight	Risk Ratio IV, Random, 95% CI
4.39.1 short term						
Boulay 2002	4	13	0	14	1.3%	9.64 [0.57 , 163.32]
Chaudhry 2003	13	132	5	144	10.4%	2.84 [1.04 , 7.74]
Gründer (NeSSy) 2012	2	27	1	25	1.9%	1.85 [0.18 , 19.19]
Krakowski 2006	4	36	1	37	2.3%	4.11 [0.48 , 35.04]
Wang 2012k	6	120	2	252	4.2%	6.30 [1.29 , 30.75]
Subtotal (95% CI)		**328**		**472**	**20.0%**	**3.63 [1.76 , 7.48]**
Total events:	29		9			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.49$, df = 4 (P = 0.83); $I^2 = 0\%$						
Test for overall effect: Z = 3.50 (P = 0.0005)						
4.39.2 medium term						
Kahn (EUFEST) 2005	12	103	5	105	10.3%	2.45 [0.89 , 6.70]
Lilly (S029) 2007	14	134	9	141	16.2%	1.64 [0.73 , 3.65]
Lilly 2006a	3	40	0	31	1.2%	5.46 [0.29 , 102.00]
Parabiaghi (GiSAS) 2010	8	97	6	103	10.0%	1.42 [0.51 , 3.93]
San 2012	2	21	2	25	3.0%	1.19 [0.18 , 7.74]
Subtotal (95% CI)		**395**		**405**	**40.8%**	**1.77 [1.07 , 2.94]**
Total events:	39		22			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.36$, df = 4 (P = 0.85); $I^2 = 0\%$						
Test for overall effect: Z = 2.21 (P = 0.03)						
4.39.3 long term						
Crespo-Facorro 2006	18	56	7	55	16.8%	2.53 [1.15 , 5.56]
Lilly (HGGN) 2000	14	97	15	159	22.4%	1.53 [0.77 , 3.03]
Subtotal (95% CI)		**153**		**214**	**39.2%**	**1.90 [1.13 , 3.18]**
Total events:	32		22			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.89$, df = 1 (P = 0.35); $I^2 = 0\%$						
Test for overall effect: Z = 2.43 (P = 0.02)						
Total (95% CI)		**876**		**1091**	**100.0%**	**2.10 [1.52 , 2.90]**
Total events:	100		53			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 6.52$, df = 11 (P = 0.84); $I^2 = 0\%$						
Test for overall effect: Z = 4.50 (P < 0.00001)						
Test for subgroup differences: $Chi^2 = 2.79$, df = 2 (P = 0.25), $I^2 = 28.3\%$						

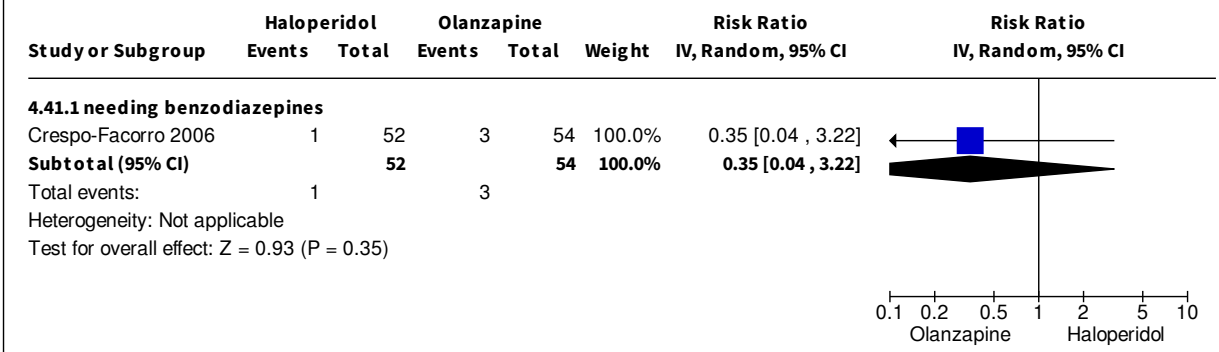
Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 39: Adverse effects/events: 1b. General - severe enough to cause withdrawal from study

Analysis 4.40



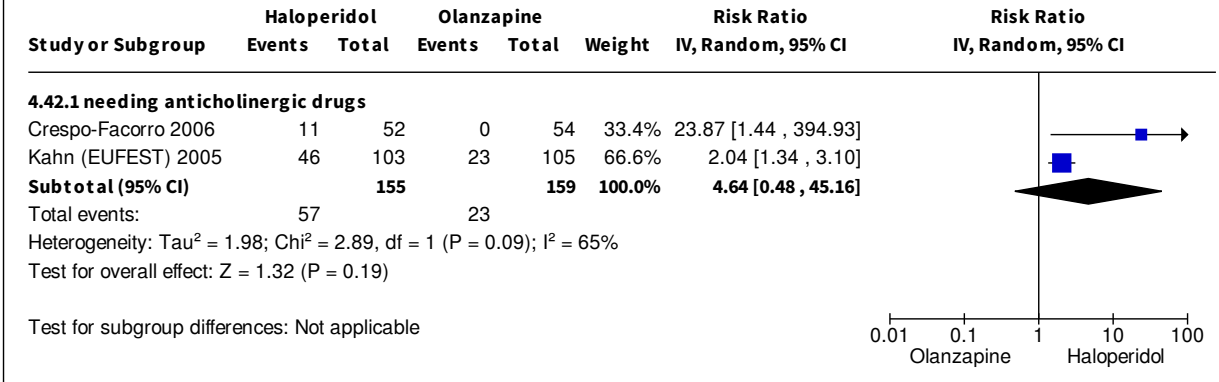
Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 40: Adverse effects/events: 2a. General - needing additional medication - short term

Analysis 4.41



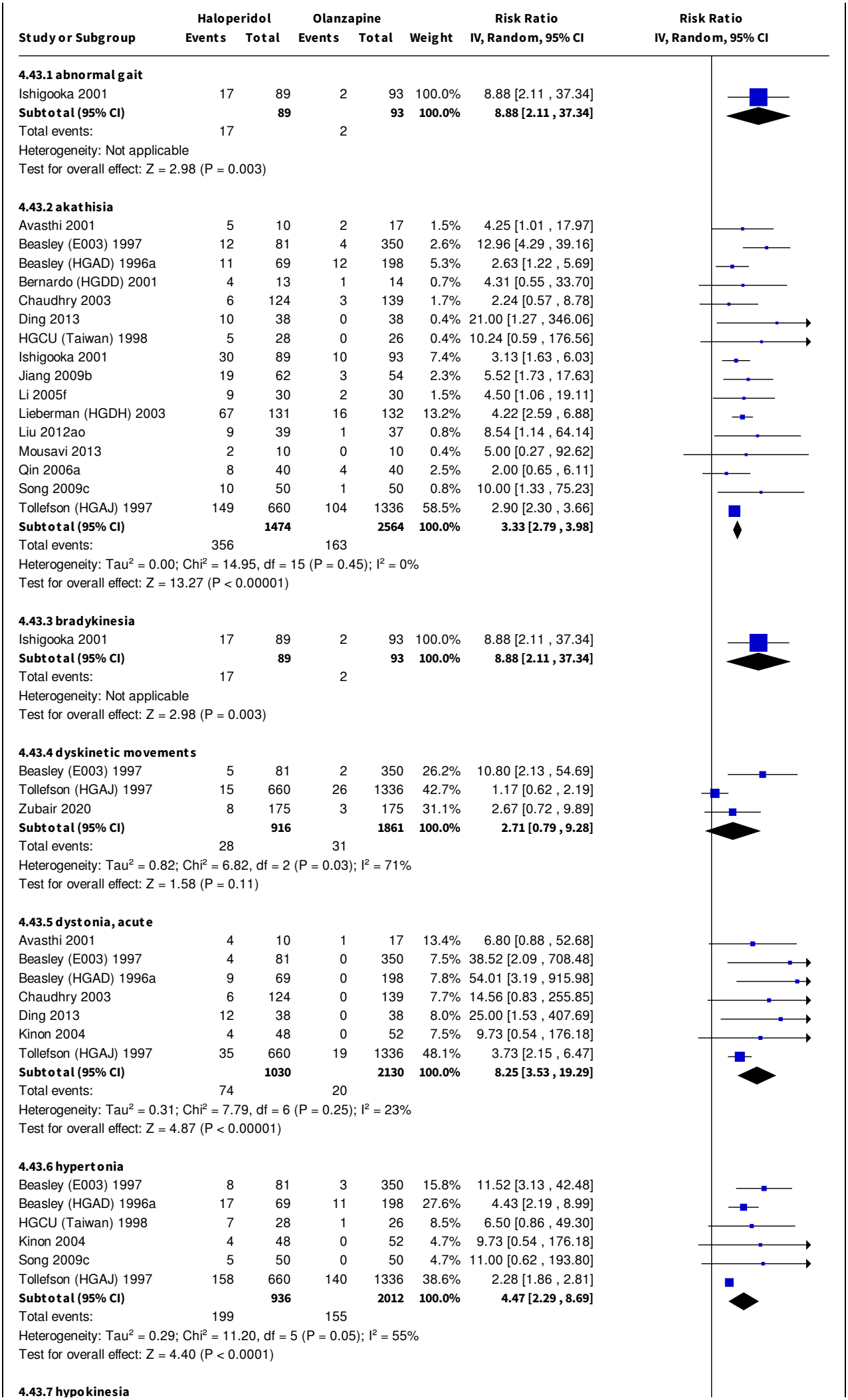
Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 41: Adverse effects/events: 2b. General - needing additional medication - medium term

Analysis 4.42



Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 42: Adverse effects/events: 2c General - needing additional medication - long term

Analysis 4.43


Haloperidol
Olanzapine
Risk Ratio
Risk Ratio
Study or Subgroup
Events Total Events Total Weight IV, Random, 95% CI
IV, Random, 95% CI
4.43.1 abnormal gait
Ishigooka 2001 17 89 2 93 100.0% 8.88 [2.11 , 37.34]
Subtotal (95% CI) 89 93 100.0% 8.88 [2.11 , 37.34]
Total events: 17 2
Heterogeneity: Not applicable
Test for overall effect: Z = 2.98 (P = 0.003)
4.43.2 akathisia
Avasthi 2001 5 10 2 17 1.5% 4.25 [1.01 , 17.97]
Beasley (E003) 1997 12 81 4 350 2.6% 12.96 [4.29 , 39.16]
Beasley (HGAD) 1996a 11 69 12 198 5.3% 2.63 [1.22 , 5.69]
Bernardo (HGDD) 2001 4 13 1 14 0.7% 4.31 [0.55 , 33.70]
Chaudhry 2003 6 124 3 139 1.7% 2.24 [0.57 , 8.78]
Ding 2013 10 38 0 38 0.4% 21.00 [1.27 , 346.06]
HGCU (Taiwan) 1998 5 28 0 26 0.4% 10.24 [0.59 , 176.56]
Ishigooka 2001 30 89 10 93 7.4% 3.13 [1.63 , 6.03]
Jiang 2009b 19 62 3 54 2.3% 5.52 [1.73 , 17.63]
Li 2005f 9 30 2 30 1.5% 4.50 [1.06 , 19.11]
Lieberman (HGDH) 2003 67 131 16 132 13.2% 4.22 [2.59 , 6.88]
Liu 2012ao 9 39 1 37 0.8% 8.54 [1.14 , 64.14]
Mousavi 2013 2 10 0 10 0.4% 5.00 [0.27 , 92.62]
Qin 2006a 8 40 4 40 2.5% 2.00 [0.65 , 6.11]
Song 2009c 10 50 1 50 0.8% 10.00 [1.33 , 75.23]
Tollefson (HGAJ) 1997 149 660 104 1336 58.5% 2.90 [2.30 , 3.66]
Subtotal (95% CI) 1474 2564 100.0% 3.33 [2.79 , 3.98]
Total events: 356 163
Heterogeneity: Tau² = 0.00; Chi² = 14.95, df = 15 (P = 0.45); I² = 0%
Test for overall effect: Z = 13.27 (P < 0.00001)
4.43.3 bradykinesia
Ishigooka 2001 17 89 2 93 100.0% 8.88 [2.11 , 37.34]
Subtotal (95% CI) 89 93 100.0% 8.88 [2.11 , 37.34]
Total events: 17 2
Heterogeneity: Not applicable
Test for overall effect: Z = 2.98 (P = 0.003)
4.43.4 dyskinetic movements
Beasley (E003) 1997 5 81 2 350 26.2% 10.80 [2.13 , 54.69]
Tollefson (HGAJ) 1997 15 660 26 1336 42.7% 1.17 [0.62 , 2.19]
Zubair 2020 8 175 3 175 31.1% 2.67 [0.72 , 9.89]
Subtotal (95% CI) 916 1861 100.0% 2.71 [0.79 , 9.28]
Total events: 28 31
Heterogeneity: Tau² = 0.82; Chi² = 6.82, df = 2 (P = 0.03); I² = 71%
Test for overall effect: Z = 1.58 (P = 0.11)
4.43.5 dystonia, acute
Avasthi 2001 4 10 1 17 13.4% 6.80 [0.88 , 52.68]
Beasley (E003) 1997 4 81 0 350 7.5% 38.52 [2.09 , 708.48]
Beasley (HGAD) 1996a 9 69 0 198 7.8% 54.01 [3.19 , 915.98]
Chaudhry 2003 6 124 0 139 7.7% 14.56 [0.83 , 255.85]
Ding 2013 12 38 0 38 8.0% 25.00 [1.53 , 407.69]
Kinon 2004 4 48 0 52 7.5% 9.73 [0.54 , 176.18]
Tollefson (HGAJ) 1997 35 660 19 1336 48.1% 3.73 [2.15 , 6.47]
Subtotal (95% CI) 1030 2130 100.0% 8.25 [3.53 , 19.29]
Total events: 74 20
Heterogeneity: Tau² = 0.31; Chi² = 7.79, df = 6 (P = 0.25); I² = 23%
Test for overall effect: Z = 4.87 (P < 0.00001)
4.43.6 hypertonia
Beasley (E003) 1997 8 81 3 350 15.8% 11.52 [3.13 , 42.48]
Beasley (HGAD) 1996a 17 69 11 198 27.6% 4.43 [2.19 , 8.99]
HGCU (Taiwan) 1998 7 28 1 26 8.5% 6.50 [0.86 , 49.30]
Kinon 2004 4 48 0 52 4.7% 9.73 [0.54 , 176.18]
Song 2009c 5 50 0 50 4.7% 11.00 [0.62 , 193.80]
Tollefson (HGAJ) 1997 158 660 140 1336 38.6% 2.28 [1.86 , 2.81]
Subtotal (95% CI) 936 2012 100.0% 4.47 [2.29 , 8.69]
Total events: 199 155
Heterogeneity: Tau² = 0.29; Chi² = 11.20, df = 5 (P = 0.05); I² = 55%
Test for overall effect: Z = 4.40 (P < 0.0001)
4.43.7 hypokinesia

Avasthi 2001	5	10	2	17	3.1%	4.25 [1.01 , 17.97]
Tollefson (HGAJ) 1997	110	660	97	1336	96.9%	2.30 [1.78 , 2.97]
Subtotal (95% CI)		**670**		**1353**	**100.0%**	**2.34 [1.82 , 3.01]**
Total events:	115		99			

Heterogeneity: Tau² = 0.00; Chi² = 0.68, df = 1 (P = 0.41); I² = 0%

Test for overall effect: Z = 6.59 (P < 0.00001)

4.43.8 myotonia

Jiang 2009b	27	62	5	54	67.8%	4.70 [1.95 , 11.36]
Li 2005f	13	30	2	30	26.9%	6.50 [1.60 , 26.36]
Qin 2006a	1	40	0	40	5.2%	3.00 [0.13 , 71.51]
Subtotal (95% CI)		**132**		**124**	**100.0%**	**5.01 [2.42 , 10.36]**
Total events:	41		7			

Heterogeneity: Tau² = 0.00; Chi² = 0.25, df = 2 (P = 0.88); I² = 0%

Test for overall effect: Z = 4.35 (P < 0.0001)

4.43.9 parkinsonism

Bernardo (HGDD) 2001	6	13	1	14	1.5%	6.46 [0.89 , 46.70]
Lieberman (HGDH) 2003	72	131	34	132	36.6%	2.13 [1.54 , 2.96]
Tollefson (HGAJ) 1997	177	660	128	1336	62.0%	2.80 [2.27 , 3.44]
Subtotal (95% CI)		**804**		**1482**	**100.0%**	**2.57 [2.02 , 3.26]**
Total events:	255		163			

Heterogeneity: Tau² = 0.01; Chi² = 2.69, df = 2 (P = 0.26); I² = 26%

Test for overall effect: Z = 7.67 (P < 0.00001)

4.43.10 rigidity

Avasthi 2001	8	10	2	17	100.0%	6.80 [1.78 , 25.92]
Subtotal (95% CI)		**10**		**17**	**100.0%**	**6.80 [1.78 , 25.92]**
Total events:	8		2			

Heterogeneity: Not applicable

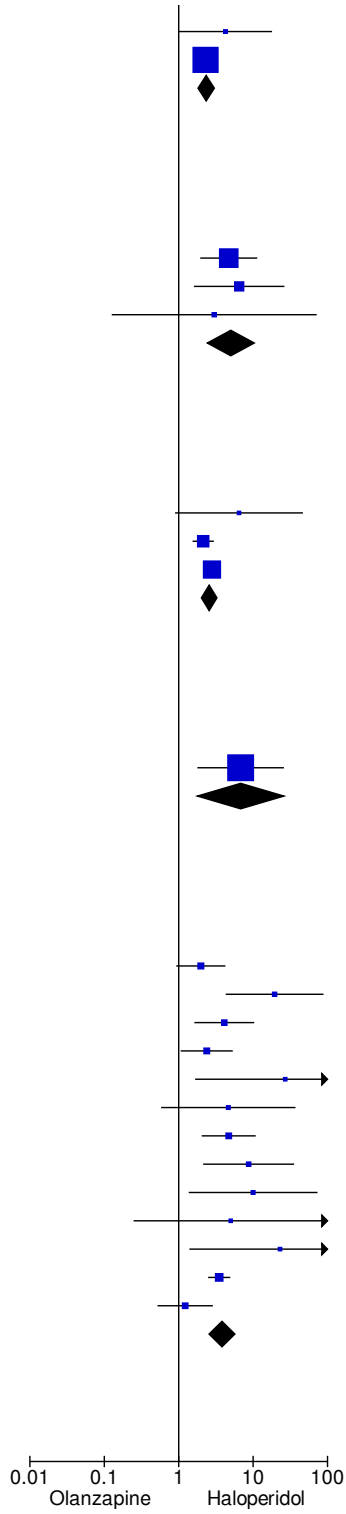
Test for overall effect: Z = 2.81 (P = 0.005)

4.43.11 tremor

Avasthi 2001	7	10	6	17	12.5%	1.98 [0.93 , 4.24]
Beasley (E003) 1997	9	81	2	350	5.3%	19.44 [4.28 , 88.28]
Beasley (HGAD) 1996a	10	69	7	198	10.3%	4.10 [1.62 , 10.35]
Chaudhry 2003	17	124	8	139	11.9%	2.38 [1.07 , 5.33]
Ding 2013	13	38	0	38	1.9%	27.00 [1.66 , 438.51]
HGCU (Taiwan) 1998	5	28	1	26	3.2%	4.64 [0.58 , 37.15]
Ishigooka 2001	27	89	6	93	11.4%	4.70 [2.04 , 10.84]
Jiang 2009b	20	62	2	54	6.0%	8.71 [2.13 , 35.57]
Li 2005f	10	30	1	30	3.4%	10.00 [1.36 , 73.33]
Qin 2006a	2	40	0	40	1.6%	5.00 [0.25 , 100.97]
Song 2009c	11	50	0	50	1.9%	23.00 [1.39 , 380.01]
Tollefson (HGAJ) 1997	83	660	48	1336	19.5%	3.50 [2.48 , 4.93]
Zubair 2020	11	175	9	175	11.2%	1.22 [0.52 , 2.88]
Subtotal (95% CI)		**1456**		**2546**	**100.0%**	**3.82 [2.56 , 5.69]**
Total events:	225		90			

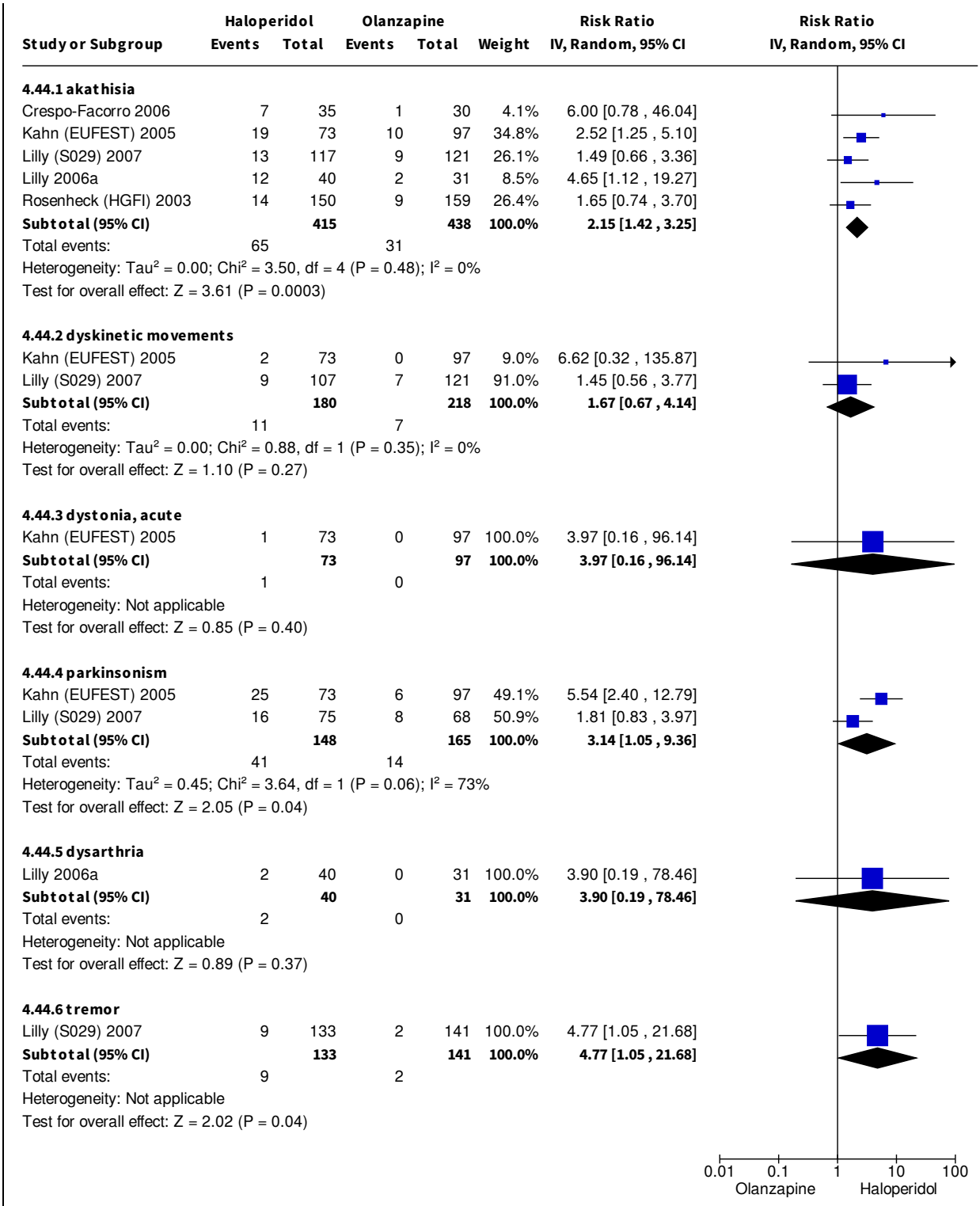
Heterogeneity: Tau² = 0.18; Chi² = 20.93, df = 12 (P = 0.05); I² = 43%

Test for overall effect: Z = 6.57 (P < 0.00001)



Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 43: Adverse effects/events: 3b. Specific - extrapyramidal - various specific effects - short term

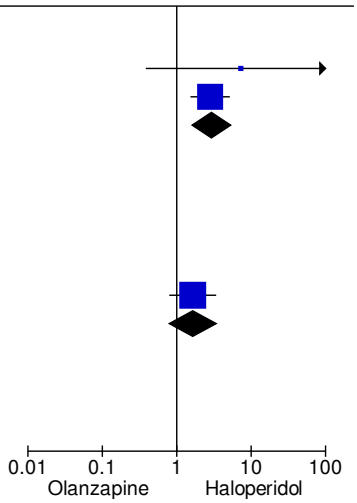
Analysis 4.44



Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 44: Adverse effects/events: 3c. Specific - extrapyramidal - various specific effects - medium term

Analysis 4.45

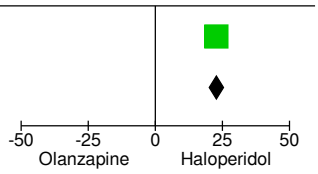
Study or Subgroup	Haloperidol Events	Total	Olanzapine Events	Total	Weight	Risk Ratio IV, Random, 95% CI
4.45.1 akathisia						
Crespo-Facorro 2006	3	53	0	55	4.1%	7.26 [0.38 , 137.25]
Lilly (HGGN) 2000	24	97	14	159	95.9%	2.81 [1.53 , 5.17]
Subtotal (95% CI)		**150**		**214**	**100.0%**	**2.92 [1.61 , 5.30]**
Total events:	27		14			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.38$, df = 1 (P = 0.54); $I^2 = 0\%$						
Test for overall effect: Z = 3.52 (P = 0.0004)						
4.45.2 tremor						
Lilly (HGGN) 2000	13	97	13	159	100.0%	1.64 [0.79 , 3.39]
Subtotal (95% CI)		**97**		**159**	**100.0%**	**1.64 [0.79 , 3.39]**
Total events:	13		13			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.33 (P = 0.18)						



Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 45: Adverse effects/events: 3d. Specific - extrapyramidal - various specific effects - long term

Analysis 4.46

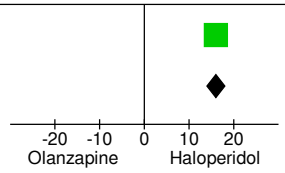
Study or Subgroup	Haloperidol Mean	SD	Total	Olanzapine Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Lilly 2006a	25	8.49	40	2.25	0.96	31	100.0%	22.75 [20.10 , 25.40]
Total (95% CI)			**40**			**31**	**100.0%**	**22.75 [20.10 , 25.40]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 16.81 (P < 0.00001)								
Test for subgroup differences: Not applicable								



Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 46: Adverse effects/events: 3e. Specific - extrapyramidal - average endpoint score - medium term (BAS total, high=poor)

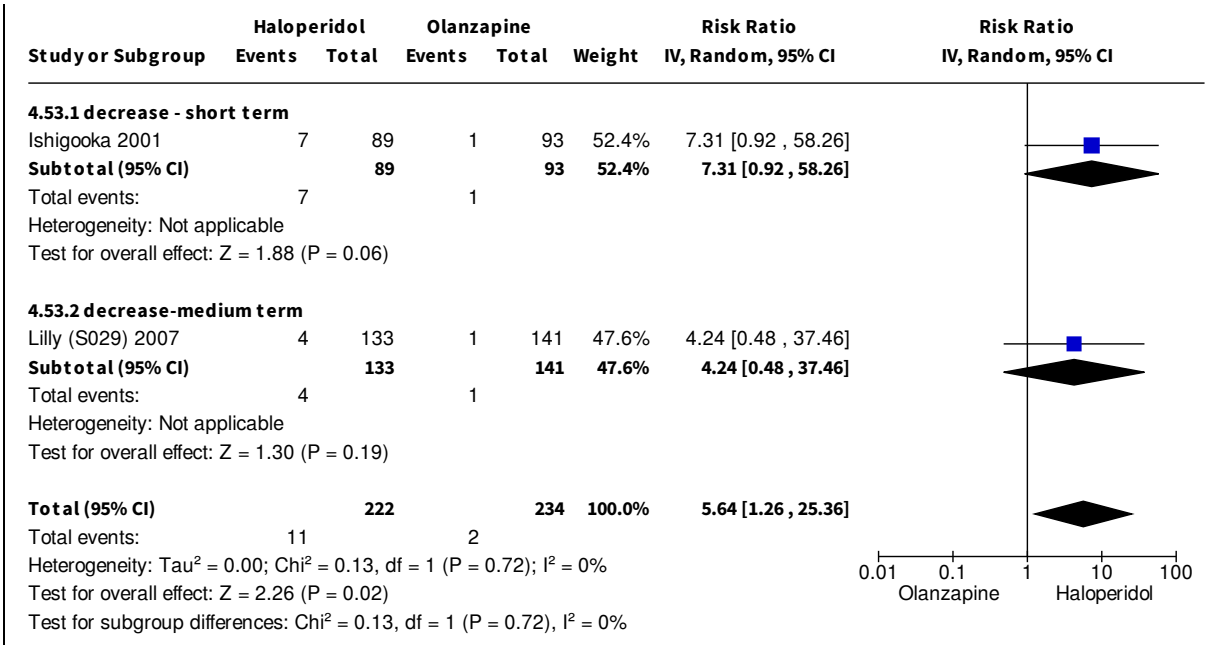
Analysis 4.47

Study or Subgroup	Haloperidol Mean	SD	Total	Olanzapine Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Lilly 2006a	22.3	6.04	40	6.3	2	31	100.0%	16.00 [14.00 , 18.00]
Total (95% CI)			**40**			**31**	**100.0%**	**16.00 [14.00 , 18.00]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 15.68 (P < 0.00001)								
Test for subgroup differences: Not applicable								



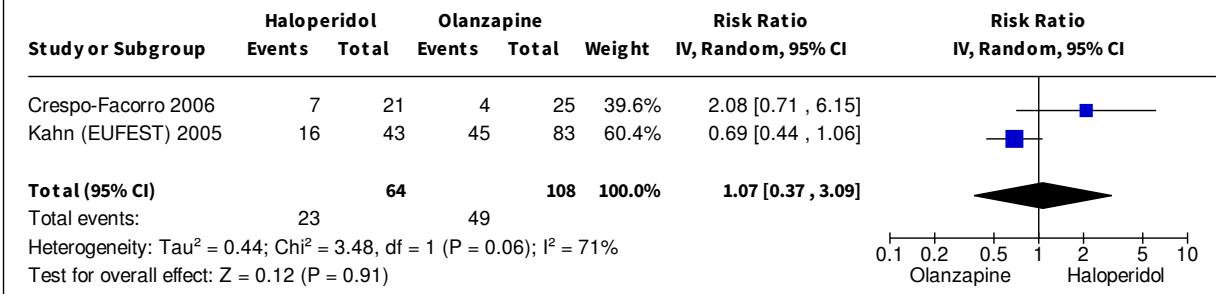
Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 47: Adverse effects/events: 3f. Specific - extrapyramidal - average endpoint score - medium term (SAS total, high=poor)

Analysis 4.53



Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 53: Adverse effects/events: 4b. Specific - metabolic - weight decrease

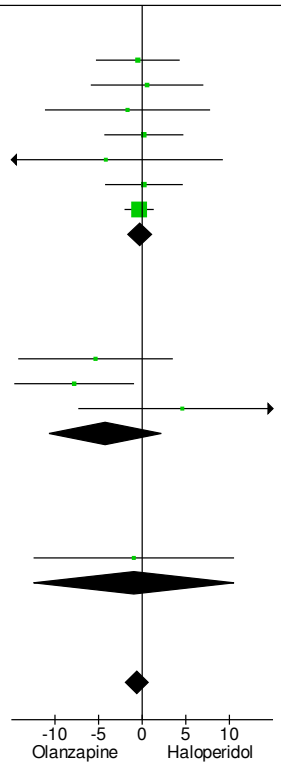
Analysis 4.54



Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 54: Adverse effects/events: 4c. Specific - metabolic - weight - high BMI (>=25kg/m2) - medium term

Analysis 4.55

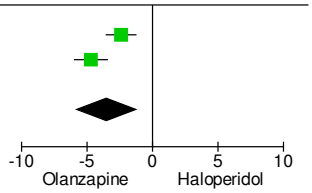
Study or Subgroup	Haloperidol Mean	SD	Total	Olanzapine Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
4.55.1 short term								
Beasley (E003) 1997	73.4	15.97	77	73.9	15.12	85	7.4%	-0.50 [-5.30 , 4.30]
Beasley (HGAD) 1996a	83.92	16.55	67	83.36	20.78	64	4.1%	0.56 [-5.89 , 7.01]
Buchanan 2003	87.27	20	31	88.95	16.78	27	1.9%	-1.68 [-11.15 , 7.79]
HGFH (Korea) 1998	60.07	10.9	39	59.88	10.83	51	8.3%	0.19 [-4.34 , 4.72]
Lindenmayer 2007	88.03	21.62	19	92.2	18.88	16	0.9%	-4.17 [-17.59 , 9.25]
Saddichha 2007	52.2	6.4	31	52	11.6	35	8.6%	0.20 [-4.25 , 4.65]
Tollefson (HGAJ) 1997	77.95	17.92	633	78.3	17.02	1303	60.6%	-0.35 [-2.02 , 1.32]
Subtotal (95% CI)			**897**			**1581**	**91.8%**	**-0.29 [-1.65 , 1.07]**
Heterogeneity: Tau² = 0.00; Chi² = 0.57, df = 6 (P = 1.00); I² = 0%								
Test for overall effect: Z = 0.42 (P = 0.68)								
4.55.2 medium term								
HGCJ (Hong Kong) 1998	59.36	11.08	14	64.71	13.67	16	2.2%	-5.35 [-14.21 , 3.51]
HGCU (Taiwan) 1998	63.05	13.15	27	70.85	11.87	24	3.6%	-7.80 [-14.67 , -0.93]
Raposo 2011	74.9	21.5	16	70.3	12.1	18	1.2%	4.60 [-7.33 , 16.53]
Subtotal (95% CI)			**57**			**58**	**7.0%**	**-4.25 [-10.68 , 2.18]**
Heterogeneity: Tau² = 11.87; Chi² = 3.13, df = 2 (P = 0.21); I² = 36%								
Test for overall effect: Z = 1.29 (P = 0.20)								
4.55.3 long term								
Jones 1998 (P022)	83.82	22.45	25	84.78	17.69	22	1.3%	-0.96 [-12.45 , 10.53]
Subtotal (95% CI)			**25**			**22**	**1.3%**	**-0.96 [-12.45 , 10.53]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.16 (P = 0.87)								
Total (95% CI)			**979**			**1661**	**100.0%**	**-0.62 [-1.92 , 0.68]**
Heterogeneity: Tau² = 0.00; Chi² = 6.83, df = 10 (P = 0.74); I² = 0%								
Test for overall effect: Z = 0.93 (P = 0.35)								
Test for subgroup differences: Chi² = 1.40, df = 2 (P = 0.50), I² = 0%								



Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 55: Adverse effects/events: 4d. Specific - metabolic - weight - average endpoint (kg)

Analysis 4.56

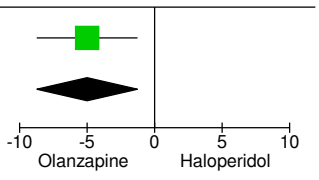
Study or Subgroup	Haloperidol Mean	SD	Total	Olanzapine Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Barak 2002	2.1	1.8	10	4.5	0.6	10	50.7%	-2.40 [-3.58 , -1.22]
Lieberman (HGDH) 2003	2.6	4.5	131	7.3	6.1	132	49.3%	-4.70 [-5.99 , -3.41]
Total (95% CI)			**141**			**142**	**100.0%**	**-3.53 [-5.79 , -1.28]**
Heterogeneity: Tau² = 2.25; Chi² = 6.64, df = 1 (P = 0.010); I² = 85%								
Test for overall effect: Z = 3.07 (P = 0.002)								
Test for subgroup differences: Not applicable								



Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 56: Adverse effects/events: 4e. Specific - metabolic - weight - average increase - short term

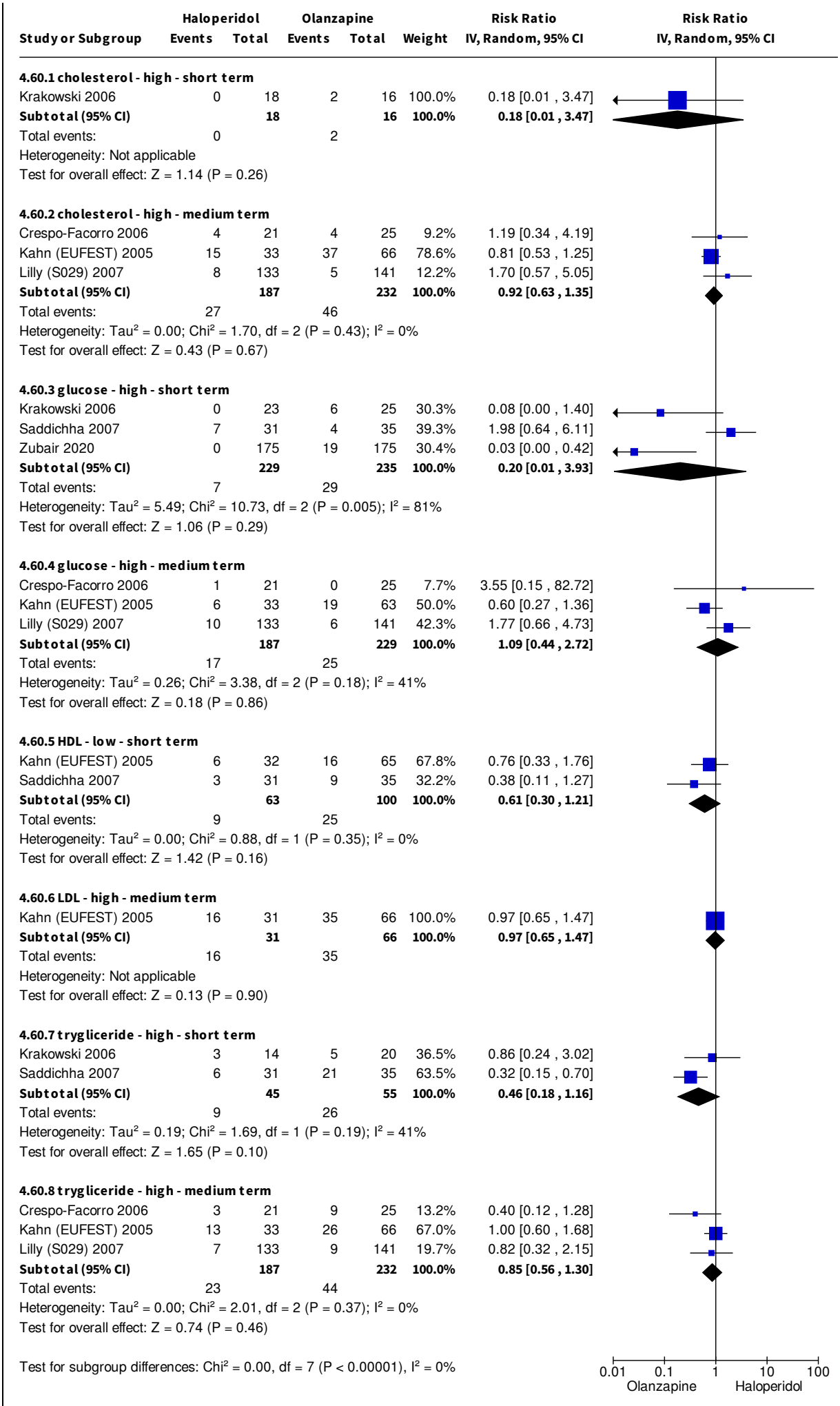
Analysis 4.57

Study or Subgroup	Haloperidol Mean	SD	Total	Olanzapine Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Saddichha 2007	76	6.5	31	81	8.9	35	100.0%	-5.00 [-8.73 , -1.27]
Total (95% CI)			**31**			**35**	**100.0%**	**-5.00 [-8.73 , -1.27]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.63 (P = 0.009)								
Test for subgroup differences: Not applicable								



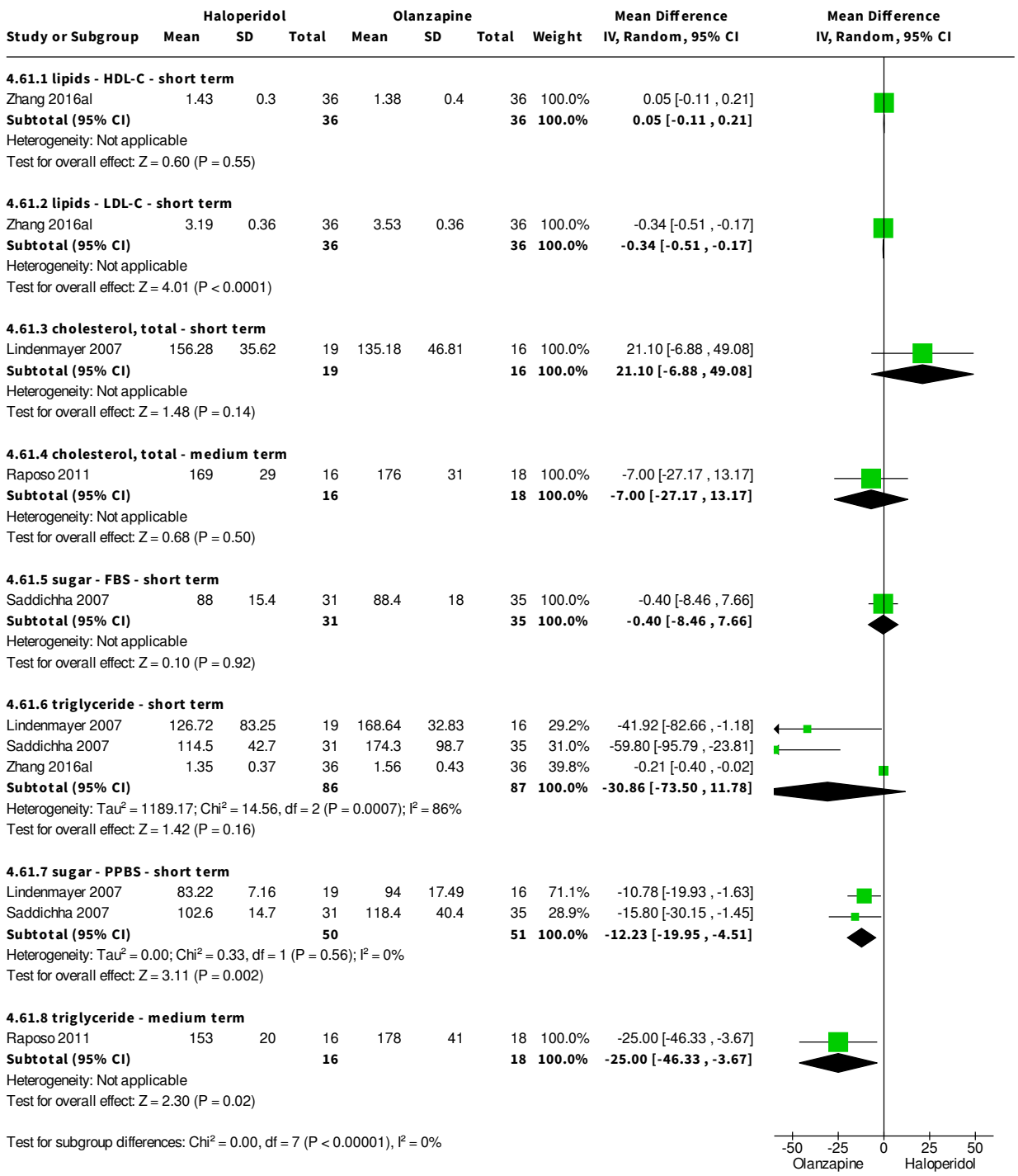
Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 57: Adverse effects/events: 4f. Specific - metabolic - weight - waist circumference at endpoint - short term (high=poor)

Analysis 4.60


Haloperidol
Olanzapine
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight IV, Random, 95% CI
IV, Random, 95% CI
4.60.1 cholesterol - high - short term
Krakowski 2006 0 18 2 16 100.0% 0.18 [0.01 , 3.47]
Subtotal (95% CI) 18 16 100.0% 0.18 [0.01 , 3.47]
Total events: 0 2
Heterogeneity: Not applicable
Test for overall effect: Z = 1.14 (P = 0.26)
4.60.2 cholesterol - high - medium term
Crespo-Facorro 2006 4 21 4 25 9.2% 1.19 [0.34 , 4.19]
Kahn (EUFEST) 2005 15 33 37 66 78.6% 0.81 [0.53 , 1.25]
Lilly (S029) 2007 8 133 5 141 12.2% 1.70 [0.57 , 5.05]
Subtotal (95% CI) 187 232 100.0% 0.92 [0.63 , 1.35]
Total events: 27 46
Heterogeneity: Tau² = 0.00; Chi² = 1.70, df = 2 (P = 0.43); I² = 0%
Test for overall effect: Z = 0.43 (P = 0.67)
4.60.3 glucose - high - short term
Krakowski 2006 0 23 6 25 30.3% 0.08 [0.00 , 1.40]
Saddichha 2007 7 31 4 35 39.3% 1.98 [0.64 , 6.11]
Zubair 2020 0 175 19 175 30.4% 0.03 [0.00 , 0.42]
Subtotal (95% CI) 229 235 100.0% 0.20 [0.01 , 3.93]
Total events: 7 29
Heterogeneity: Tau² = 5.49; Chi² = 10.73, df = 2 (P = 0.005); I² = 81%
Test for overall effect: Z = 1.06 (P = 0.29)
4.60.4 glucose - high - medium term
Crespo-Facorro 2006 1 21 0 25 7.7% 3.55 [0.15 , 82.72]
Kahn (EUFEST) 2005 6 33 19 63 50.0% 0.60 [0.27 , 1.36]
Lilly (S029) 2007 10 133 6 141 42.3% 1.77 [0.66 , 4.73]
Subtotal (95% CI) 187 229 100.0% 1.09 [0.44 , 2.72]
Total events: 17 25
Heterogeneity: Tau² = 0.26; Chi² = 3.38, df = 2 (P = 0.18); I² = 41%
Test for overall effect: Z = 0.18 (P = 0.86)
4.60.5 HDL - low - short term
Kahn (EUFEST) 2005 6 32 16 65 67.8% 0.76 [0.33 , 1.76]
Saddichha 2007 3 31 9 35 32.2% 0.38 [0.11 , 1.27]
Subtotal (95% CI) 63 100 100.0% 0.61 [0.30 , 1.21]
Total events: 9 25
Heterogeneity: Tau² = 0.00; Chi² = 0.88, df = 1 (P = 0.35); I² = 0%
Test for overall effect: Z = 1.42 (P = 0.16)
4.60.6 LDL - high - medium term
Kahn (EUFEST) 2005 16 31 35 66 100.0% 0.97 [0.65 , 1.47]
Subtotal (95% CI) 31 66 100.0% 0.97 [0.65 , 1.47]
Total events: 16 35
Heterogeneity: Not applicable
Test for overall effect: Z = 0.13 (P = 0.90)
4.60.7 trygliceride - high - short term
Krakowski 2006 3 14 5 20 36.5% 0.86 [0.24 , 3.02]
Saddichha 2007 6 31 21 35 63.5% 0.32 [0.15 , 0.70]
Subtotal (95% CI) 45 55 100.0% 0.46 [0.18 , 1.16]
Total events: 9 26
Heterogeneity: Tau² = 0.19; Chi² = 1.69, df = 1 (P = 0.19); I² = 41%
Test for overall effect: Z = 1.65 (P = 0.10)
4.60.8 trygliceride - high - medium term
Crespo-Facorro 2006 3 21 9 25 13.2% 0.40 [0.12 , 1.28]
Kahn (EUFEST) 2005 13 33 26 66 67.0% 1.00 [0.60 , 1.68]
Lilly (S029) 2007 7 133 9 141 19.7% 0.82 [0.32 , 2.15]
Subtotal (95% CI) 187 232 100.0% 0.85 [0.56 , 1.30]
Total events: 23 44
Heterogeneity: Tau² = 0.00; Chi² = 2.01, df = 2 (P = 0.37); I² = 0%
Test for overall effect: Z = 0.74 (P = 0.46)
Test for subgroup differences: Chi² = 0.00, df = 7 (P < 0.00001), I² = 0%
0.01 0.1 1 10 100
Olanzapine Haloperidol

Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 60: Adverse effects/events: 5a. Specific - metabolic - metabolism-related final serum levels (various measures)

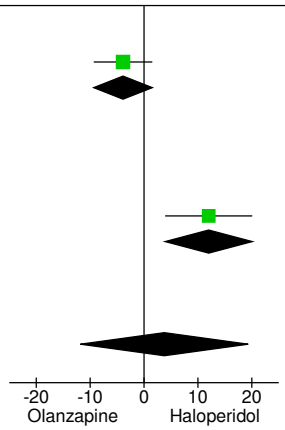
Analysis 4.61



Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 61: Adverse effects/events: 5b. Specific - metabolic - metabolism-related serum levels (high=poor)

Analysis 4.62

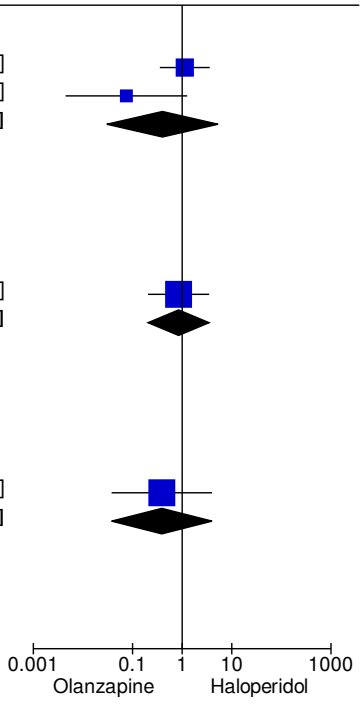
Study or Subgroup	Haloperidol Mean	SD	Total	Olanzapine Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
4.62.1 short term								
Saddichha 2007	35.6	8.2	31	39.5	13.9	35	51.8%	-3.90 [-9.33 , 1.53]
Subtotal (95% CI)			**31**			**35**	**51.8%**	**-3.90 [-9.33 , 1.53]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.41 (P = 0.16)								
4.62.2 medium term								
Raposo 2011	55	12	16	43	12	18	48.2%	12.00 [3.92 , 20.08]
Subtotal (95% CI)			**16**			**18**	**48.2%**	**12.00 [3.92 , 20.08]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.91 (P = 0.004)								
Total (95% CI)			**47**			**53**	**100.0%**	**3.76 [-11.81 , 19.33]**
Heterogeneity: Tau² = 114.06; Chi² = 10.24, df = 1 (P = 0.001); I² = 90%								
Test for overall effect: Z = 0.47 (P = 0.64)								
Test for subgroup differences: Chi² = 10.24, df = 1 (P = 0.001), I² = 90.2%								



Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 62: Adverse effects/events: 5c. Specific - metabolic - metabolism-related HDL serum levels - endpoint (high=poor)

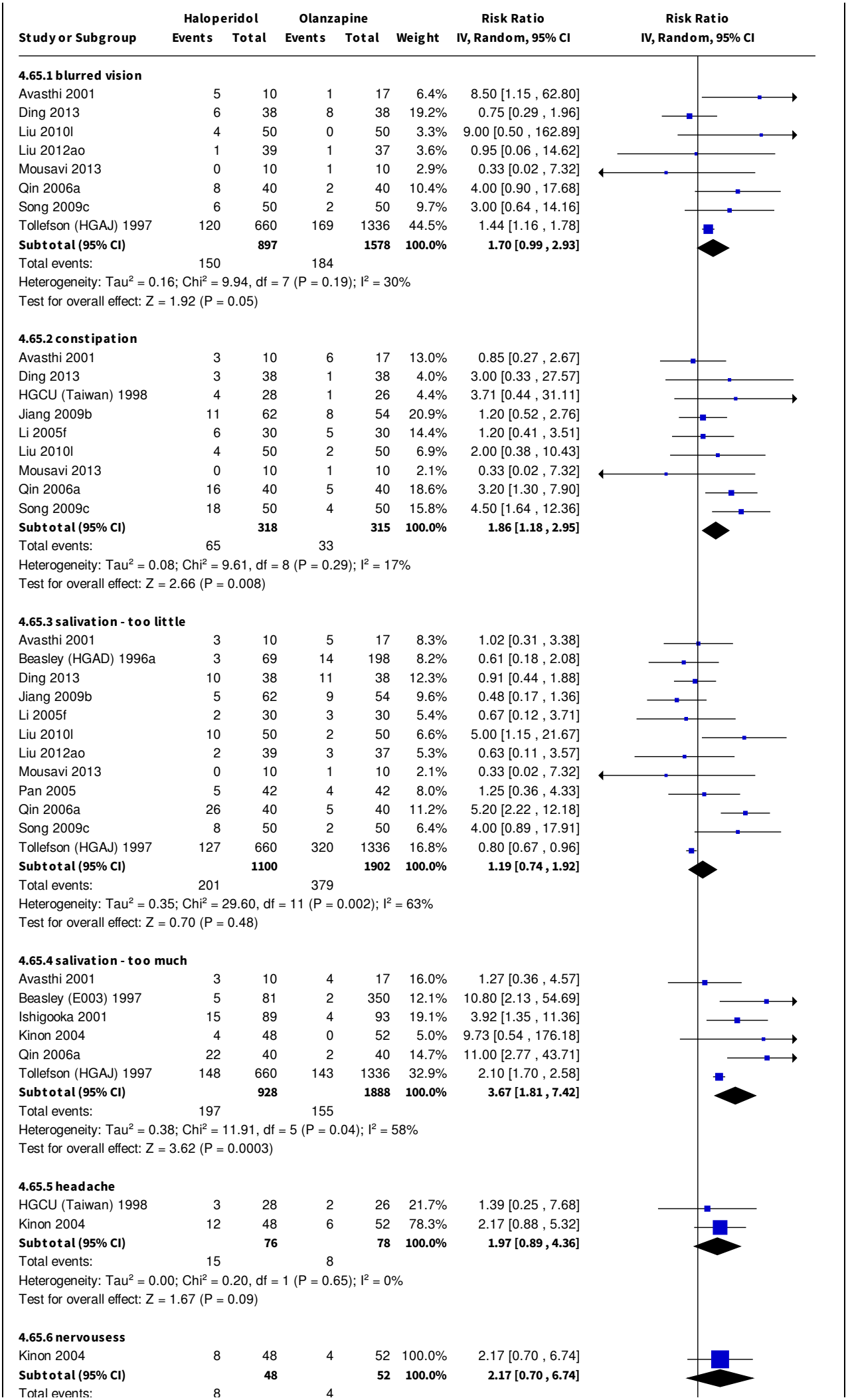
Analysis 4.64

Study or Subgroup	Haloperidol Events	Total	Olanzapine Events	Total	Weight	Risk Ratio IV, Random, 95% CI
4.64.1 metabolic syndrome						
Krakowski 2006	4	17	5	24	61.7%	1.13 [0.35 , 3.60]
Saddichha 2007	0	31	7	35	38.3%	0.07 [0.00 , 1.26]
Subtotal (95% CI)		**48**		**59**	**100.0%**	**0.40 [0.03 , 5.30]**
Total events:	4		12			
Heterogeneity: Tau² = 2.47; Chi² = 3.03, df = 1 (P = 0.08); I² = 67%						
Test for overall effect: Z = 0.70 (P = 0.49)						
4.64.2 diabetes						
Saddichha 2007	3	31	4	35	100.0%	0.85 [0.21 , 3.49]
Subtotal (95% CI)		**31**		**35**	**100.0%**	**0.85 [0.21 , 3.49]**
Total events:	3		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.23 (P = 0.82)						
4.64.3 metabolism and nutrition disorders, unspecified						
Gründer (NeSSy) 2012	1	27	2	21	100.0%	0.39 [0.04 , 4.00]
Subtotal (95% CI)		**27**		**21**	**100.0%**	**0.39 [0.04 , 4.00]**
Total events:	1		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.79 (P = 0.43)						



Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 64: Adverse effects/events: 6. Specific - metabolic - various binary - short term

Analysis 4.65


Haloperidol
Olanzapine
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight IV, Random, 95% CI
IV, Random, 95% CI
4.65.1 blurred vision
Avasthi 2001 5 10 1 17 6.4% 8.50 [1.15 , 62.80]
Ding 2013 6 38 8 38 19.2% 0.75 [0.29 , 1.96]
Liu 2010l 4 50 0 50 3.3% 9.00 [0.50 , 162.89]
Liu 2012ao 1 39 1 37 3.6% 0.95 [0.06 , 14.62]
Mousavi 2013 0 10 1 10 2.9% 0.33 [0.02 , 7.32]
Qin 2006a 8 40 2 40 10.4% 4.00 [0.90 , 17.68]
Song 2009c 6 50 2 50 9.7% 3.00 [0.64 , 14.16]
Tollefson (HGAJ) 1997 120 660 169 1336 44.5% 1.44 [1.16 , 1.78]
Subtotal (95% CI) 897 1578 100.0% 1.70 [0.99 , 2.93]
Total events: 150 184
Heterogeneity: Tau² = 0.16; Chi² = 9.94, df = 7 (P = 0.19); I² = 30%
Test for overall effect: Z = 1.92 (P = 0.05)
4.65.2 constipation
Avasthi 2001 3 10 6 17 13.0% 0.85 [0.27 , 2.67]
Ding 2013 3 38 1 38 4.0% 3.00 [0.33 , 27.57]
HGCU (Taiwan) 1998 4 28 1 26 4.4% 3.71 [0.44 , 31.11]
Jiang 2009b 11 62 8 54 20.9% 1.20 [0.52 , 2.76]
Li 2005f 6 30 5 30 14.4% 1.20 [0.41 , 3.51]
Liu 2010l 4 50 2 50 6.9% 2.00 [0.38 , 10.43]
Mousavi 2013 0 10 1 10 2.1% 0.33 [0.02 , 7.32]
Qin 2006a 16 40 5 40 18.6% 3.20 [1.30 , 7.90]
Song 2009c 18 50 4 50 15.8% 4.50 [1.64 , 12.36]
Subtotal (95% CI) 318 315 100.0% 1.86 [1.18 , 2.95]
Total events: 65 33
Heterogeneity: Tau² = 0.08; Chi² = 9.61, df = 8 (P = 0.29); I² = 17%
Test for overall effect: Z = 2.66 (P = 0.008)
4.65.3 salivation - too little
Avasthi 2001 3 10 5 17 8.3% 1.02 [0.31 , 3.38]
Beasley (HGAD) 1996a 3 69 14 198 8.2% 0.61 [0.18 , 2.08]
Ding 2013 10 38 11 38 12.3% 0.91 [0.44 , 1.88]
Jiang 2009b 5 62 9 54 9.6% 0.48 [0.17 , 1.36]
Li 2005f 2 30 3 30 5.4% 0.67 [0.12 , 3.71]
Liu 2010l 10 50 2 50 6.6% 5.00 [1.15 , 21.67]
Liu 2012ao 2 39 3 37 5.3% 0.63 [0.11 , 3.57]
Mousavi 2013 0 10 1 10 2.1% 0.33 [0.02 , 7.32]
Pan 2005 5 42 4 42 8.0% 1.25 [0.36 , 4.33]
Qin 2006a 26 40 5 40 11.2% 5.20 [2.22 , 12.18]
Song 2009c 8 50 2 50 6.4% 4.00 [0.89 , 17.91]
Tollefson (HGAJ) 1997 127 660 320 1336 16.8% 0.80 [0.67 , 0.96]
Subtotal (95% CI) 1100 1902 100.0% 1.19 [0.74 , 1.92]
Total events: 201 379
Heterogeneity: Tau² = 0.35; Chi² = 29.60, df = 11 (P = 0.002); I² = 63%
Test for overall effect: Z = 0.70 (P = 0.48)
4.65.4 salivation - too much
Avasthi 2001 3 10 4 17 16.0% 1.27 [0.36 , 4.57]
Beasley (E003) 1997 5 81 2 350 12.1% 10.80 [2.13 , 54.69]
Ishigooka 2001 15 89 4 93 19.1% 3.92 [1.35 , 11.36]
Kinon 2004 4 48 0 52 5.0% 9.73 [0.54 , 176.18]
Qin 2006a 22 40 2 40 14.7% 11.00 [2.77 , 43.71]
Tollefson (HGAJ) 1997 148 660 143 1336 32.9% 2.10 [1.70 , 2.58]
Subtotal (95% CI) 928 1888 100.0% 3.67 [1.81 , 7.42]
Total events: 197 155
Heterogeneity: Tau² = 0.38; Chi² = 11.91, df = 5 (P = 0.04); I² = 58%
Test for overall effect: Z = 3.62 (P = 0.0003)
4.65.5 headache
HGCU (Taiwan) 1998 3 28 2 26 21.7% 1.39 [0.25 , 7.68]
Kinon 2004 12 48 6 52 78.3% 2.17 [0.88 , 5.32]
Subtotal (95% CI) 76 78 100.0% 1.97 [0.89 , 4.36]
Total events: 15 8
Heterogeneity: Tau² = 0.00; Chi² = 0.20, df = 1 (P = 0.65); I² = 0%
Test for overall effect: Z = 1.67 (P = 0.09)
4.65.6 nervousess
Kinon 2004 8 48 4 52 100.0% 2.17 [0.70 , 6.74]
Subtotal (95% CI) 48 52 100.0% 2.17 [0.70 , 6.74]
Total events: 8 4

Heterogeneity: Not applicable
Test for overall effect: Z = 1.34 (P = 0.18)

4.65.7 urination difficulties

Avasthi 2001	5	10	2	17	21.0%	4.25 [1.01 , 17.97]
Tollefson (HGAJ) 1997	63	660	77	1336	79.0%	1.66 [1.20 , 2.28]
Subtotal (95% CI)		**670**		**1353**	**100.0%**	**2.02 [0.95 , 4.29]**
Total events:	68		79			

Heterogeneity: $Tau^2 = 0.16$; $Chi^2 = 1.56$, df = 1 (P = 0.21); $I^2 = 36\%$
Test for overall effect: Z = 1.83 (P = 0.07)

4.65.8 hypotension

Liu 2012ao	1	39	2	37	22.4%	0.47 [0.04 , 5.01]
Pan 2005	4	42	3	42	45.8%	1.33 [0.32 , 5.60]
Qin 2006a	3	40	0	40	15.6%	7.00 [0.37 , 131.28]
Song 2009c	5	50	0	50	16.2%	11.00 [0.62 , 193.80]
Subtotal (95% CI)		**171**		**169**	**100.0%**	**1.92 [0.56 , 6.66]**
Total events:	13		5			

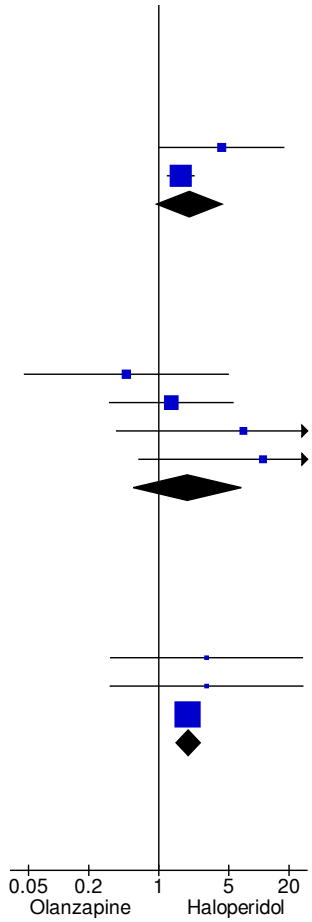
Heterogeneity: $Tau^2 = 0.34$; $Chi^2 = 3.75$, df = 3 (P = 0.29); $I^2 = 20\%$
Test for overall effect: Z = 1.03 (P = 0.30)

4.65.9 perspiration

Qin 2006a	3	40	1	40	1.6%	3.00 [0.33 , 27.63]
Song 2009c	3	50	1	50	1.6%	3.00 [0.32 , 27.87]
Tollefson (HGAJ) 1997	84	636	89	1306	96.9%	1.94 [1.46 , 2.57]
Subtotal (95% CI)		**726**		**1396**	**100.0%**	**1.96 [1.49 , 2.60]**
Total events:	90		91			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.29$, df = 2 (P = 0.87); $I^2 = 0\%$
Test for overall effect: Z = 4.76 (P < 0.00001)

Test for subgroup differences: $Chi^2 = 0.00$, df = 8 (P < 0.00001), $I^2 = 0\%$

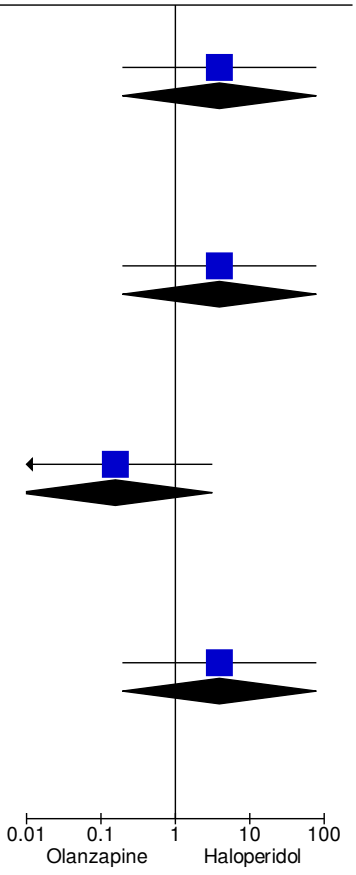


Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 65: Adverse effects/events: 7a. Specific - anticholinergic - various - short term

Analysis 4.66

Study or Subgroup	Haloperidol Events	Haloperidol Total	Olanzapine Events	Olanzapine Total	Weight	Risk Ratio IV, Random, 95% CI
4.66.1 dysarthria						
Lilly 2006a	2	40	0	31	100.0%	3.90 [0.19 , 78.46]
Subtotal (95% CI)		**40**		**31**	**100.0%**	**3.90 [0.19 , 78.46]**
Total events:	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.89 (P = 0.37)						
4.66.2 urination difficulties						
Lilly 2006a	2	40	0	31	100.0%	3.90 [0.19 , 78.46]
Subtotal (95% CI)		**40**		**31**	**100.0%**	**3.90 [0.19 , 78.46]**
Total events:	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.89 (P = 0.37)						
4.66.3 rash						
Lilly 2006a	0	40	2	31	100.0%	0.16 [0.01 , 3.14]
Subtotal (95% CI)		**40**		**31**	**100.0%**	**0.16 [0.01 , 3.14]**
Total events:	0		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.21 (P = 0.23)						
4.66.4 anemia						
Lilly 2006a	2	40	0	31	100.0%	3.90 [0.19 , 78.46]
Subtotal (95% CI)		**40**		**31**	**100.0%**	**3.90 [0.19 , 78.46]**
Total events:	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.89 (P = 0.37)						

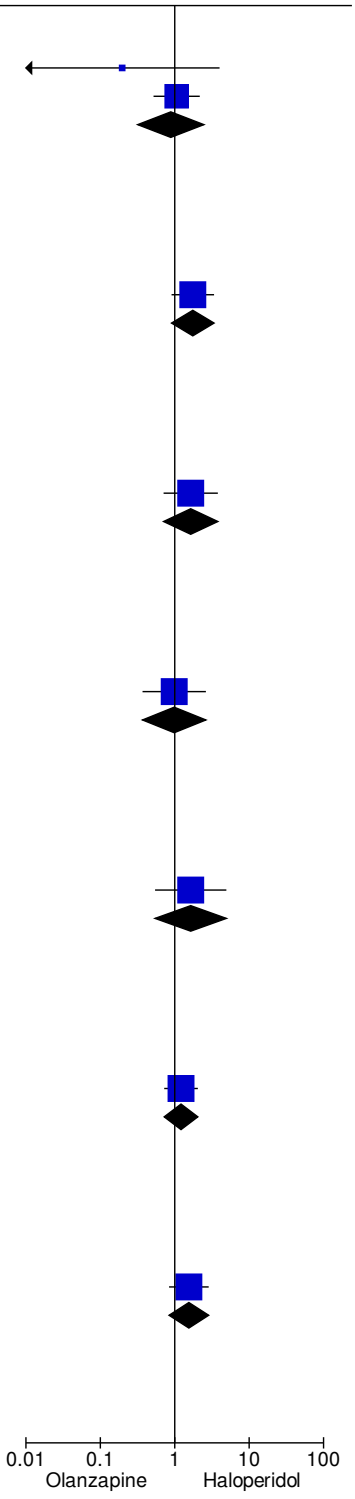
Test for subgroup differences: $Chi^2 = 0.00$, df = 3 (P < 0.00001), $I^2 = 0\%$



Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 66: Adverse effects/events: 7b. Specific - anticholinergic - various - medium term

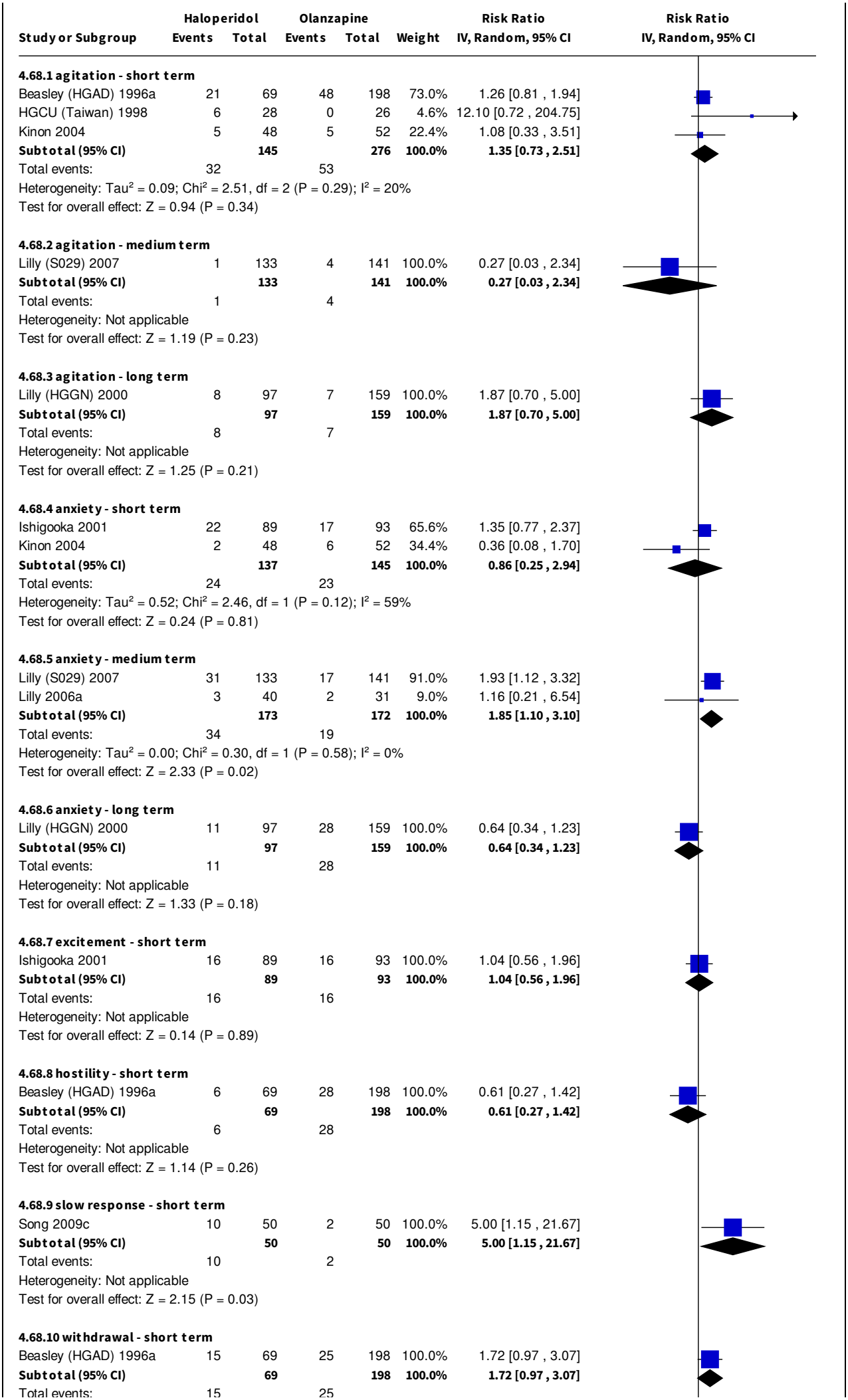
Analysis 4.67

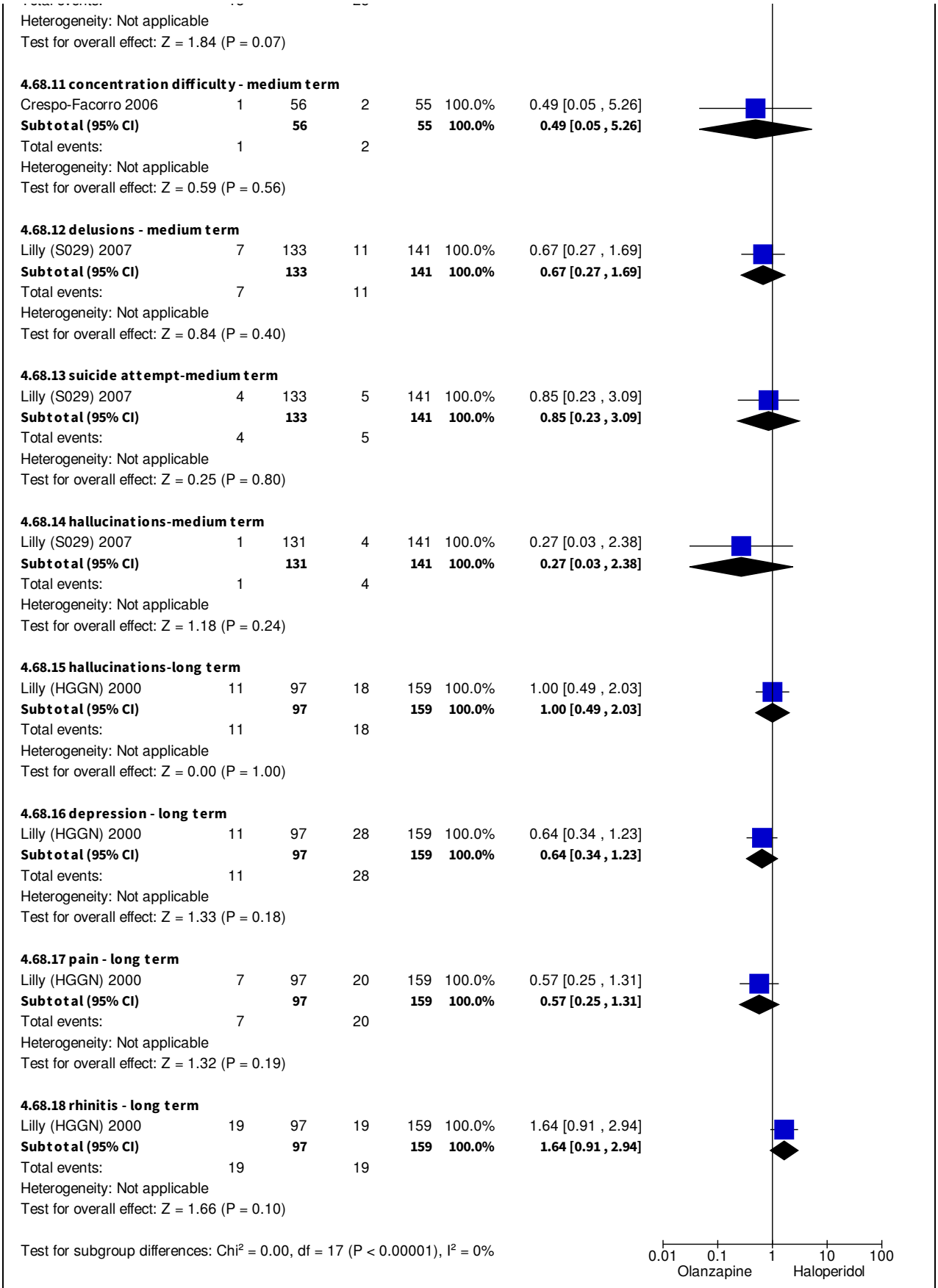
Study or Subgroup	Haloperidol Events	Haloperidol Total	Olanzapine Events	Olanzapine Total	Weight	Risk Ratio IV, Random, 95% CI
4.67.1 salivation - too little						
Crespo-Facorro 2006	0	56	2	55	10.8%	0.20 [0.01 , 4.00]
Lilly (HGGN) 2000	11	97	17	159	89.2%	1.06 [0.52 , 2.17]
Subtotal (95% CI)		**153**		**214**	**100.0%**	**0.88 [0.32 , 2.46]**
Total events:	11		19			
Heterogeneity: $Tau^2 = 0.17$; $Chi^2 = 1.14$, df = 1 (P = 0.29); $I^2 = 12\%$						
Test for overall effect: Z = 0.23 (P = 0.81)						
4.67.2 dizziness						
Lilly (HGGN) 2000	16	97	15	159	100.0%	1.75 [0.91 , 3.37]
Subtotal (95% CI)		**97**		**159**	**100.0%**	**1.75 [0.91 , 3.37]**
Total events:	16		15			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.67 (P = 0.10)						
4.67.3 paranoid reaction						
Lilly (HGGN) 2000	10	97	10	159	100.0%	1.64 [0.71 , 3.79]
Subtotal (95% CI)		**97**		**159**	**100.0%**	**1.64 [0.71 , 3.79]**
Total events:	10		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.15 (P = 0.25)						
4.67.4 abnormal thinking						
Lilly (HGGN) 2000	6	97	10	159	100.0%	0.98 [0.37 , 2.62]
Subtotal (95% CI)		**97**		**159**	**100.0%**	**0.98 [0.37 , 2.62]**
Total events:	6		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.03 (P = 0.97)						
4.67.5 constipation						
Lilly (HGGN) 2000	6	97	6	159	100.0%	1.64 [0.54 , 4.94]
Subtotal (95% CI)		**97**		**159**	**100.0%**	**1.64 [0.54 , 4.94]**
Total events:	6		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.88 (P = 0.38)						
4.67.6 headache						
Lilly (HGGN) 2000	20	97	27	159	100.0%	1.21 [0.72 , 2.04]
Subtotal (95% CI)		**97**		**159**	**100.0%**	**1.21 [0.72 , 2.04]**
Total events:	20		27			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.73 (P = 0.46)						
4.67.7 nervousness						
Lilly (HGGN) 2000	17	97	18	159	100.0%	1.55 [0.84 , 2.86]
Subtotal (95% CI)		**97**		**159**	**100.0%**	**1.55 [0.84 , 2.86]**
Total events:	17		18			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.40 (P = 0.16)						
Test for subgroup differences: $Chi^2 = 0.00$, df = 6 (P < 0.00001), $I^2 = 0\%$						



Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 67: Adverse effects/events: 7c. Specific - anticholinergic - various - long term

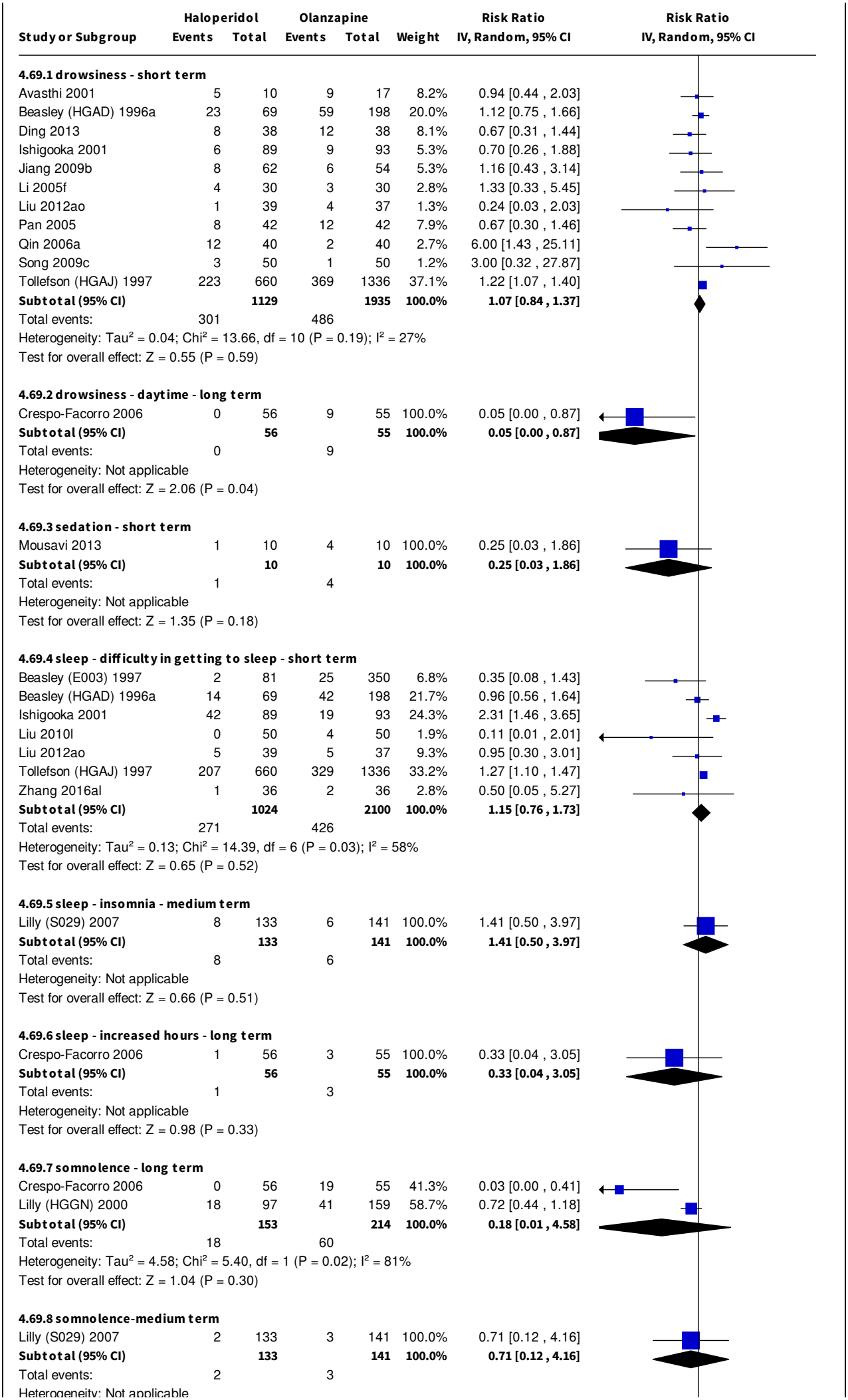
Analysis 4.68


Haloperidol
Olanzapine
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight IV, Random, 95% CI
IV, Random, 95% CI
4.68.1 agitation - short term
Beasley (HGAD) 1996a 21 69 48 198 73.0% 1.26 [0.81 , 1.94]
HGCU (Taiwan) 1998 6 28 0 26 4.6% 12.10 [0.72 , 204.75]
Kinon 2004 5 48 5 52 22.4% 1.08 [0.33 , 3.51]
Subtotal (95% CI) 145 276 100.0% 1.35 [0.73 , 2.51]
Total events: 32 53
Heterogeneity: Tau² = 0.09; Chi² = 2.51, df = 2 (P = 0.29); I² = 20%
Test for overall effect: Z = 0.94 (P = 0.34)
4.68.2 agitation - medium term
Lilly (S029) 2007 1 133 4 141 100.0% 0.27 [0.03 , 2.34]
Subtotal (95% CI) 133 141 100.0% 0.27 [0.03 , 2.34]
Total events: 1 4
Heterogeneity: Not applicable
Test for overall effect: Z = 1.19 (P = 0.23)
4.68.3 agitation - long term
Lilly (HGGN) 2000 8 97 7 159 100.0% 1.87 [0.70 , 5.00]
Subtotal (95% CI) 97 159 100.0% 1.87 [0.70 , 5.00]
Total events: 8 7
Heterogeneity: Not applicable
Test for overall effect: Z = 1.25 (P = 0.21)
4.68.4 anxiety - short term
Ishigooka 2001 22 89 17 93 65.6% 1.35 [0.77 , 2.37]
Kinon 2004 2 48 6 52 34.4% 0.36 [0.08 , 1.70]
Subtotal (95% CI) 137 145 100.0% 0.86 [0.25 , 2.94]
Total events: 24 23
Heterogeneity: Tau² = 0.52; Chi² = 2.46, df = 1 (P = 0.12); I² = 59%
Test for overall effect: Z = 0.24 (P = 0.81)
4.68.5 anxiety - medium term
Lilly (S029) 2007 31 133 17 141 91.0% 1.93 [1.12 , 3.32]
Lilly 2006a 3 40 2 31 9.0% 1.16 [0.21 , 6.54]
Subtotal (95% CI) 173 172 100.0% 1.85 [1.10 , 3.10]
Total events: 34 19
Heterogeneity: Tau² = 0.00; Chi² = 0.30, df = 1 (P = 0.58); I² = 0%
Test for overall effect: Z = 2.33 (P = 0.02)
4.68.6 anxiety - long term
Lilly (HGGN) 2000 11 97 28 159 100.0% 0.64 [0.34 , 1.23]
Subtotal (95% CI) 97 159 100.0% 0.64 [0.34 , 1.23]
Total events: 11 28
Heterogeneity: Not applicable
Test for overall effect: Z = 1.33 (P = 0.18)
4.68.7 excitement - short term
Ishigooka 2001 16 89 16 93 100.0% 1.04 [0.56 , 1.96]
Subtotal (95% CI) 89 93 100.0% 1.04 [0.56 , 1.96]
Total events: 16 16
Heterogeneity: Not applicable
Test for overall effect: Z = 0.14 (P = 0.89)
4.68.8 hostility - short term
Beasley (HGAD) 1996a 6 69 28 198 100.0% 0.61 [0.27 , 1.42]
Subtotal (95% CI) 69 198 100.0% 0.61 [0.27 , 1.42]
Total events: 6 28
Heterogeneity: Not applicable
Test for overall effect: Z = 1.14 (P = 0.26)
4.68.9 slow response - short term
Song 2009c 10 50 2 50 100.0% 5.00 [1.15 , 21.67]
Subtotal (95% CI) 50 50 100.0% 5.00 [1.15 , 21.67]
Total events: 10 2
Heterogeneity: Not applicable
Test for overall effect: Z = 2.15 (P = 0.03)
4.68.10 withdrawal - short term
Beasley (HGAD) 1996a 15 69 25 198 100.0% 1.72 [0.97 , 3.07]
Subtotal (95% CI) 69 198 100.0% 1.72 [0.97 , 3.07]
Total events: 15 25



Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 68: Adverse effects/events: 8a. Specific - arousal - various [non-sleep] measures

Analysis 4.69


Haloperidol
Olanzapine
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight IV, Random, 95% CI
IV, Random, 95% CI
4.69.1 drowsiness - short term
Avasthi 2001 5 10 9 17 8.2% 0.94 [0.44 , 2.03]
Beasley (HGAD) 1996a 23 69 59 198 20.0% 1.12 [0.75 , 1.66]
Ding 2013 8 38 12 38 8.1% 0.67 [0.31 , 1.44]
Ishigooka 2001 6 89 9 93 5.3% 0.70 [0.26 , 1.88]
Jiang 2009b 8 62 6 54 5.3% 1.16 [0.43 , 3.14]
Li 2005f 4 30 3 30 2.8% 1.33 [0.33 , 5.45]
Liu 2012ao 1 39 4 37 1.3% 0.24 [0.03 , 2.03]
Pan 2005 8 42 12 42 7.9% 0.67 [0.30 , 1.46]
Qin 2006a 12 40 2 40 2.7% 6.00 [1.43 , 25.11]
Song 2009c 3 50 1 50 1.2% 3.00 [0.32 , 27.87]
Tollefson (HGAJ) 1997 223 660 369 1336 37.1% 1.22 [1.07 , 1.40]
Subtotal (95% CI) 1129 1935 100.0% 1.07 [0.84 , 1.37]
Total events: 301 486
Heterogeneity: Tau² = 0.04; Chi² = 13.66, df = 10 (P = 0.19); I² = 27%
Test for overall effect: Z = 0.55 (P = 0.59)
4.69.2 drowsiness - daytime - long term
Crespo-Facorro 2006 0 56 9 55 100.0% 0.05 [0.00 , 0.87]
Subtotal (95% CI) 56 55 100.0% 0.05 [0.00 , 0.87]
Total events: 0 9
Heterogeneity: Not applicable
Test for overall effect: Z = 2.06 (P = 0.04)
4.69.3 sedation - short term
Mousavi 2013 1 10 4 10 100.0% 0.25 [0.03 , 1.86]
Subtotal (95% CI) 10 10 100.0% 0.25 [0.03 , 1.86]
Total events: 1 4
Heterogeneity: Not applicable
Test for overall effect: Z = 1.35 (P = 0.18)
4.69.4 sleep - difficulty in getting to sleep - short term
Beasley (E003) 1997 2 81 25 350 6.8% 0.35 [0.08 , 1.43]
Beasley (HGAD) 1996a 14 69 42 198 21.7% 0.96 [0.56 , 1.64]
Ishigooka 2001 42 89 19 93 24.3% 2.31 [1.46 , 3.65]
Liu 2010l 0 50 4 50 1.9% 0.11 [0.01 , 2.01]
Liu 2012ao 5 39 5 37 9.3% 0.95 [0.30 , 3.01]
Tollefson (HGAJ) 1997 207 660 329 1336 33.2% 1.27 [1.10 , 1.47]
Zhang 2016al 1 36 2 36 2.8% 0.50 [0.05 , 5.27]
Subtotal (95% CI) 1024 2100 100.0% 1.15 [0.76 , 1.73]
Total events: 271 426
Heterogeneity: Tau² = 0.13; Chi² = 14.39, df = 6 (P = 0.03); I² = 58%
Test for overall effect: Z = 0.65 (P = 0.52)
4.69.5 sleep - insomnia - medium term
Lilly (S029) 2007 8 133 6 141 100.0% 1.41 [0.50 , 3.97]
Subtotal (95% CI) 133 141 100.0% 1.41 [0.50 , 3.97]
Total events: 8 6
Heterogeneity: Not applicable
Test for overall effect: Z = 0.66 (P = 0.51)
4.69.6 sleep - increased hours - long term
Crespo-Facorro 2006 1 56 3 55 100.0% 0.33 [0.04 , 3.05]
Subtotal (95% CI) 56 55 100.0% 0.33 [0.04 , 3.05]
Total events: 1 3
Heterogeneity: Not applicable
Test for overall effect: Z = 0.98 (P = 0.33)
4.69.7 somnolence - long term
Crespo-Facorro 2006 0 56 19 55 41.3% 0.03 [0.00 , 0.41]
Lilly (HGGN) 2000 18 97 41 159 58.7% 0.72 [0.44 , 1.18]
Subtotal (95% CI) 153 214 100.0% 0.18 [0.01 , 4.58]
Total events: 18 60
Heterogeneity: Tau² = 4.58; Chi² = 5.40, df = 1 (P = 0.02); I² = 81%
Test for overall effect: Z = 1.04 (P = 0.30)
4.69.8 somnolence-medium term
Lilly (S029) 2007 2 133 3 141 100.0% 0.71 [0.12 , 4.16]
Subtotal (95% CI) 133 141 100.0% 0.71 [0.12 , 4.16]
Total events: 2 3
Heterogeneity: Not applicable

Test for overall effect: Z = 0.38 (P = 0.70)

4.69.9 insomnia - short term

Kinon 2004	6	48	3	52	100.0%	2.17 [0.57 , 8.19]
Subtotal (95% CI)		**48**		**52**	**100.0%**	**2.17 [0.57 , 8.19]**
Total events:	6		3			

Heterogeneity: Not applicable

Test for overall effect: Z = 1.14 (P = 0.25)

4.69.10 somnolence - short term

Kinon 2004	12	48	9	52	100.0%	1.44 [0.67 , 3.12]
Subtotal (95% CI)		**48**		**52**	**100.0%**	**1.44 [0.67 , 3.12]**
Total events:	12		9			

Heterogeneity: Not applicable

Test for overall effect: Z = 0.94 (P = 0.35)

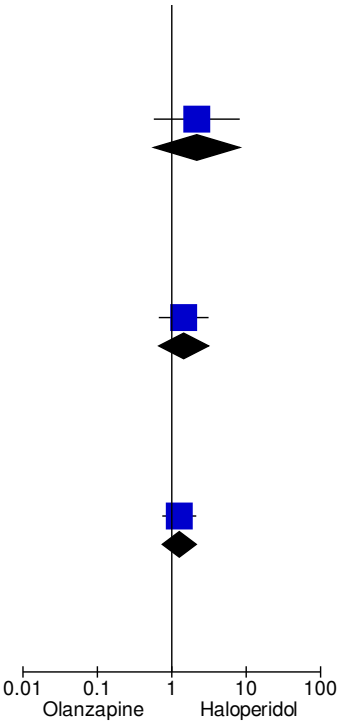
4.69.11 insomnia - long term

Lilly (HGGN) 2000	20	97	26	159	100.0%	1.26 [0.75 , 2.13]
Subtotal (95% CI)		**97**		**159**	**100.0%**	**1.26 [0.75 , 2.13]**
Total events:	20		26			

Heterogeneity: Not applicable

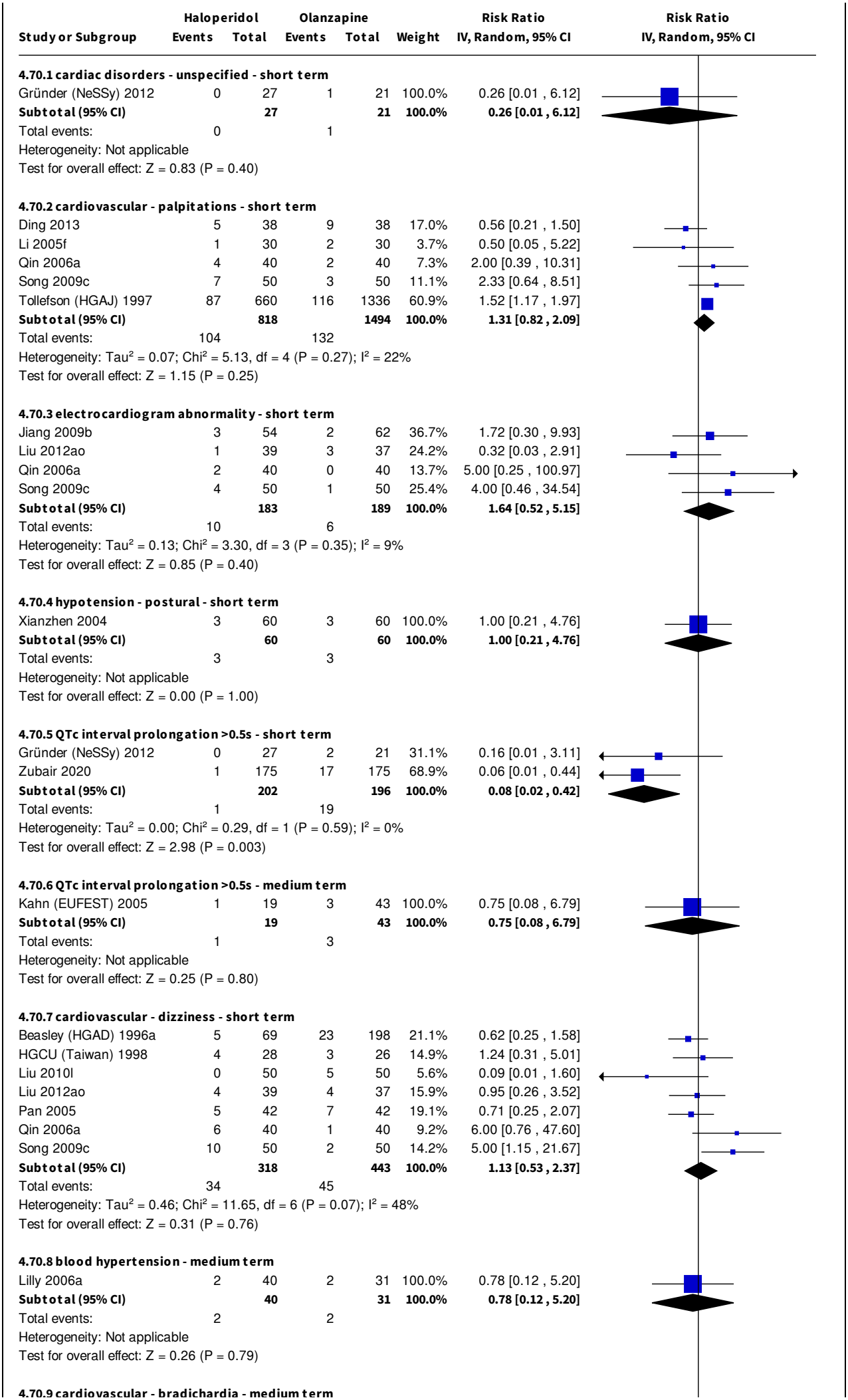
Test for overall effect: Z = 0.86 (P = 0.39)

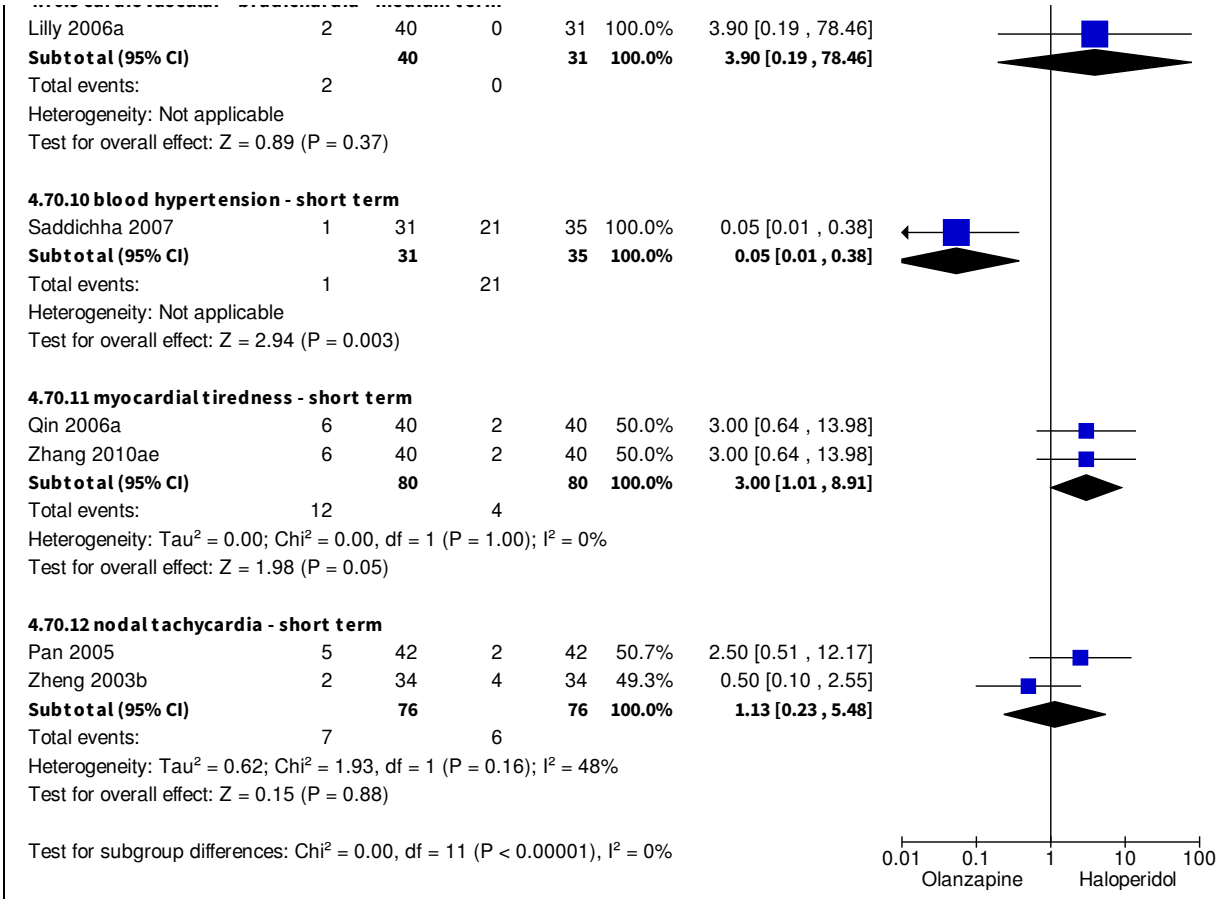
Test for subgroup differences: $Chi^2 = 0.00$, df = 10 (P < 0.00001), $I^2 = 0\%$



Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 69: Adverse effects/events: 8b. Specific - arousal - sleep/sleepiness - various binary outcomes

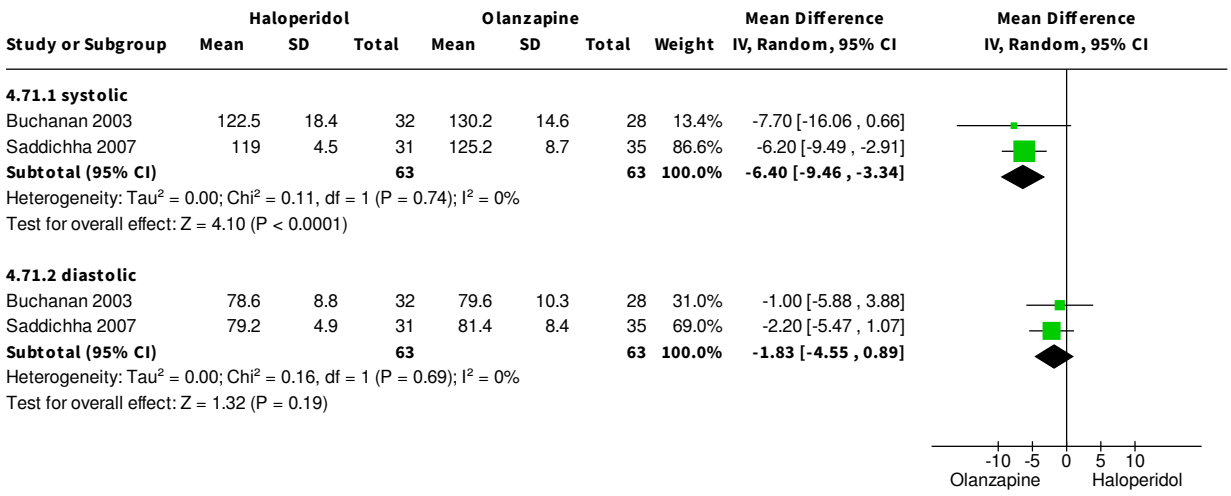
Analysis 4.70


Haloperidol
Olanzapine
Risk Ratio
Risk Ratio
Study or Subgroup
Events
Total
Events
Total
Weight
IV, Random, 95% CI
IV, Random, 95% CI
4.70.1 cardiac disorders - unspecified - short term
Gründer (NeSSy) 2012 0 27 1 21 100.0% 0.26 [0.01 , 6.12]
Subtotal (95% CI) 27 21 100.0% 0.26 [0.01 , 6.12]
Total events: 0 1
Heterogeneity: Not applicable
Test for overall effect: Z = 0.83 (P = 0.40)
4.70.2 cardiovascular - palpitations - short term
Ding 2013 5 38 9 38 17.0% 0.56 [0.21 , 1.50]
Li 2005f 1 30 2 30 3.7% 0.50 [0.05 , 5.22]
Qin 2006a 4 40 2 40 7.3% 2.00 [0.39 , 10.31]
Song 2009c 7 50 3 50 11.1% 2.33 [0.64 , 8.51]
Tollefson (HGAJ) 1997 87 660 116 1336 60.9% 1.52 [1.17 , 1.97]
Subtotal (95% CI) 818 1494 100.0% 1.31 [0.82 , 2.09]
Total events: 104 132
Heterogeneity: Tau² = 0.07; Chi² = 5.13, df = 4 (P = 0.27); I² = 22%
Test for overall effect: Z = 1.15 (P = 0.25)
4.70.3 electrocardiogram abnormality - short term
Jiang 2009b 3 54 2 62 36.7% 1.72 [0.30 , 9.93]
Liu 2012ao 1 39 3 37 24.2% 0.32 [0.03 , 2.91]
Qin 2006a 2 40 0 40 13.7% 5.00 [0.25 , 100.97]
Song 2009c 4 50 1 50 25.4% 4.00 [0.46 , 34.54]
Subtotal (95% CI) 183 189 100.0% 1.64 [0.52 , 5.15]
Total events: 10 6
Heterogeneity: Tau² = 0.13; Chi² = 3.30, df = 3 (P = 0.35); I² = 9%
Test for overall effect: Z = 0.85 (P = 0.40)
4.70.4 hypotension - postural - short term
Xianzhen 2004 3 60 3 60 100.0% 1.00 [0.21 , 4.76]
Subtotal (95% CI) 60 60 100.0% 1.00 [0.21 , 4.76]
Total events: 3 3
Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)
4.70.5 QTc interval prolongation >0.5s - short term
Gründer (NeSSy) 2012 0 27 2 21 31.1% 0.16 [0.01 , 3.11]
Zubair 2020 1 175 17 175 68.9% 0.06 [0.01 , 0.44]
Subtotal (95% CI) 202 196 100.0% 0.08 [0.02 , 0.42]
Total events: 1 19
Heterogeneity: Tau² = 0.00; Chi² = 0.29, df = 1 (P = 0.59); I² = 0%
Test for overall effect: Z = 2.98 (P = 0.003)
4.70.6 QTc interval prolongation >0.5s - medium term
Kahn (EUFEST) 2005 1 19 3 43 100.0% 0.75 [0.08 , 6.79]
Subtotal (95% CI) 19 43 100.0% 0.75 [0.08 , 6.79]
Total events: 1 3
Heterogeneity: Not applicable
Test for overall effect: Z = 0.25 (P = 0.80)
4.70.7 cardiovascular - dizziness - short term
Beasley (HGAD) 1996a 5 69 23 198 21.1% 0.62 [0.25 , 1.58]
HGCU (Taiwan) 1998 4 28 3 26 14.9% 1.24 [0.31 , 5.01]
Liu 2010l 0 50 5 50 5.6% 0.09 [0.01 , 1.60]
Liu 2012ao 4 39 4 37 15.9% 0.95 [0.26 , 3.52]
Pan 2005 5 42 7 42 19.1% 0.71 [0.25 , 2.07]
Qin 2006a 6 40 1 40 9.2% 6.00 [0.76 , 47.60]
Song 2009c 10 50 2 50 14.2% 5.00 [1.15 , 21.67]
Subtotal (95% CI) 318 443 100.0% 1.13 [0.53 , 2.37]
Total events: 34 45
Heterogeneity: Tau² = 0.46; Chi² = 11.65, df = 6 (P = 0.07); I² = 48%
Test for overall effect: Z = 0.31 (P = 0.76)
4.70.8 blood hypertension - medium term
Lilly 2006a 2 40 2 31 100.0% 0.78 [0.12 , 5.20]
Subtotal (95% CI) 40 31 100.0% 0.78 [0.12 , 5.20]
Total events: 2 2
Heterogeneity: Not applicable
Test for overall effect: Z = 0.26 (P = 0.79)
4.70.9 cardiovascular - bradichardia - medium term



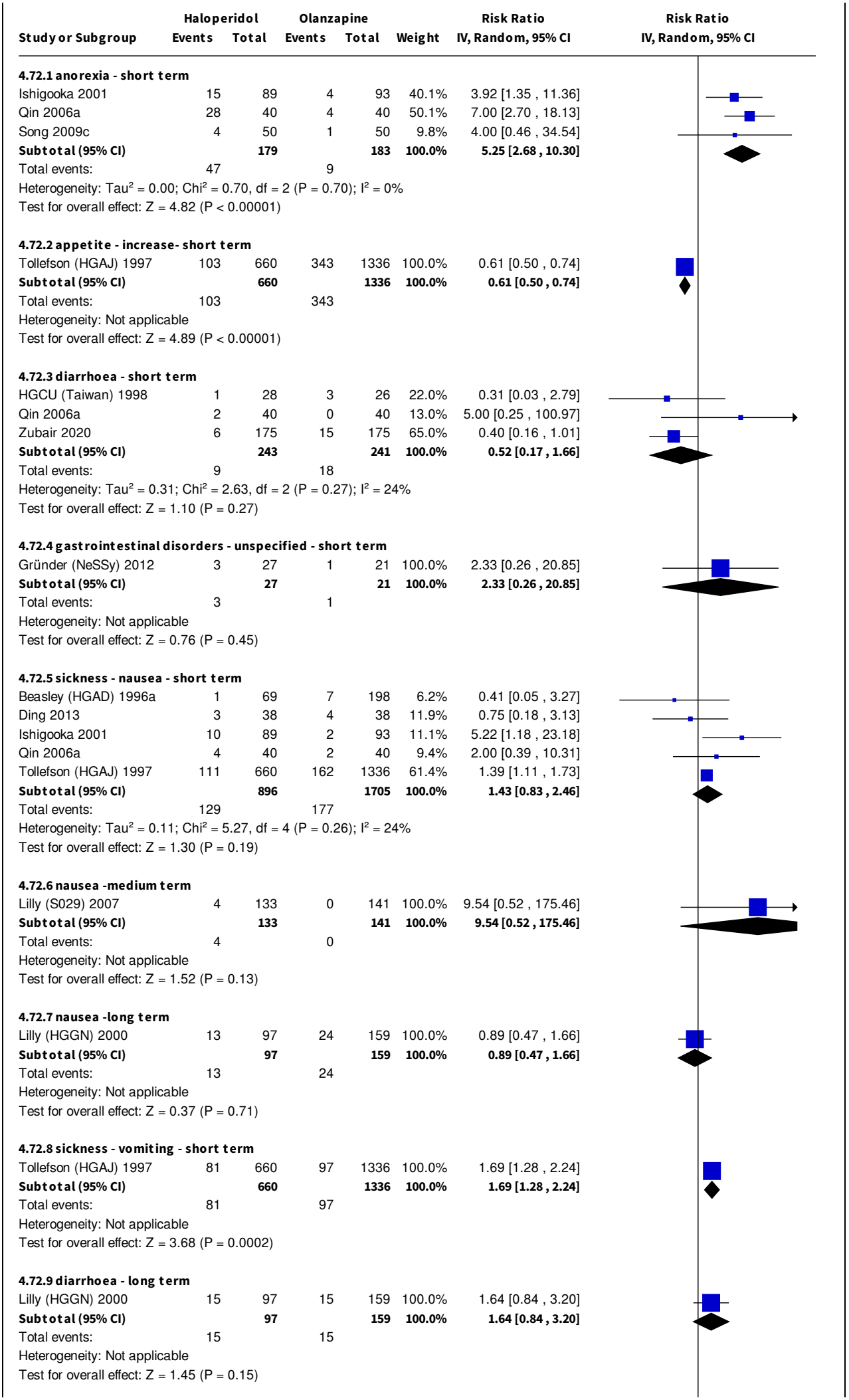
Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 70: Adverse effects/events: 9a. Specific - cardiovascular - various binary measures

Analysis 4.71



Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 71: Adverse effects/events: 9b. Specific - cardiovascular - blood pressure endpoint - short term (high=poor)

Analysis 4.72

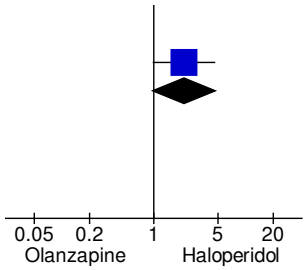

Haloperidol
Olanzapine
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight IV, Random, 95% CI
IV, Random, 95% CI
4.72.1 anorexia - short term
Ishigooka 2001 15 89 4 93 40.1% 3.92 [1.35 , 11.36]
Qin 2006a 28 40 4 40 50.1% 7.00 [2.70 , 18.13]
Song 2009c 4 50 1 50 9.8% 4.00 [0.46 , 34.54]
Subtotal (95% CI) 179 183 100.0% 5.25 [2.68 , 10.30]
Total events: 47 9
Heterogeneity: Tau² = 0.00; Chi² = 0.70, df = 2 (P = 0.70); I² = 0%
Test for overall effect: Z = 4.82 (P < 0.00001)
4.72.2 appetite - increase- short term
Tollefson (HGAJ) 1997 103 660 343 1336 100.0% 0.61 [0.50 , 0.74]
Subtotal (95% CI) 660 1336 100.0% 0.61 [0.50 , 0.74]
Total events: 103 343
Heterogeneity: Not applicable
Test for overall effect: Z = 4.89 (P < 0.00001)
4.72.3 diarrhoea - short term
HGCU (Taiwan) 1998 1 28 3 26 22.0% 0.31 [0.03 , 2.79]
Qin 2006a 2 40 0 40 13.0% 5.00 [0.25 , 100.97]
Zubair 2020 6 175 15 175 65.0% 0.40 [0.16 , 1.01]
Subtotal (95% CI) 243 241 100.0% 0.52 [0.17 , 1.66]
Total events: 9 18
Heterogeneity: Tau² = 0.31; Chi² = 2.63, df = 2 (P = 0.27); I² = 24%
Test for overall effect: Z = 1.10 (P = 0.27)
4.72.4 gastrointestinal disorders - unspecified - short term
Gründer (NeSSy) 2012 3 27 1 21 100.0% 2.33 [0.26 , 20.85]
Subtotal (95% CI) 27 21 100.0% 2.33 [0.26 , 20.85]
Total events: 3 1
Heterogeneity: Not applicable
Test for overall effect: Z = 0.76 (P = 0.45)
4.72.5 sickness - nausea - short term
Beasley (HGAD) 1996a 1 69 7 198 6.2% 0.41 [0.05 , 3.27]
Ding 2013 3 38 4 38 11.9% 0.75 [0.18 , 3.13]
Ishigooka 2001 10 89 2 93 11.1% 5.22 [1.18 , 23.18]
Qin 2006a 4 40 2 40 9.4% 2.00 [0.39 , 10.31]
Tollefson (HGAJ) 1997 111 660 162 1336 61.4% 1.39 [1.11 , 1.73]
Subtotal (95% CI) 896 1705 100.0% 1.43 [0.83 , 2.46]
Total events: 129 177
Heterogeneity: Tau² = 0.11; Chi² = 5.27, df = 4 (P = 0.26); I² = 24%
Test for overall effect: Z = 1.30 (P = 0.19)
4.72.6 nausea -medium term
Lilly (S029) 2007 4 133 0 141 100.0% 9.54 [0.52 , 175.46]
Subtotal (95% CI) 133 141 100.0% 9.54 [0.52 , 175.46]
Total events: 4 0
Heterogeneity: Not applicable
Test for overall effect: Z = 1.52 (P = 0.13)
4.72.7 nausea -long term
Lilly (HGGN) 2000 13 97 24 159 100.0% 0.89 [0.47 , 1.66]
Subtotal (95% CI) 97 159 100.0% 0.89 [0.47 , 1.66]
Total events: 13 24
Heterogeneity: Not applicable
Test for overall effect: Z = 0.37 (P = 0.71)
4.72.8 sickness - vomiting - short term
Tollefson (HGAJ) 1997 81 660 97 1336 100.0% 1.69 [1.28 , 2.24]
Subtotal (95% CI) 660 1336 100.0% 1.69 [1.28 , 2.24]
Total events: 81 97
Heterogeneity: Not applicable
Test for overall effect: Z = 3.68 (P = 0.0002)
4.72.9 diarrhoea - long term
Lilly (HGGN) 2000 15 97 15 159 100.0% 1.64 [0.84 , 3.20]
Subtotal (95% CI) 97 159 100.0% 1.64 [0.84 , 3.20]
Total events: 15 15
Heterogeneity: Not applicable
Test for overall effect: Z = 1.45 (P = 0.15)

4.72.10 vomiting - long term

Lilly (HGGN) 2000	13	97	10	159	100.0%	2.13 [0.97 , 4.67]
Subtotal (95% CI)		**97**		**159**	**100.0%**	**2.13 [0.97 , 4.67]**
Total events:	13		10			

Heterogeneity: Not applicable

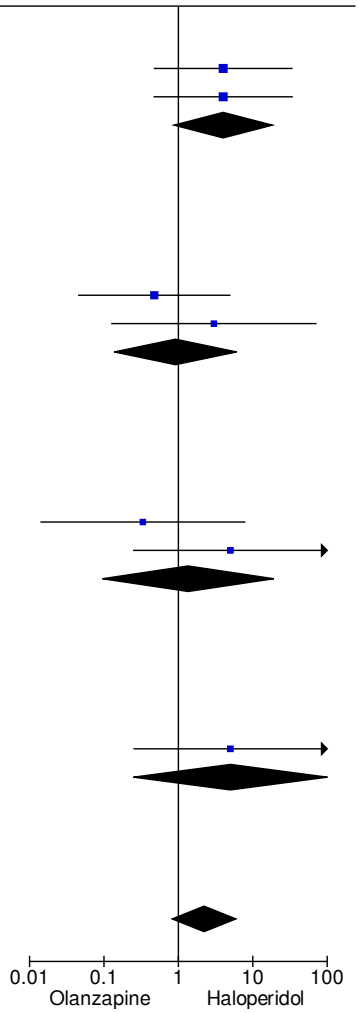
Test for overall effect: Z = 1.89 (P = 0.06)



Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 72: Adverse effects/events: 10a. Specific - gastrointestinal

Analysis 4.73

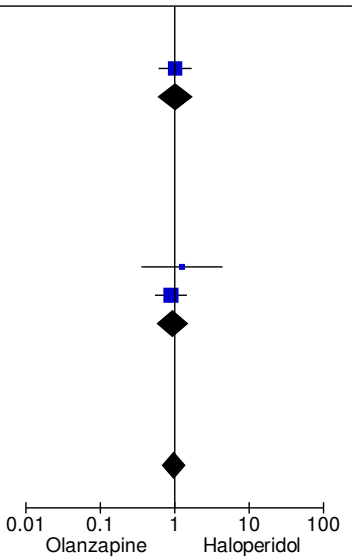
Study or Subgroup	Haloperidol Events	Total	Olanzapine Events	Total	Weight	Risk Ratio IV, Random, 95% CI
4.73.1 abnormal blood routine test						
Qin 2006a	4	40	1	40	21.0%	4.00 [0.47 , 34.24]
Song 2009c	4	50	1	50	20.8%	4.00 [0.46 , 34.54]
Subtotal (95% CI)		**90**		**90**	**41.9%**	**4.00 [0.87 , 18.31]**
Total events:	8		2			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.00$, df = 1 (P = 1.00); $I^2 = 0\%$						
Test for overall effect: Z = 1.79 (P = 0.07)						
4.73.2 abnormal liver dysfunction						
Liu 2012ao	1	39	2	37	17.4%	0.47 [0.04 , 5.01]
Song 2009c	1	50	0	50	9.6%	3.00 [0.13 , 71.92]
Subtotal (95% CI)		**89**		**87**	**27.0%**	**0.91 [0.14 , 6.07]**
Total events:	2		2			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.83$, df = 1 (P = 0.36); $I^2 = 0\%$						
Test for overall effect: Z = 0.09 (P = 0.93)						
4.73.3 transaminase increase						
Ding 2013	0	38	1	38	9.6%	0.33 [0.01 , 7.93]
Liu 2010l	2	50	0	50	10.7%	5.00 [0.25 , 101.58]
Subtotal (95% CI)		**88**		**88**	**20.3%**	**1.35 [0.10 , 19.20]**
Total events:	2		1			
Heterogeneity: $Tau^2 = 1.18$; $Chi^2 = 1.47$, df = 1 (P = 0.22); $I^2 = 32\%$						
Test for overall effect: Z = 0.22 (P = 0.82)						
4.73.4 SGPT increase						
Zheng 2003b	2	34	0	34	10.8%	5.00 [0.25 , 100.43]
Subtotal (95% CI)		**34**		**34**	**10.8%**	**5.00 [0.25 , 100.43]**
Total events:	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.05 (P = 0.29)						
Total (95% CI)		**301**		**299**	**100.0%**	**2.21 [0.83 , 5.93]**
Total events:	14		5			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4.19$, df = 6 (P = 0.65); $I^2 = 0\%$						
Test for overall effect: Z = 1.58 (P = 0.11)						
Test for subgroup differences: $Chi^2 = 1.83$, df = 3 (P = 0.61), $I^2 = 0\%$						



Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 73: Adverse effects/events: 10b. Specific - hepatic/haematological disfunction - short term

Analysis 4.74

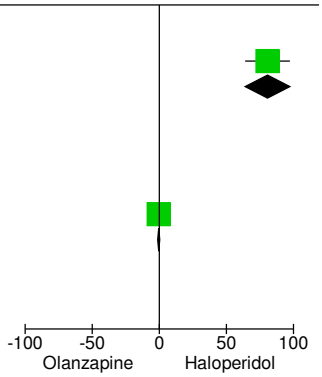
Study or Subgroup	Haloperidol Events	Total	Olanzapine Events	Total	Weight	Risk Ratio IV, Random, 95% CI
4.74.1 short term						
Crespo-Facorro 2006	17	37	15	33	44.7%	1.01 [0.61 , 1.69]
Subtotal (95% CI)		**37**		**33**	**44.7%**	**1.01 [0.61 , 1.69]**
Total events:	17		15			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.04 (P = 0.97)						
4.74.2 medium term						
Crespo-Facorro 2006	4	20	4	25	7.4%	1.25 [0.36 , 4.38]
Kahn (EUFEST) 2005	12	27	29	58	47.9%	0.89 [0.54 , 1.46]
Subtotal (95% CI)		**47**		**83**	**55.3%**	**0.93 [0.59 , 1.47]**
Total events:	16		33			
Heterogeneity: Tau² = 0.00; Chi² = 0.25, df = 1 (P = 0.62); I² = 0%						
Test for overall effect: Z = 0.31 (P = 0.76)						
Total (95% CI)		**84**		**116**	**100.0%**	**0.97 [0.69 , 1.36]**
Total events:	33		48			
Heterogeneity: Tau² = 0.00; Chi² = 0.30, df = 2 (P = 0.86); I² = 0%						
Test for overall effect: Z = 0.20 (P = 0.84)						
Test for subgroup differences: Chi² = 0.06, df = 1 (P = 0.81), I² = 0%						



Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 74: Adverse effects/events: 10c. Specific - hormonal - high prolactin levels

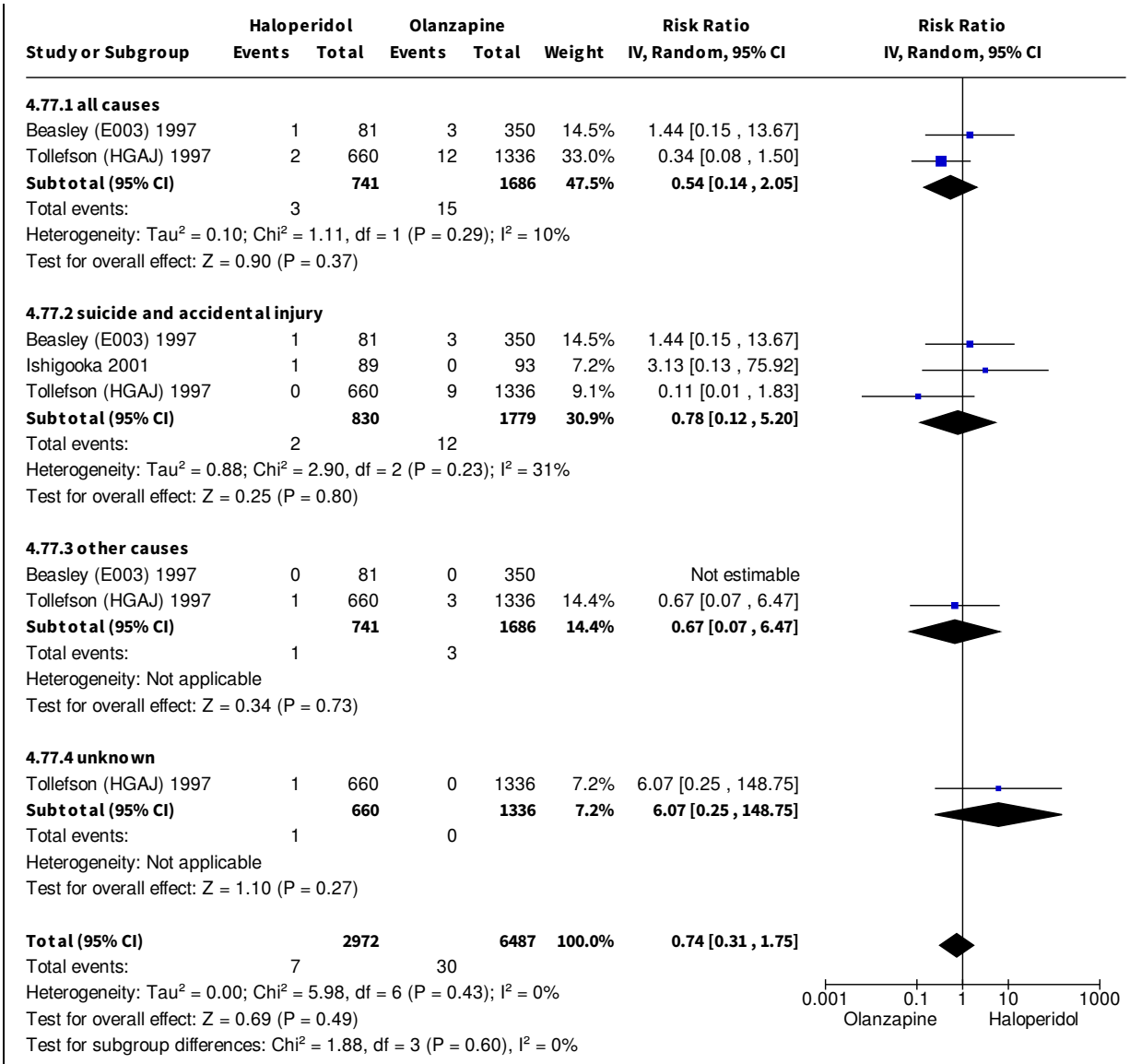
Analysis 4.75

Study or Subgroup	Haloperidol Mean	SD	Total	Olanzapine Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
4.75.1 prolactin								
Zhang 2005g	98.96	47.58	33	18.31	10.21	28	100.0%	80.65 [63.98 , 97.32]
Subtotal (95% CI)			**33**			**28**	**100.0%**	**80.65 [63.98 , 97.32]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 9.48 (P < 0.00001)								
4.75.2 growth hormone								
Zhang 2005g	1.57	1.68	33	2.01	1.32	28	100.0%	-0.44 [-1.19 , 0.31]
Subtotal (95% CI)			**33**			**28**	**100.0%**	**-0.44 [-1.19 , 0.31]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.14 (P = 0.25)								
Test for subgroup differences: Chi² = 0.00, df = 1 (P < 0.00001), I² = 0%								



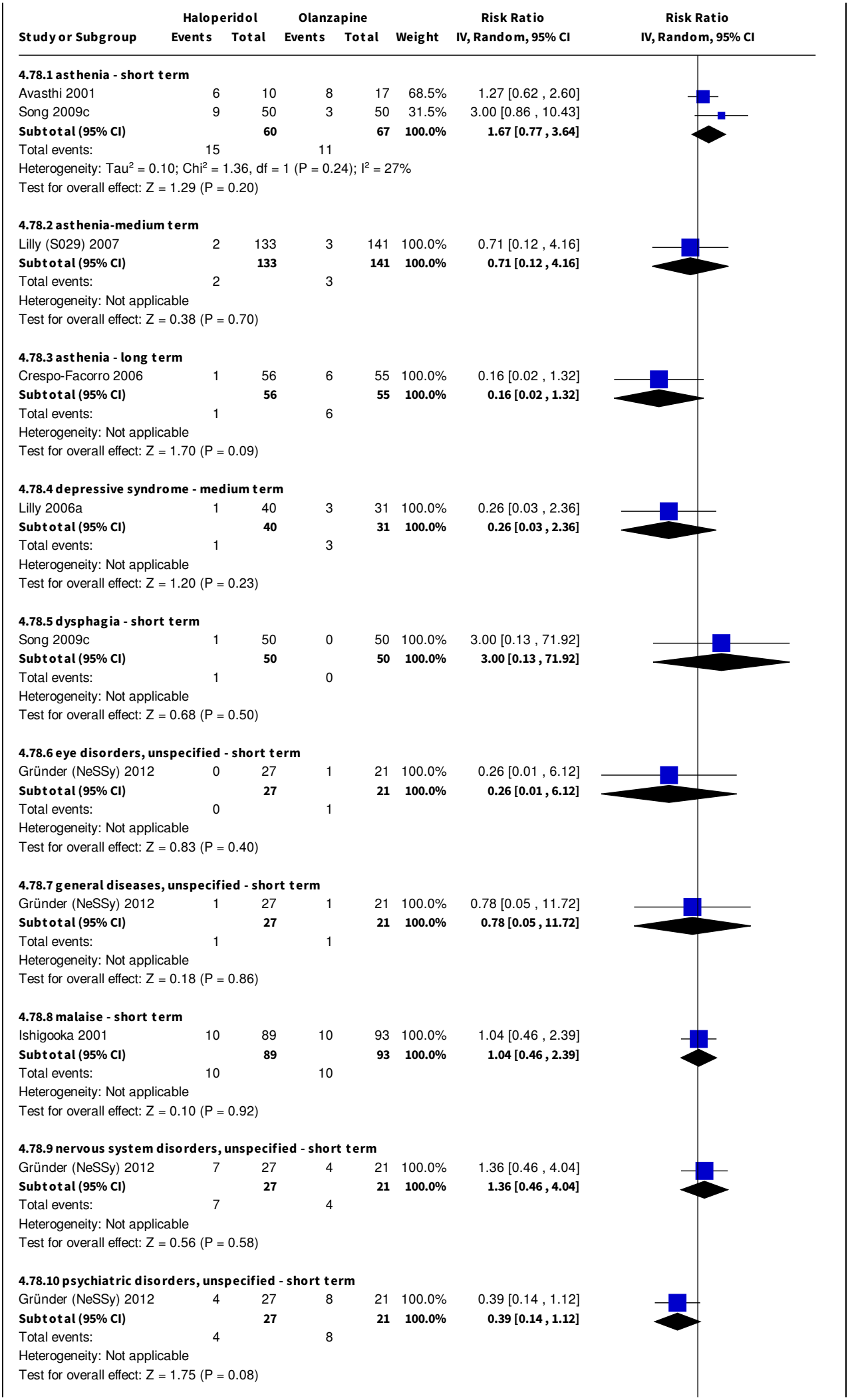
Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 75: Adverse effects/events: 10d. Specific - hormonal - serum levels - short term

Analysis 4.77



Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 77: Adverse effects/events: 12. Specific - death - during study or within 30 days of study discontinuation

Analysis 4.78


Haloperidol
Olanzapine
Risk Ratio
Risk Ratio
Study or Subgroup
Events
Total
Events
Total
Weight
IV, Random, 95% CI
IV, Random, 95% CI
4.78.1 asthenia - short term
Avasthi 2001 6 10 8 17 68.5% 1.27 [0.62 , 2.60]
Song 2009c 9 50 3 50 31.5% 3.00 [0.86 , 10.43]
Subtotal (95% CI) 60 67 100.0% 1.67 [0.77 , 3.64]
Total events: 15 11
Heterogeneity: Tau² = 0.10; Chi² = 1.36, df = 1 (P = 0.24); I² = 27%
Test for overall effect: Z = 1.29 (P = 0.20)
4.78.2 asthenia-medium term
Lilly (S029) 2007 2 133 3 141 100.0% 0.71 [0.12 , 4.16]
Subtotal (95% CI) 133 141 100.0% 0.71 [0.12 , 4.16]
Total events: 2 3
Heterogeneity: Not applicable
Test for overall effect: Z = 0.38 (P = 0.70)
4.78.3 asthenia - long term
Crespo-Facorro 2006 1 56 6 55 100.0% 0.16 [0.02 , 1.32]
Subtotal (95% CI) 56 55 100.0% 0.16 [0.02 , 1.32]
Total events: 1 6
Heterogeneity: Not applicable
Test for overall effect: Z = 1.70 (P = 0.09)
4.78.4 depressive syndrome - medium term
Lilly 2006a 1 40 3 31 100.0% 0.26 [0.03 , 2.36]
Subtotal (95% CI) 40 31 100.0% 0.26 [0.03 , 2.36]
Total events: 1 3
Heterogeneity: Not applicable
Test for overall effect: Z = 1.20 (P = 0.23)
4.78.5 dysphagia - short term
Song 2009c 1 50 0 50 100.0% 3.00 [0.13 , 71.92]
Subtotal (95% CI) 50 50 100.0% 3.00 [0.13 , 71.92]
Total events: 1 0
Heterogeneity: Not applicable
Test for overall effect: Z = 0.68 (P = 0.50)
4.78.6 eye disorders, unspecified - short term
Gründer (NeSSy) 2012 0 27 1 21 100.0% 0.26 [0.01 , 6.12]
Subtotal (95% CI) 27 21 100.0% 0.26 [0.01 , 6.12]
Total events: 0 1
Heterogeneity: Not applicable
Test for overall effect: Z = 0.83 (P = 0.40)
4.78.7 general diseases, unspecified - short term
Gründer (NeSSy) 2012 1 27 1 21 100.0% 0.78 [0.05 , 11.72]
Subtotal (95% CI) 27 21 100.0% 0.78 [0.05 , 11.72]
Total events: 1 1
Heterogeneity: Not applicable
Test for overall effect: Z = 0.18 (P = 0.86)
4.78.8 malaise - short term
Ishigooka 2001 10 89 10 93 100.0% 1.04 [0.46 , 2.39]
Subtotal (95% CI) 89 93 100.0% 1.04 [0.46 , 2.39]
Total events: 10 10
Heterogeneity: Not applicable
Test for overall effect: Z = 0.10 (P = 0.92)
4.78.9 nervous system disorders, unspecified - short term
Gründer (NeSSy) 2012 7 27 4 21 100.0% 1.36 [0.46 , 4.04]
Subtotal (95% CI) 27 21 100.0% 1.36 [0.46 , 4.04]
Total events: 7 4
Heterogeneity: Not applicable
Test for overall effect: Z = 0.56 (P = 0.58)
4.78.10 psychiatric disorders, unspecified - short term
Gründer (NeSSy) 2012 4 27 8 21 100.0% 0.39 [0.14 , 1.12]
Subtotal (95% CI) 27 21 100.0% 0.39 [0.14 , 1.12]
Total events: 4 8
Heterogeneity: Not applicable
Test for overall effect: Z = 1.75 (P = 0.08)

4.78.11 rash - short term

Mousavi 2013	1	10	0	10	100.0%	3.00 [0.14 , 65.90]
Subtotal (95% CI)		**10**		**10**	**100.0%**	**3.00 [0.14 , 65.90]**
Total events:	1		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.70 (P = 0.49)

4.78.12 rash - medium term

Lilly 2006a	0	40	2	31	100.0%	0.16 [0.01 , 3.14]
Subtotal (95% CI)		**40**		**31**	**100.0%**	**0.16 [0.01 , 3.14]**
Total events:	0		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.21 (P = 0.23)

4.78.13 reproductive system and breast disorders, unspecified - short term

Gründer (NeSSy) 2012	0	27	2	21	100.0%	0.16 [0.01 , 3.11]
Subtotal (95% CI)		**27**		**21**	**100.0%**	**0.16 [0.01 , 3.11]**
Total events:	0		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.22 (P = 0.22)

4.78.14 respiratory, thoracic, mediastinal disorders, unspecified - short term

Gründer (NeSSy) 2012	0	27	2	21	100.0%	0.16 [0.01 , 3.11]
Subtotal (95% CI)		**27**		**21**	**100.0%**	**0.16 [0.01 , 3.11]**
Total events:	0		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.22 (P = 0.22)

4.78.15 skin and subcutaneous tissue disorders, unspecified - short term

Gründer (NeSSy) 2012	0	27	1	21	100.0%	0.26 [0.01 , 6.12]
Subtotal (95% CI)		**27**		**21**	**100.0%**	**0.26 [0.01 , 6.12]**
Total events:	0		1			

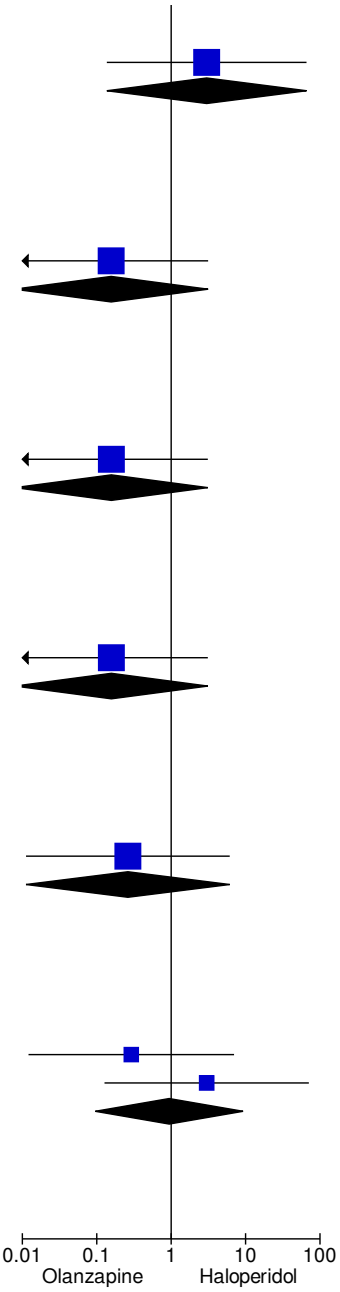
Heterogeneity: Not applicable
Test for overall effect: Z = 0.83 (P = 0.40)

4.78.16 torsion-spasm - short term

Jiang 2009b	0	62	1	54	49.7%	0.29 [0.01 , 7.00]
Li 2005f	1	30	0	30	50.3%	3.00 [0.13 , 70.83]
Subtotal (95% CI)		**92**		**84**	**100.0%**	**0.94 [0.10 , 9.25]**
Total events:	1		1			

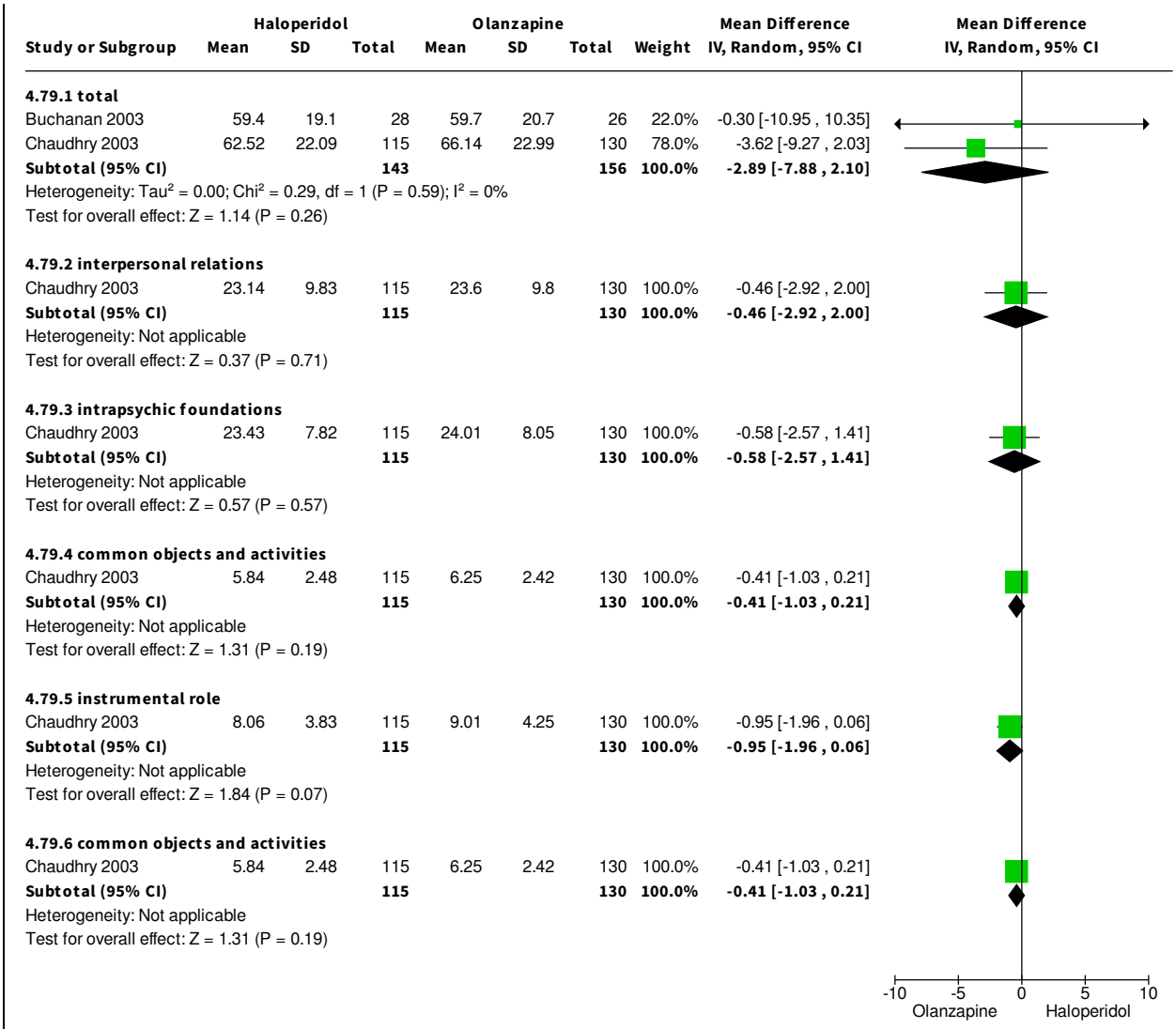
Heterogeneity: $Tau^2 = 0.10$; $Chi^2 = 1.04$, df = 1 (P = 0.31); $I^2 = 4\%$
Test for overall effect: Z = 0.05 (P = 0.96)

Test for subgroup differences: $Chi^2 = 0.00$, df = 15 (P < 0.00001), $I^2 = 0\%$



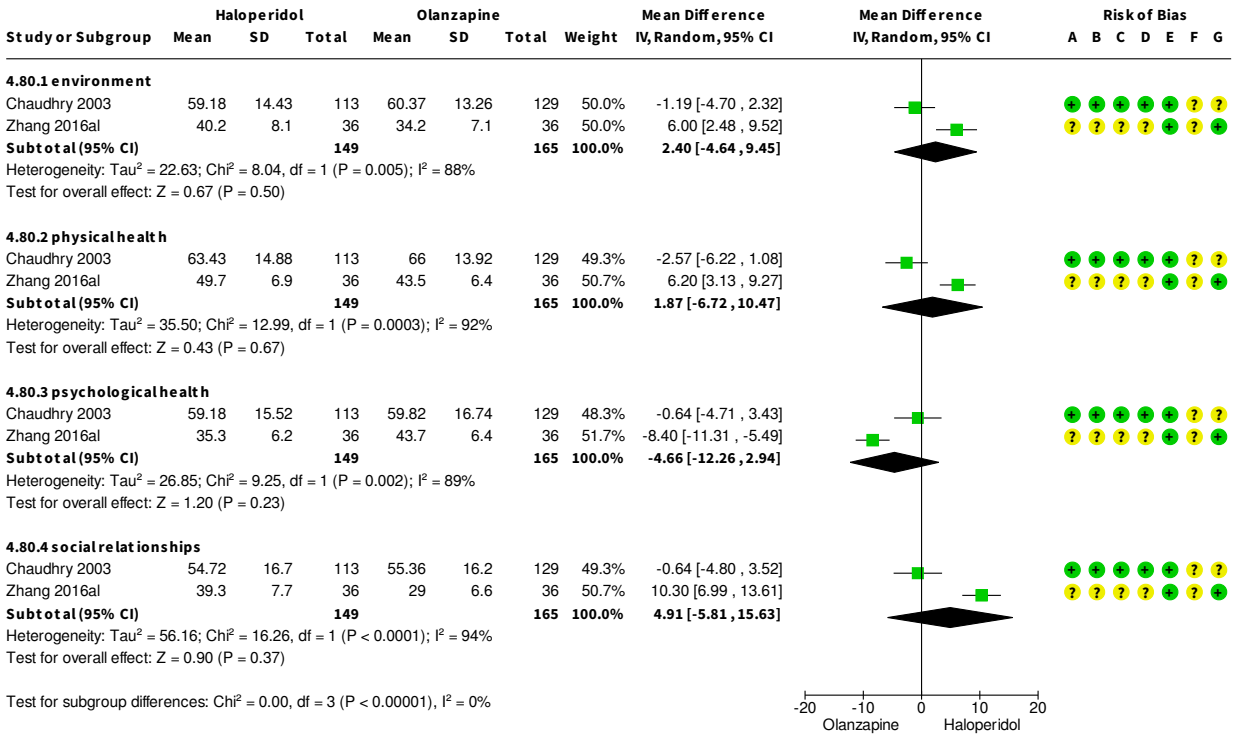
Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 78: Adverse effects/events: 13. Specific - others

Analysis 4.79



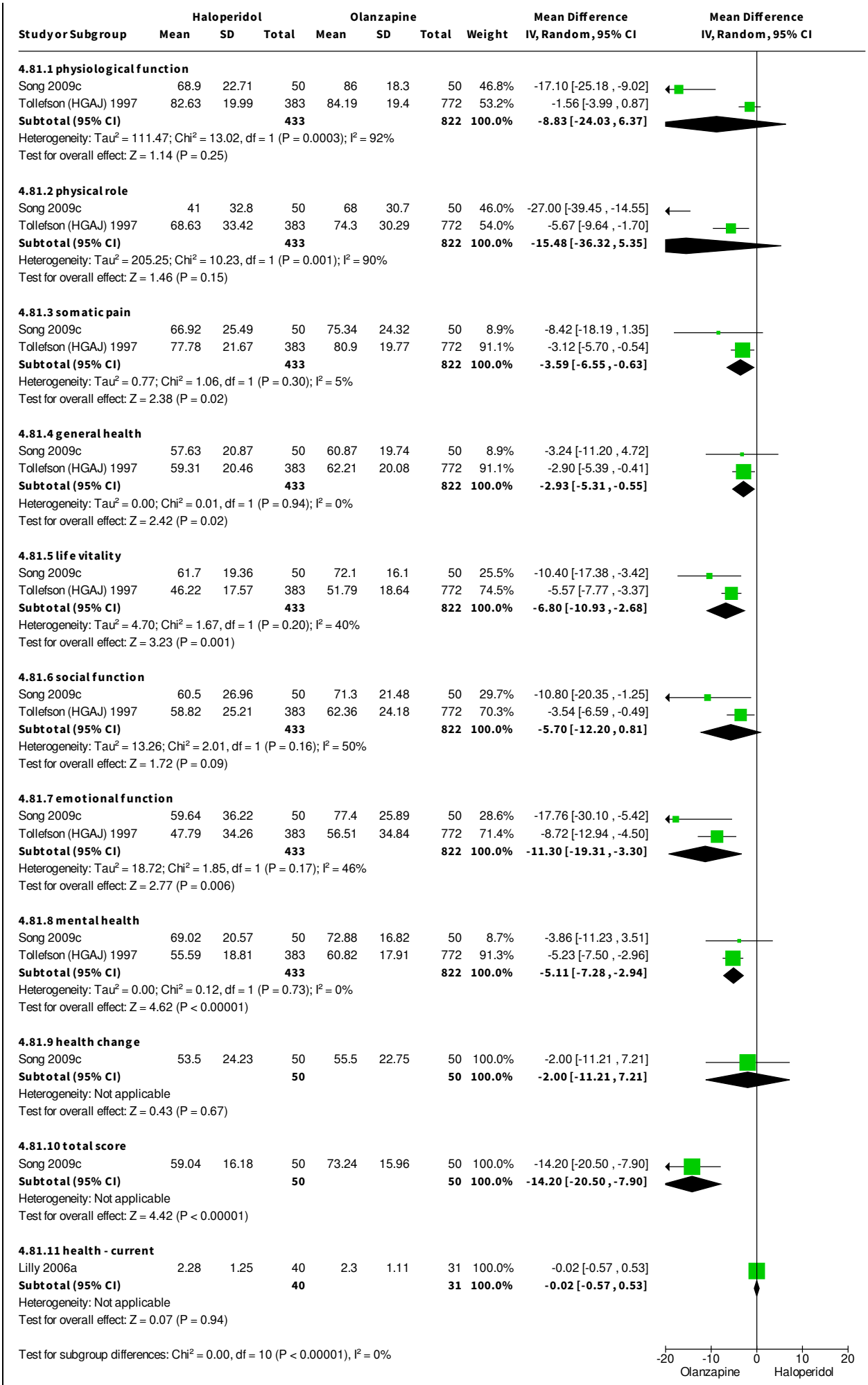
Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 79: Quality of life: 2a. Specific - average endpoint score - short term (QLS-Heinrich&Carpenter, high=good)

Analysis 4.80



Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 80: Quality of life: 2b. Specific - average endpoint score - short term (WHO-QOL-BREF, high=good)

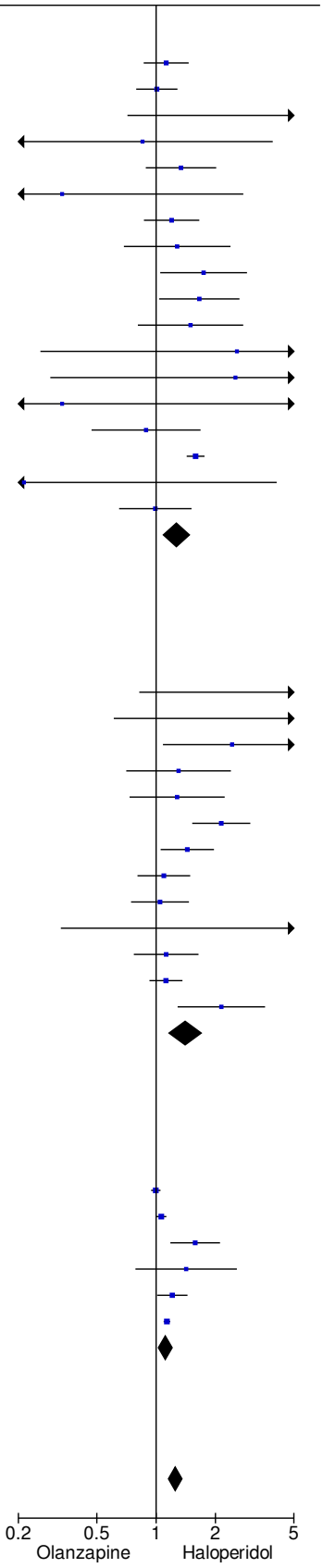
Analysis 4.81



Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 81: Quality of life: 2c. Specific - average endpoint score - short term (SF-36, high=good)

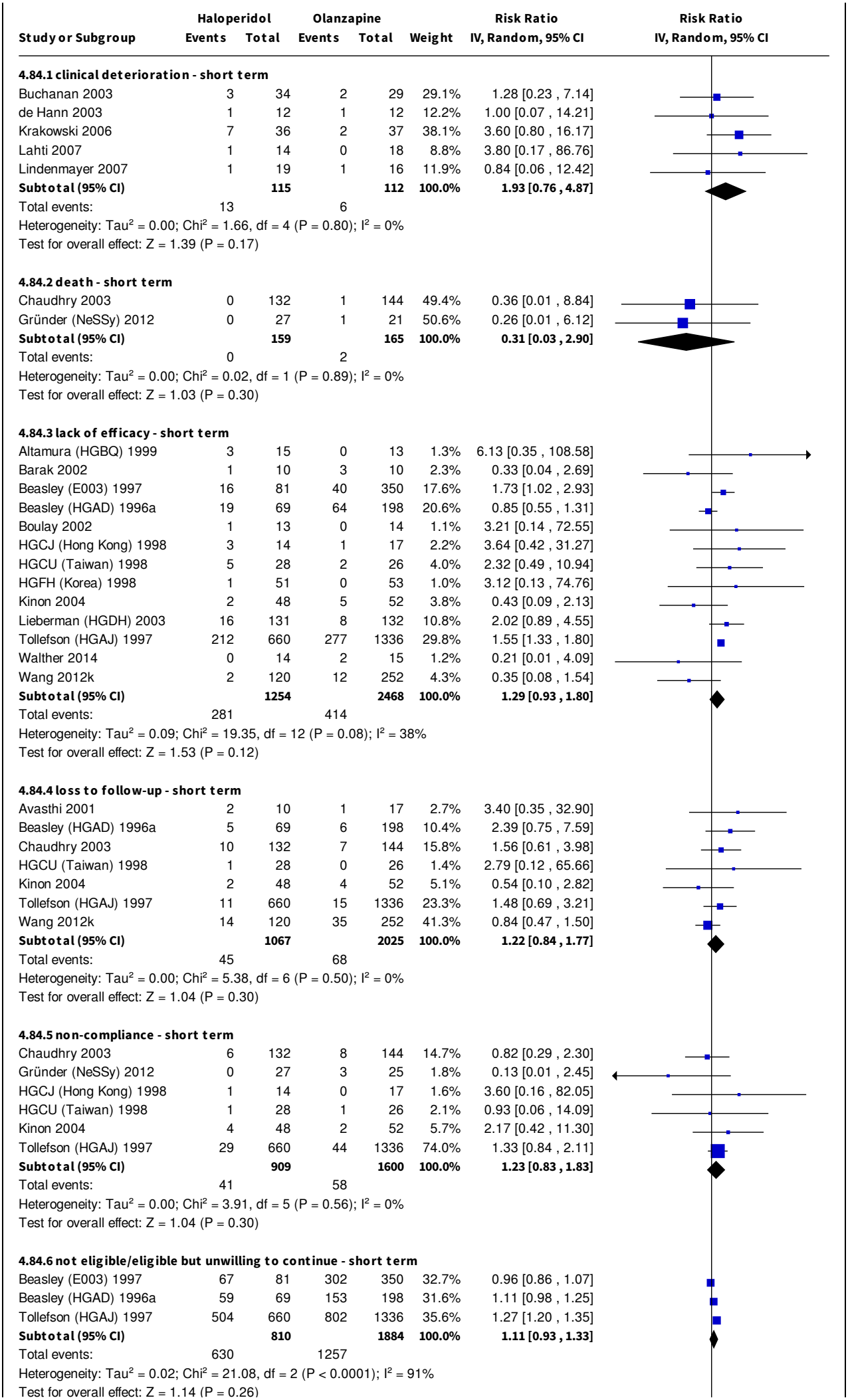
Analysis 4.83

Study or Subgroup	Haloperidol Events	Haloperidol Total	Olanzapine Events	Olanzapine Total	Weight	Risk Ratio IV, Random, 95% CI
4.83.1 short term						
Beasley (E003) 1997	38	81	146	350	4.4%	1.12 [0.86 , 1.46]
Beasley (HGAD) 1996a	39	69	111	198	4.8%	1.01 [0.79 , 1.28]
Boulay 2002	5	13	0	14	0.1%	11.79 [0.72 , 194.19]
Buchanan 2003	3	34	3	29	0.3%	0.85 [0.19 , 3.91]
Chaudhry 2003	38	132	31	144	2.6%	1.34 [0.89 , 2.02]
de Hann 2003	1	12	3	12	0.1%	0.33 [0.04 , 2.77]
Gründer (NeSSy) 2012	22	27	17	25	3.5%	1.20 [0.87 , 1.66]
HGFH (Korea) 1998	16	51	13	53	1.4%	1.28 [0.69 , 2.38]
Ishigooka 2001	30	89	18	93	1.9%	1.74 [1.05 , 2.89]
Kinon 2004	26	48	17	52	2.1%	1.66 [1.04 , 2.65]
Krakowski 2006	16	36	11	37	1.4%	1.49 [0.81 , 2.77]
Lahti 2007	2	14	1	18	0.1%	2.57 [0.26 , 25.56]
Lindenmayer 2007	3	19	1	16	0.1%	2.53 [0.29 , 21.98]
Mousavi 2013	0	10	1	10	0.1%	0.33 [0.02 , 7.32]
Sergi 2007	8	20	18	40	1.3%	0.89 [0.47 , 1.68]
Tollefson (HGAJ) 1997	351	660	448	1336	7.6%	1.59 [1.43 , 1.76]
Walther 2014	0	14	2	15	0.1%	0.21 [0.01 , 4.09]
Wang 2012k	25	120	53	252	2.5%	0.99 [0.65 , 1.51]
Subtotal (95% CI)		**1449**		**2694**	**34.4%**	**1.27 [1.09 , 1.48]**
Total events:	623		894			
Heterogeneity: Tau² = 0.03; Chi² = 29.43, df = 17 (P = 0.03); I² = 42%						
Test for overall effect: Z = 3.04 (P = 0.002)						
4.83.2 medium term						
Altamura (HGBQ) 1999	7	15	0	13	0.1%	13.12 [0.82 , 209.75]
Avasthi 2001	3	10	1	17	0.1%	5.10 [0.61 , 42.66]
HGCJ (Hong Kong) 1998	10	14	5	17	0.9%	2.43 [1.08 , 5.45]
HGCU (Taiwan) 1998	14	28	10	26	1.4%	1.30 [0.71 , 2.40]
Jones 1998 (P022)	14	23	10	21	1.6%	1.28 [0.73 , 2.23]
Kahn (EUFEST) 2005	63	103	30	105	3.3%	2.14 [1.52 , 3.01]
Lieberman (HGDH) 2003	60	131	42	132	3.7%	1.44 [1.05 , 1.97]
Lilly (S029) 2007	52	134	50	141	3.7%	1.09 [0.80 , 1.49]
Lilly 2006a	27	40	20	31	3.3%	1.05 [0.75 , 1.47]
Malyarov 1999	3	18	0	15	0.1%	5.89 [0.33 , 105.81]
Parabiaghi (GiSAS) 2010	36	97	34	103	2.9%	1.12 [0.77 , 1.64]
Rosenheck (HGFI) 2003	91	150	86	159	5.7%	1.12 [0.93 , 1.36]
San 2012	18	21	10	25	1.9%	2.14 [1.29 , 3.57]
Subtotal (95% CI)		**784**		**805**	**28.8%**	**1.40 [1.16 , 1.69]**
Total events:	398		298			
Heterogeneity: Tau² = 0.05; Chi² = 25.61, df = 12 (P = 0.01); I² = 53%						
Test for overall effect: Z = 3.53 (P = 0.0004)						
4.83.3 long term						
Beasley (E003) 1997	77	81	334	350	8.4%	1.00 [0.94 , 1.05]
Beasley (HGAD) 1996a	67	69	181	198	8.3%	1.06 [1.00 , 1.13]
Crespo-Facorro 2006	45	56	28	55	4.0%	1.58 [1.18 , 2.11]
Jones 1998 (P022)	14	23	9	21	1.5%	1.42 [0.79 , 2.57]
Lilly (HGGN) 2000	70	97	95	159	6.1%	1.21 [1.01 , 1.44]
Tollefson (HGAJ) 1997	590	660	1053	1336	8.6%	1.13 [1.09 , 1.18]
Subtotal (95% CI)		**986**		**2119**	**36.8%**	**1.11 [1.03 , 1.21]**
Total events:	863		1700			
Heterogeneity: Tau² = 0.01; Chi² = 23.60, df = 5 (P = 0.0003); I² = 79%						
Test for overall effect: Z = 2.60 (P = 0.009)						
Total (95% CI)		**3219**		**5618**	**100.0%**	**1.25 [1.15 , 1.35]**
Total events:	1884		2892			
Heterogeneity: Tau² = 0.02; Chi² = 119.67, df = 36 (P < 0.00001); I² = 70%						
Test for overall effect: Z = 5.54 (P < 0.00001)						
Test for subgroup differences: Chi² = 6.13, df = 2 (P = 0.05), I² = 67.4%						



Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 83: Leaving the study early: 2. Any reason

Analysis 4.84


Haloperidol
Olanzapine
Risk Ratio
Risk Ratio
Study or Subgroup
Events
Total
Events
Total
Weight
IV, Random, 95% CI
IV, Random, 95% CI
4.84.1 clinical deterioration - short term
Buchanan 2003 3 34 2 29 29.1% 1.28 [0.23 , 7.14]
de Hann 2003 1 12 1 12 12.2% 1.00 [0.07 , 14.21]
Krakowski 2006 7 36 2 37 38.1% 3.60 [0.80 , 16.17]
Lahti 2007 1 14 0 18 8.8% 3.80 [0.17 , 86.76]
Lindenmayer 2007 1 19 1 16 11.9% 0.84 [0.06 , 12.42]
Subtotal (95% CI) 115 112 100.0% 1.93 [0.76 , 4.87]
Total events: 13 6
Heterogeneity: Tau² = 0.00; Chi² = 1.66, df = 4 (P = 0.80); I² = 0%
Test for overall effect: Z = 1.39 (P = 0.17)
4.84.2 death - short term
Chaudhry 2003 0 132 1 144 49.4% 0.36 [0.01 , 8.84]
Gründer (NeSSy) 2012 0 27 1 21 50.6% 0.26 [0.01 , 6.12]
Subtotal (95% CI) 159 165 100.0% 0.31 [0.03 , 2.90]
Total events: 0 2
Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.89); I² = 0%
Test for overall effect: Z = 1.03 (P = 0.30)
4.84.3 lack of efficacy - short term
Altamura (HGBQ) 1999 3 15 0 13 1.3% 6.13 [0.35 , 108.58]
Barak 2002 1 10 3 10 2.3% 0.33 [0.04 , 2.69]
Beasley (E003) 1997 16 81 40 350 17.6% 1.73 [1.02 , 2.93]
Beasley (HGAD) 1996a 19 69 64 198 20.6% 0.85 [0.55 , 1.31]
Boulay 2002 1 13 0 14 1.1% 3.21 [0.14 , 72.55]
HGCJ (Hong Kong) 1998 3 14 1 17 2.2% 3.64 [0.42 , 31.27]
HGCU (Taiwan) 1998 5 28 2 26 4.0% 2.32 [0.49 , 10.94]
HGFH (Korea) 1998 1 51 0 53 1.0% 3.12 [0.13 , 74.76]
Kinon 2004 2 48 5 52 3.8% 0.43 [0.09 , 2.13]
Lieberman (HGDH) 2003 16 131 8 132 10.8% 2.02 [0.89 , 4.55]
Tollefson (HGAJ) 1997 212 660 277 1336 29.8% 1.55 [1.33 , 1.80]
Walther 2014 0 14 2 15 1.2% 0.21 [0.01 , 4.09]
Wang 2012k 2 120 12 252 4.3% 0.35 [0.08 , 1.54]
Subtotal (95% CI) 1254 2468 100.0% 1.29 [0.93 , 1.80]
Total events: 281 414
Heterogeneity: Tau² = 0.09; Chi² = 19.35, df = 12 (P = 0.08); I² = 38%
Test for overall effect: Z = 1.53 (P = 0.12)
4.84.4 loss to follow-up - short term
Avasthi 2001 2 10 1 17 2.7% 3.40 [0.35 , 32.90]
Beasley (HGAD) 1996a 5 69 6 198 10.4% 2.39 [0.75 , 7.59]
Chaudhry 2003 10 132 7 144 15.8% 1.56 [0.61 , 3.98]
HGCU (Taiwan) 1998 1 28 0 26 1.4% 2.79 [0.12 , 65.66]
Kinon 2004 2 48 4 52 5.1% 0.54 [0.10 , 2.82]
Tollefson (HGAJ) 1997 11 660 15 1336 23.3% 1.48 [0.69 , 3.21]
Wang 2012k 14 120 35 252 41.3% 0.84 [0.47 , 1.50]
Subtotal (95% CI) 1067 2025 100.0% 1.22 [0.84 , 1.77]
Total events: 45 68
Heterogeneity: Tau² = 0.00; Chi² = 5.38, df = 6 (P = 0.50); I² = 0%
Test for overall effect: Z = 1.04 (P = 0.30)
4.84.5 non-compliance - short term
Chaudhry 2003 6 132 8 144 14.7% 0.82 [0.29 , 2.30]
Gründer (NeSSy) 2012 0 27 3 25 1.8% 0.13 [0.01 , 2.45]
HGCJ (Hong Kong) 1998 1 14 0 17 1.6% 3.60 [0.16 , 82.05]
HGCU (Taiwan) 1998 1 28 1 26 2.1% 0.93 [0.06 , 14.09]
Kinon 2004 4 48 2 52 5.7% 2.17 [0.42 , 11.30]
Tollefson (HGAJ) 1997 29 660 44 1336 74.0% 1.33 [0.84 , 2.11]
Subtotal (95% CI) 909 1600 100.0% 1.23 [0.83 , 1.83]
Total events: 41 58
Heterogeneity: Tau² = 0.00; Chi² = 3.91, df = 5 (P = 0.56); I² = 0%
Test for overall effect: Z = 1.04 (P = 0.30)
4.84.6 not eligible/eligible but unwilling to continue - short term
Beasley (E003) 1997 67 81 302 350 32.7% 0.96 [0.86 , 1.07]
Beasley (HGAD) 1996a 59 69 153 198 31.6% 1.11 [0.98 , 1.25]
Tollefson (HGAJ) 1997 504 660 802 1336 35.6% 1.27 [1.20 , 1.35]
Subtotal (95% CI) 810 1884 100.0% 1.11 [0.93 , 1.33]
Total events: 630 1257
Heterogeneity: Tau² = 0.02; Chi² = 21.08, df = 2 (P < 0.0001); I² = 91%
Test for overall effect: Z = 1.14 (P = 0.26)

4.84.7 patient's decision - short term

Chaudhry 2003	1	132	0	144	1.2%	3.27 [0.13 , 79.59]
de Hann 2003	0	10	2	12	1.5%	0.24 [0.01 , 4.42]
HGCJ (Hong Kong) 1998	2	14	0	17	1.4%	6.00 [0.31 , 115.56]
HGCU (Taiwan) 1998	2	28	2	26	3.5%	0.93 [0.14 , 6.12]
Kinon 2004	6	48	3	52	7.1%	2.17 [0.57 , 8.19]
Lindenmayer 2007	1	19	0	16	1.3%	2.55 [0.11 , 58.60]
Tollefson (HGAJ) 1997	49	660	48	1336	83.9%	2.07 [1.40 , 3.04]
Subtotal (95% CI)		**911**		**1603**	**100.0%**	**2.00 [1.40 , 2.85]**
Total events:	61		55			

Heterogeneity: Tau² = 0.00; Chi² = 3.36, df = 6 (P = 0.76); I² = 0%

Test for overall effect: Z = 3.83 (P = 0.0001)

4.84.8 physician decision - short term

Chaudhry 2003	3	132	1	144	20.7%	3.27 [0.34 , 31.08]
HGCJ (Hong Kong) 1998	1	14	0	17	10.7%	3.60 [0.16 , 82.05]
HGCU (Taiwan) 1998	3	28	3	26	46.0%	0.93 [0.21 , 4.20]
Kinon 2004	4	48	1	52	22.5%	4.33 [0.50 , 37.42]
Subtotal (95% CI)		**222**		**239**	**100.0%**	**1.97 [0.71 , 5.49]**
Total events:	11		5			

Heterogeneity: Tau² = 0.00; Chi² = 1.81, df = 3 (P = 0.61); I² = 0%

Test for overall effect: Z = 1.30 (P = 0.19)

4.84.9 protocol violation - short term

Beasley (HGAD) 1996a	2	69	10	198	68.2%	0.57 [0.13 , 2.55]
Buchanan 2003	0	34	1	29	15.2%	0.29 [0.01 , 6.76]
Chaudhry 2003	0	132	2	144	16.6%	0.22 [0.01 , 4.50]
Subtotal (95% CI)		**235**		**371**	**100.0%**	**0.44 [0.13 , 1.51]**
Total events:	2		13			

Heterogeneity: Tau² = 0.00; Chi² = 0.40, df = 2 (P = 0.82); I² = 0%

Test for overall effect: Z = 1.31 (P = 0.19)

4.84.10 unspecified - short term

Gründer (NeSSy) 2012	20	27	12	25	100.0%	1.54 [0.97 , 2.46]
Subtotal (95% CI)		**27**		**25**	**100.0%**	**1.54 [0.97 , 2.46]**
Total events:	20		12			

Heterogeneity: Not applicable

Test for overall effect: Z = 1.83 (P = 0.07)

4.84.11 violent behavior - short term

Lindenmayer 2007	1	19	0	16	100.0%	2.55 [0.11 , 58.60]
Subtotal (95% CI)		**19**		**16**	**100.0%**	**2.55 [0.11 , 58.60]**
Total events:	1		0			

Heterogeneity: Not applicable

Test for overall effect: Z = 0.59 (P = 0.56)

4.84.12 withdrawal of informed consent - short term

Gründer (NeSSy) 2012	0	27	1	25	7.8%	0.31 [0.01 , 7.26]
Krakowski 2006	4	36	4	37	45.7%	1.03 [0.28 , 3.80]
Lahti 2007	1	14	1	18	10.9%	1.29 [0.09 , 18.80]
Wang 2012k	3	120	4	252	35.6%	1.57 [0.36 , 6.93]
Subtotal (95% CI)		**197**		**332**	**100.0%**	**1.12 [0.46 , 2.70]**
Total events:	8		10			

Heterogeneity: Tau² = 0.00; Chi² = 0.87, df = 3 (P = 0.83); I² = 0%

Test for overall effect: Z = 0.24 (P = 0.81)

4.84.13 personal conflict - short term

Chaudhry 2003	5	132	7	144	100.0%	0.78 [0.25 , 2.40]
Subtotal (95% CI)		**132**		**144**	**100.0%**	**0.78 [0.25 , 2.40]**
Total events:	5		7			

Heterogeneity: Not applicable

Test for overall effect: Z = 0.44 (P = 0.66)

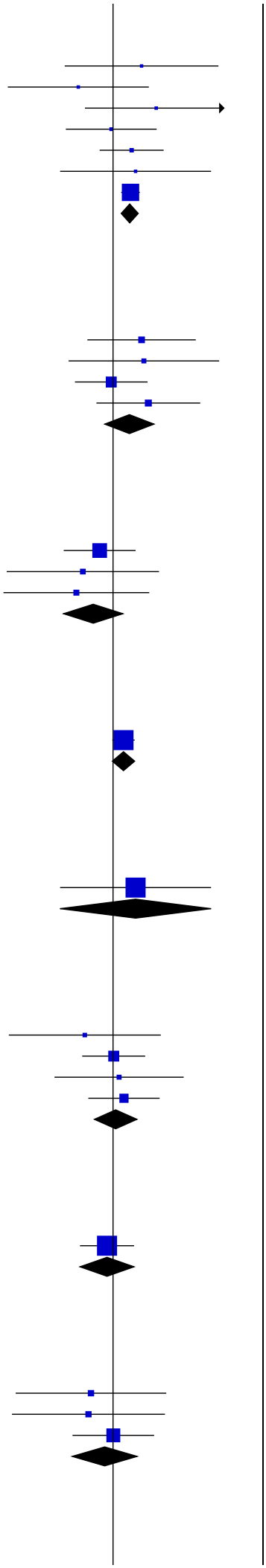
4.84.14 sponsor decision - short term

HGCJ (Hong Kong) 1998	0	14	1	17	18.6%	0.40 [0.02 , 9.12]
Kinon 2004	0	48	1	52	18.0%	0.36 [0.02 , 8.64]
Tollefson (HGAJ) 1997	2	660	4	1336	63.4%	1.01 [0.19 , 5.51]
Subtotal (95% CI)		**722**		**1405**	**100.0%**	**0.71 [0.18 , 2.72]**
Total events:	2		6			

Heterogeneity: Tau² = 0.00; Chi² = 0.47, df = 2 (P = 0.79); I² = 0%

Test for overall effect: Z = 0.50 (P = 0.61)

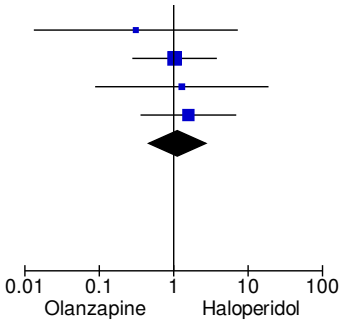
4.84.15 withdrawal of informed consent - short term



Gründer (NeSSy) 2012	0	27	1	25	7.8%	0.31 [0.01 , 7.26]
Krakowski 2006	4	36	4	37	45.7%	1.03 [0.28 , 3.80]
Lahti 2007	1	14	1	18	10.9%	1.29 [0.09 , 18.80]
Wang 2012k	3	120	4	252	35.6%	1.57 [0.36 , 6.93]
Subtotal (95% CI)		**197**		**332**	**100.0%**	**1.12 [0.46 , 2.70]**
Total events:	8		10			

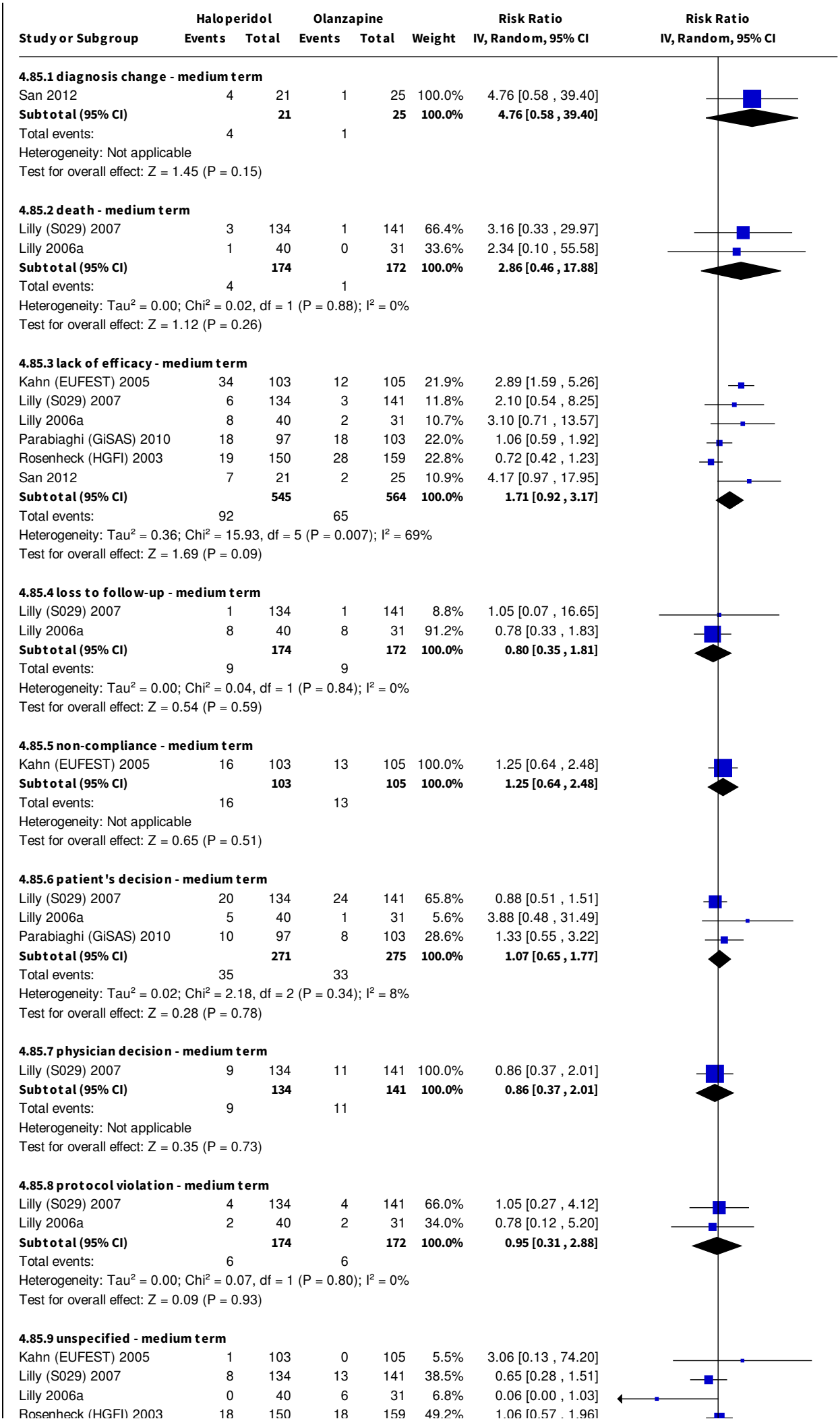
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.87$, df = 3 (P = 0.83); $I^2 = 0\%$

Test for overall effect: Z = 0.24 (P = 0.81)

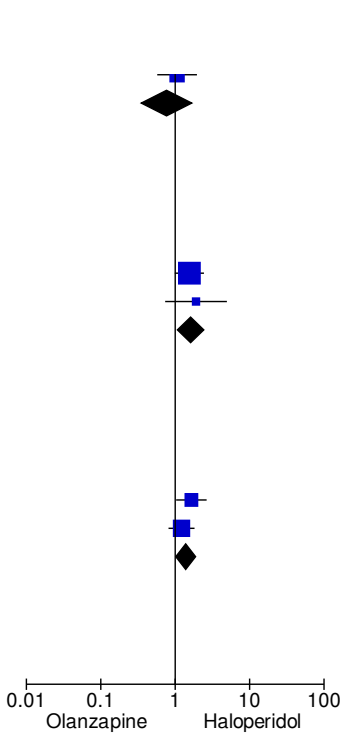


Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 84: Leaving the study early: 3a. Various reasons - short term

Analysis 4.85

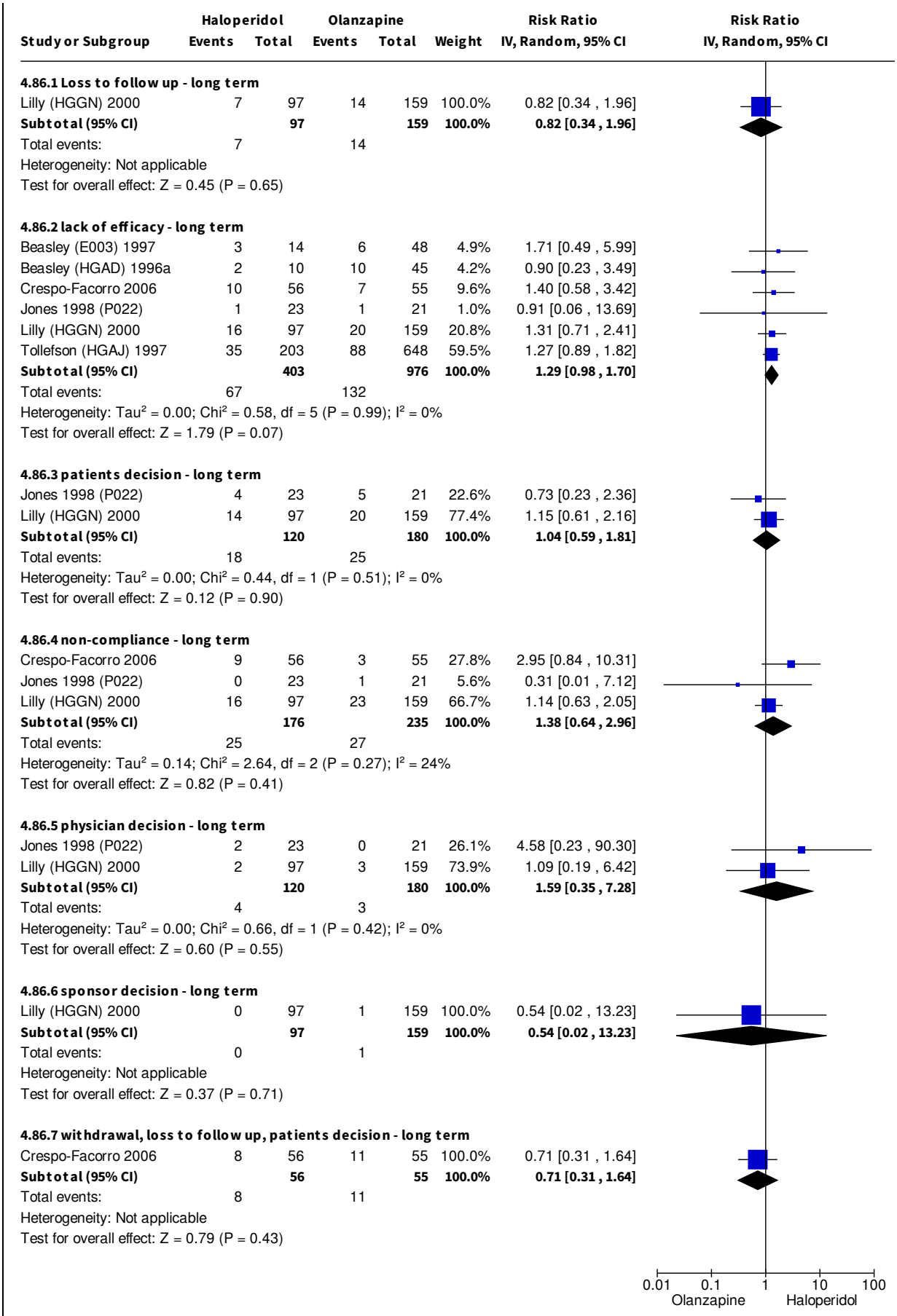

Haloperidol
Olanzapine
Risk Ratio
Risk Ratio
Study or Subgroup
Events Total Events Total Weight IV, Random, 95% CI
IV, Random, 95% CI
4.85.1 diagnosis change - medium term
San 2012 4 21 1 25 100.0% 4.76 [0.58 , 39.40]
Subtotal (95% CI) 21 25 100.0% 4.76 [0.58 , 39.40]
Total events: 4 1
Heterogeneity: Not applicable
Test for overall effect: Z = 1.45 (P = 0.15)
4.85.2 death - medium term
Lilly (S029) 2007 3 134 1 141 66.4% 3.16 [0.33 , 29.97]
Lilly 2006a 1 40 0 31 33.6% 2.34 [0.10 , 55.58]
Subtotal (95% CI) 174 172 100.0% 2.86 [0.46 , 17.88]
Total events: 4 1
Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.88); I² = 0%
Test for overall effect: Z = 1.12 (P = 0.26)
4.85.3 lack of efficacy - medium term
Kahn (EUFEST) 2005 34 103 12 105 21.9% 2.89 [1.59 , 5.26]
Lilly (S029) 2007 6 134 3 141 11.8% 2.10 [0.54 , 8.25]
Lilly 2006a 8 40 2 31 10.7% 3.10 [0.71 , 13.57]
Parabiaghi (GiSAS) 2010 18 97 18 103 22.0% 1.06 [0.59 , 1.92]
Rosenheck (HGFI) 2003 19 150 28 159 22.8% 0.72 [0.42 , 1.23]
San 2012 7 21 2 25 10.9% 4.17 [0.97 , 17.95]
Subtotal (95% CI) 545 564 100.0% 1.71 [0.92 , 3.17]
Total events: 92 65
Heterogeneity: Tau² = 0.36; Chi² = 15.93, df = 5 (P = 0.007); I² = 69%
Test for overall effect: Z = 1.69 (P = 0.09)
4.85.4 loss to follow-up - medium term
Lilly (S029) 2007 1 134 1 141 8.8% 1.05 [0.07 , 16.65]
Lilly 2006a 8 40 8 31 91.2% 0.78 [0.33 , 1.83]
Subtotal (95% CI) 174 172 100.0% 0.80 [0.35 , 1.81]
Total events: 9 9
Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.84); I² = 0%
Test for overall effect: Z = 0.54 (P = 0.59)
4.85.5 non-compliance - medium term
Kahn (EUFEST) 2005 16 103 13 105 100.0% 1.25 [0.64 , 2.48]
Subtotal (95% CI) 103 105 100.0% 1.25 [0.64 , 2.48]
Total events: 16 13
Heterogeneity: Not applicable
Test for overall effect: Z = 0.65 (P = 0.51)
4.85.6 patient's decision - medium term
Lilly (S029) 2007 20 134 24 141 65.8% 0.88 [0.51 , 1.51]
Lilly 2006a 5 40 1 31 5.6% 3.88 [0.48 , 31.49]
Parabiaghi (GiSAS) 2010 10 97 8 103 28.6% 1.33 [0.55 , 3.22]
Subtotal (95% CI) 271 275 100.0% 1.07 [0.65 , 1.77]
Total events: 35 33
Heterogeneity: Tau² = 0.02; Chi² = 2.18, df = 2 (P = 0.34); I² = 8%
Test for overall effect: Z = 0.28 (P = 0.78)
4.85.7 physician decision - medium term
Lilly (S029) 2007 9 134 11 141 100.0% 0.86 [0.37 , 2.01]
Subtotal (95% CI) 134 141 100.0% 0.86 [0.37 , 2.01]
Total events: 9 11
Heterogeneity: Not applicable
Test for overall effect: Z = 0.35 (P = 0.73)
4.85.8 protocol violation - medium term
Lilly (S029) 2007 4 134 4 141 66.0% 1.05 [0.27 , 4.12]
Lilly 2006a 2 40 2 31 34.0% 0.78 [0.12 , 5.20]
Subtotal (95% CI) 174 172 100.0% 0.95 [0.31 , 2.88]
Total events: 6 6
Heterogeneity: Tau² = 0.00; Chi² = 0.07, df = 1 (P = 0.80); I² = 0%
Test for overall effect: Z = 0.09 (P = 0.93)
4.85.9 unspecified - medium term
Kahn (EUFEST) 2005 1 103 0 105 5.5% 3.06 [0.13 , 74.20]
Lilly (S029) 2007 8 134 13 141 38.5% 0.65 [0.28 , 1.51]
Lilly 2006a 0 40 6 31 6.8% 0.06 [0.00 , 1.03]
Rosenheck (HGFI) 2003 18 150 18 159 49.2% 1.06 [0.57 , 1.96]

Subtotal (95% CI)		**427**		**436**	**100.0%**	**0.76 [0.35 , 1.67]**
Total events:	27		37			
Heterogeneity: Tau² = 0.22; Chi² = 4.86, df = 3 (P = 0.18); I² = 38%						
Test for overall effect: Z = 0.68 (P = 0.50)						
4.85.10 withdrawal, loss to follow up, patients decision - medium term						
Kahn (EUFEST) 2005	35	103	23	105	81.8%	1.55 [0.99 , 2.43]
San 2012	8	21	5	25	18.2%	1.90 [0.73 , 4.95]
Subtotal (95% CI)		**124**		**130**	**100.0%**	**1.61 [1.07 , 2.42]**
Total events:	43		28			
Heterogeneity: Tau² = 0.00; Chi² = 0.15, df = 1 (P = 0.70); I² = 0%						
Test for overall effect: Z = 2.29 (P = 0.02)						
4.85.11 withdrawal of informed consent - medium term						
Kahn (EUFEST) 2005	34	103	21	105	42.1%	1.65 [1.03 , 2.64]
Rosenheck (HGFI) 2003	39	150	34	159	57.9%	1.22 [0.81 , 1.82]
Subtotal (95% CI)		**253**		**264**	**100.0%**	**1.38 [1.02 , 1.88]**
Total events:	73		55			
Heterogeneity: Tau² = 0.00; Chi² = 0.93, df = 1 (P = 0.33); I² = 0%						
Test for overall effect: Z = 2.08 (P = 0.04)						



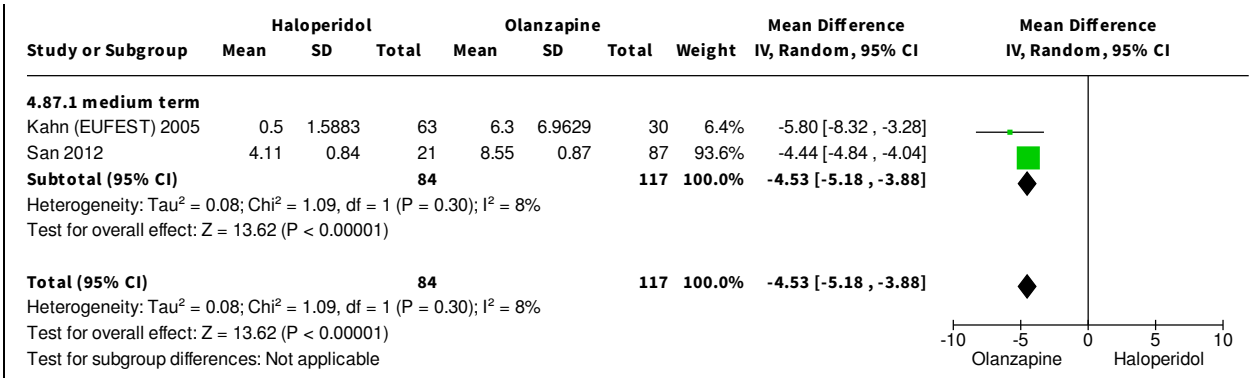
Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 85: Leaving the study early: 3b. Various reasons - medium term

Analysis 4.86



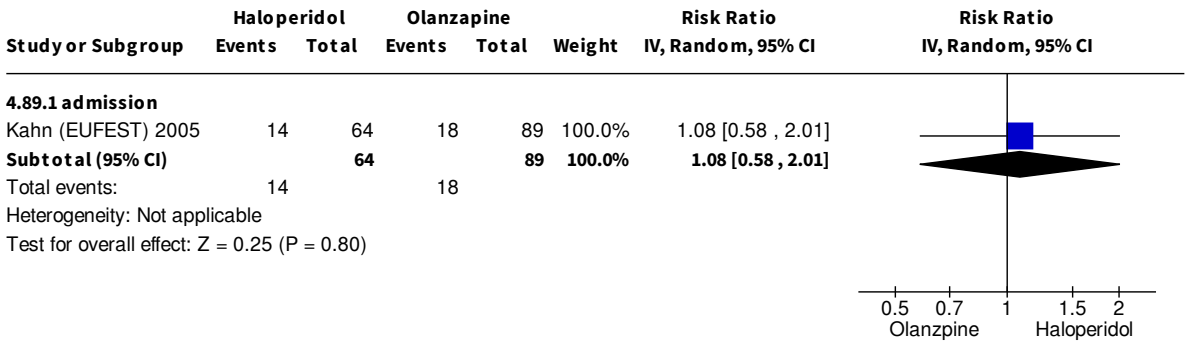
Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 86: Leaving the study early: 3c. Various reasons - long term

Analysis 4.87



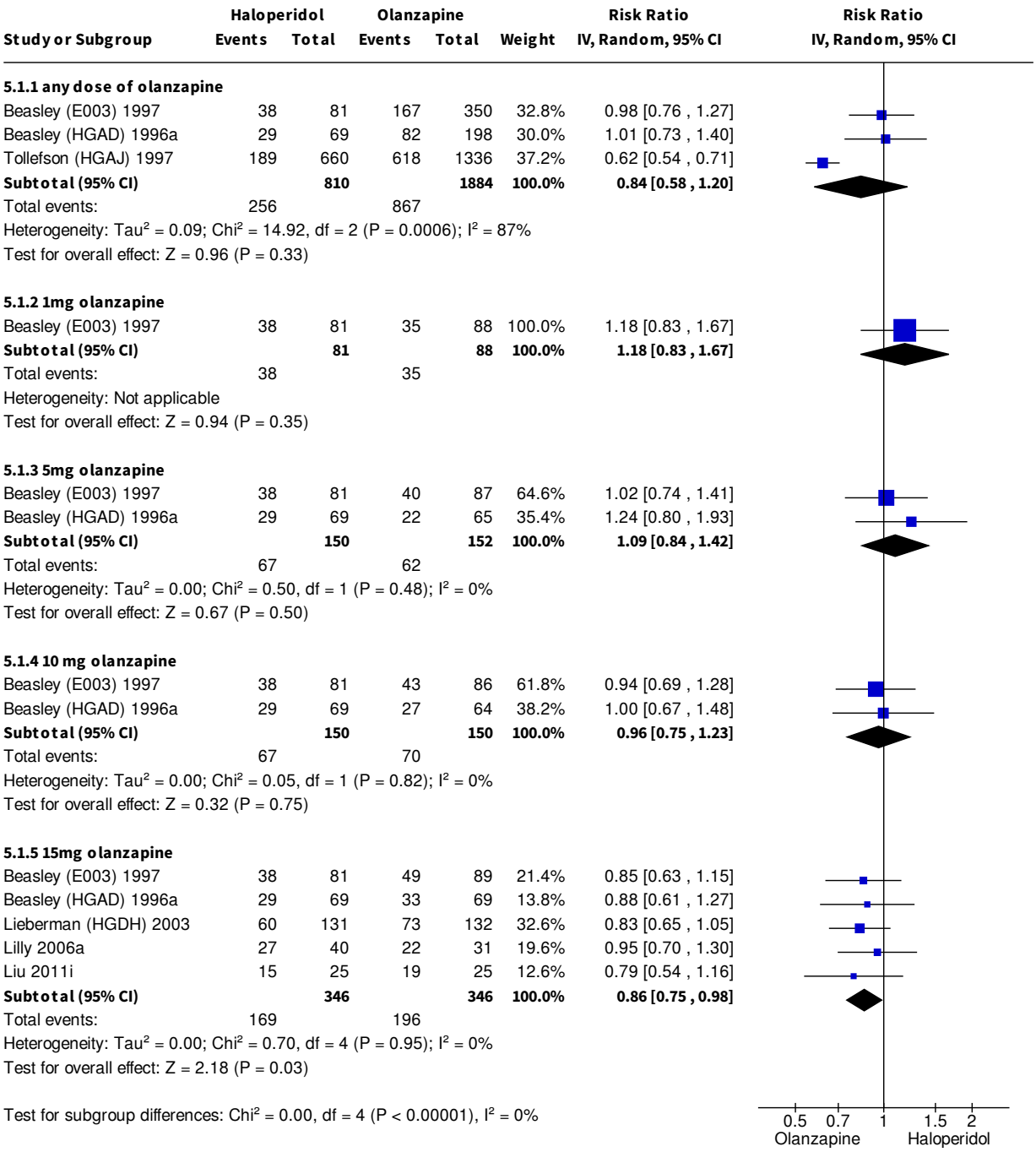
Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 87: Leaving study early: 4a. Average time until discontinuation - medium term (months)

Analysis 4.89



Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 89: Service use: 1a. Admission to hospital after randomisation

Analysis 5.1



Comparison 5: COMPARISON HALOPERIDOL vs OLANZAPINE: OLANZAPINE DOSE STUDY, Outcome 1: Global state: Clinically important (short term)

Analysis 4.2

Global state: 1b. Average endpoint score (CGI-S, high=poor, skewed data)				
Study	**Intervention**	**Mean**	**SD**	**N**
Avasthi 2001	Haloperidol	2.86	1.57	7
	Olanzapine	3.19	0.98	16
Kahn (EUFEST) 2005	Haloperidol	3.0	3.05	103
	Olanzapine	2.4	3.07	105
Lilly 2006a	Haloperidol	3.49	1.77	40
	Olanzapine	2.96	1.68	31

Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 2: Global state: 1b. Average endpoint score (CGI-S, high=poor, skewed data)

Analysis 4.10

Mental state: 2c. Overall - average endpoint score (BPRS total, high=poor, skewed data)				
Study	**Intervention**	**Mean**	**SD**	**N**
Avasthi 2001	Haloperidol	12.57	13.39	7
	Olanzapine	9.5	7.06	16
Beasley (E003) 1997	Haloperidol	28.78	15.41	79
	Olanzapine	25.95	16.2	85
Beasley (HGAD) 1996a	Haloperidol	28.99	15.86	68
	Olanzapine	27.43	17.28	65

HGCJ (Hong Kong) 1998	Haloperidol	26.86	13.71	14
	Olanzapine	12.75	8.81	16
HGCU (Taiwan) 1998	Haloperidol	20.32	12.21	28
	Olanzapine	15.83	11.33	24
Lilly 2006a	Haloperidol	26.83	14.04	40
	Olanzapine	13.06	4.8	31
Tollefson (HGAJ) 1997	Haloperidol	26.16	13.34	636
	Olanzapine	22.16	13.36	1312

Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 10: Mental state: 2c. Overall - average endpoint score (BPRS total, high=poor, skewed data)

Analysis 4.12

Mental state: 3b. Overall - average change score - short term (PANSS total, high=poor, skewed data)				
Study	**Intervention**	**mean**	**SD**	**N**
Krakowski 2006	Haloperidol	0.58	15.2	36
	Olanzapine	4.83	9.7	37

Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 12: Mental state: 3b. Overall - average change score - short term (PANSS total, high=poor, skewed data)

Analysis 4.14

Mental state: 4b. Specific - average endpoint score - depression (MADRS, high=poor, skewed data)				
Study	**Intervention**	**Mean**	**SD**	**N**
short term				
Avasthi 2001	Haloperidol	5.00	4.58	7
	Olanzapine	3.00	2.42	16
HGCJ (Hong Kong) 1998	Haloperidol	12.29	10.56	14
	Olanzapine	4.06	4.39	16
HGCU (Taiwan) 1998	Haloperidol	4.79	5.14	28
	Olanzapine	3.67	5.43	24
Lieberman (HGDH) 2003	Haloperidol	8.38	8.21	126
	Olanzapine	6.95	7.01	125
Tollefson (HGAJ) 1997	Haloperidol	13.64	9.82	428
	Olanzapine	10.65	8.3	1053
de Hann 2003	Haloperidol	7.91	5.39	9
	Olanzapine	10.56	9.81	11
long term change score				
Lilly (HGGN) 2000	Haloperidol	-1.7	7.9	92
	Olanzapine	-2.9	8.3	153

Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 14: Mental state: 4b. Specific - average endpoint score - depression (MADRS, high=poor, skewed data)

Analysis 4.15

Mental state: 4c. Specific - average endpoint score - aggression - short term (MOAS, high=poor, skewed data)				
Study	**Intervention**	**Mean**	**SE**	**N**
Total score				
Krakowski 2006	Haloperidol	40.9	24	3-48
	Olanzapine	32.7	29	6-51
Mean change total score				
Krakowski 2006	Haloperidol	38.2	50.7	34
	Olanzapine	33.3	32.2	36
Change in Physical agression score				
Krakowski 2006	Haloperidol	141.9	0.20	28
	Olanzapine	-13.4	0.06	31
Physical aggression score				
Krakowski 2006	Haloperidol	20.7	6	0-20
	Olanzapine	14.1	12	0-20
Aggression against property				
Krakowski 2006	Haloperidol	4.7	0	0-6
	Olanzapine	2.7	0	0-4
Verbal aggression score				
Krakowski 2006	Haloperidol	15.6	7.5	2-25
	Olanzapine	16.0	11	4-23

Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 15: Mental state: 4c. Specific - average endpoint score - aggression - short term (MOAS, high=poor, skewed data)

Analysis 4.16

Mental state: 4d. Specific - average endpoint score - depression (various scales, high=poor, skewed data)				
Study	**Intervention**	**Mean**	**SD**	**N**
medium term (CDSS)				
Crespo-Facorro 2006	Haloperidol	0.9	1.9	24
	Olanzapine	0.7	2.0	37
Kahn (EUFEST) 2005	Haloperidol	1.9	2.03	103
	Olanzapine	1.8	2.05	105

long term (CDSS)				
Crespo-Facorro 2006	Haloperidol	1.29	2.89	28
	Olanzapine	0.55	1.54	23
short term (HAM-DRS)				
Buchanan 2003	Haloperidol	9.8	8.2	34
	Olanzapine	9.4	6.2	29
Lindenmayer 2007	Haloperidol	5.74	4.0	19
	Olanzapine	4.50	3.23	16
medium term (HAM-DRS)				
Crespo-Facorro 2006	Haloperidol	4.8	4.4	24
	Olanzapine	3.9	5.5	37

Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 16: Mental state: 4d. Specific - average endpoint score - depression (various scales, high=poor, skewed data)

Analysis 4.21

Mental state: 5e. Specific - negative symptoms - average endpoint score (various scales, high=poor, skewed data)

Study	Intervention	Mean	SD	N
BPRS - short term				
Beasley (E003) 1997	Haloperidol	6.23	2.97	79
	Olanzapine	5.26	3.27	85
Beasley (HGAD) 1996a	Haloperidol	4.87	3.44	68
	Olanzapine	4.42	3.56	65
Tollefson (HGAJ) 1997	Haloperidol	5.55	3.22	636
	Olanzapine	4.62	3.0	1312
PANSS-N - short term				
Avasthi 2001	Haloperidol	16.86	8.71	7
	Olanzapine	15.62	7.93	16
SANS - short term				
Avasthi 2001	Haloperidol	27.43	19.48	7
	Olanzapine	21.87	19.47	16
Beasley (HGAD) 1996a	Haloperidol	11.22	4.8	68
	Olanzapine	9.32	5.39	65
SANS - medium term				
Crespo-Facorro 2006	Haloperidol	4.8	5.3	24
	Olanzapine	3.5	3.8	37
SANS - long term				
Crespo-Facorro 2006	Haloperidol	4.39	4.47	28
	Olanzapine	4.31	4.96	23

Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 21: Mental state: 5e. Specific - negative symptoms - average endpoint score (various scales, high=poor, skewed data)

Analysis 4.22

Mental state: 5f. Specific - negative symptoms - average change scores - long term (PANSS-N, high=poor, skewed data)

Study	Intervention	mean	SD	N
Lilly (HGGN) 2000	Haloperidol	-1.5	4.8	94
	Olanzapine	-2.5	5.3	153

Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 22: Mental state: 5f. Specific - negative symptoms - average change scores - long term (PANSS-N, high=poor, skewed data)

Analysis 4.26

Mental state: 6d. Specific - positive symptoms - average endpoint score (various scales, high=poor, skewed data)

Study	Interventions	Mean	SD	N
short term (BPRS)				
Beasley (E003) 1997	Haloperidol	7.91	4.74	79
	Olanzapine	7.87	4.89	85
Beasley (HGAD) 1996a	Haloperidol	8.59	5.32	68
	Olanzapine	9.12	6.21	65
Buchanan 2003	Haloperidol	10.1	5.3	34
	Olanzapine	9.8	5.3	29
Tollefson (HGAJ) 1997	Haloperidol	7.61	4.54	636
	Olanzapine	6.83	4.66	1312
short term (PANSS-P)				
Avasthi 2001	Haloperidol	10.86	8.49	7
	Olanzapine	11.44	4.11	16
Barak 2002	Haloperidol	17.3	6.1	10
	Olanzapine	15.4	7.8	10
medium term (SAPS)				
Crespo-Facorro 2006	Haloperidol	1.7	2.5	24
	Olanzapine	1.0	2.0	37
long term (SAPS)				
Crespo-Facorro 2006	Haloperidol	1.93	2.93	28
	Olanzapine	3.41	5.36	23

Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 26: Mental state: 6d. Specific - positive symptoms - average endpoint score (various scales, high=poor, skewed data)

Analysis 4.27

Mental state: 6e. Specific - positive symptoms - average change score (PANSS-P, high=poor, skewed data)				
Study	**Intervention**	**Mean**	**SD**	**N**
short term				
Dhar 2010	Haloperidol	-16.5	6.6	20
	Olanzapine	-20.6	13.2	20
Krakowski 2006	Haloperidol	-0.50	5.3	36
	Olanzapine	1.41	3.6	37
long term				
Lilly (HGGN) 2000	Haloperidol	-3.1	5.8	94
	Olanzapine	-4.3	4.9	153

Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 27: Mental state: 6e. Specific - positive symptoms - average change score (PANSS-P, high=poor, skewed data)

Analysis 4.33

Functioning: 1b. General - average endpoint score - medium term (GAF, high=good, skewed data)				
Study	**Interventions**	**Mean**	**SD**	**N**
Kahn (EUFEST) 2005	Haloperidol	64.3	35.52	103
	Olanzapine	68.3	35.86	105

Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 33: Functioning: 1b. General - average endpoint score - medium term (GAF, high=good, skewed data)

Analysis 4.37

Functioning: 2d. Specific - cognition - average change scores - medium term (various domains, high=good, skewed data)				
Study	**Interventions**	**Mean**	**SD**	**N**
Composite score				
Kahn (EUFEST) 2005	Haloperidol	0.36	0.76	52
	Olanzapine	0.46	0.55	74
Global Cognitive Index				
Krakowski 2006	Haloperidol	-0.17	0.49	22
	Olanzapine	0.34	0.72	30
Lindenmayer 2007	Haloperidol	-0.09	0.25	19
	Olanzapine	0.13	0.47	16
Purdue Pegboard Test				
Kahn (EUFEST) 2005	Haloperidol	0.32	0.9	59
	Olanzapine	0.25	0.76	81
Rey Auditory Verbal Learning Test				
Kahn (EUFEST) 2005	Haloperidol	0.38	0.87	56
	Olanzapine	0.51	0.68	58
Trail Making Test part A				
Kahn (EUFEST) 2005	Haloperidol	0.23	0.82	59
	Olanzapine	0.28	0.73	81
Trail Making Test part B				
Kahn (EUFEST) 2005	Haloperidol	0.13	0.42	55
	Olanzapine	0.33	0.6	81
WAIS III digit symbol				
Kahn (EUFEST) 2005	Haloperidol	0.22	0.8	58
	Olanzapine	0.39	0.71	80

Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 37: Functioning: 2d. Specific - cognition - average change scores - medium term (various domains, high=good, skewed data)

Analysis 4.48

Adverse effects/events: 3g. Specific - extrapyramidal - average endpoint score (BAS, high=poor, skewed data)				
Study	**Intervention**	**Mean**	**SD**	**N**
akathisia - short term				
Avasthi 2001	Haloperidol	0.29	0.49	7
	Olanzapine	0.0	0.0	16
Beasley (E003) 1997	Haloperidol	0.91	1.24	79
	Olanzapine	0.38	0.79	85
Beasley (HGAD) 1996a	Haloperidol	0.87	1.12	68
	Olanzapine	0.42	0.66	65
Bernardo (HGDD) 2001	Haloperidol	0.8	1.0	13
	Olanzapine	0.4	1.1	14
total score - medium term				
Crespo-Facorro 2006	Haloperidol	0.58	1.02	24
	Olanzapine	0.0	0.0	37
total score - long term				
Crespo-Facorro 2006	Haloperidol	0.25	0.7	28
	Olanzapine	0.0	0.0	23
total - endpoint change score- long term				

Lilly (HGGN) 2000	Haloperidol	0.41	1.26	93
	Olanzapine	-0.18	0.92	153

Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 48: Adverse effects/events: 3g. Specific - extrapyramidal - average endpoint score (BAS, high=poor, skewed data)

Analysis 4.49

Adverse effects/events: 3h. Specific - extrapyramidal - average endpoint score (SAS, high=poor, skewed data)				
Study	**Intervention**	**Mean**	**SD**	**N**
parkinsonism - short term				
Avasthi 2001	Haloperidol	0.86	1.86	7
	Olanzapine	0.75	1.39	16
Beasley (E003) 1997	Haloperidol	5.59	7.93	79
	Olanzapine	1.8	3.10	85
Beasley (HGAD) 1996a	Haloperidol	3.34	4.39	67
	Olanzapine	1.35	2.44	63
Bernardo (HGDD) 2001	Haloperidol	4.5	3.4	13
	Olanzapine	0.2	1.7	14
total - short term				
Buchanan 2003	Haloperidol	3.1	3.6	33
	Olanzapine	1.5	1.9	29
Lindenmayer 2007	Haloperidol	0.89	1.15	19
	Olanzapine	1	1.37	16
Taraskina 2017	Haloperidol	6.6	4.37	30
	Olanzapine	0.85	1.5	30
total - medium term				
Crespo-Facorro 2006	Haloperidol	0.75	1.59	24
	Olanzapine	0.24	0.76	37
Lilly (S029) 2007	Haloperidol	2.4	3.6	119
	Olanzapine	1.9	3.6	126
total - long term				
Crespo-Facorro 2006	Haloperidol	0.68	1.12	28
	Olanzapine	0.48	1.41	23
total- endpoint change- long term				
Lilly (HGGN) 2000	Haloperidol	-0.22	3.65	94
	Olanzapine	-0.73	2.92	153

Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 49: Adverse effects/events: 3h. Specific - extrapyramidal - average endpoint score (SAS, high=poor, skewed data)

Analysis 4.50

Adverse effects/events: 3i. Specific - extrapyramidal - average endpoint score - short term (AIMS, high=poor, skewed data)				
Study	**Intervention**	**Mean**	**SD**	**N**
dyskinesia				
Beasley (E003) 1997	Haloperidol	1.90	3.64	78
	Olanzapine	1.38	2.8	85
Beasley (HGAD) 1996a	Haloperidol	2.49	3.93	68
	Olanzapine	2.09	3.53	65
total				
Lindenmayer 2007	Haloperidol	0.53	1.47	19
	Olanzapine	0.94	2.57	16
AIMS total - endpoint change - long term				
Lilly (HGGN) 2000	Haloperidol	1.13	4.36	93
	Olanzapine	0.09	2.91	152

Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 50: Adverse effects/events: 3i. Specific - extrapyramidal - average endpoint score - short term (AIMS, high=poor, skewed data)

Analysis 4.51

Adverse effects/events: 3j. Specific - extrapyramidal - average endpoint score - short term (DIEPSS, high=poor, skewed data)				
Study	**Intervention**	**Mean**	**SD**	**N**
akathisia				
Ishigooka 2001	Haloperidol	0.50	0.9	80
	Olanzapine	0.20	0.5	81
dyskinesia				
Ishigooka 2001	Haloperidol	0.20	0.50	80
	Olanzapine	0.10	0.40	81
dystonia				
Ishigooka 2001	Haloperidol	0.10	0.40	80
	Olanzapine	0.10	0.30	81
overall severity				
Ishigooka 2001	Haloperidol	1.00	0.90	80
	Olanzapine	0.70	0.70	81
parkinsonism				
Ishigooka 2001	Haloperidol	2.60	3.30	80
	Olanzapine	1.70	2.50	81
total score				

Ishigooka 2001	Haloperidol	3.3	3.9	80
	Olanzapine	2.0	3.0	81

Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 51: Adverse effects/events: 3j. Specific - extrapyramidal - average endpoint score - short term (DIEPSS, high=poor, skewed data)

Analysis 4.52

Adverse effects/events: 3k. Specific - extrapyramidal - average endpoint score (ESRS, high score=poor, skewed data)				
Study	**Intervention**	**Mean**	**SD**	**N**
ESRS total - short term				
Taraskina 2017	Haloperidol	22.6	14.9	30
	Olanzapine	3.2	5.2	30
parkinsonism - short term				
Boulay 2002	Haloperidol	6.80	6.73	13
	Olanzapine	7.79	7.75	14
Dhar 2010	Haloperidol	2.4	2.3	20
	Olanzapine	0.8	2.5	20
parkinsonism, dyskinesia, dystonia (subjective) - short term				
Dhar 2010	Haloperidol	2.0	1.7	20
	Olanzapine	0.4	1.4	20
parkinsonism - long term				
Jones 1998 (P022)	Haloperidol	2.57	2.61	23
	Olanzapine	1.19	1.86	21

Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 52: Adverse effects/events: 3k. Specific - extrapyramidal - average endpoint score (ESRS, high score=poor, skewed data)

Analysis 4.58

Adverse effects/events: 4g. Specific - metabolic - weight - waist circumference change data- medium term (high=poor, skewed data)				
Study	**Intervention**	**Mean**	**SD**	**N**
Gründer (NeSSy) 2012	Haloperidol	-0.26	2.84	27
	Olanzapine	1.87	5.61	21

Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 58: Adverse effects/events: 4g. Specific - metabolic - weight - waist circumference change data- medium term (high=poor, skewed data)

Analysis 4.59

Adverse effects/events: 4h. Specific - metabolic - weight - average change various measures (skewed data)				
Study	**Intervention**	**Mean**	**SD**	**N**
BMI - short term				
Gründer (NeSSy) 2012	Haloperidol	0.49	1.56	27
	Olanzapine	0.86	1.72	21
Krakowski 2006	Haloperidol	-0.60	1.4	28
	Olanzapine	1.31	1.6	31
BMI - medium term				
Crespo-Facorro 2006	Haloperidol	3.74	2.6	52
	Olanzapine	3.97	2.79	54
weight gain (kg) - short term				
Krakowski 2006	Haloperidol	-2.0	4.7	28
	Olanzapine	3.59	4.2	31
weight gain (kg) - medium term				
Crespo-Facorro 2006	Haloperidol	10.65	7.66	52
	Olanzapine	11.22	7.99	54
Lilly (S029) 2007	Haloperidol	0.4	6.4	120
	Olanzapine	1.8	6.6	131
Raposo 2011	Haloperidol	5.9	5.5	16
	Olanzapine	7.0	7.7	18
weight gain (kg) - lomg term				
Lilly (HGGN) 2000	Haloperidol	-2.34	4.80	94
	Olanzapine	3.0	7.87	152

Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 59: Adverse effects/events: 4h. Specific - metabolic - weight - average change various measures (skewed data)

Analysis 4.63

Adverse effects/events: 5d. Specific - metabolic - metabolism-related serum levels - average change (high=poor, skewed data)				
Study	**Intervention**	**mean**	**SD**	**N**
cholesterol - short term				
Gründer (NeSSy) 2012	Haloperidol	0.76	0.80	27
	Olanzapine	-0.04	1.16	21
Krakowski 2006	Haloperidol	-6.7	24.6	28
	Olanzapine	-1.2	34.5	31
cholesterol - medium term				
Crespo-Facorro 2006	Haloperidol	19.3	37.3	52
	Olanzapine	23.6	35.1	54
cholesterol - long term				
Lilly (HGGN) 2000	Haloperidol	-3.72	24.41	71

	Olanzapine	8.97	31.41	111
glucose (mg/dl) - short term				
Krakowski 2006	Haloperidol	-0.8	7.18	26
	Olanzapine	-0.1	18.8	29
glucose (mg/dl) - medium term				
Crespo-Facorro 2006	Haloperidol	3.3	11.8	52
	Olanzapine	2.7	16.2	54
glucose (mg/dl) - long term				
Lilly (HGGN) 2000	Haloperidol	0.6	57.26	71
	Olanzapine	40.44	51.46	111
HDL - medium term				
Crespo-Facorro 2006	Haloperidol	-2.2	10.8	52
	Olanzapine	-2.6	12	54
Gründer (NeSSy) 2012	Haloperidol	0.12	0.37	27
	Olanzapine	0.05	0.21	21
insulin (mU/ml) - medium term				
Crespo-Facorro 2006	Haloperidol	3.0	6.4	52
	Olanzapine	3.4	16.6	54
LDL - medium term				
Crespo-Facorro 2006	Haloperidol	14.4	25.4	52
	Olanzapine	15.7	28.3	54
Gründer (NeSSy) 2012	Haloperidol	0.52	0.93	27
	Olanzapine	0.13	1.02	21
triglyceride - short term				
Gründer (NeSSy) 2012	Haloperidol	0.05	0.86	27
	Olanzapine	-0.26	0.89	21
Krakowski 2006	Haloperidol	-6.8	65.7	28
	Olanzapine	10.7	56.2	30
triglyceride - medium term				
Crespo-Facorro 2006	Haloperidol	40.3	70.1	52
	Olanzapine	28.9	56.8	54
triglyceride - long term				
Lilly (HGGN) 2000	Haloperidol	-22.27	117.38	40
	Olanzapine	31.58	131.61	96
prolactine - long term				
Lilly (HGGN) 2000	Haloperidol	-2.37	25.89	81
	Olanzapine	-9.73	23.15	136

Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 63: Adverse effects/events: 5d. Specific - metabolic - metabolism-related serum levels - average change (high=poor, skewed data)

Analysis 4.76

Adverse effects/events: 11. Specific - renal - average creatinine change - short term (skewed data)				
Study	**Intervention**	**Mean**	**SD**	**N**
Gründer (NeSSy) 2012	Haloperidol	6.41	6.79	27
	Olanzapine	-0.65	9.20	21

Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 76: Adverse effects/events: 11. Specific - renal - average creatinine change - short term (skewed data)

Analysis 4.82

Quality of life: 2d. Specific - average endpoint score - short term (QLS total, high score=good, skewed data)				
Study	**Intervention**	**Mean**	**SD**	**N**
Avasthi 2001	Haloperidol	49.14	33.88	7
	Olanzapine	51.19	23.38	16

Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 82: Quality of life: 2d. Specific - average endpoint score - short term (QLS total, high score=good, skewed data)

Analysis 4.88

Leaving study early: 4b. Average time until discontinuation - long term (months, skewed data)				
Study	**Intervention**	**Mean**	**SD**	**N**
Crespo-Facorro 2006	Haloperidol	15.4	13.44	56
	Olanzapine	23.8	13.68	55

Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 88: Leaving study early: 4b. Average time until discontinuation - long term (months, skewed data)

Analysis 4.90

Service use: 1b. Hospitalisation (skewed data)				
Study	**Intervention**	**median**	**SD**	**N**
prior psychiatric hospitalisation (number of patients)				
Krakowski 2006	Haloperidol	8.5	4.4	28
	Olanzapine	12.1	10.1	31
median length of hospitalisation				
Krakowski 2006	Haloperidol	36	no data	28
	Olanzapine	48	no data	31

Comparison 4: COMPARISON HALOPERIDOL vs OLANZAPINE: SECONDARY OUTCOMES, Outcome 90: Service use: 1b. Hospitalisation (skewed data)