

Comparative Outcomes of Commonly Used Off-Label Atypical Antipsychotics in the Treatment of Dementia-Related Psychosis: A Network Meta-analysis

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Supplementary Table 1. Study and Patient characteristics

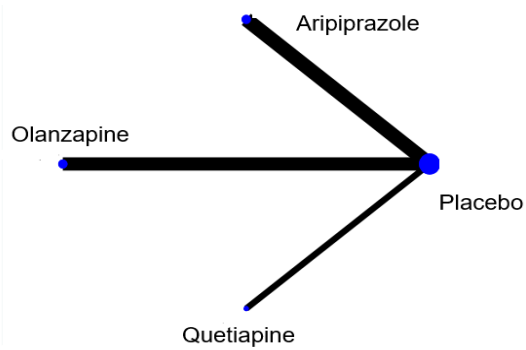
Study Name	Study design	Population	N	Study Period (weeks)	Age Mean age (\pm SD)	Study Setting	Comparison
Ballard, 2005	RCT (double blind)	AD, dementia, and clinically significant agitation.	93	26	83.8 \pm 7.7	NH	Quetiapine vs. Placebo
Brody, 2003	RCT (double blind)	Elderly patients with a DSM-IV diagnosis of dementia of the AD, vascular dementia, or a combination of the 2 (i.e., mixed dementia) and significant aggressive behaviors	309	12	83 \pm 10	NH	Risperidone vs. Placebo
De Deyn, 2004	RCT (double blind)	Psychotic AD dementia patients with or without behavioral disturbances	652	10	76.6 \pm 10.4	NH	Olanzapine vs. Placebo
De Deyn, 2005	RCT (double blind)	AD patients with psychosis	208	10	81.5	Assisted living facilities or adult communities, or with a caregiver	Aripiprazole vs. Placebo
Deberdt, 2005	RCT (double blind)	Patients with dementia-related psychosis	494	10	78.6 \pm 7.3	NH or assisted living centers	Risperidone/ Olanzapine vs. Placebo
Devanand (ADAD trial), 2011	Randomized open label	Patients with AD and psychosis or agitation–aggression who responded to risperidone therapy for 16 weeks	110	48	79.6 \pm 7.6	Memory and geriatric psychiatry clinics	Risperidone vs. Placebo
Ellingrod, 2002	Observational study	Elderly patients with dementia and psychosis	19	8	84 \pm 3.17	NH	Risperidone/ Olanzapine vs. Placebo
Gareri, 2004	RCT (double blind)	AD/ VaD patients with behavioral and psychological symptoms	60	8	76.6 \pm 6	NA	Risperidone/ Olanzapine vs. Promazine
Grossberg (Study 1), 2019	RCT (double blind)	AD with symptoms of agitation and aggression	433	12	73.8 \pm 8.7	Care facility or community-based setting	Brexpiprazole vs. Placebo
Grossberg (Study 2), 2019	RCT (double blind)	AD with symptoms of agitation and aggression	270	12	73.7 \pm 8.2	Care facility or community-based setting	Brexpiprazole vs. Placebo
Katz, 1999	RCT (double blind)	AD, VaD, Mixed dementia	625	12	82.7 \pm 7.7	NH	Risperidone vs. Placebo
Kurlan, 2007	RCT (double blind)	Probable AD with psychosis/agitation and extrapyramidal symptoms	40	10	73.8 \pm 5.9	NH or own residence	Quetiapine vs. Placebo

Mintzer, 2007	RCT (double blind)	Institutionalized patients with psychosis associated with AD	487	10	82.7	NH or residential assisted-living facilities	Aripiprazole vs. Placebo
Mintzer, 2006	RCT (double blind)	Nursing home residents diagnosed with AD and psychosis	473	8	83.3 ± 7.3	NH	Risperidone vs. Placebo
Mulsant, 2004	RCT (double blind)	Probable AD, VaD, or mixed	86	6		NH	Risperidone vs. Olanzapine
Paleacu, 2008	RCT (double blind)	AD patients with psycho behavioral symptoms	40	6	82.2 ± 6.4	NA	Quetiapine vs. Placebo
Rainer, 2007	RCT (Rater-blinded)	Elderly patients with dementia and neurobehavioral symptoms	72	8	77.7 ± 5.90	Outpatient clinic	Risperidone vs. Quetiapine
Street, 2000	RCT (double blind)	AD patients who exhibited psychotic and/or behavioral symptoms	206	6	82.9 ± 6.5	NH	Olanzapine vs. Placebo
Streim, 2008	RCT (double blind)	Institutionalized subjects with AD and psychotic symptoms	256	10	83 (59 - 96)	NH	Aripiprazole vs. Placebo
Sultzer (CATIE-AD), 2008	RCT (double blind)	AD and psychosis or agitated/aggressive behavior	421	36	77.9 ± 7.5	Outpatient living at home or in an assisted living facility	Olanzapine vs. Placebo, Quetiapine vs. Placebo, Risperidone vs. Placebo
Tariot, 2006	RCT (double blind)	Probable/possible AD with psychosis	284	10	83.2	NH	Quetiapine vs. Placebo
Zhong, 2007	RCT (double blind)	Probable or possible AD or VaD with agitation	333	10	83.2 ± 7.2	NH and assisted living facilities	Quetiapine vs. Placebo

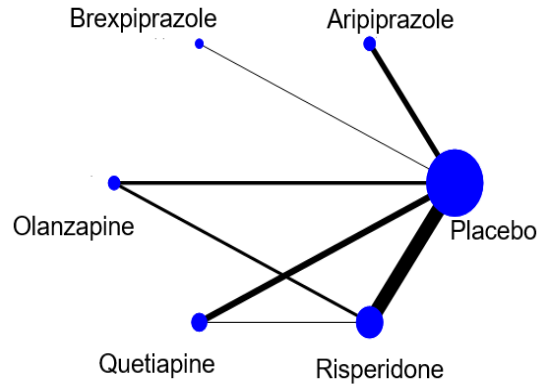
Abbreviation: SD (Standard deviation); RCT (Randomized controlled trial); AD (Alzheimer disease); VaD (Vascular dementia); DSM (Diagnostic and Statistical Manual of Mental Disorders); NH (Nursing home); NA (Not Applicable)

Supplementary Figure 1. Network diagram for efficacy and primary safety outcomes

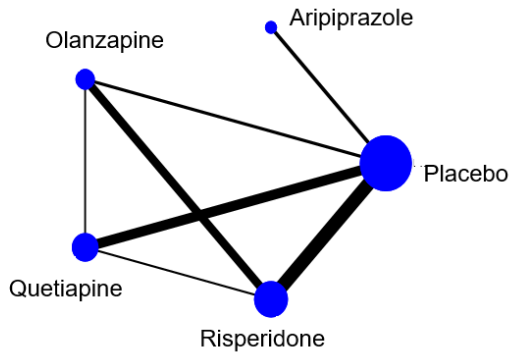
a. NPI-NH Psychosis subscale



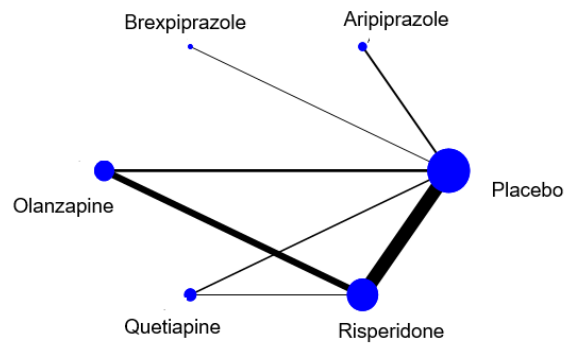
b. Mortality



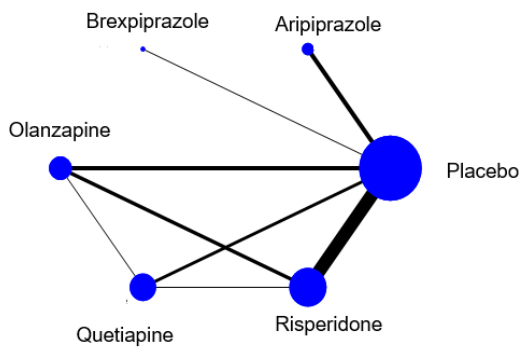
c. CVAE



d. Somnolence

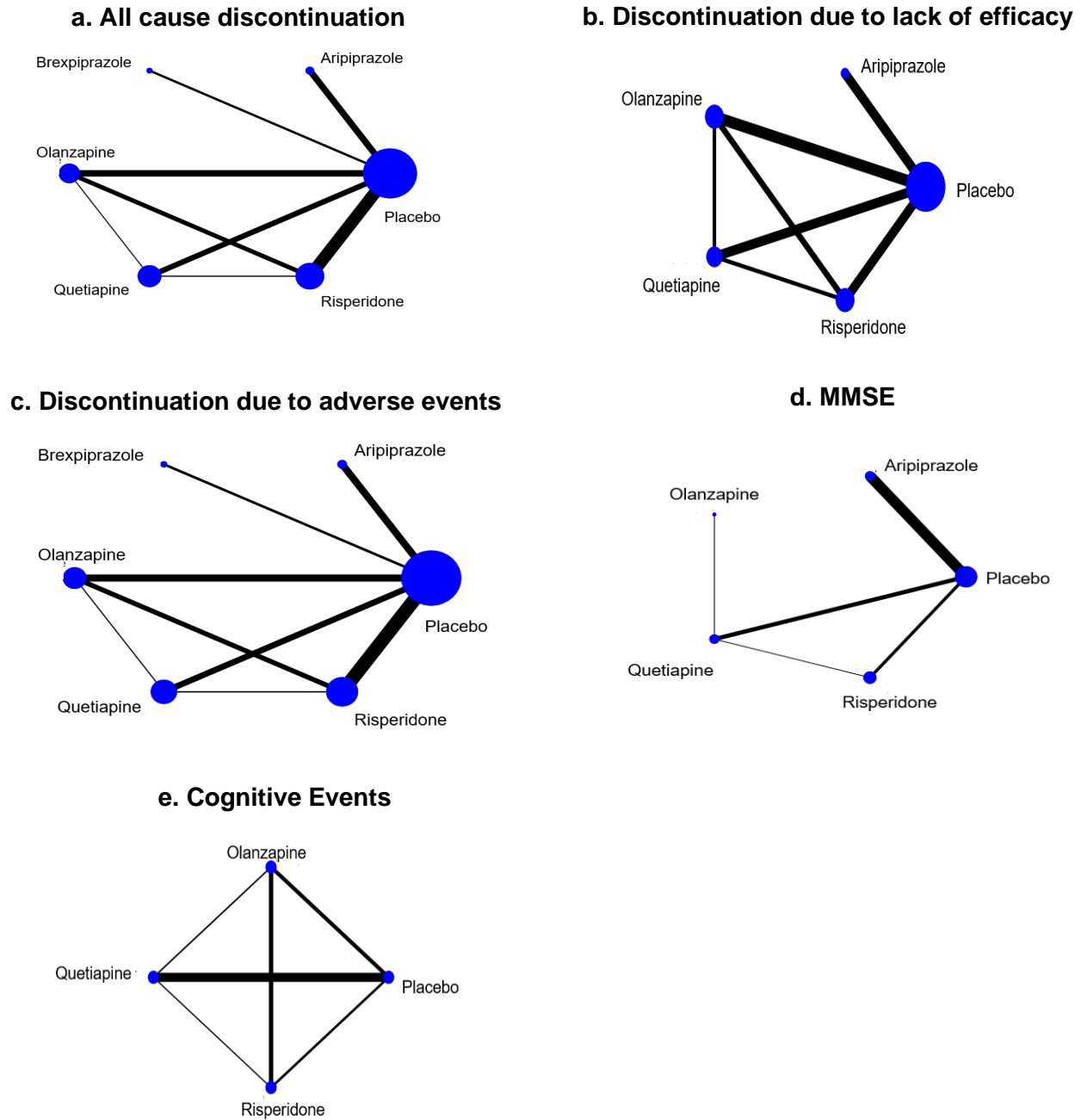


e. Falls, Fractures, and Injuries (FFI)



Network diagram depicting AAPs compared in the efficacy and primary safety analysis. The width of each line corresponds to number of trials which compared every pair of treatment while the size of every dot corresponds to the number of patients receiving the AAP (sample size).

Supplementary Figure 2. Network diagram for acceptability and other outcomes



Network diagram depicting AAPs compared in the acceptability and other outcome analysis. The width of each line corresponds to number of trials which compared every pair of treatment while the size of every dot corresponds to the number of patients receiving the AAP (sample size).

Supplementary Table 2. Summary table for efficacy and primary safety outcomes of atypical antipsychotics in comparison with each other

Efficacy Outcome				
Comparing Atypical Antipsychotics with Respect to change in NPI-NH				
Treatment	Aripiprazole	Brexpiprazole	Olanzapine	Quetiapine
Aripiprazole				
Brexpiprazole	N/A			
Olanzapine	-0.05 (-0.32, 0.22) ^a	N/A		
Quetiapine	0.16 (-0.17, 0.49) ^a	N/A	0.21 (-0.13, 0.55) ^a	
Risperidone	N/A	N/A	N/A	N/A
Primary Safety Outcomes				
Comparing Atypical Antipsychotics with respect to Mortality				
Treatment	Aripiprazole	Brexpiprazole	Olanzapine	Quetiapine
Aripiprazole				
Brexpiprazole	1.41 (0.15, 12.95) ^b			
Olanzapine	1.40 (0.36, 5.42) ^b	0.99 (0.11, 9.26) ^b		
Quetiapine	1.06 (0.29, 3.85) ^b	0.76 (0.08, 6.76) ^b	0.76 (0.21, 2.80) ^b	
Risperidone	1.03 (0.34, 3.08) ^b	0.73 (0.09, 5.89) ^b	0.74 (0.28, 1.96) ^b	0.97 (0.35, 2.70) ^b
Comparing Atypical Antipsychotics with respect to CVAE				
Treatment	Aripiprazole	Brexpiprazole	Olanzapine	Quetiapine
Aripiprazole				
Brexpiprazole				
Olanzapine	3.53 (0.44, 28.10) ^b	N/A		
Quetiapine	1.51 (0.21, 10.75) ^b	N/A	0.43 (0.10, 1.76) ^b	
Risperidone	3.07 (0.46, 20.37) ^b	N/A	0.87 (0.31, 2.47) ^b	2.03 (0.62, 6.67) ^b
Comparing Atypical Antipsychotics with respect to Somnolence				
Treatment	Aripiprazole	Brexpiprazole	Olanzapine	Quetiapine
Aripiprazole				
Brexpiprazole	0.62 (0.15, 2.65) ^b			
Olanzapine	1.36 (0.52, 3.74) ^b	2.23 (0.60, 8.30) ^b		
Quetiapine	2.44 (0.73, 8.10) ^b	3.90 (0.89, 17.16) ^b	1.75 (0.62, 4.94) ^b	
Risperidone	0.89 (0.37, 2.18) ^b	1.43 (0.41, 4.96) ^b	0.64 (0.40, 1.05) ^b	0.37 (0.14, 0.94) ^b
Comparing Atypical Antipsychotics with respect to falls, fractures, and injuries				
Treatment	Aripiprazole	Brexpiprazole	Olanzapine	Quetiapine
Aripiprazole				
Brexpiprazole	0.38 (0.07, 2.09) ^b			
Olanzapine	1.20 (0.72, 2.00) ^b	3.14 (0.58, 17.06) ^b		
Quetiapine	0.73 (0.40, 1.34) ^b	1.91 (0.34, 10.73) ^b	0.61 (0.34, 1.06) ^b	
Risperidone	0.74 (0.48, 1.17) ^b	1.95 (0.37, 10.43) ^b	0.62 (0.44, 0.88) ^b	0.93 (0.57, 1.52) ^b

Comparisons should be read from left to right and are point estimate of ^astandardized mean differences (95% confidence interval) or odds ratio (95% confidence interval). The estimate is in the cell shared between the column defining-treatment and row defining treatment. Significant results do not include 0 in the 95% confidence interval. ^bSignificant results do not include 1 in the 95% confidence interval. Abbreviations: NPI-NH (Neuropsychiatric inventory- nursing home); N/A (Not applicable)

Supplementary Table 3. Summary table for acceptability outcomes of atypical antipsychotics in comparison with each other

Comparing Atypical Antipsychotics with Respect to all cause discontinuation				
Treatment	Aripiprazole	Brexpiprazole	Olanzapine	Quetiapine
Aripiprazole				
Brexpiprazole	1.65 (0.90, 3.03)			
Olanzapine	1.60 (1.04, 2.46)	0.97 (0.54, 1.73)		
Quetiapine	1.42 (0.90, 2.24)	0.89 (0.47, 1.56)	0.89 (0.59, 1.33)	
Risperidone	1.40 (0.94, 2.09)	0.85 (0.49, 1.48)	0.88 (0.65, 1.19)	0.99 (0.68, 1.43)
Comparing Atypical Antipsychotics with Respect to discontinuation due to lack of efficacy				
Treatment	Aripiprazole	Brexpiprazole	Olanzapine	Quetiapine
Aripiprazole				
Brexpiprazole	1.30 (0.52, 3.28)			
Olanzapine	1.90 (1.05, 3.43)	1.45 (0.59, 3.61)		
Quetiapine	0.90 (0.49, 1.66)	0.69 (0.28, 1.74)	0.48 (0.29, 0.79)	
Risperidone	1.02 (0.60, 1.74)	0.78 (0.33, 1.88)	0.54 (0.36, 0.80)	1.13 (0.70, 1.82)
Comparing Atypical Antipsychotics with Respect to discontinuation due to adverse events				
Treatment	Aripiprazole	Brexpiprazole	Olanzapine	Quetiapine
Aripiprazole				
Brexpiprazole	1.30 (0.52, 3.28)			
Olanzapine	1.90 (1.05, 3.43)	1.45 (0.59, 3.61)		
Quetiapine	0.90 (0.49, 1.66)	0.69 (0.28, 1.74)	0.48 (0.29, 0.79)	
Risperidone	1.02 (0.60, 1.74)	0.78 (0.33, 1.88)	0.54 (0.36, 0.80)	1.13 (0.70, 1.82)

Comparisons should be read from left to right and are point estimate of odds ratio (95% confidence interval). The estimate is in the cell shared between the column defining-treatment and row defining treatment. Significant results do not include 1 in the 95% confidence interval. N/A: Not applicable

Supplementary Table 4. Summary table for other outcomes

Comparing Atypical Antipsychotics with Respect to change in MMSE				
Treatment	Aripiprazole	Olanzapine	Quetiapine	Placebo
Aripiprazole				-0.09 (-0.23, 0.06)^a
Olanzapine	0.32 (-0.63, 1.27) ^a			0.23 (-0.71, 1.17)^a
Quetiapine	0.04 (-0.22, 0.29) ^a	-0.28, (-1.20, 0.63) ^a		-0.05 (-0.26, 0.16)^a
Risperidone	-0.063 (-0.34, 0.22) ^a	-0.38 (-1.34, 0.58) ^a	-0.10 (-0.38, 0.19) ^a	-0.15 (-0.39, 0.09)^a
Comparing Atypical Antipsychotics with respect to Cognitive events				
Treatment	Aripiprazole	Olanzapine	Quetiapine	Placebo
Aripiprazole				N/A
Olanzapine	N/A			7.29 (1.39, 38.24)^b
Quetiapine	N/A	0.27 (0.04, 1.73) ^b		1.941 (0.56, 6.68)^b
Risperidone	N/A	0.38 (0.07, 1.99) ^b	1.43 (0.15, 13.50) ^b	2.76 (0.35, 21.90)^b

Comparisons should be read from left to right and are point estimate of ^astandardized mean differences (95% confidence interval) or ^bodds ratio (95% confidence interval). The estimate is in the cell shared between the column defining-treatment and row defining treatment. ^aSignificant results do not include 0 in the 95% confidence interval. ^bSignificant results do not include 1 in the 95% confidence interval. N/A: Not applicable

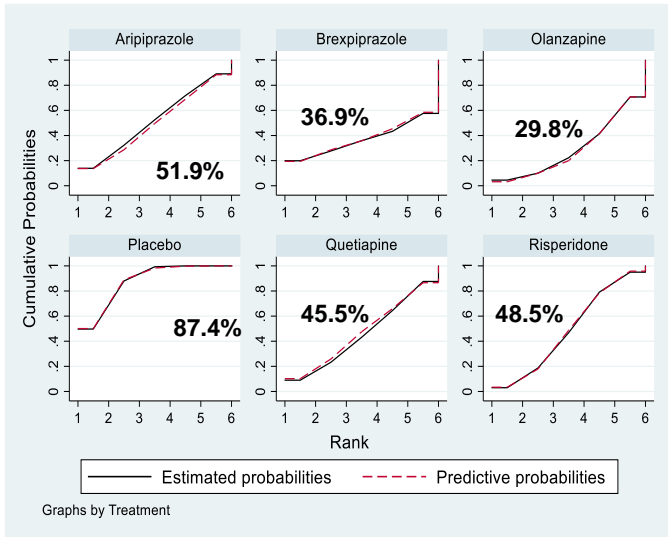
Supplementary Table 5. Loop specific approach-based inconsistency tests

Loop	IF	S.E(IF)	z_value	p_value	cr_95	Loop_Heterg_tau2
All cause discontinuation						
1-5-6	0.422	0.391	1.078	0.281	(0.00, 1.19)	0.000
1-4-5	0.305	0.612	0.498	0.619	(0.00, 1.50)	0.116
4-5-6	0.103	0.539	0.191	0.849	(0.00, 1.16)	0.000
1-4-6	0.015	0.357	0.042	0.966	(0.00, 0.71)	0.056
Discontinuation due to lack of efficacy						
1-3-5	0.865	0.398	2.174	0.030	(0.09, 1.64)	0.000
1-4-5	0.366	0.811	0.451	0.652	(0.00, 1.95)	0.250
1-3-4	0.098	0.800	0.123	0.902	(0.00, 1.67)	0.180
3-4-5	0.070	0.569	0.122	0.903	(0.00, 1.19)	0.000
Discontinuation due to adverse events						
1-4-5	0.925	0.535	1.728	0.084	(0.00, 1.97)	0.000
1-4-6	0.724	0.408	1.773	0.076	(0.00, 1.53)	0.000
1-5-6	0.404	0.504	0.801	0.423	(0.00, 1.39)	0.000
4-5-6	0.089	0.607	0.146	0.884	(0.00, 1.28)	0.000
Mortality						
1-5-6	0.133	2.086	0.064	0.949	(0.00, 4.22)	0.000
1-4-6	0.099	0.954	0.104	0.917	(0.00, 1.97)	0.000
CVAE						
1-4-5	0.974	1.361	0.715	0.474	(0.00, 3.64)	0.000
3-4-5	0.506	2.429	0.208	0.835	(0.00, 5.27)	0.000
1-3-5	0.470	1.213	0.388	0.698	(0.00, 2.85)	0.000
1-3-4	0.289	1.885	0.153	0.878	(0.00, 3.98)	0.429
Somnolence						
1-5-6	0.581	1.649	0.352	0.725	(0.00, 3.81)	0.020
1-4-6	0.112	0.495	0.226	0.821	(0.00, 1.08)	0.032
FFI						
1-4-5	0.543	0.613	0.885	0.376	(0.00, 1.74)	0.013
4-5-6	0.241	0.726	0.332	0.740	(0.00, 1.66)	0.000
1-5-6	0.104	0.843	0.123	0.902	(0.00, 1.76)	0.115
1-4-6	0.062	0.407	0.152	0.879	(0.00, 0.86)	0.027

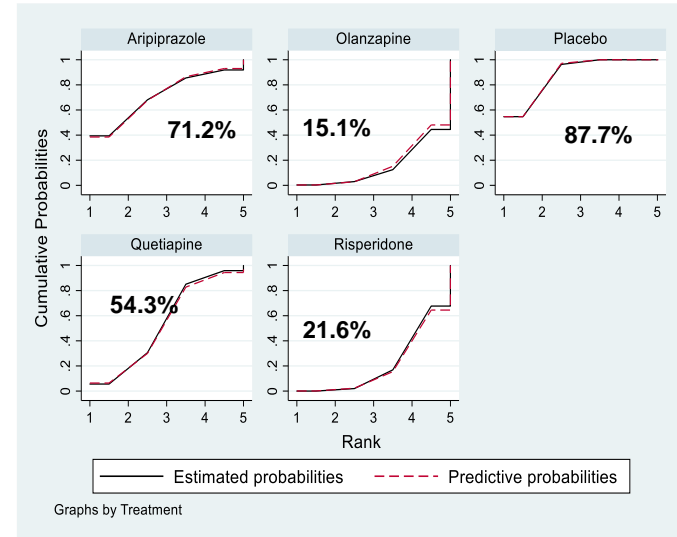
Inconsistency factors (IF) are ratios of odds ratios (RORs). S.E(IF): Standard error of inconsistency factor. Cr_95: 95% confidence interval; Loop_Heterog_tau2: loop-specific heterogeneity. The p-value for inconsistency was 0.1. Loops with p-value > 0.1 showed evidence of consistency. In loop column; 1= Placebo; 2= Aripiprazole; 3= Brepiprazole; 4= Olanzapine; 5= Quetiapine; 6= Risperidone

Supplementary Figure 3. Percentage as shown in the surface under the cumulative ranking curves (SUCRAs) against an imaginary treatment demonstrating no uncertainty and highest ranking. The highest-ranking treatment with no uncertainty will have a SUCRA of 100% while the worst will be 0%. The closer a treatment's SUCRA value is to 100%, the more likely it is to be the more acceptable or safe alternative; the lower and closer the SUCRA value is to 0%, the less likely it is to be the most acceptable or safe alternative.

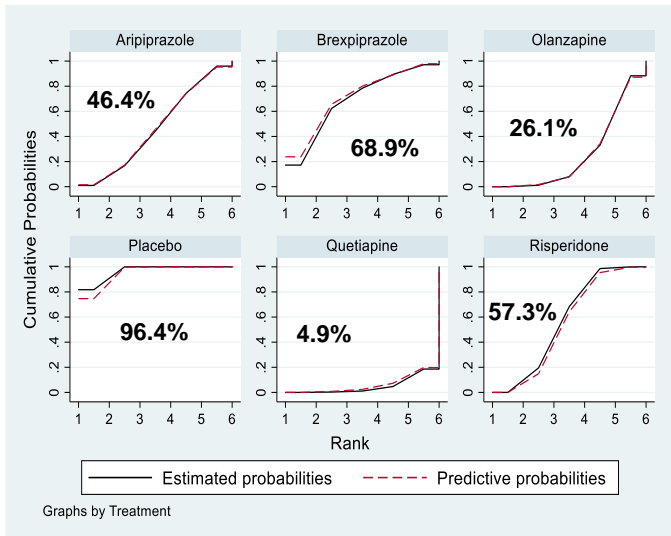
a. Mortality



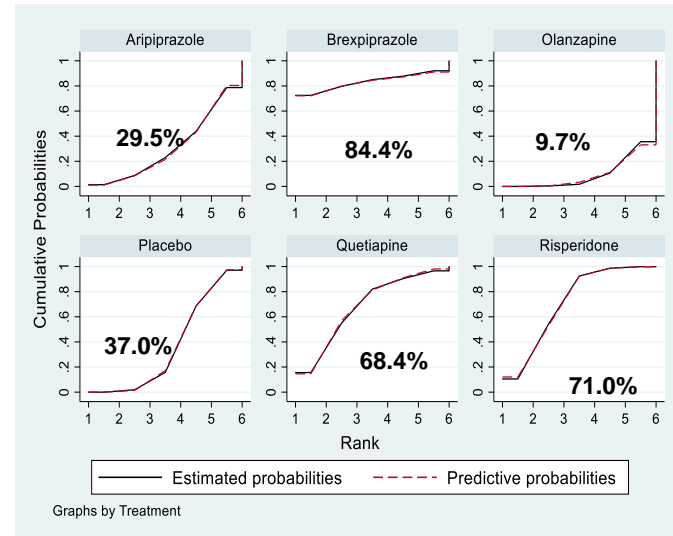
b. CVAE



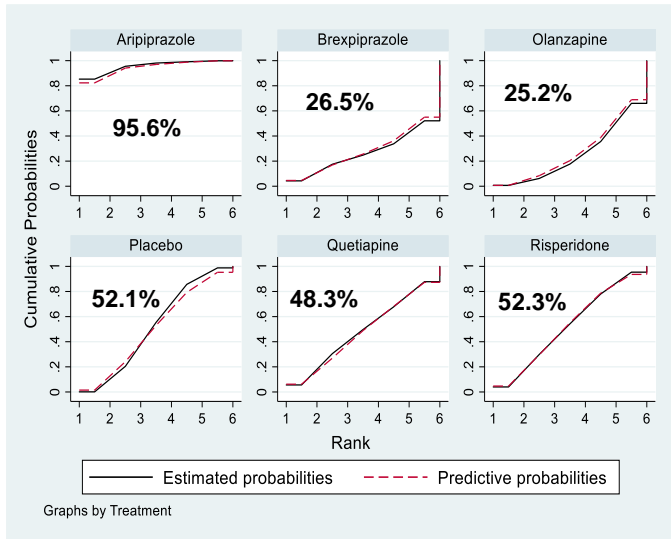
c. Somnolence



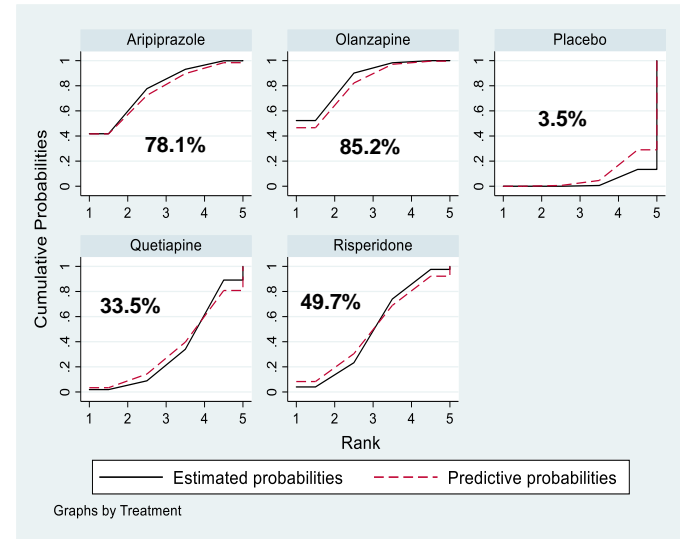
d. FFI



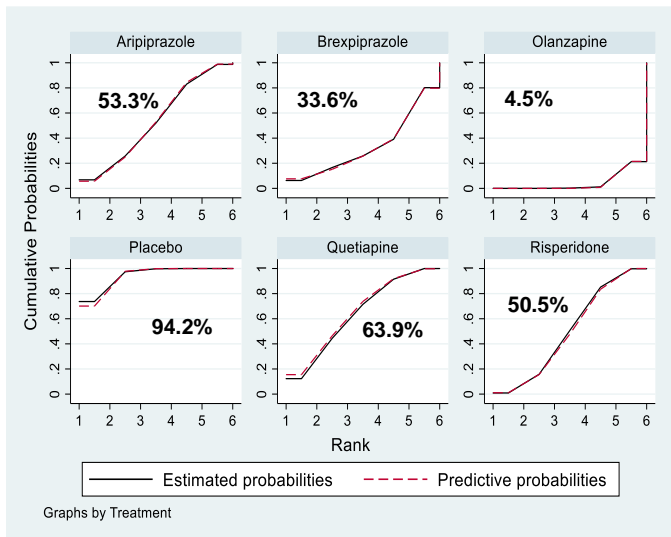
e. All cause discontinuation



f. Discontinuation due to lack of efficacy



g. Discontinuation due to adverse events



Supplementary Table 6. Summary table for secondary safety outcomes

Comparing Atypical Antipsychotics with respect to Cardiovascular					
Treatment	Aripiprazole	Brexpiprazole	Olanzapine	Quetiapine	Placebo
Aripiprazole					
Brexpiprazole					
Olanzapine					4.33 (0.22, 84.37)
Quetiapine			0.21 (0.01, 5.02)		0.90 (0.29, 2.84)
Risperidone			1.00 (0.13, 7.89)	4.81 (0.43, 54.14)	4.33 (0.51, 36.56)
Comparing Atypical Antipsychotics with respect to EPS					
Treatment	Aripiprazole	Brexpiprazole	Olanzapine	Quetiapine	Placebo
Aripiprazole					1.20 (0.22, 6.72)
Brexpiprazole	1.77 (0.23, 13.40)				2.14 (0.74, 6.20)
Olanzapine	4.36 (0.57, 33.50)	2.46 (0.54, 11.29)			5.25 (1.75, 15.73)
Quetiapine	0.89 (0.13, 6.01)	0.50 (0.13, 1.94)	0.20 (0.06, 0.70)		1.07 (0.46, 2.47)
Risperidone	3.15 (0.51, 19.62)	1.78 (0.52, 6.07)	0.72 (0.25, 2.06)	3.55 (1.45, 8.69)	3.80 (2.04, 7.07)
Comparing Atypical Antipsychotics with respect to Akathisia					
Treatment	Aripiprazole	Brexpiprazole	Olanzapine	Quetiapine	Placebo
Aripiprazole					N/A
Brexpiprazole	N/A				1.95 (0.27, 13.94)
Olanzapine	N/A	N/A			N/A
Quetiapine	N/A	0.16 (0.007, 7.35)	N/A		0.32 (0.01, 8.26)
Risperidone	N/A	0.97 (0.11, 8.69)	N/A	5.95 (0.20, 178.27)	1.89 (0.72, 4.96)

Comparisons should be read from left to right and are point estimate of odds ratio (95% confidence interval). The estimate is in the cell shared between the column defining-treatment and row defining treatment. Significant results do not include 1 in the 95% confidence interval. Abbreviation: EPS (Extrapyramidal symptoms); N/A (Not applicable)