Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

Online-Only Supplements

eTable 1. Newcastle-Ottawa Quality Assessment Scale of studies with co-primary outcomes

Study	Selection				Comparability	Outcome			Total score
	1	2	3	4	1	1	2	3	
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	
Ascher-Svanum et al. 2008	1	1	1	1	0	1	1	1	7
Bitter et al. 2013	1	1	1	1	0	1	1	1	7
Buoli et al. 2016	1	1	1	1	0	1	1	1	7
Castro et al. 2007	0	1	1	1	0	1	1	0	5
Conley et al. 1999	0	1	1	1	0	1	1	1	6
Conley et al. 2003	0	1	1	1	0	1	1	0	5
Cooper et al. 2007	1	1	1	1	0	1	1	1	7
Green et al. 2003	0	1	1	1	0	1	1	1	6
Guo_Fang et al. 2011	1	1	1	1	0	1	1	0	6
Haro et al. 2007	1	1	1	1	0	1	1	1	7
Herceg et al. 2008	0	1	1	1	0	1	1	1	6
Hodgson et al. 2005	1	1	1	1	2	1	1	1	9
Karagianis et al. 2009	1	1	1	1	0	1	1	1	7
Kim et al. 2008	0	1	1	1	0	1	1	1	6
Lin et al. 2006	0	1	1	1	0	1	1	1	6
Lindenmayer et al. 1998	0	1	1	1	0	1	1	1	6
Novick et al. 2012	1	1	1	1	0	1	1	1	7
Nyakyoma et al. 2010	0	1	1	1	0	1	1	1	6
Ringback et al. 2014	1	1	1	1	0	1	1	1/0 (ACD/HOS)	7/6 (ACD/HOS)
Sharma et al. 2003	0	1	1	1	0	1	1	1	6
Stroup et al. 2015	0	1	1	1	2	1	1	1/0 (ACD/HOS)	8/7 (ACD/HOS)
Taylor et al. 2008	1	1	1	1/0 (ACD/HOS)	0	1	1	1	7/6 (ACD/HOS)
Tiihonen et al. 2006	0	1	1	1	0	1	1	1	6
Treuer et al. 2010	1	1	1	1	0	1	1	1	7

Vanasse et al. 2016	1	1	1	1	0	1	1	1	7
Velligan et al. 2015	1	1	1	0	0	1	1	1	6
Werneck et al. 2011	0	1	1	1	0	1	1	1	6
Williams et al. 2006	0	1	1	1	0	1	1	1	6

ACD, all-cause discontinuation, HOS, hospitalization

eTable 2-1. Results of secondary outcomes related to effectiveness using different types of pre/post coefficients

Outcome	pre/post correlation coefficients	Effect size				Heterogeneity	
		SMD	Lower 95%CI	Upper 95%CI	*P* Value	I^2 (%)	*P* Value
Overall symptoms	High	-0.521	-0.988	-0.053	**0.029**	91.9	**<0.001**
	Medium	-0.302	-0.572	-0.032	**0.028**	74.8	**<0.001**
	Low	-0.248	-0.472	-0.025	**0.029**	62.6	**0.004**
Positive symptoms	High	-0.516	-1.102	0.069	0.084	92.9	**<0.001**
	Medium	-0.253	-0.574	0.069	0.124	76.3	**<0.001**
	Low	-0.185	-0.438	0.068	0.153	61.1	**0.012**
Negative symptoms	High	-0.322	-0.759	0.115	0.148	87.5	**<0.001**
	Medium	-0.227	-0.568	0.113	0.190	79.5	**<0.001**
	Low	-0.194	-0.502	0.113	0.216	74.9	**<0.001**
General symptoms	High	-0.166	-0.733	0.401	0.565	81.1	**<0.001**
	Medium	-0.050	-0.351	0.251	0.746	45.4	0.120
	Low	-0.022	-0.253	0.209	0.852	12.6	0.333
Depressive symptoms	High	-0.038	-0.343	0.266	0.805	77.0	**<0.001**
	Medium	-0.008	-0.178	0.163	0.931	30.9	0.181
	Low	-0.013	-0.118	0.091	0.803	1.7	0.416
Cognitive symptoms	High	-0.354	-0.635	-0.074	**0.013**	41.5	0.181
	Medium	-0.124	-0.235	-0.014	**0.027**	<0.1	0.603
	Low	-0.093	-0.203	0.017	0.098	<0.1	0.744
Clinical global impressions	High	-2.062	-3.514	-0.611	**0.005**	92.0	**<0.001**
	Medium	-1.182	-2.243	-0.122	**0.029**	87.7	**<0.001**
	Low	-0.911	-1.809	-0.014	**0.047**	83.8	**<0.001**

Bolded *P* values indicate *P*<0.05; The pre/post correlation coefficients (High=0.9, Medium=0.5, Low=0.1)

CI, confidence interval; SMD, standardized mean difference

eTable 2-2. Results of secondary outcomes related to safety using different types of pre/post coefficients

Outcome	pre/post correlation coefficients	Effect size				Heterogeneity		Effect size					Heterogeneity	
		SMD	Lower 95%CI	Upper 95%CI	*P* Value	I^2 (%)	*P* Value	MD	Lower 95%CI	Upper 95%CI	*P* Value	Unit	I^2 (%)	*P* Value
Waist circumference	High	0.429	-0.25	1.107	0.216	86.4	**0.001**	1.16	-0.97	3.29	0.286	cm	88.1	**<0.001**
	Medium	0.272	-0.042	0.586	0.090	37.7	0.201	1.21	-0.78	3.20	0.234		51.1	0.129
	Low	0.237	-0.014	0.488	0.064	3.4	0.355	0.83	-0.52	2.17	0.228		14.4	0.311
Blood pressure (Systolic)	High	0.313	0.067	0.559	**0.013**	22.8	0.274	1.98	0.45	3.50	**0.011**	mmHg	15.9	0.304
	Medium	0.247	0.034	0.459	**0.023**	<0.1	0.372	2.22	0.15	4.28	**0.035**		9.3	0.332
	Low	0.228	0.007	0.449	**0.043**	6.2	0.344	2.31	0.08	4.54	**0.042**		6.9	0.342
Blood pressure (Diastolic)	High	0.387	0.173	0.600	**<0.001**	<0.1	0.616	1.71	0.05	3.37	**0.044**	mmHg	63.9	0.063
	Medium	0.336	0.111	0.561	**0.003**	9.0	0.333	1.92	0.03	3.81	**0.047**		53.8	0.115
	Low	0.32	0.076	0.565	**0.010**	22.0	0.278	2.03	0.02	4.03	**0.048**		50.2	0.134
Total cholesterol	High	0.704	-0.162	1.569	0.111	92.3	**<0.001**	12.98	-4.77	30.72	0.152	mg/dL	87.0	**<0.001**
	Medium	0.297	-0.186	0.781	0.228	75.3	0.007	11.06	-7.66	29.78	0.247		72.8	**0.012**
	Low	0.199	-0.201	0.599	0.330	64.0	0.04	9.47	-9.32	28.25	0.323		63.7	**0.041**
Glucose	High	0.898	0.411	1.385	**<0.001**	87.4	**<0.001**	9.00	5.80	12.21	**<0.001**	mg/dL	64.8	**0.009**
	Medium	0.486	0.230	0.743	**<0.001**	55.6	**0.036**	8.09	4.56	11.62	**<0.001**		32.4	0.181
	Low	0.377	0.168	0.586	**<0.001**	35.0	0.161	7.71	3.98	11.44	**<0.001**		20.1	0.276
Insulin	High	0.662	0.311	1.013	**<0.001**	31.9	0.230	3.09	0.49	5.70	**0.020**	microU/mL	49.5	0.138
	Medium	0.391	0.115	0.667	**0.005**	<0.1	0.409	3.50	-1.04	8.04	0.131		36.2	0.209
	Low	0.317	0.041	0.592	**0.024**	<0.1	0.444	3.70	-1.72	9.11	0.181		28.8	0.245
HOMA-IR	High	0.584	0.287	0.881	**<0.001**	15.5	0.314	1.05	0.40	1.69	**0.001**		21.3	0.282
	Medium	0.382	0.119	0.645	**0.004**	<0.1	0.493	0.99	0.01	1.96	**0.047**		15.6	0.314
	Low	0.311	0.049	0.574	**0.020**	<0.1	0.547	0.95	-0.15	2.05	0.091		10.9	0.338
EPS score	High	0.145	-0.127	0.416	0.296	14.8	0.309							
	Medium	0.068	-0.179	0.314	0.590	<0.1	0.720							
	Low	0.051	-0.195	0.298	0.683	<0.1	0.825							

Bolded *P* values indicate *P*<0.05; The pre/post correlation coefficients (High=0.9, Medium=0.5, Low=0.1)

CI, confidence interval; EPS, extrapyramidal side effects; HOMA-IR, homeostatic model assessment of insulin resistance; MD, mean difference; SMD, standardized mean difference

eTable 3. Study and patient characteristics with analyzed outcomes

Study	Country	Study design /Data source	Study duration (month)	Diagnosis	TRS (yes, no, N.R.)	Patients (n) Total (CLO/NC-SGAs)	Compara-tor	Mean age /Illness duration (year)	% Male	Supported by Pharma Company	Co-primary outcomes	Secondary outcomes
Advokat et al, 2004[1]	US.	Retrospective /Single-site	3	All diagnoses were made by the treating psychiatrist, using the (DSM-III-R).	N.R.	100 (7/93)	OLZ QTP RIS	40.6 /N.R.	31.0	No	N.D.	Response rate Anti-chol
Agid et al, 2007[2]	Canada	Prospective /Single-site	6	All patients were receiving treatment of a first episode of schizophrenia or schizoaffective disorder (DSM-IV)	Yes	22 (13/9)	OLZ RIS	25.7 /N.R.	78.3	No	N.D.	Psy (O, P, N), CGI
Ascher-Svanum et al, 2008[3]	US	Prospective /Multi-site	12	All patients were diagnosed with schizophrenia, schizoaffective, or schizophreniform disorders based on DSM-IV criteria	N.R.	768 (74/694)	OLZ QTP RIS	42.0 /21.8	57.3	Yes	ACD (main, pyr, RIS, OLZ, QTP, HR)	N.D.
Bai et al, 2009[4]	Taiwan	Retrospective /Single-site	Mean 45.8 (CLO:56, NC-SGAs:38.8)	Schizophrenia, as diagnosed according to DSM-IV.	N.R.	567 (231/336)	OLZ RIS	48.7 /N.R.	65.8	No	N.D.	Weight, BMI

Bitter et al, (IC-SOHO) 2005[5]	27 Countries[a]	Prospective /Multi-site	6	Clinical diagnosis of schizophrenia (ICD-10 or DSM-IV).	N.R.	4762 (236/4526)	OLZ QTP RIS	35.2[b] /N.R.	54.3[b]	Yes	ACD (6mo)	N.D.
Bitter et al, (IC-SOHO) 2008[6]	27 Countries[a]	Prospective /Multi-site	24	Diagnosed with schizophrenia according to either ICD-10 or DSM-IV	N.R.	4764 (236/4528)	OLZ QTP RIS	35.1 /8.7	55.0	Yes	ACD (24mo, aOR)	Anti-cho
Bitter et al, 2013[7]	Hungary	Prospective /Data base	12	All patients in Hungary who had at least one record of schizophrenia diagnosis (F20.0-F20.9 according to ICD-10)	N.R.	8472 (790/7682)	AMI APZ OLZ QTP RIS ZIP	48.2 /N.R.	39.3	Yes	ACD (main, 6, 12mo, RIS, OLZ, QTP, APZ, AMI, HR) HOS (main, 12mo, RIS, OLZ, QTP, APZ, AMI)	Death, Suicide-attempt
Bobo et al, 2010[8]	US	Retrospective /Single-site	3	Patients who met DSM-IV criteria for schizophrenia or schizoaffective disorder.	Partly (SGA:62.9 %)	159 (146/13)	Melperone	35.8 /13.0	71.8	No	N.D.	WG-risk, weight, BMI
Buoli et al, 2016[9]	Netherlands and Italy	Prospective /Multi-site	36	All patients with a diagnosis of schizophrenia according to DSM-IV-TR	N.R.	193 (36/157)	APZ OLZ QTP RIS	30.5 /6.3	67.4	No	ACD (main, 36mo, pyr, RIS, OLZ, QTP, APZ)	EPS-risk, WG-risk, DM-risk
Bushe et al, (SOHO+IC-SOHO) 2012[10]		Prospective /Multi-site	36	The patients populations consisted of outpatients aged 18 years or older with schizophrenia	N.R.	3906 (187/3719)	AMI OLZ QTP RIS	37.9 /N.R.	54.6	Yes	N.D.	WG risk Weight, BMI

Castro and Elkis, 2007[11]	Brazil	Retrospective /Single-site	36	All patients with schizophrenia (ICD-10)	Yes	53 (31/22)	RIS	36.4 /17.2	58.5	No	HOS (6, 12, 24mo, pyr, RIS)	N.D.
Chitaia et al, 2009[12]	Russia	Prospective /Single-site	6	Most of patients are schizophrenia according to ICD-10	N.R.	40 (20/20)	RIS	36.3 /7.3	0.0	No	N.D.	WG-risk
Conley et al, 1999[13]	US.	Prospective /Multi-site	24	Patients had a diagnosis of schizophrenia.	N.R.	124 (49/75)	RIS	40.4 /N.R.	60.5	No	HOS (main, 6, 12, 24mo, pyr, RIS)	N.D.
Conley et al, 2003[14]	US	Prospective /Multi-site	12	Patients with a DSM-IV diagnosis of SCZ	N.R.	293 (41/252)	OLZ RIS	38.4 /N.R.	61.0	No	HOS (main, 6, 12mo, pyr, RIS, OLZ)	N.D.
Cooper et al, 2007[15]	Canada	Retrospective /Data base	12	Patients diagnosed with schizophrenia (ICD-9).	N.R.	6662 (164/6498)	OLZ QTP RIS	N.R. /N.R.	57.4	Yes	ACD (main, 12mo, RIS, OLZ, QTP, aOR)	N.D.
Danilov, 2010[16]	Russia	Prospective /Unclear	2.5	Patients with schizophrenia	N.R.	403 (106/297)	OLZ QTP RIS	34.1 /6.7	N.R.	No	N.D.	EPS-risk
De Hert et al, 2008[17]	Belgium	Prospective /Single-site	36	The first-episode schizophrenia patients	N.R.	108 (12/96)	OLZ QTP RIS	22.1 /N.R.	71.6	No	N.D.	Mets-risk
Flynn et al, 1998[18]	Canada	Prospective /Single site	3	Patients met DSM-IV criteria for schizophrenia	Yes	86 (57/29)	RIS	33.9 /13.3	69.8	No	N.D.	Psy (O, P, N, G, D, C), CGI Response-rate Anti-cho

Franza et al, 2015[19]	Italy	Prospective /Single-site	12	Schizophrenia or schizoaffective disorder (DSM-5 criteria).	Yes	42 (12/30)	APZ OLZ PAL QTP	45.6 /N.R.	71.4	No	N.D.	Psy (O, N, D)
Gau et al, 2008[20]	Taiwan	Prospective /Data base	Mean 21.2 (CLO: 24.0, NC-SGAs: 20.9)	Subjects who were diagnosed as new cases of schizophrenia (ICD-9-CM)	No	2521 (224/2297)	OLZ QTP RIS ZOT	34.6 /1.7	52.6	No	N.D.	# of Hos, Hos-days, Anti-cho
Gautam and Meena, 2011[21]	India	Prospective /Single-site	4	Subjects were cases of schizophrenia diagnosed as per the ICD-10 criteria.	No	90 (30/60)	OLZ RIS	N.R. /N.R.	N.R.	No	N.D.	Mets-risk, Weight, Waist, BP, TG, Glu
Green et al, 2003[22]	US.	Retrospective /Single-site	12	Subjects were comorbid for alcohol and/or cannabis use disorder and schizophrenia or schizoaffective disorder.	N.R.	53 (35/18)	RIS	42.2 /N.R.	75.6	Yes	ACD (main, 12mo, RIS)	N.D.
Guo et al, 2011[23]	China	Prospective /Multi-site	12	DSM-IV criteria for schizophrenia or schizophreniform disorder	No	802 (177/625)	APZ OLZ QTP RIS	25.9 /1.9	55.9	No	HOS (Main, 12mo, pyr, RIS, OLZ, QTP, APZ)	N.D.
Gupta et al, 2014[24]	India	Prospective /Multi-site	4	They were screened and classified as schizophrenics if they met the ICD-10 diagnostic criteria	No	180 (30/150)	AMI APZ OLZ QTP RIS	N.R. /N.R.	N.R.	No	N.D.	Mets-risk, Weight, Waist, BP, TG, Glu, Insulin, HOMA-IR

Haro et al, (SOHO) 2005[25]	10 European countries[c]	Prospective /Multi-site	6	Patients with a clinical diagnosis of schizophrenia	N.R.	7700 (301/7399)	AMI OLZ QTP RIS	40.0 /N.R.	58.3	Yes	ACD (6mo)	Psy (P, N, D, C)
Haro et al, (SOHO) 2007[26]	10 European countries[c]	Prospective /Multi-site	36	Patients with a clinical diagnosis of schizophrenia	N.R.	6909 (274/6635)	AMI OLZ QTP RIS	39.6 /N.R.	57.3	Yes	ACD (main, 24, 36mo, pyr, RIS, OLZ, QTP, AMI, HR) HOS (HR)	Suicide-attempt, # of Hos
Hennessy et al, 2002[27]	US	Retrospective /Data base	Mean:7.5 (CLO: 12.6, RIS:5.5)	At least two instances of a schizophrenia diagnosis.	N.R.	30387 (8330/22057)	RIS	N.R. /N.R.	54.0	Yes	N.D.	Death
Herceg et al, (chronic) 2008[28]	Croatia	Retrospective /Single-site	24	Diagnosis of schizophrenia was established by licensed psychiatrists according to ICD-10, DSM-IV.	N.R.	167 (60/107)	OLZ RIS	median 42 /N.R.	59.9	No	HOS (6, 12, 24mo, RIS, OLZ)	N.D.
Herceg et al, (acute) 2008[28]	Croatia	Retrospective /Single-site	24	Diagnosis of schizophrenia was established by licensed psychiatrists according to ICD-10, DSM-IV.	N.R.	63 (13/50)	OLZ RIS	median 31 /N.R.	58.7	No	HOS (6, 12, 24mo, RIS, OLZ)	N.D.
Hodgson et al, 2005[29]	U.K.	Retrospective /Data base	96	Only patients with a diagnosis of schizophrenia/schizo affective (ICD10)	N.R.	253 (44/209)	OLZ RIS	40.5 /N.R.	64.8	Yes	ACD (main, 6, 12, 24, 36mo, RIS, OLZ, HR)	N.D.

Huang et al, 2011[30]	Taiwan	Prospective /Single-site	Mean 49.9 (range 4-120)	According to the DSM-IV criteria for schizophrenia	N.R.	500 (275/225)	OLZ RIS	43.9 /N.R.	60.2	No	N.D.	WG-risk
Innamorati et al, 2013[31]	Italy	Retrospective /Single-site	Mean 60.7 (CLO: 64.3, NC-SGAs: 56.4)	Eighty-seven percent of them were diagnosed with schizophrenia (most with paranoid schizophrenia) and 13% with a Psychotic Disorder Not Otherwise Specified.	Yes	46 (23/23)	APZ OLZ QTP RIS etc.,	41.9 /16.9	67.4	No	N.D.	Psy (P, N, G, D) Suicide-attempt
Karagianis et al, 2009[32]	Canada	Prospective /Multi-site	12	Schizophrenia, schizoaffective disorder, schizophreniform disorder, or psychosis not otherwise specified, using DSM-IV	N.R.	929 (19/910)	OLZ QTP RIS	43.1 /N.R.	52.9	Yes	ACD (main,12mo, RIS, OLZ, QTP)	N.D.
Karki et al, 2001[33]	US.	Prospective /Single-site	6	78% had a diagnosis of schizophrenia, and 22% had a diagnosis of schizoaffective disorder.	Yes	150 (50/100)	OLZ RIS	45.0 /N.R.	72.0	No	N.D.	Psy(O)
Kelly et al, 2003[34]	US.	Retrospective /Single-site	6	Identified all patients with a DSM-IV	N.R.	107 (10/97)	RIS OLZ QTP	43.0 /N.R.	68.4	Yes	N.D.	Weight, T-cho, TG, Glu

				diagnosis of Schizophrenia								
Kelly et al, 2010[35]	US.	Retrospective /Data base	132	The study population consisted of persons with a DSM-III or DSM-IV diagnosis of schizophrenia, schizoaffective disorder of psychosis not otherwise specified	Yes	1686 (1084/602)	RIS	39.8 /N.R.	62.8	Yes	N.D.	Death
Kim et al, 2008[36]	Korea	Prospective /Multi-site	24	DSM-IV diagnosis of both schizophrenia	N.R.	61 (25/36)	RIS	39.5 /11.9	100.0	No	HOS (main, 6, 12, 24mo, pyr, RIS)	N.D.
Konrad et al, 2000[37]	Germany	Prospective /Multi-site	1.5	Diagnosis of schizophrenia according to ICD-10	Yes	64 (27/37)	RIS	N.R. /N.R.	45.3	No	N.D.	Psy (O, P, N, G, D) Response-rate EPS
Lin et al, 2006[38]	Taiwan	Retrospective /Single-site	24	The study's subjects consisted of all the schizophrenic patients	Yes	110 (61/49)	RIS	43.9 /14.7	66.4	No	HOS (6, 12, 24mo, pyr, RIS)	N.D.
Lindenmayer et al, 1998[39]	US.	Prospective /Multi-site	3	DSM-IV criteria for schizophrenia.	Yes	35 (21/14)	RIS	39.3 /N.R.	74.3	No	ACD (main, RIS)	Psy (O, P, N, D, C), CGI

Mauri et al, 2008[40]	Italy	Retrospective /Single-site	1.5	Subjects diagnosed as being affected by schizophrenia on the basis of the DSM IV criteria,	N.R.	111 (19/92)	OLZ QTP RIS	36.6 /10.4	73.9	No	N.D.	Psy (O, D) EPS
Nakamura and Nagamine[41] 2018	Japan	Retrospective /Single site	3	Patients with schizophrenia	N.R.	22 (12/10)	ASE	41.9 /N.R.	73.3	No	N.D.	Weight, TG, Glu
Nikolac et al, 2014[42]	Croatia	Prospective /Single-site	2	Patients with schizophrenia, diagnosed using a structured clinical interview for DSM-IV.	N.R.	445 (120/325)	OLZ RIS	40.2 /N.R.	70.0	No	N.D.	Response-rate
Novick et al, (SOHO) 2010[43]	10 European countries[c]	Prospective /Multi-site	36	Patients with a clinical diagnosis of schizophrenia	N.R.	4357 (169/4188)	AMI OLZ QTP RIS	38.2 /N.R.	56.3	Yes	N.D.	EPS-risk
Novick et al, (SOHO) 2012[44]	10 European countries[c]	Prospective /Multi-site	12	Patients with a clinical diagnosis of schizophrenia	N.R.	8162 (316/8146)	AMI OLZ QTP RIS	39.9 /N.R.	58.3	Yes	ACD (12mo) HOS (main, 12mo, RIS, OLZ, QTP, AMI, aOR)	Response-rate, Psy (O)
Nyakyoma and Morriss, 2010[45]	UK	Retrospective /Single-site	24	A diagnosis of either schizophrenia or schizoaffective (ICD-10)	Yes	160 (126/34)	AMI OLZ QTP RIS etc. (Majority is NC-SGAs)	36.4[d] /N.R.	77.3[d]	No	HOS (6, 12, 24mo, pyr, HR, aOR)	N.D.
Ollendorf et al, 2004[46]	US	Retrospective /Data base	Mean 13.7 (CLO: 12.8, NC-SGAs: 13.8)	A listed diagnosis of schizophrenia (ICD-9-CM)	N.R.	1826 (35/1791)	OLZ QTP RIS	39.1 /N.R.	48.2	No	N.D.	DM-risk

Pridan et al, 2015[47]	US	Retrospective /Single-site	60	Schizophrenia (DSM-IV-TR)	Yes	369 (43/326)	NC- SGAs	67.4[d] /N.R.	46.5[d]	No	N.D.	Death
Remington and Khramov, 2001[48]	Canada	Retrospective /Single-site	18	DSM-IV diagnosis of schizophrenia	N.R.	30 (15/15)	RIS	32.6 /10.5	60.0	No	N.D.	CGI, # of Hos, Hos-days
Rettenbacher et al, 2007[49]	Austria.	Prospective /Single-site	4	A diagnosis of schizophrenic disorder according to ICD-10	N.R.	31 (14/17)	AMI	34.9 /N.R.	64.5	No	N.D.	BMI, Insulin, HOMA-IR
Ringback et al, 2014[50]	Sweden	Retrospective /Data base	12	Schizophrenia (F20) or schizoaffective syndromes (F25) according to ICD- 10	N.R.	10849 (2112/8737)	APZ OLZ QTP RIS ZIP	46.8 /N.R.	56.2	No	ACD (main, 6, 12, 24mo, RIS, OLZ, QTP, APZ) HOS (main, 12mo, RIS, OLZ, QTP, APZ)	N.D.
Schulte et al, 2016[51]	Netherlands	Retrospective /Single-site	Mean 154.8	Schizophrenia or schizoaffective disorder as recorded in the medical administration	N.R.	167 (94/73)	APZ OLZ QTP RIS SER	39.0[d] /N.R.	78.2[d]	No	N.D.	DM-risk
Schuster et al, 2012[52]	France	Prospective /Multi-site	6	Patients meet the DSM-IV TR criteria for schizophrenia	N.R.	3629 (39/3590)	AMI APZ OLZ RIS	37.5[d] /N.R.	61.3[d]	Yes	N.D.	BMI
Sharma et al, 2003[53]	U.K.	Prospective /Single-site	6	Chronic schizophrenia (DSM IV)	Yes	48 (20/28)	OLZ	35.2 /11.3	64.6	Yes	ACD (main, 6mo, OLZ)	Psy(O, P, N, G)

Shermock et al, 2001[54]	US	Retrospective /Data base	12	Schizophrenia diagnosis (ICD-9- CM)	N.R.	928 (66/862)	RIS	38.8 /N.R.	51.1	Yes	N.D.	# of Hos
Stip et al, 1999[55]	Canada	Prospective /Single-site	6	Diagnosis was made according to the DSM-IV criteria	N.R.	25 (7/18)	RIS QTP	36.5 /11.8	32.0	No	N.D.	Response-rate
Stroup et al, 2016[56]	US	Retrospective /Data base	12	Inpatient claim for schizophrenia (ICD-9-CM 295.3) prior to their index date,	Yes	4358 (2179/2179)	NC-SGAs	38.9[d] /N.R.	51.9[d]	No	ACD (main, 12mo) HOS (main, 12mo, pyr)	Death, suicide-attempt, DM-risk
Strous et al, 2006[57]	Israel	Prospective /Multi-site	3	The study population consisted of chronic schizophrenia or schizoaffective disorder (as defined by DSM-IV criteria)	N.R.	131 (55/76)	OLZ RIS	36.7 /12.5	58.0	Yes	N.D.	Psy (O, P, N, G, D) Weight, BMI, T-chol, TG, Glu
Taylor et al, 2007[58]	UK	Retrospective /Single-site	36	A diagnosis of schizophrenia or schizoaffective disorder.	N.R.	36 (7/29)	OLZ RIS	43.6 /N.R.	58.0	No	N.D.	#of Hos, Hos-days
Taylor et al, 2008[59]	U.K.	Retrospective /Data base	Mean 21.7 (CLO:23.2, NC-SGAs:21.6)	Only those cases with a diagnosis of schizophrenia or related psychoses (F2 category, ICD-10) were selected	N.R.	400 (40/360)	AMI OLZ QTP RIS	40.4 /N.R.	58.8	No	ACD (main, pyr, RIS, OLZ, QTP, AMI) HOS (main, pyr, RIS, OLZ, QTP, AMI)	N.D.

Tiihonen et al, 2006[60]	Finland	Prospective /Data base	Mean 9.8 (CLO:17.0, RIS:7.3)	Schizophrenia or schizoaffective disorder (ICD-9, 10/DSM-IV)	N.R.	587 (150/437)	OLZ RIS	30.7[d] /N.R.	62.0[d]	No	ACD (main, pyr, RIS, OLZ) HOS (main, pyr, RIS, OLZ)	N.D.
Treuer et al, (IC-SOHO) 2010[61]	27 countries[a]	Prospective /Multi-site	36	Subjects who met criteria for schizophrenia (ICD-10 or DSM-IV)	N.R.	4765 (237/4528)	OLZ QTP RIS	35.1 /8.7	55.0	Yes	ACD (main, 36mo, RIS, OLZ, QTP)	N.D.
Tschoner et al, 2009[62]	Austria	Prospective /Single-site	1	Diagnosed with schizophrenic disorder according to ICD-10	N.R.	28 (7/21)	AMI OLZ QTP RIS ZIP	34.2 /N.R.	57.1	Yes	N.D.	BMI, T-chol, TG, HOMA-IR
van Winkel et al, 2008[63]	Belgium	Prospective /Single-site	3	Patients were included if they had a DSM-IV diagnosis of schizophrenia or schizoaffective disorder as established by their treating psychiatrist;	N.R.	183 (21/162)	AMI APZ OLZ QTP RIS	33.7 /7.5	60.7	Yes	N.D.	DM-risk, BMI, Waist, Glu, Insulin, HOMA-IR
Vanasse et al, 2016[64]	Canada	Retrospective /Data base	24	A prior diagnosis of schizophrenia or schizoaffective disorder (ICD-9: 295)	N.R.	11980 (324/11656)	OLZ QTP RIS	44.2 /0.22	54.3	No	ACD (main, 24mo, RIS, OLZ, QTP, HR) HOS (main, 24mo, RIS, OLZ, QTP)	N.D.
Velligan et al, 2015[65]	US.	Retrospective /Data base	12	At least one diagnosis of schizophrenic disorder (ICD-9-	N.R.	2919 (479/2440)	APZ OLZ PAL QTP	39.2 /N.R.	50.7	Yes	HOS (main, 12mo, aOR)	N.D.

				CM code 295.XX)			RIS ZIP					
Werneck et al, 2011[66]	Brazil	Retrospective /Single-site	36	The diagnosis of schizophrenia based on ICD-10.	N.R.	172 (59/113)	AMI APZ OLZ RIS ZIP	37.3 /16.3	61.6	No	HOS (main, 6, 12 24mo, pyr, RIS)	N.D.
Williams et al, 2006[67]	Canada	Prospective /Multi-site	24	Patients diagnosed with schizophrenia and other psychotic disorders (DSM-IV).	N.R.	217 (51/166)	OLZ QTP RIS	37.9[d] /N.R.	68.0[d]	Yes	HOS (main, 12, 24mo, RIS, OLZ, QTP)	N.D.
Woo et al, 2009[68]	Korea	Retrospective /Multi-site	2	All patients with a DSM-IV diagnosis of schizophrenia	N.R.	167 (70/97)	OLZ	38.7 /N.R.	52.1	No	N.D.	Weight, BP, T-cho, TG, Glu

For study references, see e-reference list at the end of the supplemental file.

Abbreviations:

# of Hos, number of hospitalization; 6mo, at 6month; 12mo, at 12month; 24mo, at 24month; 36mo, at 36month; ACD, all cause discontinuation; AMI, amisulpride; Anti-cho, anticholinergic use; aOR, adjusted odds ratio ASE, asenapine; BMI, body mass index; BP, blood pressure; CGI, clinical global impressions; CI, confidence intervals; CLO, clozapine; CM, clinical modification; DM-risk, diabetes mellitus-risk; DSM, the Diagnostic and Statistical Manual of Mental Disorders ; EPS, extrapyramidal symptoms; Glu, glucose; Hos days, hospitalization days; HOS, hospitalization risk; HR, hazard ratio; ICD, the International Classification of Diseases; Main, main analysis ; NC-SGAs, non-clozapine second-generation antipsychotics; N.D., No data; N.R., Not reported; OLZ, olanzapine; PAL; paliperidone; Psy, psychopathology; Psy(C), cognitive symptom; Psy(D), depressive symptom; Psy(G), general symptom; Psy(N), negative symptom; Psy(O), overall symptom; Psy(P), positive symptom; pyr, person years; QTP, quetiapine; RIS, risperidone; SER, sertindole; T-cho, total cholesterol; TG, triglycerides; TRS, treatment-resistant schizophrenia; WG risk, weight gain risk; ZIP, ziprasidone; ZOT, zotepine

[a] Africa, the Middle East, Asia, Central and Eastern Europe, and Latin America

[b] Characteristics of the part of analyzed patients

[c] Germany, Italy Spain Denmark, France, Greece, Ireland, the Netherlands, Portugal and the UK

[d] Characteristics including non-analyzed patients

eTable 4. Sensitivity analyses of co-primary outcomes removing studies with unequal observation periods for comparing clozapine with specific non-clozapine SGAs.

Outcome	Studies (N)	Patients (n)	Effect size				Heterogeneity		Effect size		
			Risk Ratio	Lower 95%CI	Upper 95%CI	*P* Value	I^2 (%)	*P* Value	NNT[a]	Lower 95%CI	Upper 95%CI
Hospitalization (vs specific non-clozapine SGAs)											
CLO vs RIS	14	17,228	0.842	0.720	0.984	**0.030**	60.4	**0.002**	20	12	195
CLO vs OLZ	9	19,803	0.914	0.732	1.142	0.429	79.2	**<0.001**	-	-	-
CLO vs QTP	6	8,062	0.686	0.535	0.880	**0.003**	81.0	**<0.001**	13	9	33
CLO vs APZ	3	4,529	0.698	0.559	0.872	**0.002**	46.1	0.157	-	-	-
CLO vs AMI	2	2,308	0.633	0.543	0.739	**<0.001**	<0.1	0.725	11	8	15
All-cause discontinuation (vs specific non-clozapine SGAs)											
CLO vs RIS	12	20,367	0.688	0.590	0.802	**<0.001**	88.9	**<0.001**	7	5	10
CLO vs OLZ	11	26,677	0.800	0.659	0.971	**0.024**	93.9	**<0.001**	11	7	72
CLO vs QTP	9	8,524	0.668	0.495	0.902	**0.009**	97.2	**<0.001**	6	4	18
CLO vs APZ	3	4,070	0.712	0.338	1.501	0.372	99.0	**<0.001**	-	-	-
CLO vs AMI	2	2,240	0.792	0.598	1.049	0.104	86.0	**0.008**	-	-	-

Bolded *P* values indicate *P*<0.05; AMI, amisulpride; APZ, aripiprazole; Cl, confidence intervals; CLO, clozapine; N, number; NNT, numbers-needed-to-treat; OLZ, olanzapine; RIS, risperidone; QTP, quetiapine; SGA, second-generation antipsychotic

[a] NNTs were only calculated when the risk ratio analysis was significant (*P*<0.05) The mean risk for the non-clozapine SGAs treatment was used as the assumed control group risk.

eTable 5-1. Results of subgroup analyses for hospitalization

Variables	Subgroup	Studies (N)	Patients (n)	Effect size				Heterogeneity		Effect size			Between subgroup difference
				Risk Ratio	Lower 95%CI	Upper 95%CI	*P* Value	I^2 (%)	*P* Value	NNT[a]	Lower 95%CI	Upper 95%CI	
Baseline setting	Index discharge	11	12,639	0.777	0.669	0.903	**0.001**	23.9	0.216	13	9	28	*P*=0.572
	Outpatients	6	33,495	0.883	0.727	1.073	0.210	81.2	**<0.001**	-	-	-	
	Unclear	2	3,319	0.919	0.408	2.069	0.838	90.9	**0.001**	-	-	-	
Study design	Prospective	8	18,222	0.818	0.627	1.068	0.140	69.4	**0.002**	-	-	-	*P*=0.986
	Retrospective	11	31,231	0.820	0.717	0.938	**0.004**	65.9	**0.001**	16	10	45	
Hospitalization definition	All cause	3	804	1.089	0.883	1.343	0.426	<0.1	0.469	-	-	-	*P*=0.382
	Mental health	14	48,089	0.762	0.673	0.861	**<0.001**	64.8	**<0.001**	14	10	28	
	Unclear	2	560	0.953	0.426	2.133	0.908	82.7	**0.016**	-	-	-	
Data source	Database	7	39,565	0.803	0.691	0.934	**0.004**	81.2	**<0.001**	19	12	57	*P*=0.770
	Multi center	6	9,163	0.885	0.653	1.199	0.430	47.4	0.091	-	-	-	
	One site	6	725	0.759	0.564	1.019	0.067	49.3	0.080	-	-	-	
Region	Asia	3	973	0.822	0.638	1.059	0.129	<0.1	0.418	-	-	-	*P*=0.540
	EU	8	28,364	0.886	0.723	1.086	0.245	75.0	**<0.001**	-	-	-	
	Other	4	12,422	0.756	0.464	1.232	0.261	72.0	**0.014**	-	-	-	
	U.S.	4	7,694	0.702	0.551	0.895	**0.004**	68.4	**0.023**	13	9	36	
Supported by company	No	15	30,179	0.843	0.758	0.938	**0.002**	37.0	0.074	19	13	48	*P*=0.841
	Yes	4	19,274	0.815	0.596	1.115	0.201	86.3	**<0.001**	-	-	-	
Treatment Resistant Schizophrenia	No/Not Reported	15	44,772	0.836	0.718	0.973	**0.021**	72.0	**<0.001**	22	13	130	*P*=0.616
	Yes	4	4,681	0.782	0.635	0.965	**0.022**	33.9	0.209	11	7	67	

Bolded *P* values indicate *P*<0.05; CI, confidence interval; NNT, numbers-needed-to-treat

[a] NNTs were only calculated when the risk ratio analysis was significant (*P*<0.05) The mean risk for the non-clozapine SGAs treatment was used as the assumed control group risk.

eTable 5-2. Results of subgroup analyses for all-cause discontinuation

Variable	Subgroup	Studies (N)	Patients (N)	Effect size				Heterogeneity		Effect size			Between subgroup difference
				Risk Ratio	Lower 95%CI	Upper 95%CI	*P* Value	I^2 (%)	*P* Value	NNT[a]	Lower 95%CI	Upper 95%CI	
Baseline setting	Inpatients	1	587	0.853	0.766	0.950	**0.004**	NA	NA	9	6	24	***P*<0.001**
	Mixed	2	10,724	0.535	0.493	0.580	**<0.001**	<0.1	0.587	5	5	6	
	Outpatients	9	44,321	0.784	0.680	0.904	**0.001**	91.4	**<0.001**	9	6	20	
	Unclear	4	736	0.678	0.490	0.938	**0.019**	9.4	0.346	8	6	42	
Study design	Prospective	9	22,706	0.899	0.842	0.960	**0.001**	31.1	0.169	20	13	49	***P*<0.001**
	Retrospective	7	33,662	0.600	0.504	0.714	**<0.001**	87.0	**<0.001**	5	4	7	
Data source	Database	8	42,668	0.686	0.574	0.819	**<0.001**	95.9	**<0.001**	6	4	10	*P*=0.073
	Multi center	6	13,599	0.873	0.752	1.013	0.074	42.3	0.123	-	-	-	
	One site	2	101	0.294	0.045	1.910	0.200	81.5	**0.020**	-	-	-	
Region	EU	8	26,818	0.743	0.590	0.936	**0.012**	95.0	**<0.001**	8	5	29	*P*=0.682
	Other	4	24,336	0.761	0.571	1.016	0.064	89.6	**<0.001**	-	-	-	
	U.S.	4	5,214	0.607	0.390	0.946	**0.028**	68.6	**0.023**	6	4	41	
Supported by company	No	7	22,706	0.692	0.584	0.820	**<0.001**	89.8	**<0.001**	7	5	11	*P*=0.219
	Yes	9	33,662	0.795	0.690	0.916	**0.001**	74.9	**<0.001**	10	7	23	
Treatment Resistant Schizophrenia	No/Not Reported	13	51,927	0.723	0.613	0.852	**<0.001**	93.4	**<0.001**	7	5	13	*P*=0.954
	Yes	3	4,441	0.719	0.682	0.758	**<0.001**	<0.1	0.543	9	8	11	

Bolded *P* values indicate *P*<0.05; CI, confidence interval; NA, not available; NNT, numbers-needed-to-treat

[a] NNTs were only calculated when the risk ratio analysis was significant (*P*<0.05) The mean risk for the non-clozapine SGAs treatment was used as the assumed control group risk.

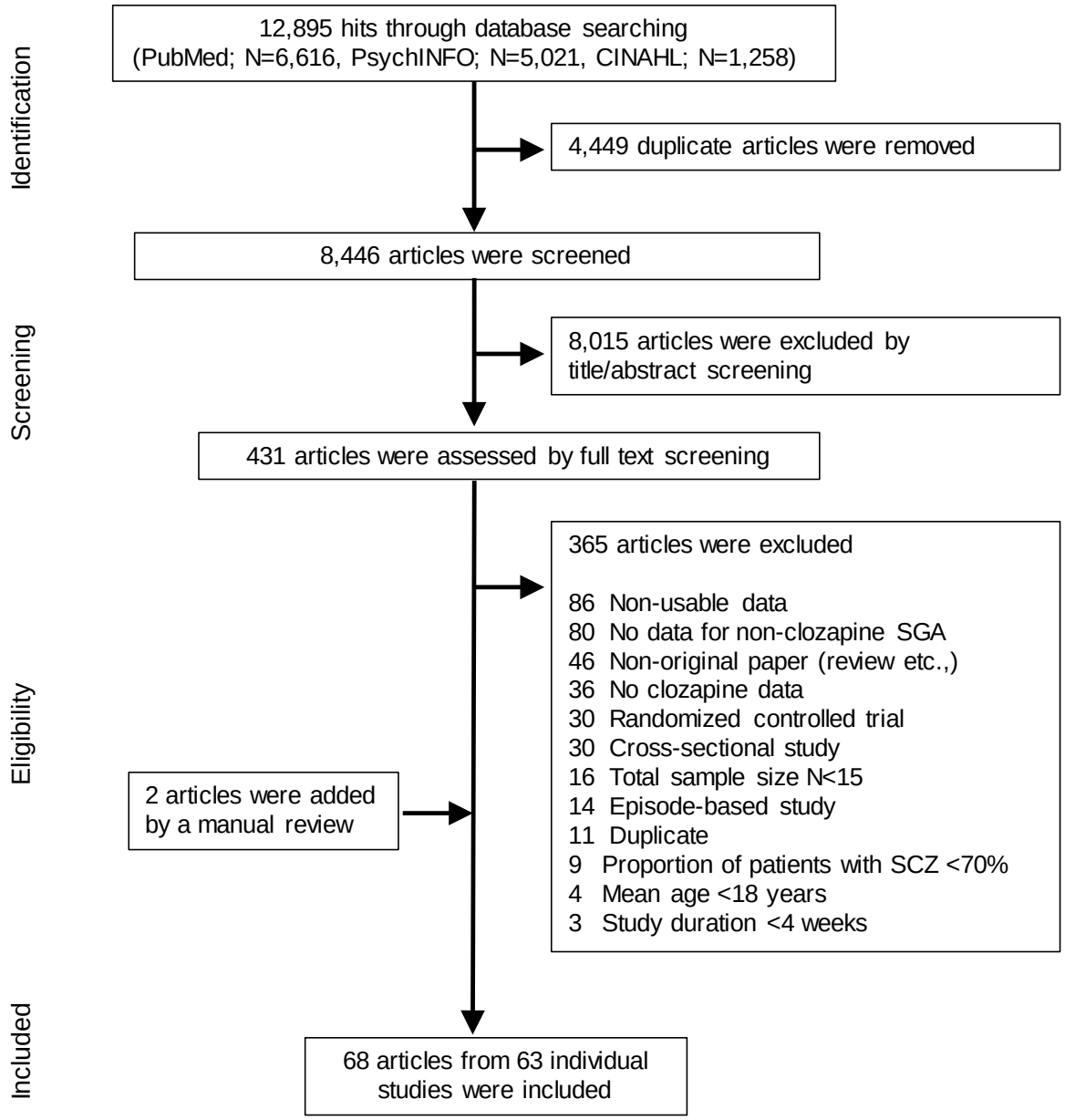
eTable 6. Results of meta-regression analyses for co-primary outcomes

Moderator or Mediator Variable	Studies (N)	Results			
		Coefficient	Lower 95%CI	Upper 95%CI	*P* Value
Meta-regression analyses for hospitalization					
Male (%)	19	0.001	-0.009	0.011	0.802
Sample size	19	0.000	0.000	0.000	0.809
Publication year	19	-0.006	-0.037	0.026	0.721
Mean age	18	-0.007	-0.032	0.017	0.551
Illness duration	6	-0.028	-0.058	0.003	0.080
Study duration	17	-0.055	-0.268	0.158	0.616
Follow up duration	11	-0.129	-0.505	0.248	0.504
Study quality	19	0.090	-0.148	0.328	0.458
Baseline illness severity (Hedges' g)*	12	0.201	-0.143	0.544	0.253
Meta-regression analyses for all-cause discontinuation					
Male (%)	16	-0.011	-0.029	0.008	0.250
Sample size	16	0.000	0.000	0.000	0.659
Publication year	16	0.001	-0.032	0.034	0.942
Mean age	15	-0.015	-0.043	0.014	0.315
Illness duration	5	-0.008	-0.047	0.031	0.679
Study duration	14	0.011	-0.076	0.097	0.811
Follow up duration	5	0.055	-0.319	0.428	0.774
Study quality	16	0.011	-0.205	0.227	0.920
Baseline illness severity (Hedges' g)*	8	-0.284	-0.792	0.224	0.274

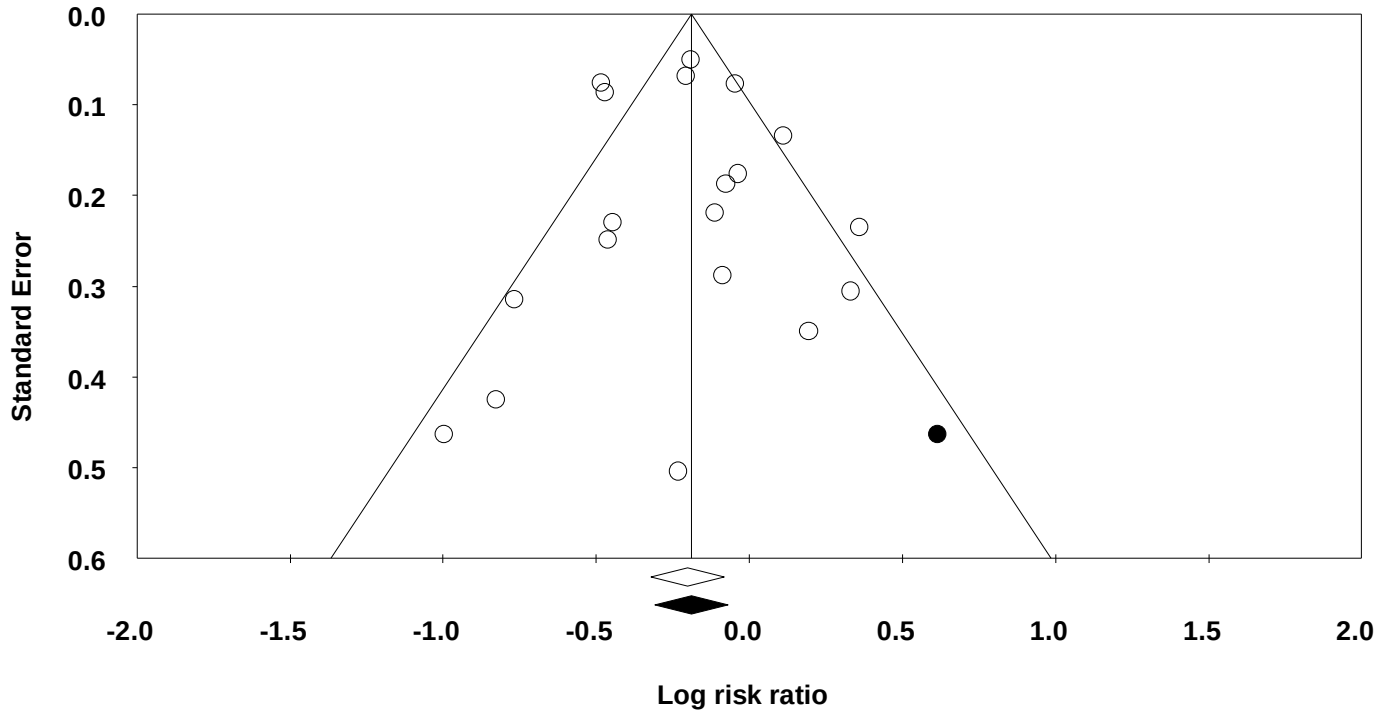
CI, confidence interval

*We used four types of data (choosing in descending order when multiple data were available): 1) psychopathology score (Positive and Negative Syndrome Scale (PANSS), Brief Psychiatric Rating Scale (BPRS) or Clinical Global Impressions scale (CGI) at baseline, 2) a prior number of hospitalizations, 3) prior hospitalization days, and 4) proportion of hospitalized patients at baseline.

eFigure 1. PRISMA Diagram of the Systematic Literature Search



eFigure 2-1. Funnel plot for hospitalization



Egger's regression test

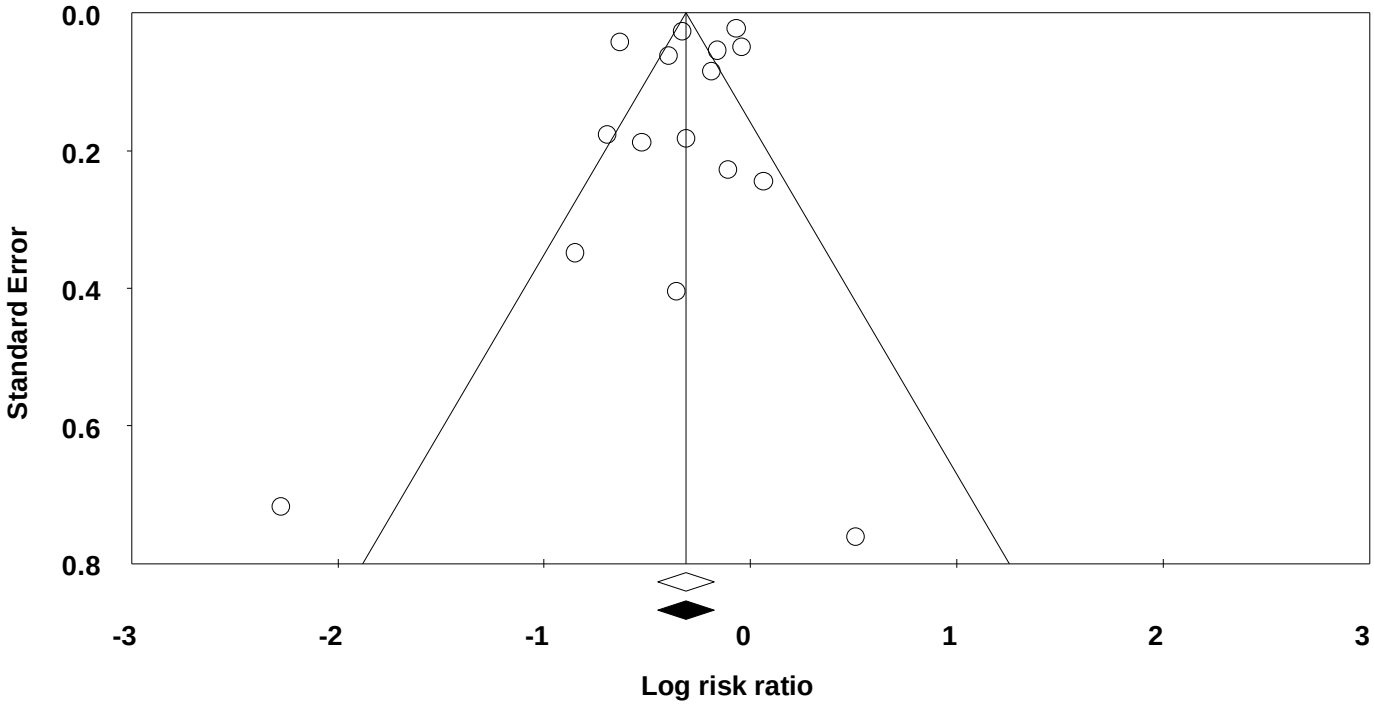
Intercept=0.138, 95%CI (-1.309 to 1.585), *P*=0.843

One data imputed by Duval and Tweedie's trim and fill method

Observed values: Risk Ratio=0.817, 95% confidence interval (0.725-0.920)

Adjusted values: Risk Ratio=0.827, 95% confidence interval (0.733-0.933)

eFigure 2-2. Funnel plot for all-cause discontinuation



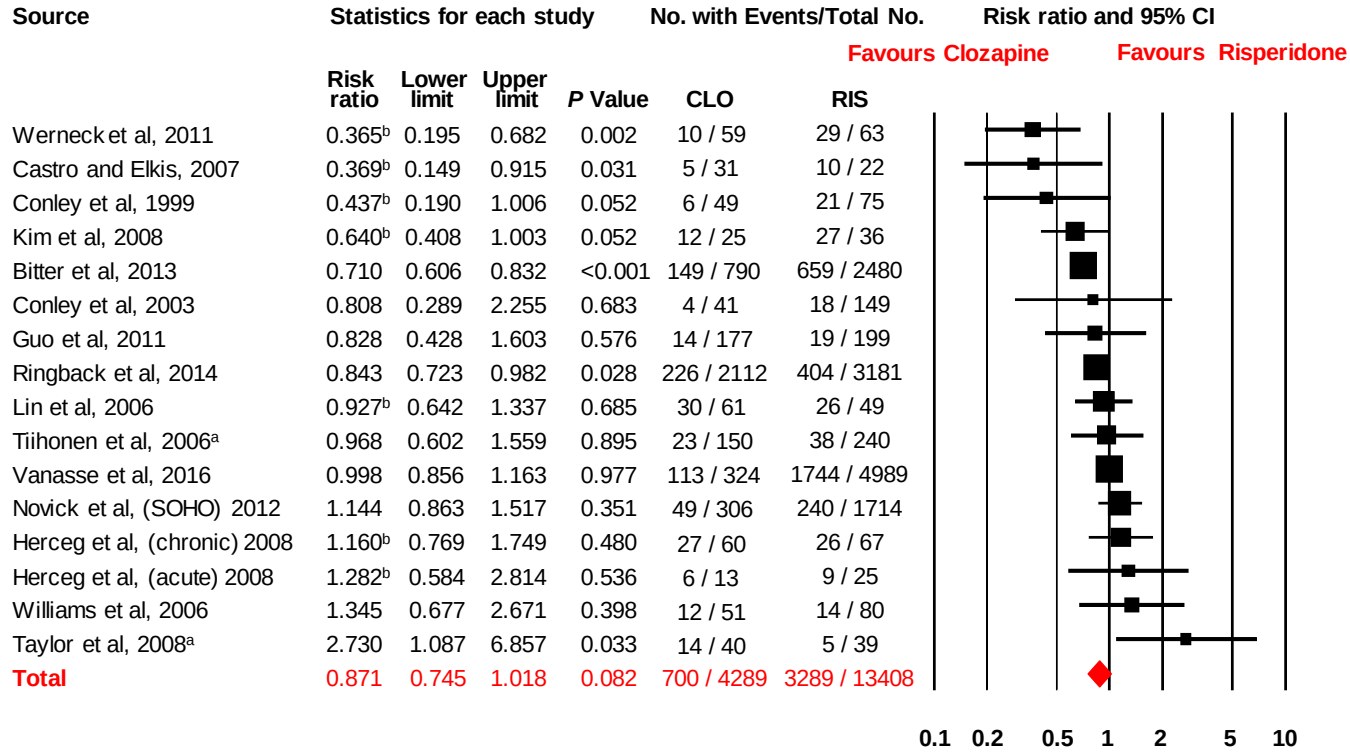
Egger's regression test

Intercept=-1.215, 95%CI (-4.015 to 1.584), *P*=0.368

No imputed data by Duval and Tweedie's trim and fill method

Observed values: Risk Ratio=0.732, 95% confidence interval (0.639-0.838)

eFigure 3-1. Forest plot of risk ratio for hospitalization (clozapine vs risperidone)



CI, confidence intervals; CLO, clozapine; RIS, risperidone

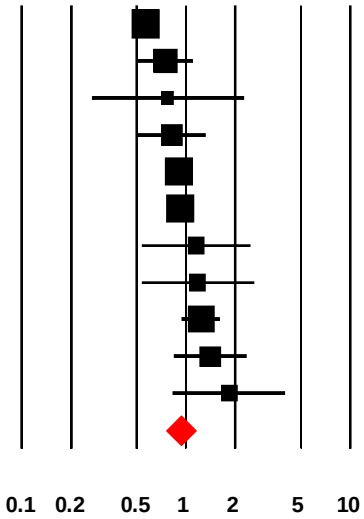
[a] The Study with unequal observation periods between clozapine and risperidone

The mean of observation period (months); Tiihonen et al. 2006, (CLO=17.0, RIS=6.5), Taylor et al, 2008, (CLO=23.2, RIS=17.4)

[b] Data from Kaplan-Meier estimates

eFigure 3-2. Forest plot of risk ratio for hospitalization (clozapine vs olanzapine)

Source	Statistics for each study				No. with Events/Total No.	
	Risk ratio	Lower limit	Upper limit	*P* Value	CLO	OLZ
Bitter et al, 2013	0.569	0.485	0.668	<0.001	149 / 790	541 / 1633
Herceg et al, (chronic) 2008	0.750[b]	0.514	1.094	0.135	27 / 60	24 / 40
Conley et al, 2003	0.773	0.268	2.232	0.634	4 / 41	13 / 103
Tiihonen et al, 2006[a]	0.816	0.508	1.313	0.403	23 / 150	37 / 197
Ringback et al, 2014	0.907	0.779	1.055	0.206	226 / 2112	438 / 3712
Vanasse et al, 2016	0.922	0.792	1.074	0.297	113 / 324	2091 / 5528
Herceg et al, (acute) 2008	1.154[b]	0.540	2.463	0.712	6 / 13	10 / 25
Guo et al, 2011	1.179	0.539	2.575	0.680	14 / 177	10 / 149
Novick et al, (SOHO) 2012	1.232	0.943	1.609	0.126	49 / 306	607 / 4669
Taylor et al, 2008[a]	1.400	0.844	2.323	0.193	14 / 40	37 / 148
Williams et al, 2006	1.830	0.834	4.014	0.131	12 / 51	9 / 70
Total	0.936	0.765	1.146	0.522	637 / 4064	3817 / 16274



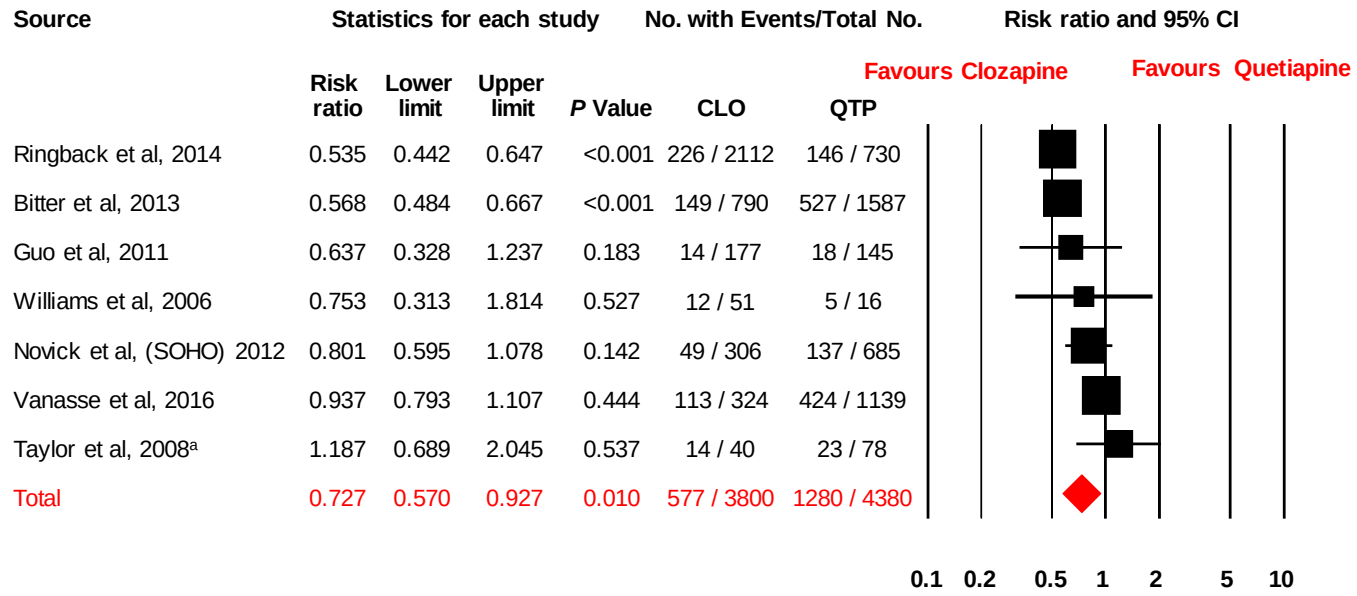
Cl, confidence intervals; CLO, clozapine; OLZ, olanzapine

[a] The Study with unequal observation periods between clozapine and olanzapine

The mean of observation period (months); Tiihonen et al. 2006, (CLO=17.0, OLZ=8.4), Taylor et al, 2008, (CLO=23.2, OLZ=21.1)

[b] Data from Kaplan-Meier estimates

eFigure 3-3. Forest plot of risk ratio for hospitalization (clozapine vs quetiapine)

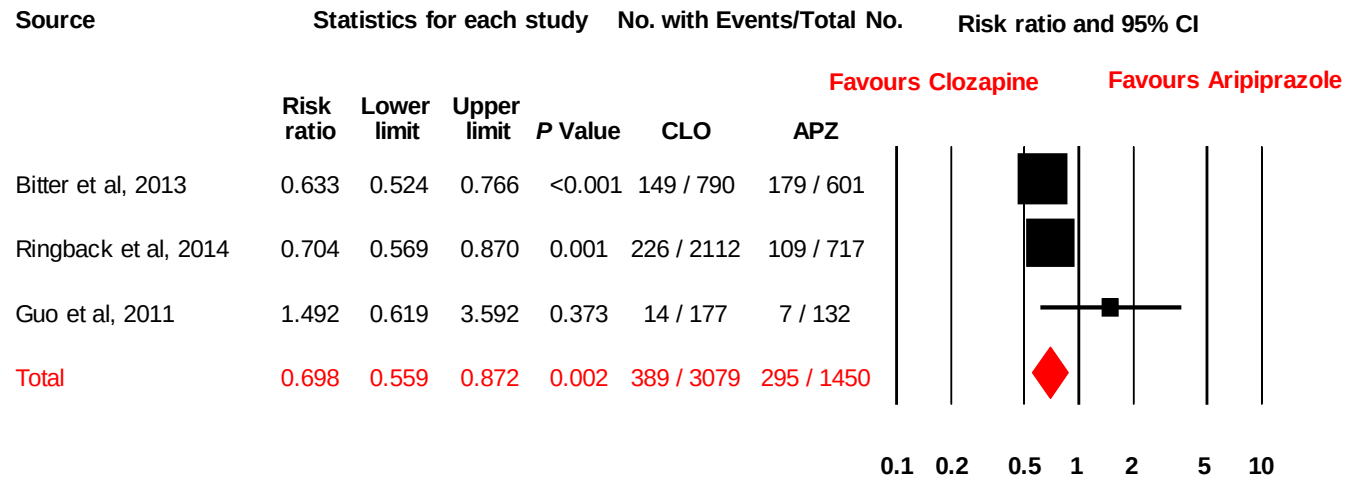


CI, confidence intervals; CLO, clozapine; QTP, quetiapine

[a] The Study with unequal observation periods between clozapine and quetiapine

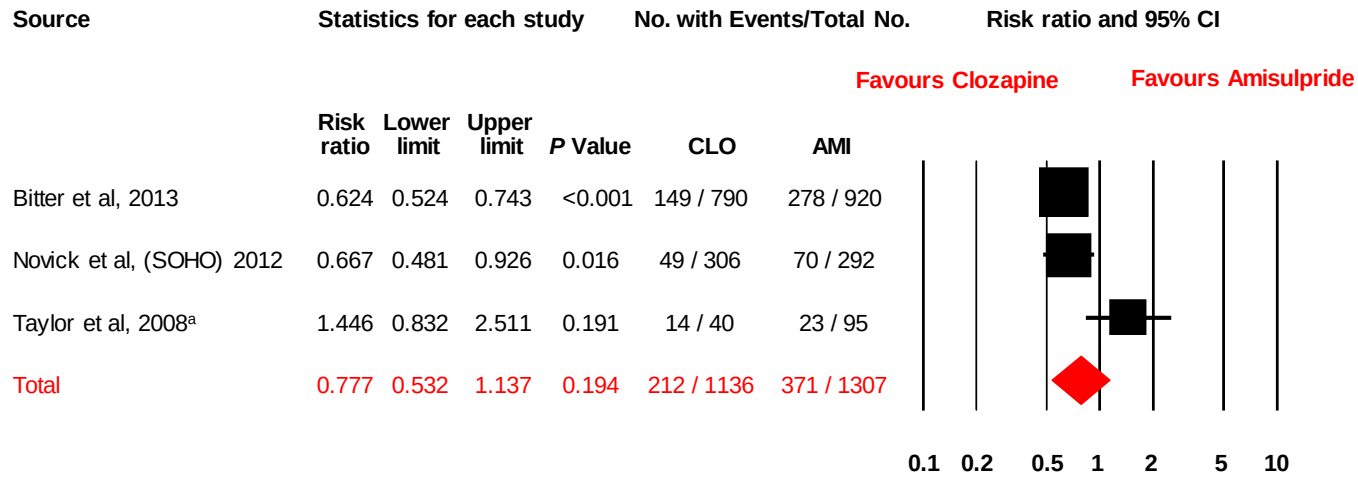
The mean of observation period (months); Taylor et al, 2008, (CLO=23.2, QTP=22.0)

eFigure 3-4. Forest plot of risk ratio for hospitalization (clozapine vs aripiprazole)



APZ, aripiprazole; CI, confidence intervals; CLO, clozapine

eFigure 3-5. Forest plot of risk ratio for hospitalization (clozapine vs amisulpride)



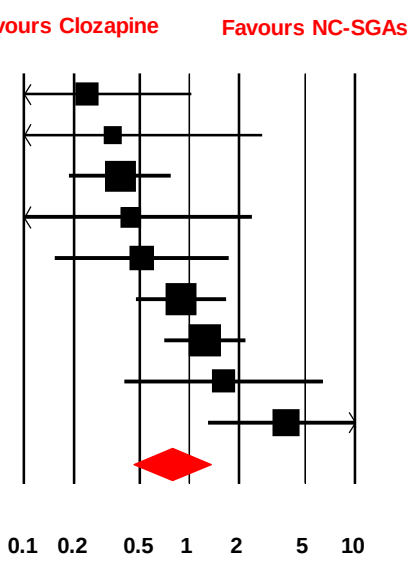
AMI, amisulpride; CI, confidence intervals; CLO, clozapine

[a]The Study with unequal observation periods between clozapine and amisulpride

The mean of observation period (months); Taylor et al, 2008, (CLO=23.2, AMI=23.5)

eFigure 3-6. Forest plot of risk ratio for hospitalization (at 6 months)

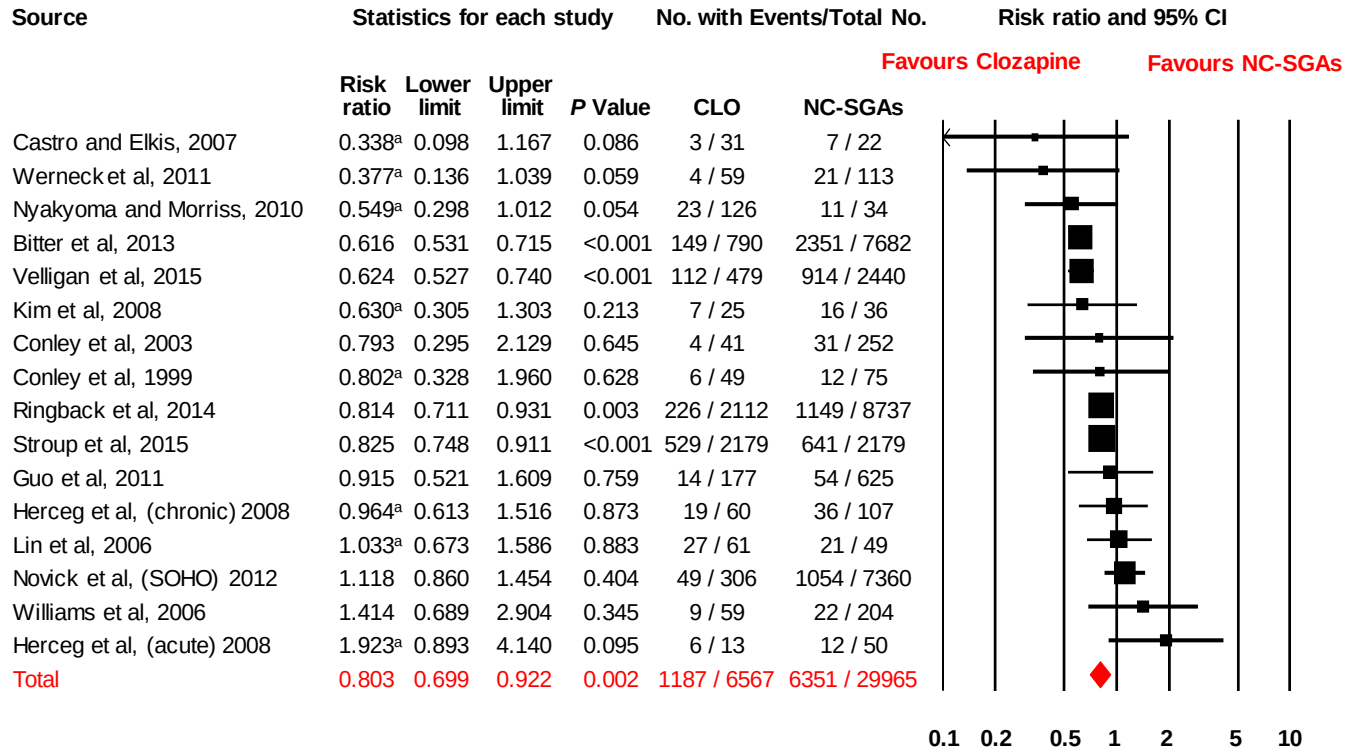
Source	Statistics for each study				No. with Events/Total No.	
	Risk ratio	Lower limit	Upper limit	*P* Value	CLO	NC-SGAs
Werneck et al, 2011	0.239[a]	0.056	1.026	0.054	2 / 59	16 / 113
Conley et al, 2003	0.342	0.043	2.722	0.311	1 / 41	17 / 252
Nyakyoma and Morriss, 2010	0.381[a]	0.188	0.773	0.007	14 / 126	10 / 34
Castro and Elkis, 2007	0.444[a]	0.083	2.380	0.343	2 / 31	3 / 22
Kim et al, 2008	0.512[a]	0.152	1.722	0.280	3 / 25	8 / 36
Herceg et al, (chronic) 2008	0.888[a]	0.472	1.672	0.712	12 / 60	23 / 107
Lin et al, 2006	1.234[a]	0.706	2.156	0.461	22 / 61	14 / 49
Conley et al, 1999	1.609[a]	0.408	6.351	0.497	4 / 49	4 / 75
Herceg et al, (acute) 2008	3.846[a]	1.307	11.314	0.014	5 / 13	5 / 50
Total	0.791	0.462	1.354	0.393	64 / 465	100 / 738



CI, confidence intervals; CLO, clozapine; NC-SGAs, non-clozapine second-generation antipsychotics

[a] Data from Kaplan-Meier estimates

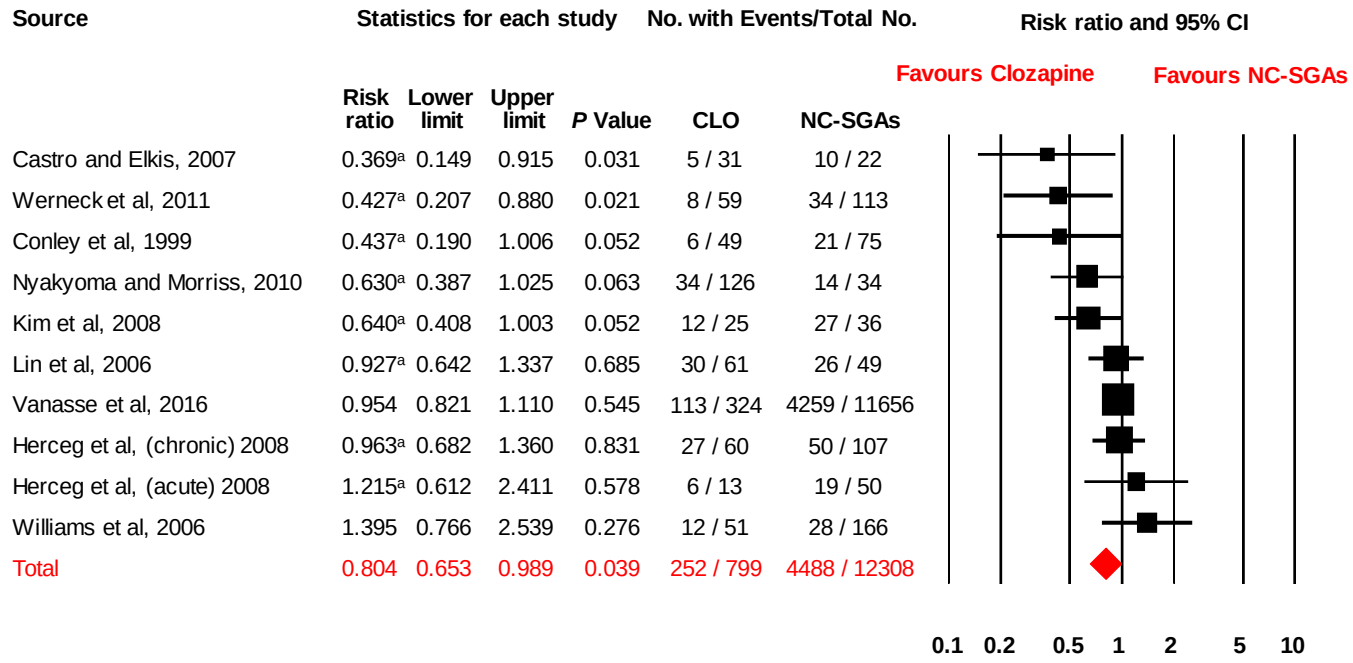
eFigure 3-7. Forest plot of risk ratio for hospitalization (at 12 months)



CI, confidence intervals; CLO, clozapine; NC-SGAs, non-clozapine second-generation antipsychotics

[a] Data from Kaplan-Meier estimates

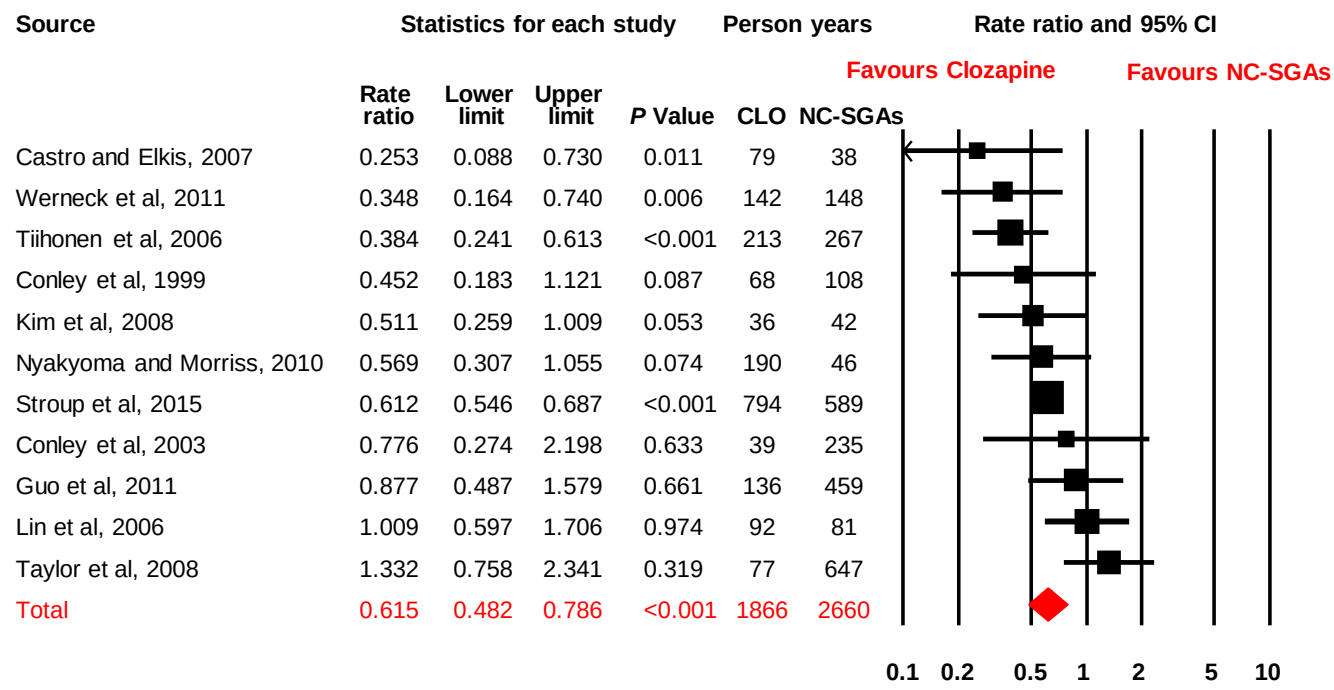
eFigure 3-8. Forest plot of risk ratio for hospitalization (at 24 months)



CI, confidence intervals; CLO, clozapine; NC-SGAs, non-clozapine second-generation antipsychotics

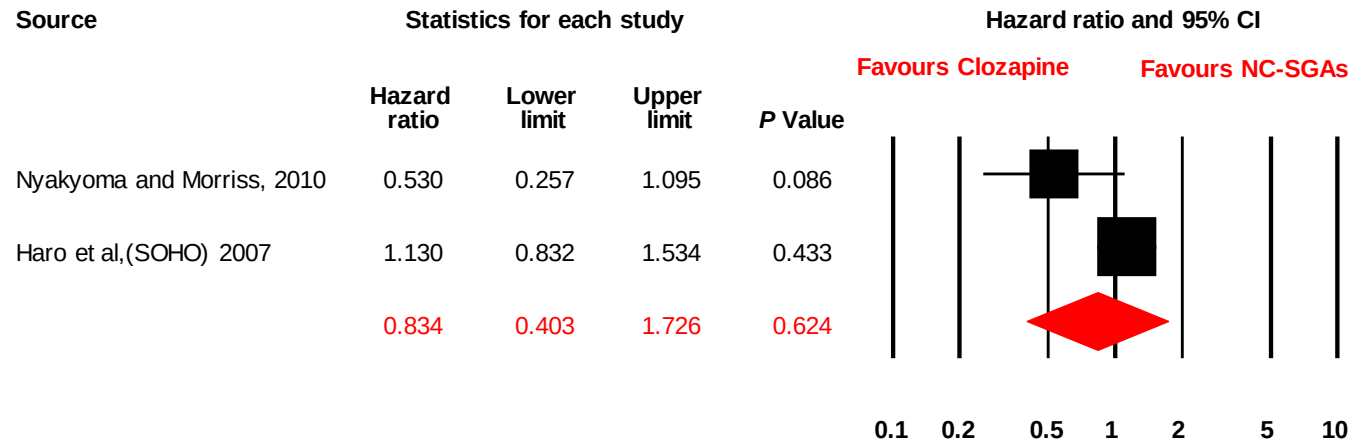
[a] Data from Kaplan-Meier estimates

eFigure 3-9. Forest plot of risk ratio for hospitalization (adjusted for follow-up duration)



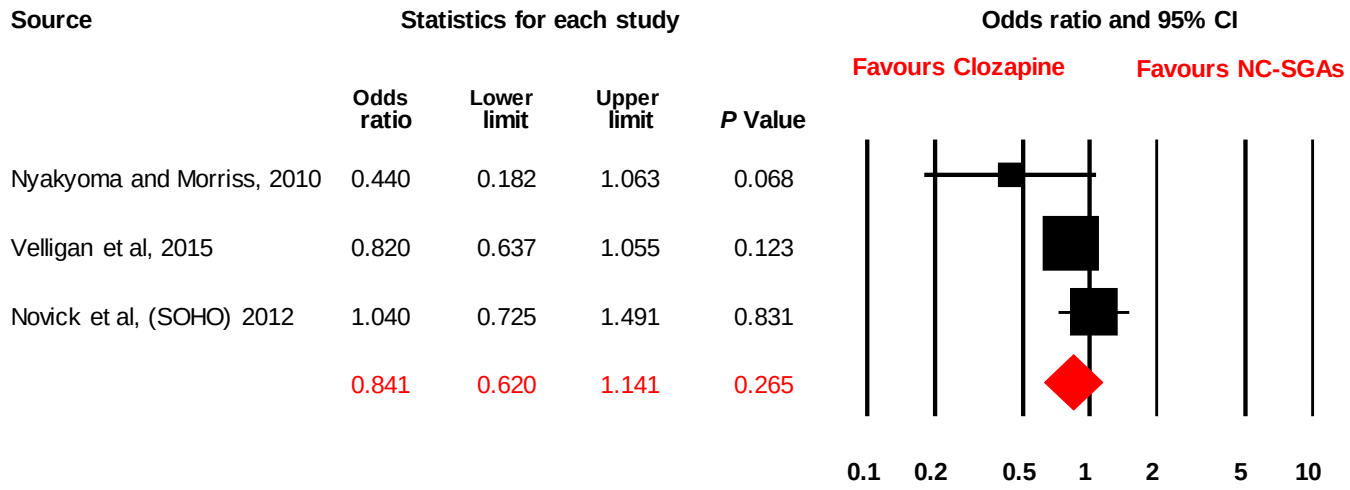
CI, confidence intervals; CLO, clozapine; NC-SGAs, non-clozapine second-generation antipsychotics

eFigure 3-10. Forest plot of hazard ratio for hospitalization



CI, confidence intervals; NC-SGAs, non-clozapine second-generation antipsychotics

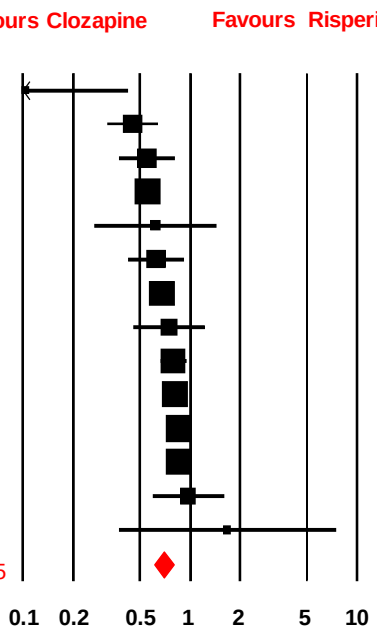
eFigure 3-11. Forest plot of adjusted odds ratio for hospitalization



CI, confidence intervals; CLO, clozapine; NC-SGAs, non-clozapine second-generation antipsychotics

eFigure 3-12. Forest plot of risk ratio for all-cause discontinuation (clozapine vs risperidone)

Source	Risk ratio	Lower limit	Upper limit	*P* Value	CLO	RIS
Green et al, 2003	0.103	0.025	0.420	0.002	2 / 35	10 / 18
Cooper et al, 2007	0.451	0.318	0.639	<0.001	27 / 164	983 / 2694
Ascher-Svanum et al, 2008	0.551	0.376	0.808	0.002	21 / 74	121 / 235
Ringback et al, 2014	0.559	0.511	0.611	<0.001	464 / 1973	1232 / 2927
Taylor et al, 2008[a]	0.620	0.268	1.435	0.265	7 / 40	11 / 39
Hodgson et al, 2005	0.623[b]	0.426	0.911	0.015	19 / 44	40 / 57
Vanasse et al, 2016	0.677	0.599	0.766	<0.001	144 / 324	3273 / 4989
Buoli et al, 2016	0.747	0.457	1.220	0.244	14 / 36	25 / 48
Haro et al, (SOHO) 2007	0.795[b]	0.668	0.947	0.010	93 / 274	661 / 1549
Tiihonen et al, 2006[a]	0.807	0.724	0.901	<0.001	108 / 150	214 / 240
Bitter et al, 2013	0.852	0.814	0.892	<0.001	573 / 790	2111 / 2480
Treuer et al, (IC-SOHO) 2010	0.860	0.777	0.952	0.003	152 / 237	833 / 1117
Karagianis et al, 2009	0.971	0.594	1.586	0.906	9 / 19	121 / 248
Lindenmayer et al, 1998	1.667	0.374	7.424	0.503	5 / 21	2 / 14
Total	0.702	0.615	0.800	<0.001	1638 / 4181	9637 / 16655



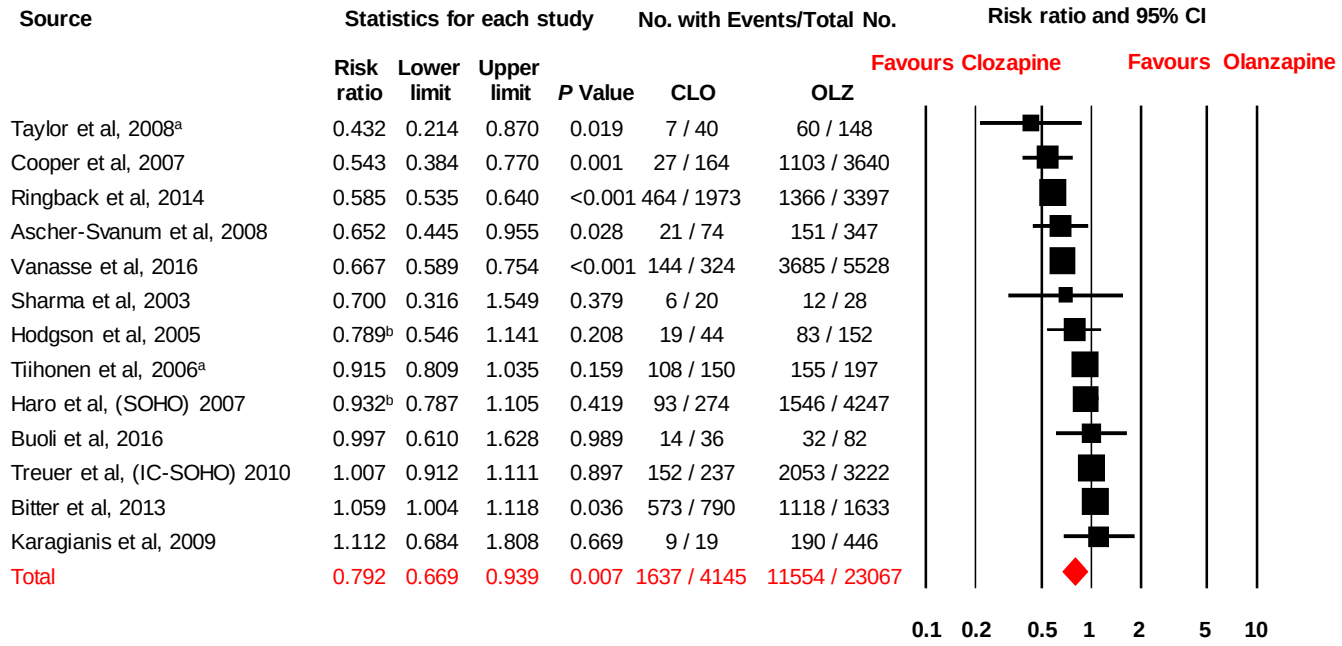
CI, confidence intervals; CLO, clozapine; RIS, risperidone

[a]The Study with unequal observation periods between clozapine and risperidone

The mean of observation period (months); Tiihonen et al. 2006, (CLO=17.0, RIS=6.5), Taylor et al, 2008, (CLO=23.2, RIS=17.4)

[b] Data from Kaplan-Meier estimates

eFigure 3-13. Forest plot of risk ratio for all-cause discontinuation (clozapine vs olanzapine)



CI, confidence intervals; CLO, clozapine; OLZ, olanzapine

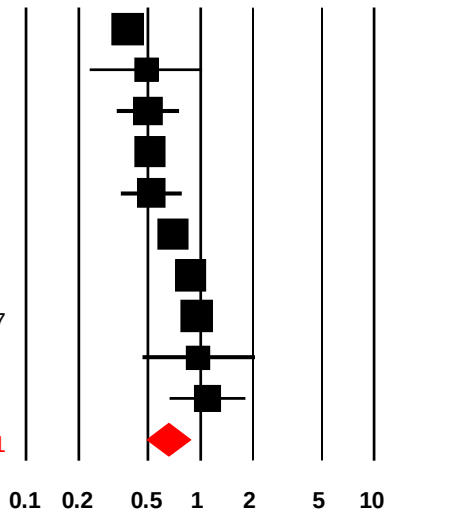
[a]The Study with unequal observation periods between clozapine and olanzapine

The mean of observation period (months); Tiihonen et al. 2006, (CLO=17.0, OLZ=8.4), Taylor et al, 2008, (CLO=23.2, OLZ=21.1)

[b] Data from Kaplan-Meier estimates

eFigure 3-14. Forest plot of risk ratio for all-cause discontinuation (clozapine vs quetiapine)

Source	Risk ratio	Lower limit	Upper limit	*P* Value	CLO	QTP
Ringback et al, 2014	0.382	0.345	0.422	<0.001	464 / 1973	387 / 628
Taylor et al, 2008[a]	0.488	0.234	1.017	0.055	7 / 40	28 / 78
Cooper et al, 2007	0.500	0.332	0.752	0.001	27 / 164	54 / 164
Haro et al, (SOHO) 2007	0.514[b]	0.431	0.612	<0.001	93 / 274	385 / 583
Ascher-Svanum et al, 2008	0.521	0.349	0.777	0.001	21 / 74	61 / 112
Vanasse et al, 2016	0.697	0.613	0.794	<0.001	144 / 324	726 / 1139
Treuer et al, (IC-SOHO) 2010	0.878	0.772	0.999	0.048	152 / 237	138 / 189
Bitter et al, 2013	0.952	0.905	1.002	0.059	573 / 790	1209 / 1587
Buoli et al, 2016	0.972	0.463	2.044	0.941	14 / 36	6 / 15
Karagianis et al, 2009	1.100	0.669	1.811	0.707	9 / 19	93 / 216
Total	0.654	0.490	0.874	0.004	1504 / 3931	3087 / 4711



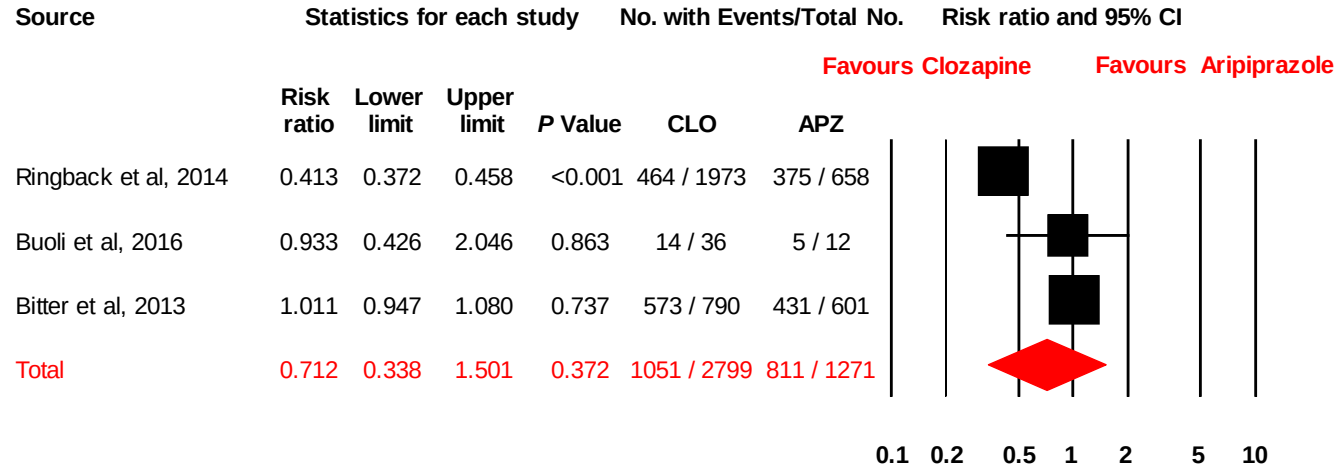
CI, confidence intervals; CLO, clozapine; QTP, quetiapine

[a]The Study with unequal observation periods between clozapine and quetiapine

The mean of observation period (months); Taylor et al, 2008, (CLO=23.2, QTP=22.0)

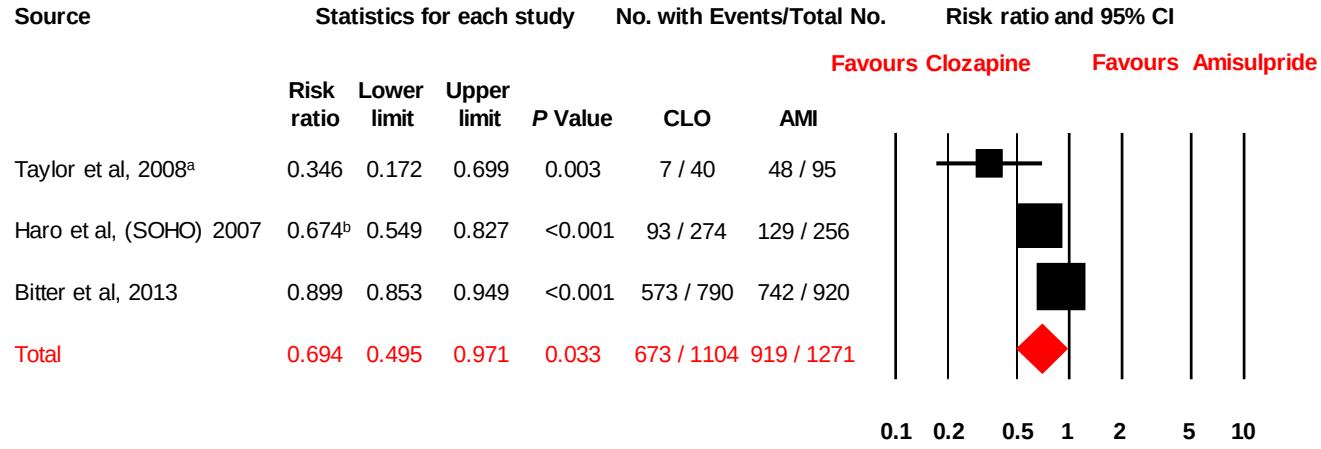
[b] Data from Kaplan-Meier estimates

eFigure 3-15. Forest plot of risk ratio for all-cause discontinuation (clozapine vs aripiprazole)



APZ, aripiprazole; CI, confidence intervals; CLO, clozapine

eFigure 3-16. Forest plot of risk ratio for all-cause discontinuation (clozapine vs amisulpride)



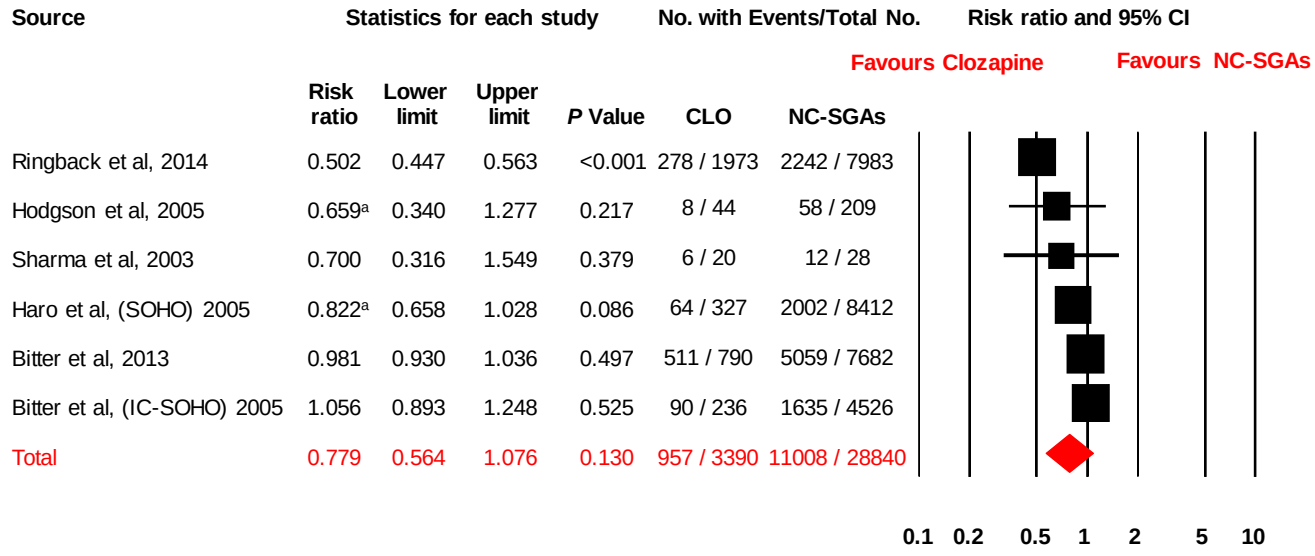
AMI, amisulpride; CI, confidence intervals; CLO, clozapine

[a]The Study with unequal observation periods between clozapine and amisulpride

The mean of observation period (months); Taylor et al, 2008, (CLO=23.2, AMI=23.5)

[b] Data from Kaplan-Meier estimates

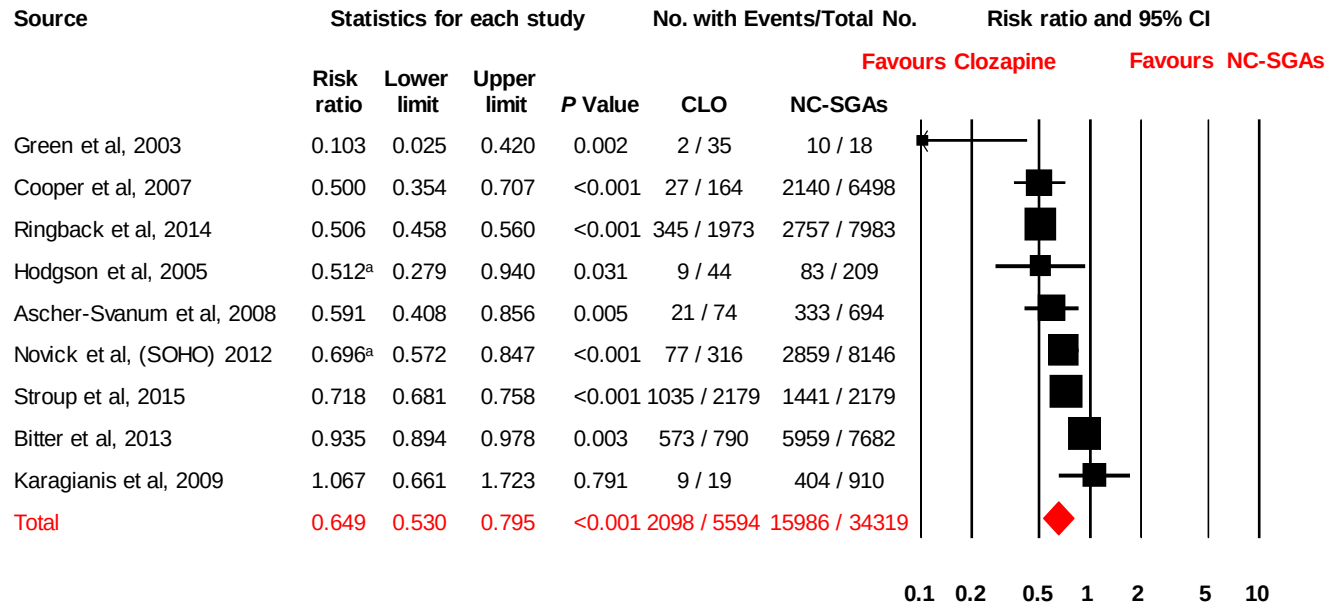
eFigure 3-17. Forest plot of risk ratio for all-cause discontinuation (at 6 months)



CI, confidence intervals; CLO, clozapine; NC-SGAs, non-clozapine second-generation antipsychotics

[a] Data from Kaplan-Meier estimates

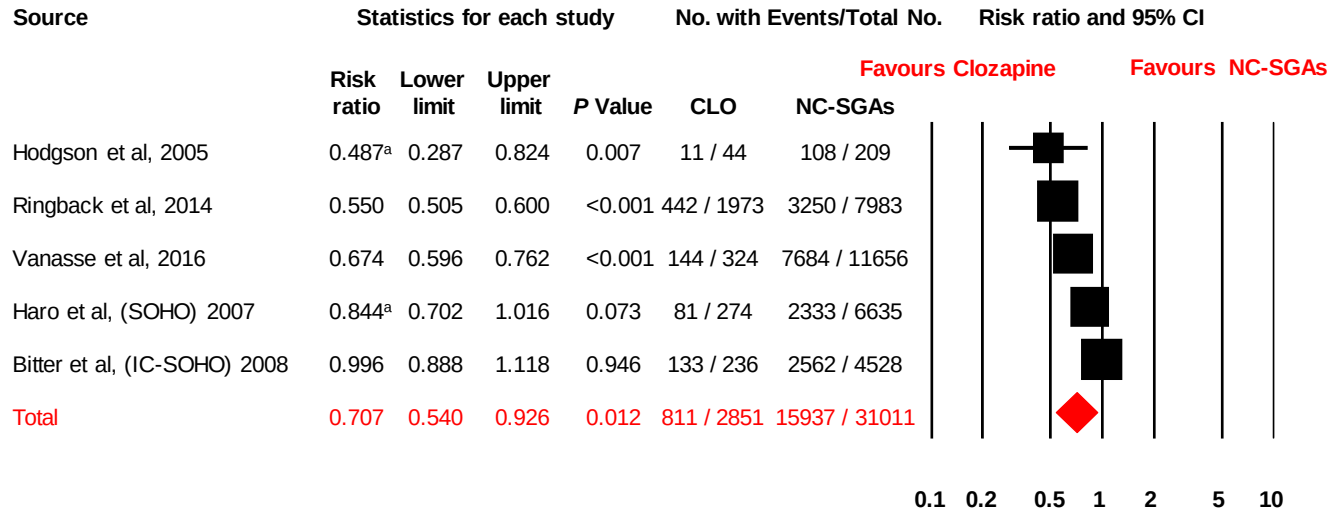
eFigure 3-18. Forest plot of risk ratio for all-cause discontinuation (at 12 months)



CI, confidence intervals; CLO, clozapine; NC-SGAs, non-clozapine second-generation antipsychotics

[a] Data from Kaplan-Meier estimates

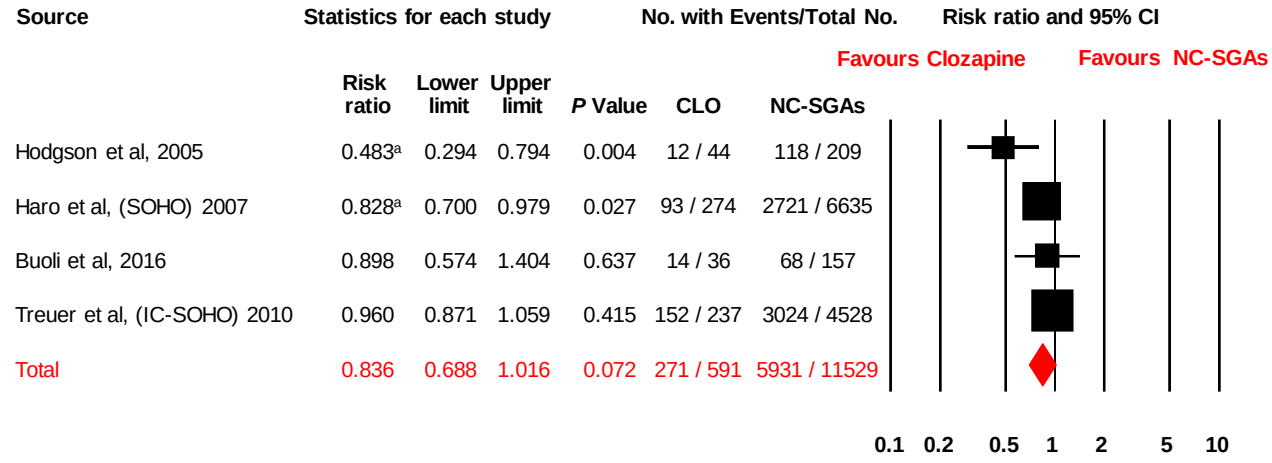
eFigure 3-19. Forest plot of risk ratio for all-cause discontinuation (at 24 months)



CI, confidence intervals; CLO, clozapine; NC-SGAs, non-clozapine second-generation antipsychotics

[a] Data from Kaplan-Meier estimates

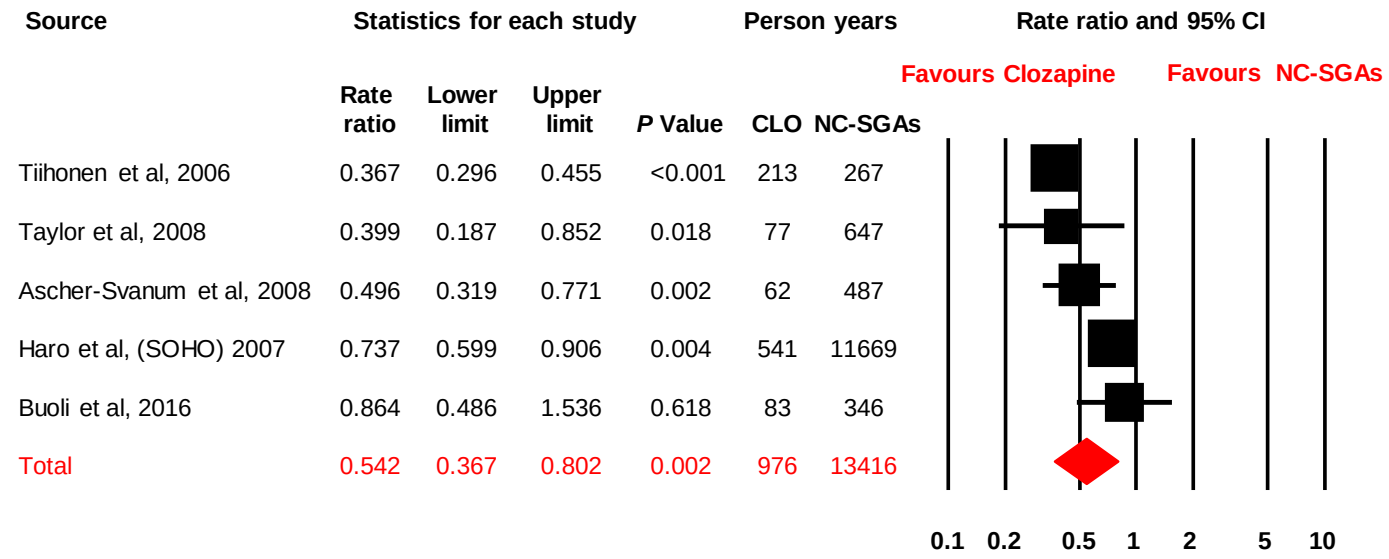
eFigure 3-20. Forest plot of risk ratio for all-cause discontinuation (at 36 months)



CI, confidence intervals; CLO, clozapine; NC-SGAs, non-clozapine second-generation antipsychotics

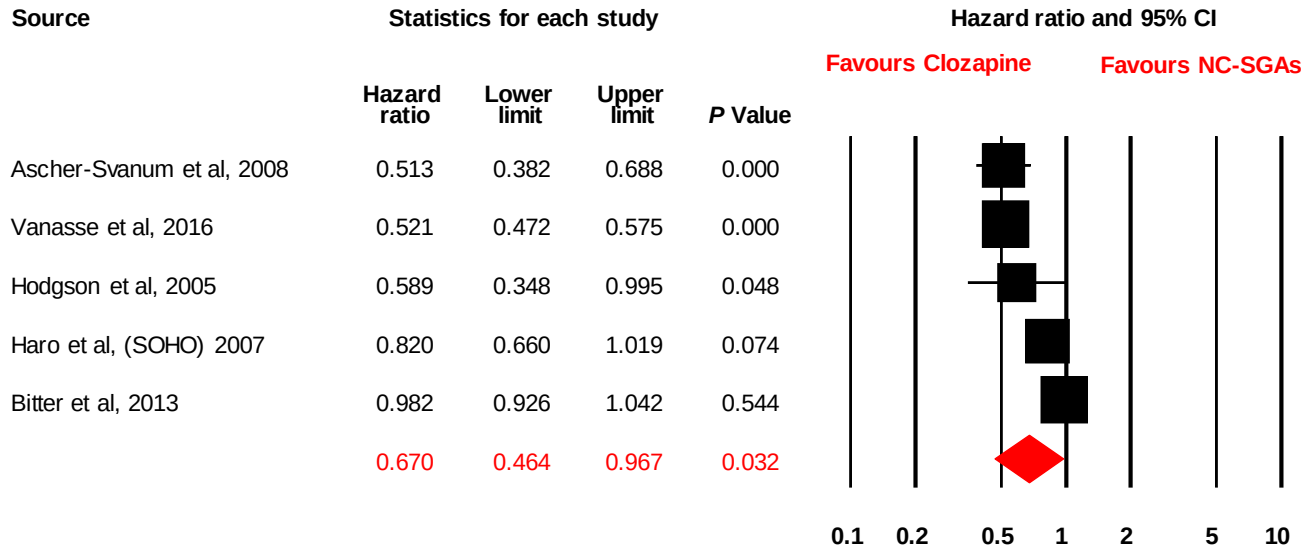
[a] Data from Kaplan-Meier estimates

eFigure 3-21. Forest plot of risk ratio for all-cause discontinuation (adjusted for follow-up duration)



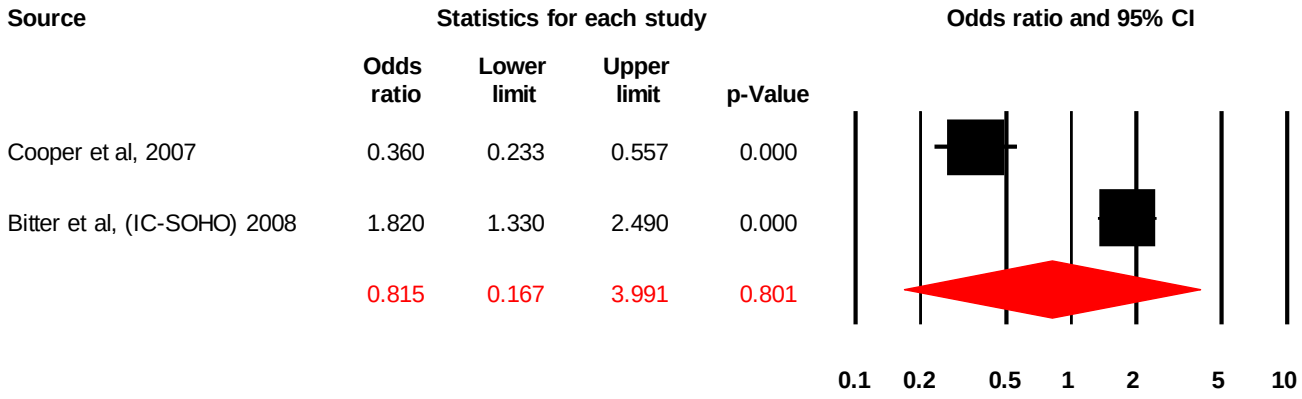
CI, confidence intervals; CLO, clozapine; NC-SGAs, non-clozapine second-generation antipsychotics

eFigure 3-22. Forest plot of hazard ratio for all-cause discontinuation



CI, confidence intervals; CLO, clozapine; NC-SGAs, non-clozapine second-generation antipsychotics

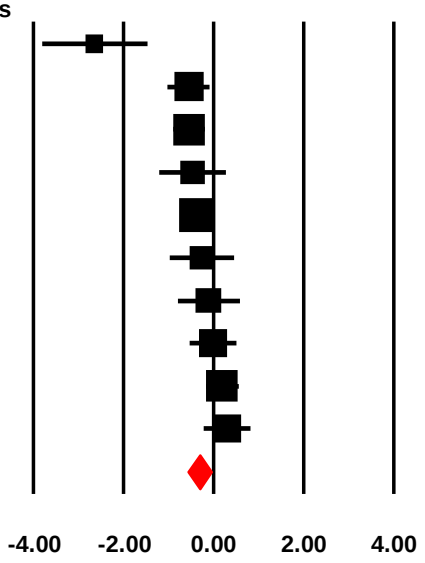
eFigure 3-23. Forest plot of adjusted odds ratio for all-cause discontinuation



CI, confidence intervals; CLO, clozapine; NC-SGAs, non-clozapine second-generation antipsychotics

eFigure 4-1. Forest plot of standardized mean difference for overall symptoms

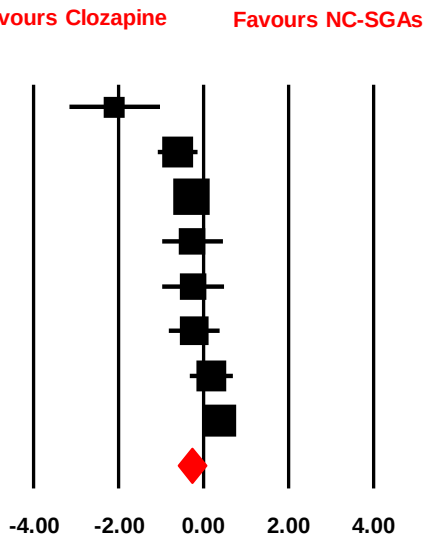
Source	Std diff in means	Lower limit	Upper limit	*P* Value	CLO	NC-SGAs
Agid et al, 2007	-2.639	-3.792	-1.486	<0.001	13	9
Flynn et al, 1998	-0.546	-1.000	-0.091	0.019	57	29
Karki et al, 2001	-0.538	-0.883	-0.193	0.002	50	100
Sharma et al, 2003	-0.449	-1.175	0.277	0.225	14	16
Novick et al, (SOHO) 2012	-0.384	-0.502	-0.266	<0.001	289	6810
Lindenmayer et al, 1998	-0.255	-0.963	0.453	0.480	19	13
Franza et al, 2015	-0.105	-0.775	0.565	0.758	12	30
Mauri et al, 2008	-0.010	-0.503	0.484	0.970	19	92
Strous et al, 2006	0.193	-0.155	0.541	0.276	55	76
Konrad et al, 2000	0.309	-0.190	0.808	0.225	27	37
Total	-0.302	-0.572	-0.032	0.028	555	7212



CI, confidence intervals; CLO, clozapine; NC-SGAs, non-clozapine second-generation antipsychotics; Std diff, standardized difference

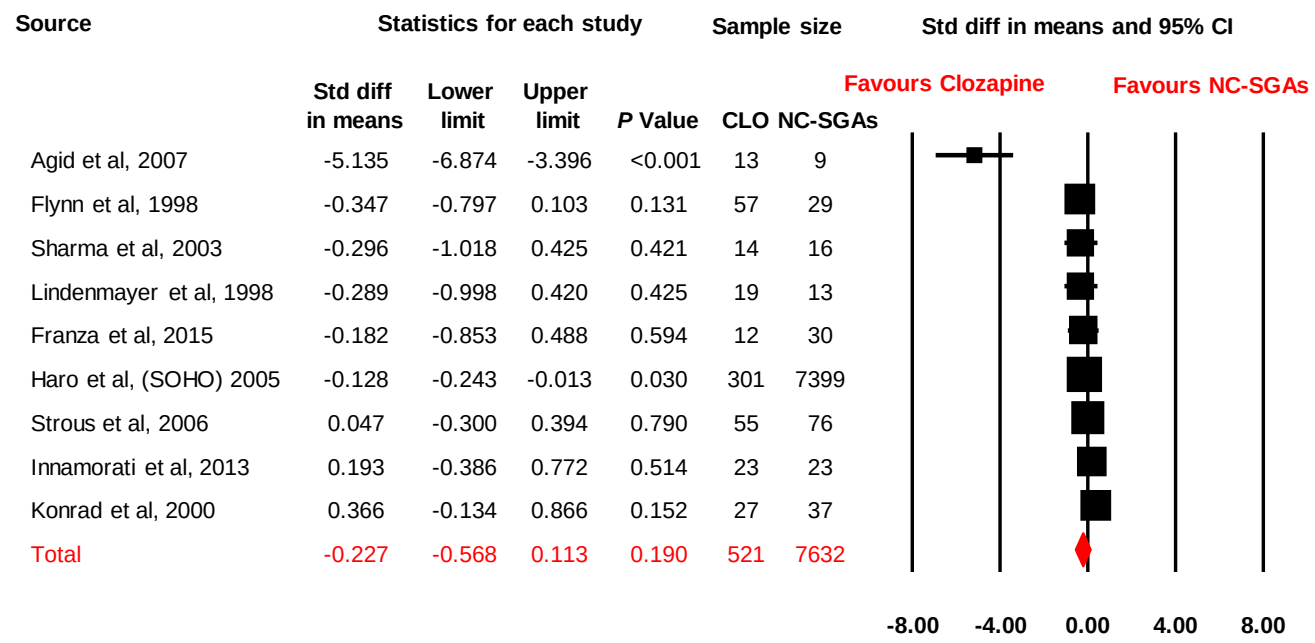
eFigure 4-2. Forest plot of standardized mean difference for positive symptoms

Source	Statistics for each study				Sample size	
	Std diff in means	Lower limit	Upper limit	*P* Value	CLO	NC-SGAs
Agid et al, 2007	-2.081	-3.130	-1.032	<0.001	13	9
Flynn et al, 1998	-0.601	-1.057	-0.145	0.010	57	29
Haro et al, (SOHO) 2005	-0.268	-0.384	-0.153	<0.001	301	7399
Lindenmayer et al, 1998	-0.246	-0.954	0.462	0.495	19	13
Sharma et al, 2003	-0.237	-0.957	0.483	0.519	14	16
Innamorati et al, 2013	-0.210	-0.789	0.370	0.478	23	23
Konrad et al, 2000	0.199	-0.299	0.696	0.433	27	37
Strous et al, 2006	0.383	0.033	0.733	0.032	55	76
Total	-0.253	-0.574	0.069	0.124	509	7602



CI, confidence intervals; CLO, clozapine; NC-SGAs, non-clozapine second-generation antipsychotics; Std diff, standardized difference

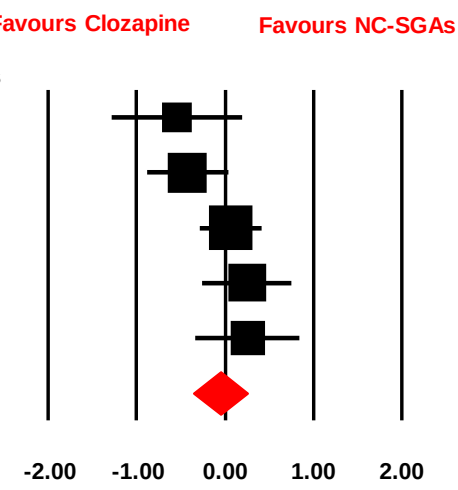
eFigure 4-3. Forest plot of standardized mean difference for negative symptoms



CI, confidence intervals; CLO, clozapine; NC-SGAs, non-clozapine second-generation antipsychotics; Std diff, standardized difference

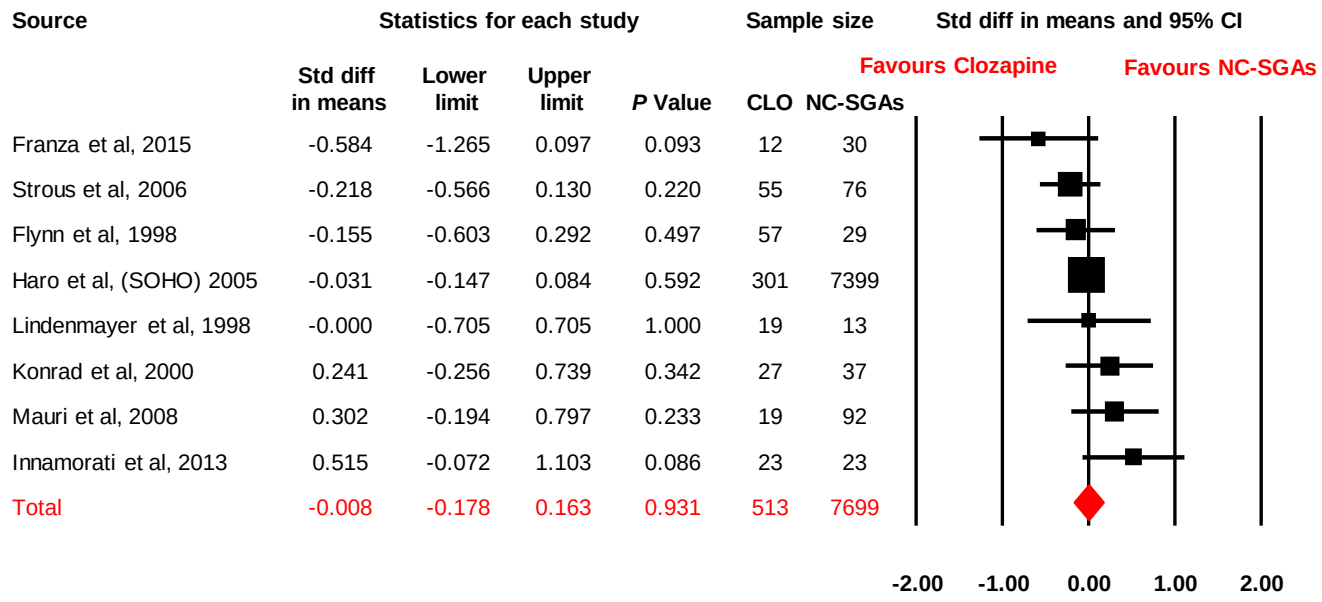
eFigure 4-4. Forest plot of standardized mean difference for general symptoms

Source	Statistics for each study				Sample size	
	Std diff in means	Lower limit	Upper limit	*P* Value	CLO	NC-SGAs
Sharma et al, 2003	-0.546	-1.277	0.184	0.143	14	16
Flynn et al, 1998	-0.425	-0.877	0.027	0.065	57	29
Strous et al, 2006	0.067	-0.280	0.414	0.707	55	76
Konrad et al, 2000	0.252	-0.246	0.750	0.322	27	37
Innamorati et al, 2013	0.256	-0.324	0.837	0.386	23	23
Total	-0.050	-0.351	0.251	0.746	176	181



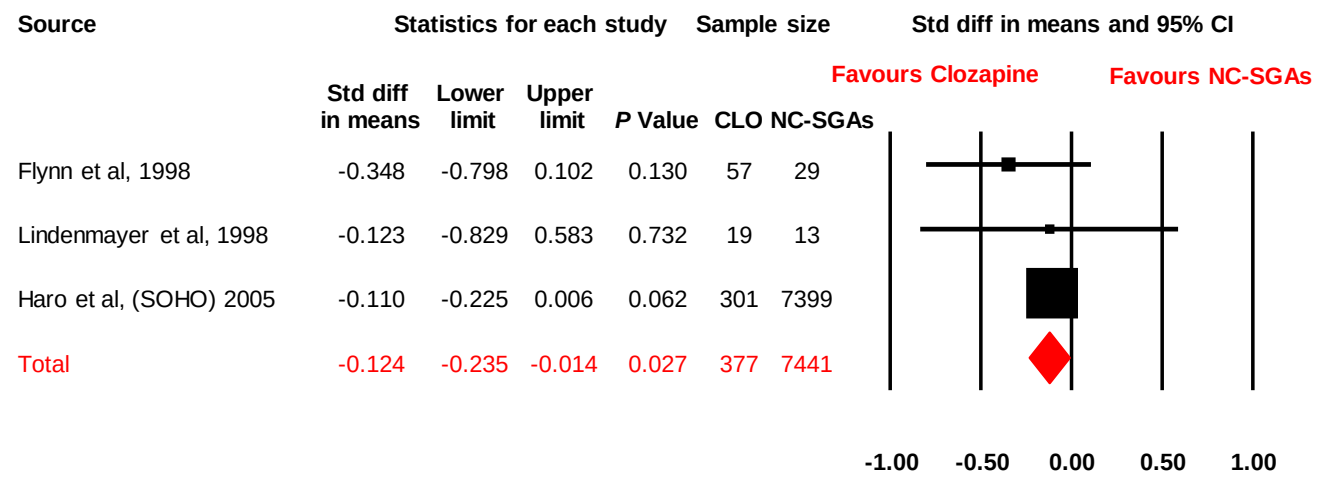
CI, confidence intervals; CLO, clozapine; NC-SGAs, non-clozapine second-generation antipsychotics; Std diff, standardized difference

eFigure 4-5. Forest plot of standardized mean difference for depressive symptoms



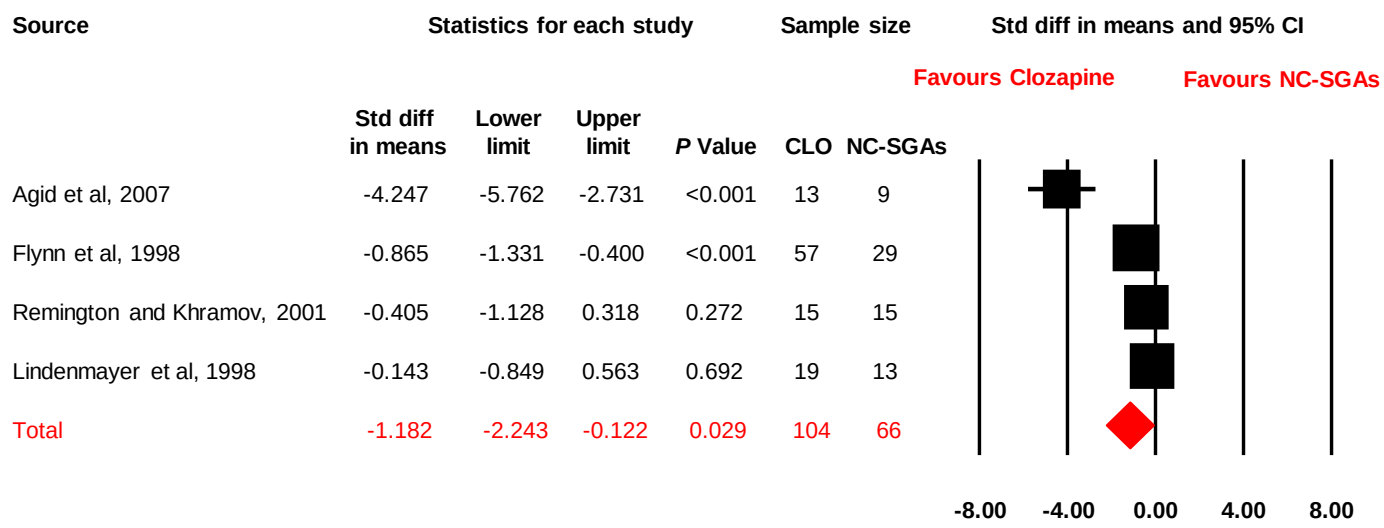
CI, confidence intervals; CLO, clozapine; NC-SGAs, non-clozapine second-generation antipsychotics; Std diff, standardized difference

eFigure 4-6. Forest plot of standardized mean difference for cognitive symptoms



CI, confidence intervals; CLO, clozapine; NC-SGAs, non-clozapine second-generation antipsychotics; Std diff, standardized difference

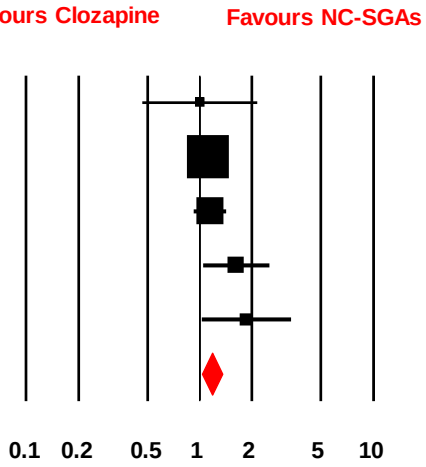
eFigure 4-7. Forest plot of standardized mean difference for clinical global impressions



CI, confidence intervals; CLO, clozapine; NC-SGAs, non-clozapine second-generation antipsychotics; Std diff, standardized difference

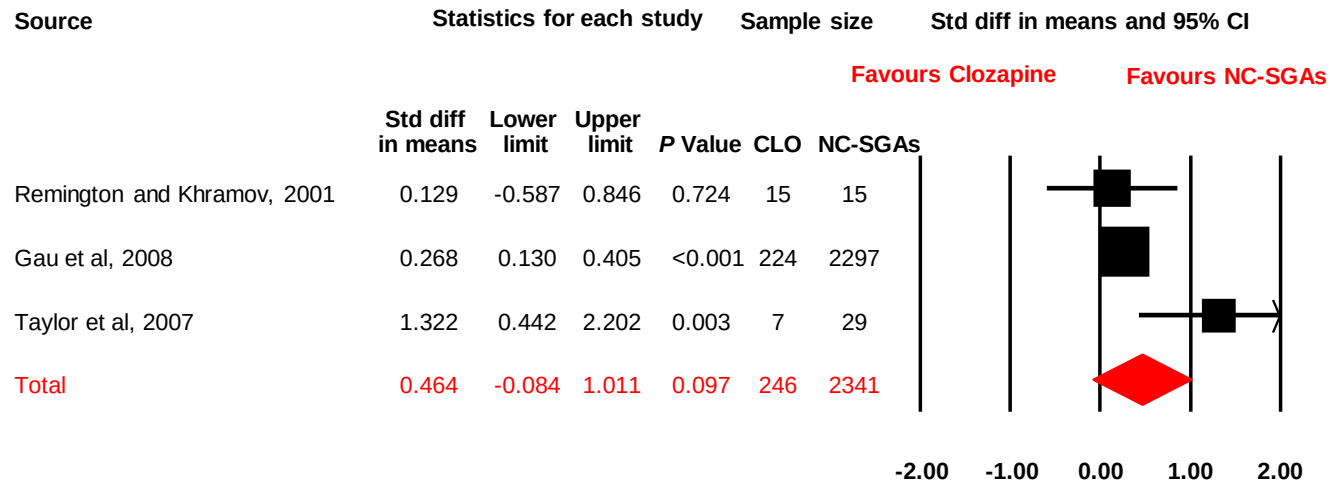
eFigure 4-8. Forest plot of rate ratio for frequency of hospitalization

Source	Rate ratio	Lower limit	Upper limit	*P* Value	CLO	NC-SGAs
Remington and Khramov, 2001	1.000	0.470	2.126	1.000	23	23
Gau et al, 2008	1.117	1.045	1.193	0.001	448	4008
Haro et al, (SOHO) 2007	1.139	0.924	1.405	0.223	541	11669
Shermock et al, 2001	1.619	1.044	2.511	0.031	66	862
Taylor et al, 2007	1.845	1.024	3.324	0.041	21	87
Total	1.180	1.034	1.346	0.014	1099	16648



CI, confidence intervals; CLO, clozapine; NC-SGAs, non-clozapine second-generation antipsychotics

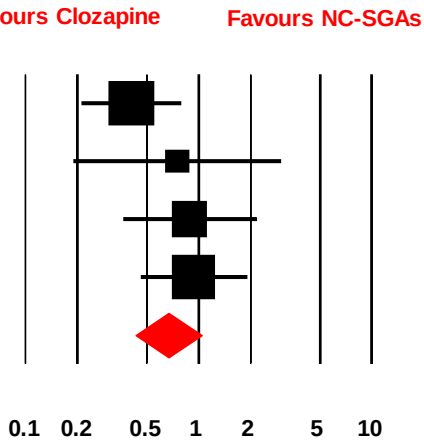
eFigure 4-9. Forest plot of standardized mean difference for length of hospitalization



CI, confidence intervals; CLO, clozapine; NC-SGAs, non-clozapine second-generation antipsychotics; Std diff, standardized difference

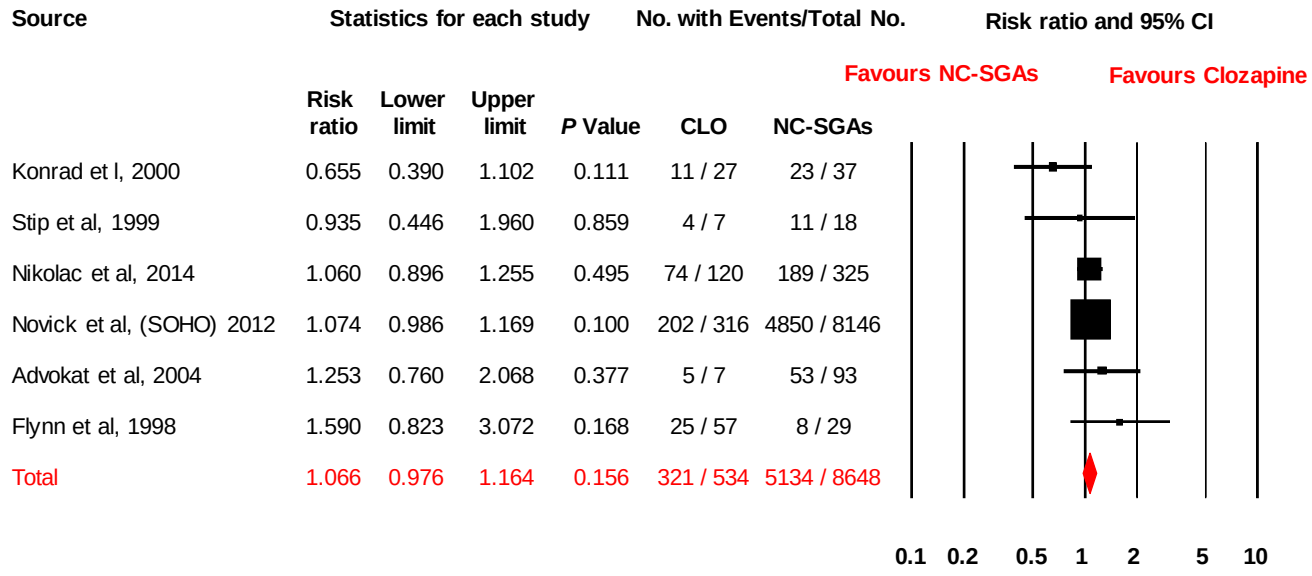
eFigure 4-10. Forest plot of risk ratio for suicide attempt/self-injurious behavior

Source	Statistics for each study				No. with Events/Total No.		Risk ratio and 95% CI
	Risk ratio	Lower limit	Upper limit	*P* Value	CLO	NC-SGAs	
Bitter et al, 2013	0.407	0.210	0.790	0.008	9 / 790	215 / 7682	
Innamorati et al, 2013	0.750	0.189	2.984	0.683	3 / 23	4 / 23	
Haro et al, (SOHO) 2007	0.885	0.365	2.144	0.787	5 / 278	133 / 6546	
Stroup et al, 2015	0.938	0.465	1.891	0.857	15 / 2179	16 / 2179	
Total	0.672	0.432	1.046	0.078	32 / 3270	368 / 16430	



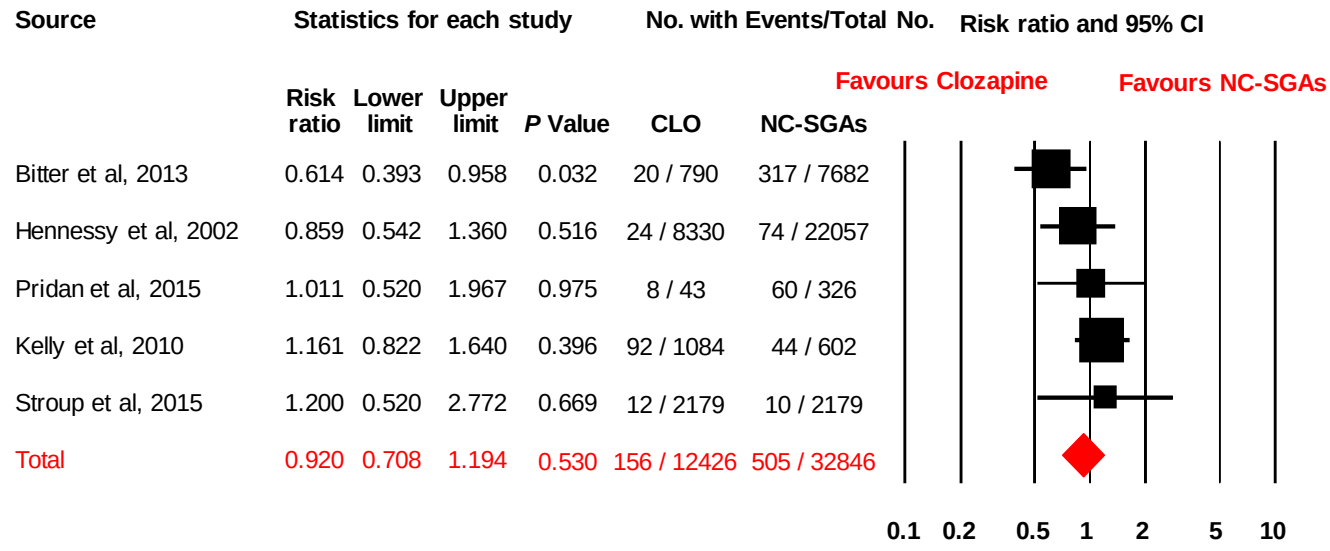
CI, confidence intervals; CLO, clozapine; NC-SGAs, non-clozapine second-generation antipsychotics

eFigure 4-11. Forest plot of risk ratio for response



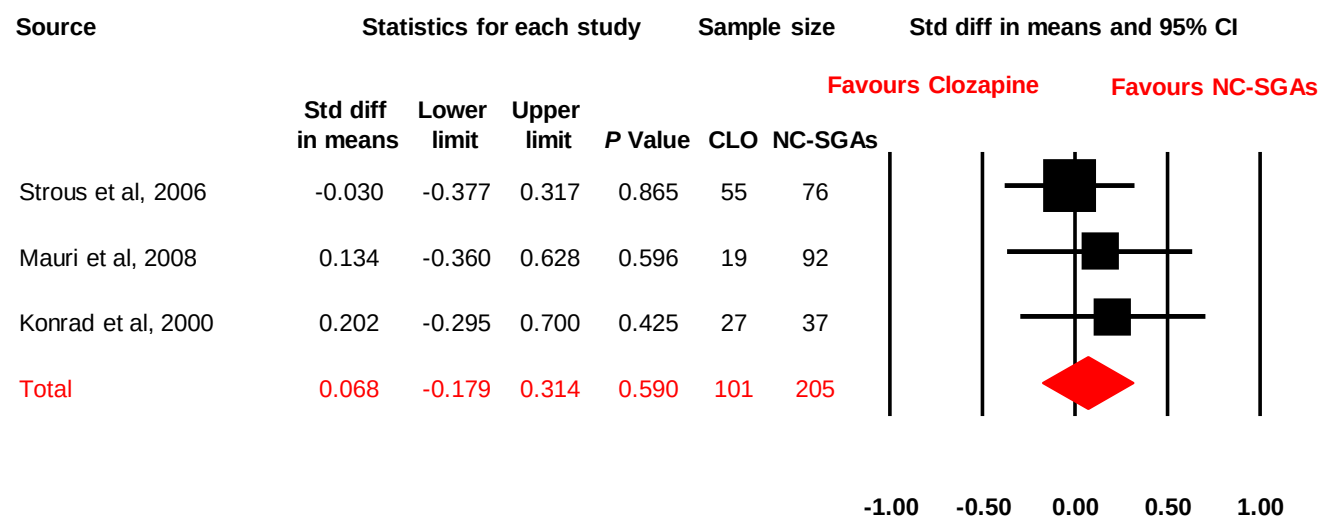
CI, confidence intervals; CLO, clozapine; NC-SGAs, non-clozapine second-generation antipsychotics

eFigure 4-12. Forest plot of risk ratio for death



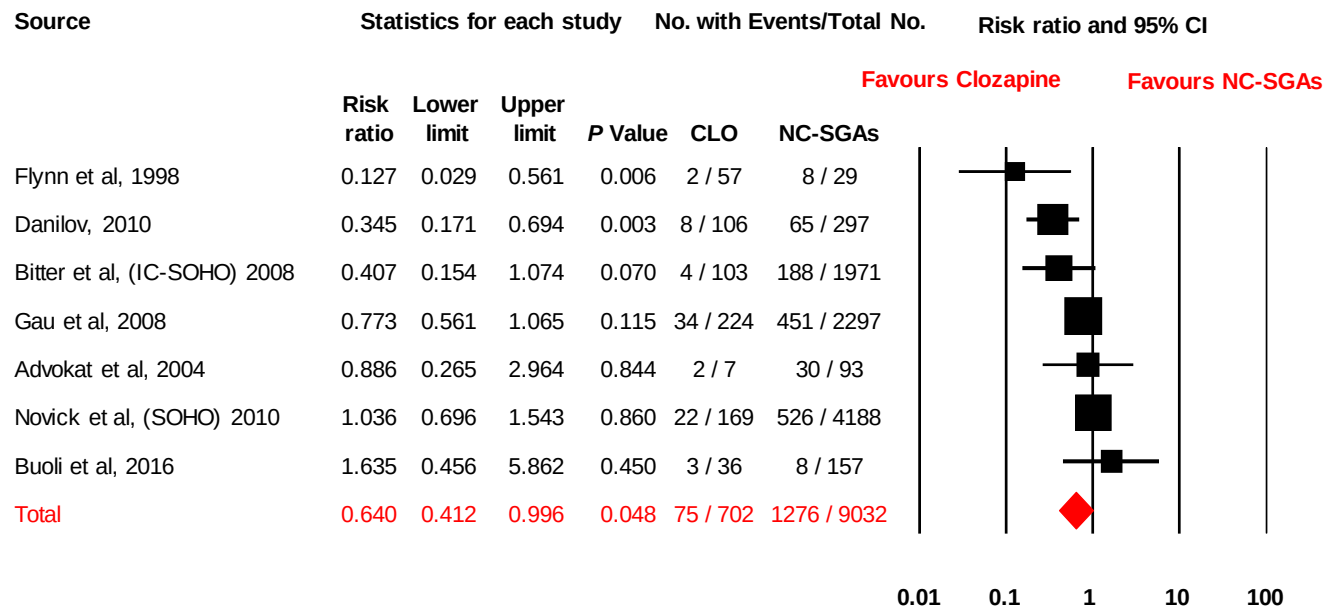
CI, confidence intervals; CLO, clozapine; NC-SGAs, non-clozapine second-generation antipsychotics

eFigure 4-13. Forest plot of standardized mean difference for EPS score



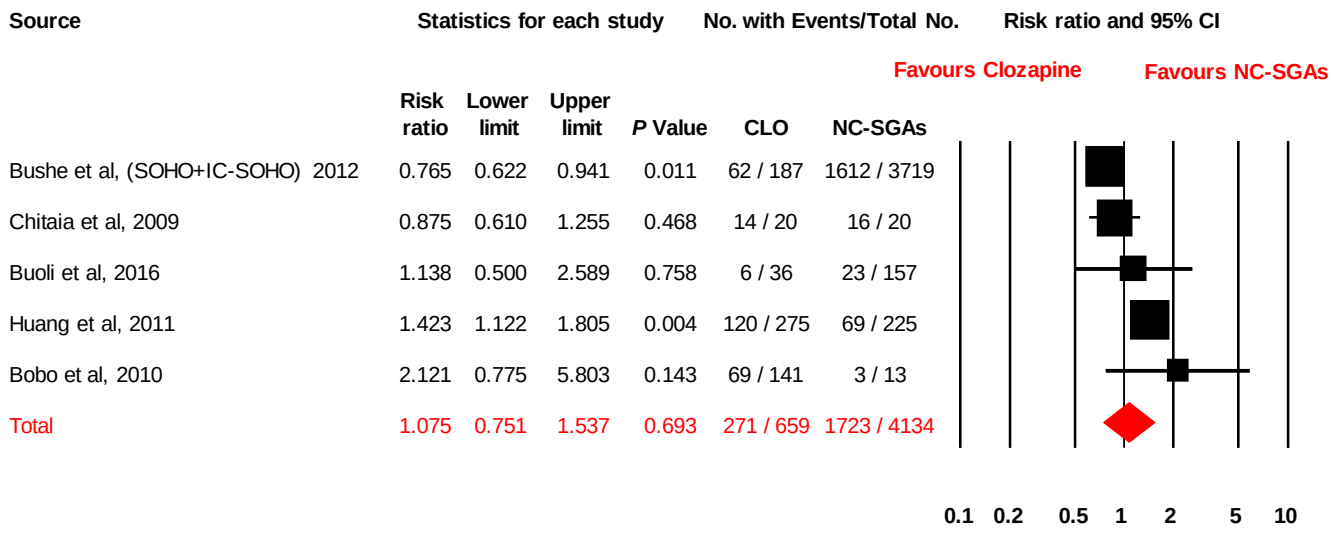
CI, confidence intervals; CLO, clozapine; EPS, extrapyramidal symptoms; NC-SGAs, non-clozapine second-generation antipsychotics; Std diff, standardized difference

eFigure 4-14. Forest plot of risk ratio for EPS risk/Anticholinergic use



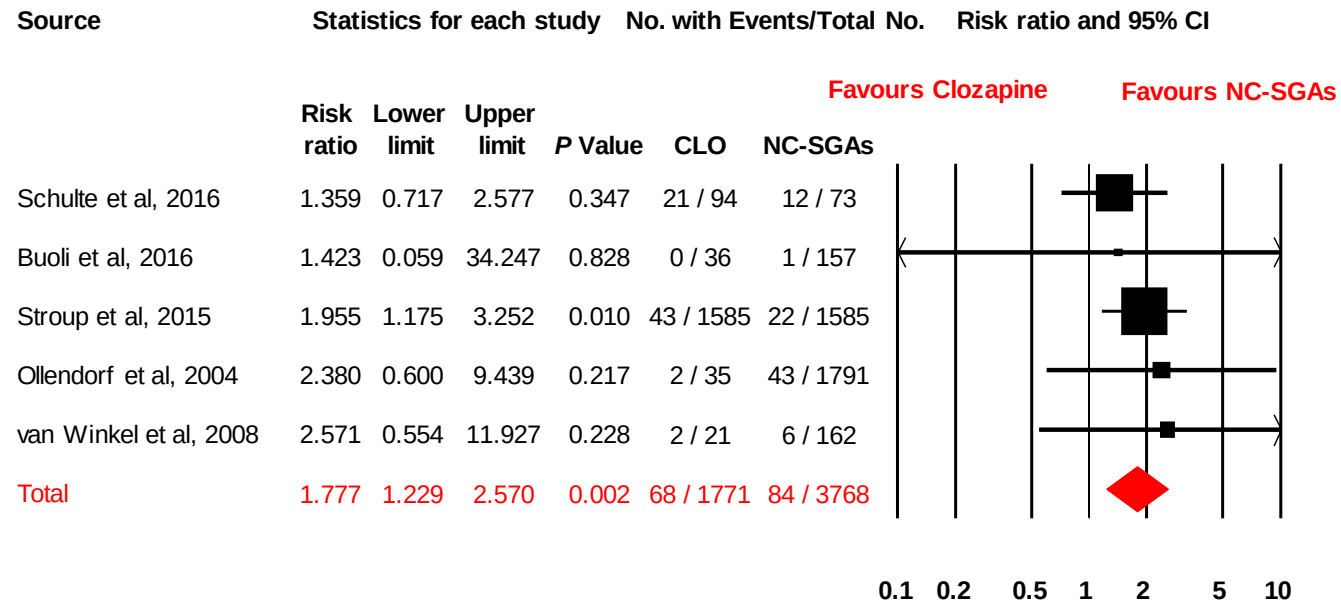
CI, confidence intervals; CLO, clozapine; EPS, extrapyramidal symptoms; NC-SGAs, non-clozapine second-generation antipsychotics; Std diff, standardized difference

eFigure 4-15. Forest plot of risk ratio for weight gain



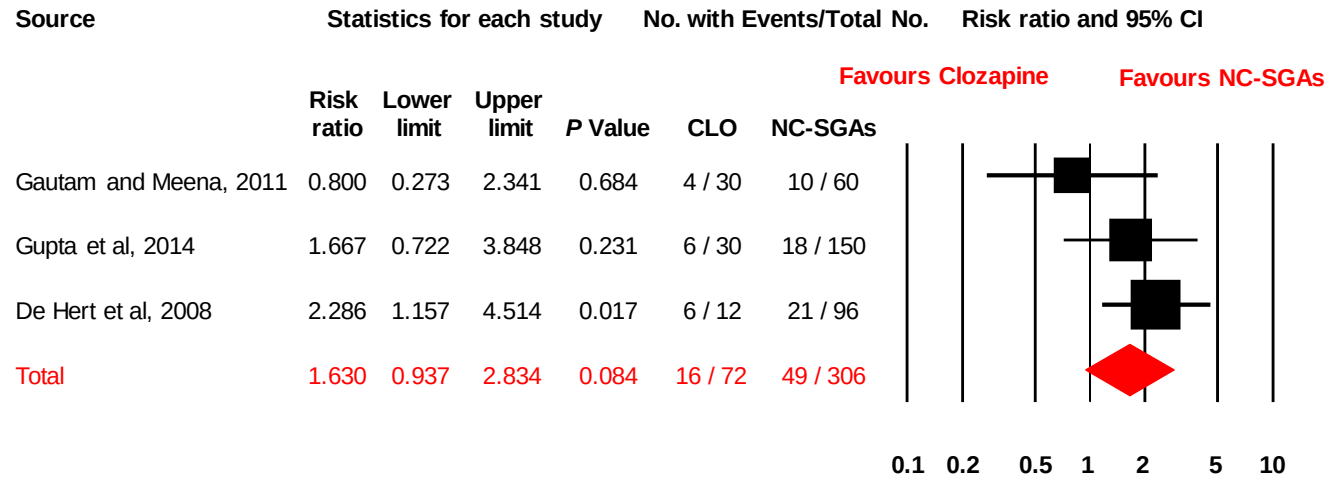
CI, confidence intervals; CLO, clozapine; NC-SGAs, non-clozapine second-generation antipsychotics; Std diff, standardized difference

eFigure 4-16. Forest plot of risk ratio for diabetes mellitus



CI, confidence intervals; CLO, clozapine; NC-SGAs, non-clozapine second-generation antipsychotics

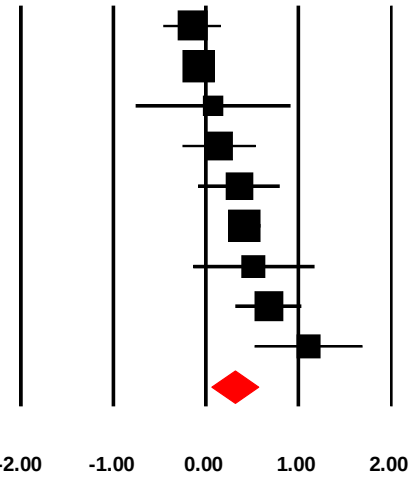
eFigure 4-17. Forest plot of risk ratio for metabolic syndrome



CI, confidence intervals; CLO, clozapine; NC-SGAs, non-clozapine second-generation antipsychotics

eFigure 4-18. Forest plot of standardized mean difference for body weight

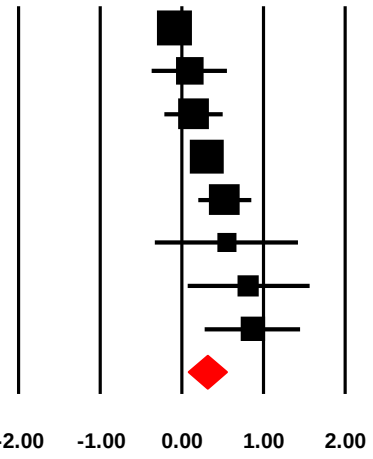
Source	Std diff in means	Lower limit	Upper limit	*P* Value	CLO	NC-SGAs
Woo et al, 2009	-0.148	-0.455	0.160	0.347	70	97
Bushe et al, (SOHO+IC-SOHO) 2012	-0.075	-0.222	0.072	0.316	187	3719
Nakamura and Nagamine 2018	0.075	-0.764	0.915	0.860	12	10
Gupta et al, 2014	0.137	-0.255	0.529	0.493	30	150
Gautam and Meena, 2011	0.358	-0.083	0.799	0.112	30	60
Bai et al, 2009	0.414	0.245	0.584	0.000	231	336
Kelly et al, 2003	0.512	-0.143	1.166	0.125	10	97
Strous et al, 2006	0.676	0.319	1.032	0.000	55	76
Bobo et al, 2010	1.107	0.527	1.687	0.000	146	13
Total	0.308	0.057	0.560	0.016	771	4558



CI, confidence intervals; CLO, clozapine; NC-SGAs, non-clozapine second-generation antipsychotics; Std diff, standardized difference

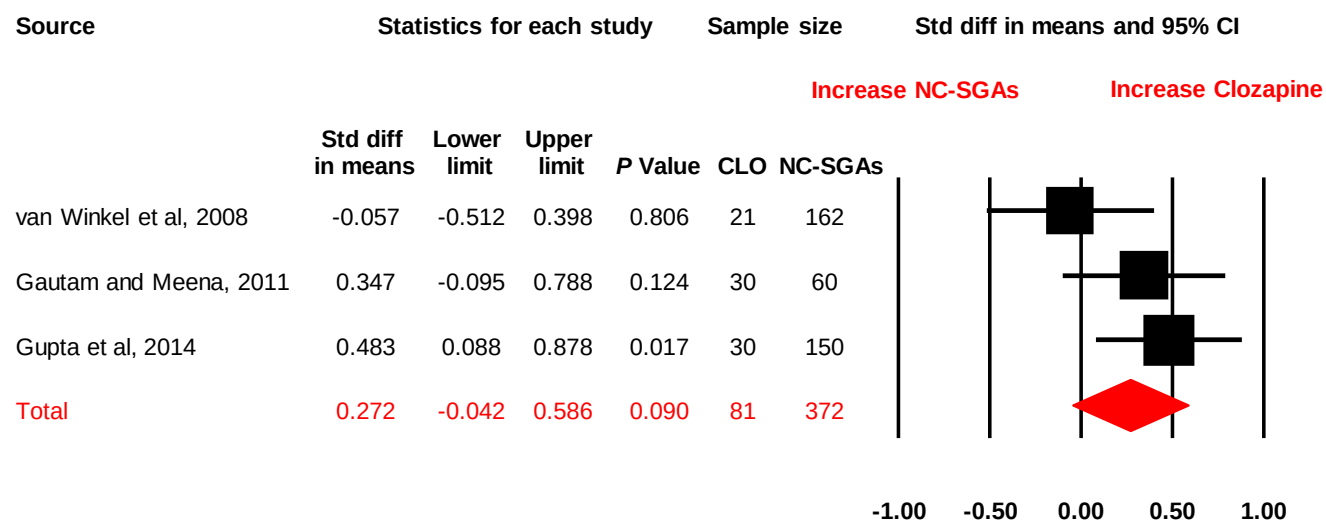
eFigure 4-19. Forest plot of standardized mean difference for body mass index

Source	Std diff in means	Lower limit	Upper limit	*P* Value	CLO	NC-SGAs
Bushe et al, (SOHO+IC-SOHO) 2012	-0.088	-0.236	0.059	0.240	186	3692
van Winkel et al, 2008	0.094	-0.361	0.549	0.686	21	162
Strous et al, 2006	0.143	-0.205	0.490	0.420	55	76
Bai et al, 2009	0.304	0.136	0.473	<0.001	231	336
Schuster et al, 2012	0.525	0.209	0.841	0.001	39	3590
Tschoner et al, 2009	0.550	-0.318	1.417	0.214	7	21
Rettenbacher et al, 2007	0.817	0.081	1.553	0.030	14	17
Bobo et al, 2010	0.868	0.293	1.444	0.003	146	13
Total	0.317	0.079	0.554	0.009	699	7907



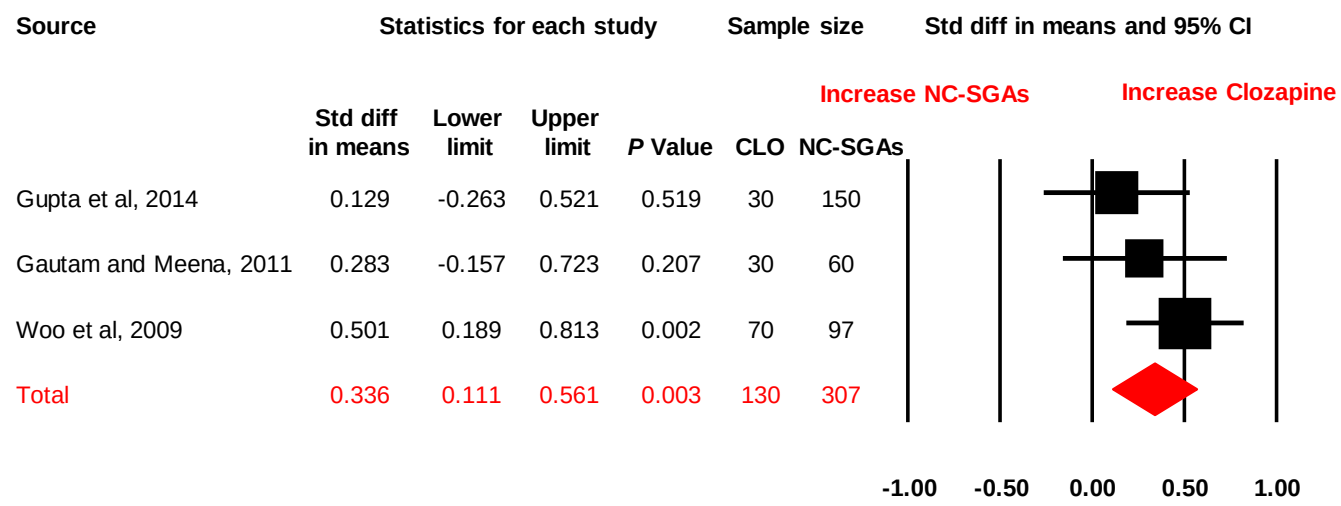
CI, confidence intervals; CLO, clozapine; NC-SGAs, non-clozapine second-generation antipsychotics; Std diff, standardized difference

eFigure 4-20. Forest plot of standardized mean difference for waist circumference



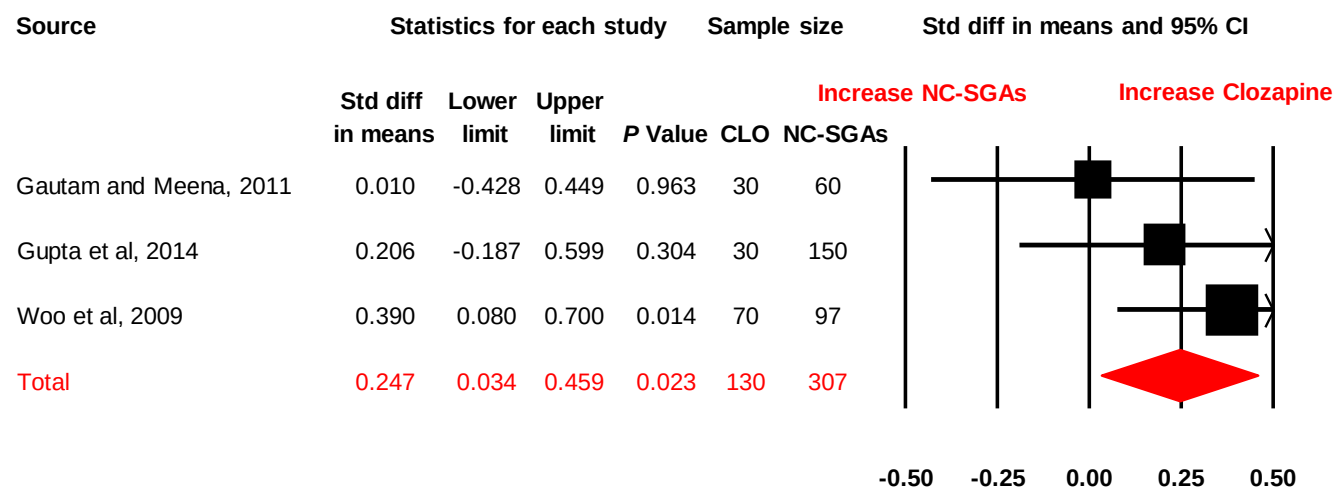
CI, confidence intervals; CLO, clozapine; NC-SGAs, non-clozapine second-generation antipsychotics; Std diff, standardized difference

eFigure 4-21. Forest plot of standardized mean difference for blood pressure (diastolic)



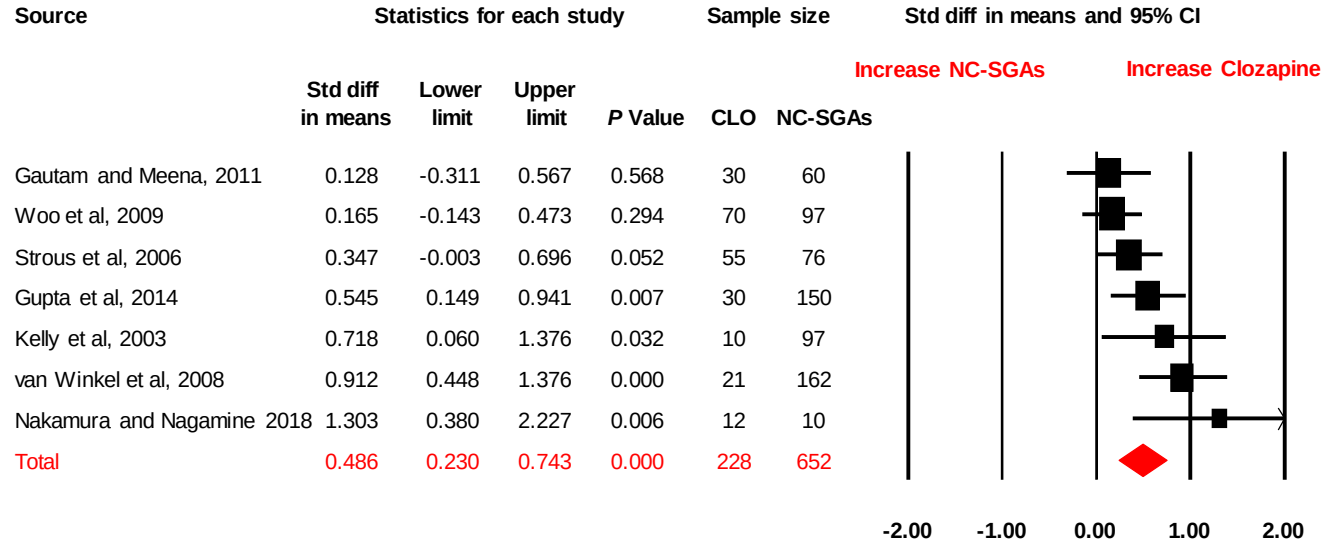
CI, confidence intervals; CLO, clozapine; NC-SGAs, non-clozapine second-generation antipsychotics; Std diff, standardized difference

eFigure 4-22. Forest plot of standardized mean difference for blood pressure (systolic)



CI, confidence intervals; CLO, clozapine; NC-SGAs, non-clozapine second-generation antipsychotics; Std diff, standardized difference

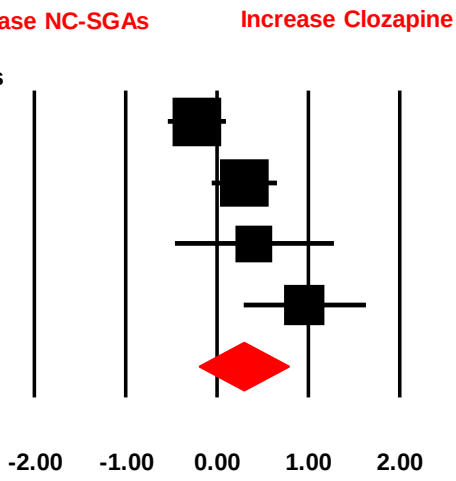
eFigure 4-23. Forest plot of standardized mean difference for glucose



CI, confidence intervals; CLO, clozapine; NC-SGAs, non-clozapine second-generation antipsychotics; Std diff, standardized difference

eFigure 4-24. Forest plot of standardized mean difference for total cholesterol

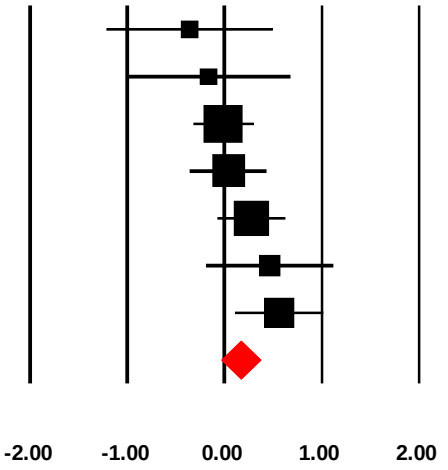
Source	Std diff in means	Lower limit	Upper limit	*P* Value	CLO	NC-SGAs
Woo et al, 2009	-0.215	-0.524	0.093	0.171	70	97
Strous et al, 2006	0.301	-0.048	0.650	0.091	55	76
Tschoner et al, 2009	0.405	-0.457	1.267	0.357	7	21
Kelly et al, 2003	0.959	0.295	1.622	0.005	10	97
Total	0.297	-0.186	0.781	0.228	142	291



CI, confidence intervals; CLO, clozapine; NC-SGAs, non-clozapine second-generation antipsychotics; Std diff, standardized difference

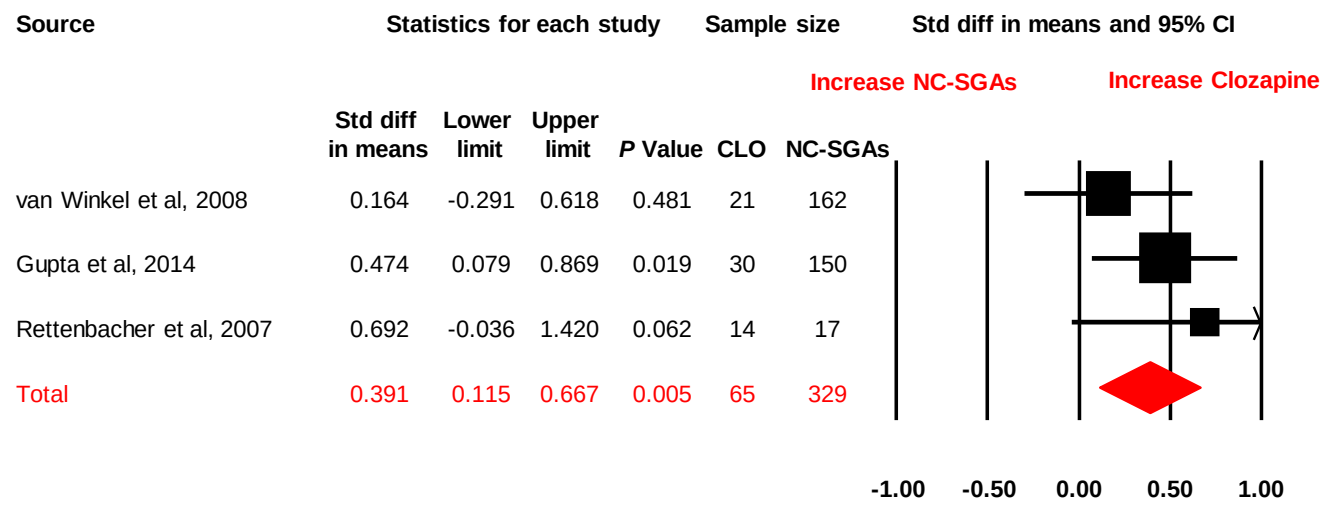
eFigure 4-25. Forest plot of standardized mean difference for triglycerides

Source	Std diff in means	Lower limit	Upper limit	*P* Value	CLO	NC-SGAs
Tschoner et al, 2009	-0.360	-1.221	0.501	0.412	7	21
Nakamura and Nagamine 2018	-0.159	-1.000	0.681	0.710	12	10
Woo et al, 2009	-0.014	-0.321	0.294	0.930	70	97
Gupta et al, 2014	0.040	-0.352	0.432	0.843	30	150
Strous et al, 2006	0.275	-0.074	0.623	0.122	55	76
Kelly et al, 2003	0.461	-0.193	1.115	0.167	10	97
Gautam and Meena, 2011	0.561	0.115	1.007	0.014	30	60
Total	0.162	-0.041	0.365	0.117	214	511



CI, confidence intervals; CLO, clozapine; NC-SGAs, non-clozapine second-generation antipsychotics; Std diff, standardized difference

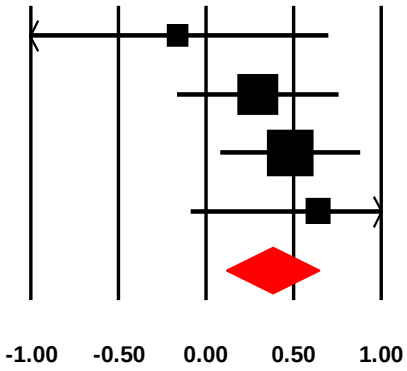
eFigure 4-26. Forest plot of standardized mean difference for insulin



CI, confidence intervals; CLO, clozapine; NC-SGAs, non-clozapine second-generation antipsychotics; Std diff, standardized difference

eFigure 4-27. Forest plot of standardized mean difference for HOMA-IR

Source	Std diff in means	Lower limit	Upper limit	*P* Value	CLO	NC-SGAs
Tschoner et al, 2009	-0.158	-1.014	0.699	0.718	7	21
van Winkel et al, 2008	0.298	-0.158	0.753	0.200	21	162
Gupta et al, 2014	0.482	0.087	0.878	0.017	30	150
Rettenbacher et al, 2007	0.643	-0.082	1.368	0.082	14	17
Total	0.382	0.119	0.645	0.004	72	350



CI, confidence intervals; CLO, clozapine; HOMA-IR: homeostatic model assessment of insulin resistance; NC-SGAs, non-clozapine second-generation antipsychotics; Std diff, standardized difference

eReference list

1. Advokat C, Dixon D, Schneider J, Comaty JE, Jr. Comparison of risperidone and olanzapine as used under "real-world" conditions in a state psychiatric hospital. *Prog Neuropsychopharmacol Biol Psychiatry.* 2004;28(3):487-495.
2. Agid O, Remington G, Kapur S, Arenovich T, Zipursky RB. Early use of clozapine for poorly responding first-episode psychosis. *J Clin Psychopharmacol.* 2007;27(4):369-373.
3. Ascher-Svanum H, Zhu B, Faries DE, Lacro JP, Dolder CR, Peng X. Adherence and persistence to typical and atypical antipsychotics in the naturalistic treatment of patients with schizophrenia. *Patient Prefer Adherence.* 2008;2:67-77.
4. Bai YM, Chen TT, Yang WS, et al. Association of adiponectin and metabolic syndrome among patients taking atypical antipsychotics for schizophrenia: a cohort study. *Schizophr Res.* 2009;111(1-3):1-8.
5. Bitter I, Czobor P, Dossenbach M, Volavka J. Effectiveness of clozapine, olanzapine, quetiapine, risperidone, and haloperidol monotherapy in reducing hostile and aggressive behavior in outpatients treated for schizophrenia: a prospective naturalistic study (IC-SOHO). *Eur Psychiatry.* 2005;20(5-6):403-408.
6. Bitter I, Treuer T, Dyachkova Y, Martenyi F, McBride M, Ungvari GS. Antipsychotic prescription patterns in outpatient settings: 24-month results from the Intercontinental Schizophrenia Outpatient Health Outcomes (IC-SOHO) study. *Eur Neuropsychopharmacol.* 2008;18(3):170-180.
7. Bitter I, Katona L, Zambori J, et al. Comparative effectiveness of depot and oral second generation antipsychotic drugs in schizophrenia: a nationwide study in Hungary. *Eur Neuropsychopharmacol.* 2013;23(11):1383-1390.
8. Bobo WV, Jayathilake K, Lee MA, Meltzer HY. Changes in weight and body mass index during treatment with melperone, clozapine and typical neuroleptics. *Psychiatry Res.* 2010;176(2-3):114-119.
9. Buoli M, Kahn RS, Serati M, Altamura AC, Cahn W. Haloperidol versus second-generation antipsychotics in the long-term treatment of schizophrenia. *Hum Psychopharmacol.* 2016;31(4):325-331.
10. Bushe CJ, Slooff CJ, Haddad PM, Karagianis JL. Weight change from 3-year observational data: findings from the worldwide schizophrenia outpatient health outcomes database. *J Clin Psychiatry.* 2012;73(6):e749-755.
11. Castro AP, Elkis H. Rehospitalization rates of patients with schizophrenia discharged on haloperidol, risperidone or clozapine. *Rev Bras Psiquiatr.* 2007;29(3):207-212.
12. Chitaia NN, Danilov DS, Tiuvina NA. [Peculiarities of neuroleptic syndrome in women treated with typical and atypical neuroleptics]. *Zh Nevrol Psikhiatr Im S S Korsakova.* 2009;109(3):37-43.
13. Conley RR, Love RC, Kelly DL, Bartko JJ. Rehospitalization rates of patients recently discharged on a regimen of risperidone or clozapine. *Am J Psychiatry.* 1999;156(6):863-868.
14. Conley RR, Kelly DL, Love RC, McMahon RP. Rehospitalization risk with second-generation and depot antipsychotics. *Ann Clin Psychiatry.* 2003;15(1):23-31.
15. Cooper D, Moisan J, Gregoire JP. Adherence to atypical antipsychotic treatment among newly treated patients: a population-based study in schizophrenia. *J Clin Psychiatry.* 2007;68(6):818-825.
16. Danilov DS. [Effect of side-effects and complications caused by atypical neuroleptics on the effectiveness of therapy in patients with schizophrenia]. *Zh Nevrol Psikhiatr Im S S Korsakova.* 2010;110(3):48-55.
17. De Hert M, Schreurs V, Sweers K, et al. Typical and atypical antipsychotics differentially affect long-term incidence rates of the metabolic syndrome in first-episode patients with schizophrenia: a retrospective chart

review. *Schizophr Res.* 2008;101(1-3):295-303.

18. Flynn SW, MacEwan GW, Altman S, et al. An open comparison of clozapine and risperidone in treatment-resistant schizophrenia. *Pharmacopsychiatry.* 1998;31(1):25-29.
19. Franza F, Fasano V, De Guglielmo S, Solomita B. Management of primary negative symptoms in schizophrenia: an one-year observational study. *Psychiatr Danub.* 2015;27 Suppl 1:S245-249.
20. Gau SS, Chung CH, Gau CS. A pharmacoeconomic analysis of atypical antipsychotics and haloperidol in first-episode schizophrenic patients in taiwan. *J Clin Psychopharmacol.* 2008;28(3):271-278.
21. Gautam S, Meena PS. Drug-emergent metabolic syndrome in patients with schizophrenia receiving atypical (second-generation) antipsychotics. *Indian J Psychiatry.* 2011;53(2):128-133.
22. Green AI, Burgess ES, Dawson R, Zimmet SV, Strous RD. Alcohol and cannabis use in schizophrenia: effects of clozapine vs. risperidone. *Schizophr Res.* 2003;60(1):81-85.
23. Guo X, Fang M, Zhai J, et al. Effectiveness of maintenance treatments with atypical and typical antipsychotics in stable schizophrenia with early stage: 1-year naturalistic study. *Psychopharmacology (Berl).* 2011;216(4):475-484.
24. Gupta A, Dadheech G, Yadav D, Sharma P, Gautam S. Metabolic issues in schizophrenic patients receiving antipsychotic treatment. *Indian J Clin Biochem.* 2014;29(2):196-201.
25. Haro JM, Edgell ET, Novick D, et al. Effectiveness of antipsychotic treatment for schizophrenia: 6-month results of the Pan-European Schizophrenia Outpatient Health Outcomes (SOHO) study. *Acta Psychiatr Scand.* 2005;111(3):220-231.
26. Haro JM, Suarez D, Novick D, Brown J, Usall J, Naber D. Three-year antipsychotic effectiveness in the outpatient care of schizophrenia: observational versus randomized studies results. *Eur Neuropsychopharmacol.* 2007;17(4):235-244.
27. Hennessy S, Bilker WB, Knauss JS, et al. Cardiac arrest and ventricular arrhythmia in patients taking antipsychotic drugs: cohort study using administrative data. *BMJ.* 2002;325(7372):1070.
28. Herceg M, Jukic V, Vidovic D, et al. Two-year rehospitalization rates of patients with newly diagnosed or chronic schizophrenia on atypical or typical antipsychotic drugs: retrospective cohort study. *Croat Med J.* 2008;49(2):215-223.
29. Hodgson R, Belgamwar R, Al-tawarah Y, MacKenzie G. The use of atypical antipsychotics in the treatment of schizophrenia in North Staffordshire. *Hum Psychopharmacol.* 2005;20(2):141-147.
30. Huang HH, Wang YC, Wu CL, et al. TNF-alpha -308 G>A polymorphism and weight gain in patients with schizophrenia under long-term clozapine, risperidone or olanzapine treatment. *Neurosci Lett.* 2011;504(3):277-280.
31. Innamorati M, Baratta S, Di Vittorio C, et al. Atypical antipsychotics in the treatment of depressive and psychotic symptoms in patients with chronic schizophrenia: a naturalistic study. *Schizophr Res Treatment.* 2013;2013:423205.
32. Karagianis J, Williams R, Davis L, et al. Antipsychotic switching: results from a one-year prospective, observational study of patients with schizophrenia. *Curr Med Res Opin.* 2009;25(9):2121-2132.
33. Karki SD, Bellnier TJ, Patil K, Oretega T. Cost-effectiveness of atypical antipsychotics in severely and persistently mentally ill patients with schizophrenia and schizoaffective disorders. *Drug Benefit Trends.*

2001;13(2):7BH-15BH.

34. Kelly DL, Kreyenbuhl J, Love RC, Van-Duong Q, Conley RR. Six-month review of weight and metabolic parameters in patients receiving clozapine, risperidone, olanzapine, or quetiapine. *J Clin Psychiatry.* 2003;64(9):1133-1134.
35. Kelly DL, McMahon RP, Liu F, et al. Cardiovascular disease mortality inpatients with chronics schizophrenia treated with clozapine: A retrospective cohort study. *J Clin Psychiatry.* 2010;71(3):304-311.
36. Kim JH, Kim D, Marder SR. Time to rehospitalization of clozapine versus risperidone in the naturalistic treatment of comorbid alcohol use disorder and schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry.* 2008;32(4):984-988.
37. Konrad C, Schormair C, Ophaus P, Knickelbein U, Eikelmann B. Risperidone and clozapine in treatment resistant schizophrenia. Clinical observations on psychopathology, side effects and subjective well-being. *Krankenhauspsychiatrie.* 2000;11(3):89-93.
38. Lin CH, Lin SC, Chen MC, Wang SY. Comparison of time to rehospitalization among schizophrenic patients discharged on typical antipsychotics, clozapine or risperidone. *J Chin Med Assoc.* 2006;69(6):264-269.
39. Lindenmayer JP, Iskander A, Park M, et al. Clinical and neurocognitive effects of clozapine and risperidone in treatment-refractory schizophrenic patients: a prospective study. *J Clin Psychiatry.* 1998;59(10):521-527.
40. Mauri MC, Moliterno D, Rossattini M, Colasanti A. Depression in schizophrenia: comparison of first- and second-generation antipsychotic drugs. *Schizophr Res.* 2008;99(1-3):7-12.
41. Nakamura M, Nagamine T. Metabolic Changes in Patients with Schizophrenia Switched From Olanzapine to Asenapine or Clozapine. *Innov Clin Neurosci.* 2018;15(7-8):11-12.
42. Nikolac Perkovic M, Nedic Erjavec G, Zivkovic M, et al. Association between the brain-derived neurotrophic factor Val66Met polymorphism and therapeutic response to olanzapine in schizophrenia patients. *Psychopharmacology (Berl).* 2014;231(18):3757-3764.
43. Novick D, Haro JM, Bertsch J, Haddad PM. Incidence of extrapyramidal symptoms and tardive dyskinesia in schizophrenia: thirty-six-month results from the European schizophrenia outpatient health outcomes study. *J Clin Psychopharmacol.* 2010;30(5):531-540.
44. Novick D, Ascher-Svanum H, Haro JM, Bertsch J, Takahashi M. Schizophrenia Outpatient Health Outcomes study: twelve-month findings. *Pragmat Obs Res.* 2012;3:27-40.
45. Nyakyoma K, Morriss R. Effectiveness of clozapine use in delaying hospitalization in routine clinical practice: a 2 year observational study. *Psychopharmacol Bull.* 2010;43(2):67-81.
46. Ollendorf DA, Joyce AT, Rucker M. Rate of new-onset diabetes among patients treated with atypical or conventional antipsychotic medications for schizophrenia. *MedGenMed.* 2004;6(1):5.
47. Pridan S, Swartz M, Baruch Y, Tadger S, Plopski I, Barak Y. Effectiveness and safety of clozapine in elderly patients with chronic resistant schizophrenia. *Int Psychogeriatr.* 2015;27(1):131-134.
48. Remington G, Khramov I. Health care utilization in patients with schizophrenia maintained on atypical versus conventional antipsychotics. *Prog Neuropsychopharmacol Biol Psychiatry.* 2001;25(2):363-369.
49. Rettenbacher MA, Hummer M, Hofer A, et al. Alterations of glucose metabolism during treatment with clozapine or amisulpride: results from a prospective 16-week study. *J Psychopharmacol.* 2007;21(4):400-404.
50. Ringback Weitoft G, Berglund M, Lindstrom EA, Nilsson M, Salmi P, Rosen M. Mortality, attempted suicide, re-

hospitalisation and prescription refill for clozapine and other antipsychotics in Sweden-a register-based study. *Pharmacoepidemiol Drug Saf.* 2014;23(3):290-298.

51. Schulte PF, Bocxe JT, Doodeman HJ, van Haelst IM, Cohen D. Risk of New-Onset Diabetes After Long-Term Treatment With Clozapine in Comparison to Other Antipsychotics in Patients With Schizophrenia. *J Clin Psychopharmacol.* 2016;36(2):115-119.
52. Schuster JP, Raucher-Chene D, Lemogne C, et al. Impact of switching or initiating antipsychotic treatment on body weight during a 6-month follow-up in a cohort of patients with schizophrenia. *J Clin Psychopharmacol.* 2012;32(5):672-677.
53. Sharma T, Hughes C, Soni W, Kumari V. Cognitive effects of olanzapine and clozapine treatment in chronic schizophrenia. *Psychopharmacology (Berl).* 2003;169(3-4):398-403.
54. Shermock K, Sadik M, Kozma C, Sesti A, Reeder C. Risperidone, haloperidol and clozapine in the South Carolina medicaid program: a comparative analysis of utilisation and expenditure. *Disease Management & Health Outcomes.* 2001;9(4):203-213 211p.
55. Stip E, Lussier I, Ngan E, Mendrek A, Liddle P. Discriminant cognitive factors in responder and non-responder patients with schizophrenia. *Eur Psychiatry.* 1999;14(8):442-450.
56. Stroup TS, Gerhard T, Crystal S, Huang C, Olfson M. Comparative Effectiveness of Clozapine and Standard Antipsychotic Treatment in Adults With Schizophrenia. *Am J Psychiatry.* 2016;173(2):166-173.
57. Strous RD, Kupchik M, Roitman S, et al. Comparison between risperidone, olanzapine, and clozapine in the management of chronic schizophrenia: a naturalistic prospective 12-week observational study. *Hum Psychopharmacol.* 2006;21(4):235-243.
58. Taylor D, Hayhurst K, Kerwin R. A controlled, mirror-image study of second-generation antipsychotics in the treatment of schizophrenia. *Int Clin Psychopharmacol.* 2007;22(3):133-136.
59. Taylor M, Shajahan P, Lawrie SM. Comparing the use and discontinuation of antipsychotics in clinical practice: an observational study. *J Clin Psychiatry.* 2008;69(2):240-245.
60. Tiihonen J, Wahlbeck K, Lonnqvist J, et al. Effectiveness of antipsychotic treatments in a nationwide cohort of patients in community care after first hospitalisation due to schizophrenia and schizoaffective disorder: observational follow-up study. *BMJ.* 2006;333(7561):224.
61. Treuer T, Martenyi F, Saylan M, Dyachkova Y. Factors associated with achieving minimally symptomatic status by patients with schizophrenia: results from the 3-year intercontinental schizophrenia outpatients health outcomes study. *Int J Clin Pract.* 2010;64(6):697-706.
62. Tschoner A, Engl J, Rettenbacher M, et al. Effects of six second generation antipsychotics on body weight and metabolism: Risk assessment and results from a prospective study. *Pharmacopsychiatry.* 2009;42(1):29-34.
63. van Winkel R, De Hert M, Wampers M, et al. Major changes in glucose metabolism, including new-onset diabetes, within 3 month after initiation of or switch to atypical antipsychotic medication in patients with schizophrenia and schizoaffective disorder. *J Clin Psychiatry.* 2008;69(3):472-479.
64. Vanasse A, Blais L, Courteau J, et al. Comparative effectiveness and safety of antipsychotic drugs in schizophrenia treatment: a real-world observational study. *Acta Psychiatr Scand.* 2016.
65. Velligan DI, Carroll C, Lage MJ, Fairman K. Outcomes of medicaid beneficiaries with schizophrenia receiving clozapine only or antipsychotic combinations. *Psychiatr Serv.* 2015;66(2):127-133.

66. Werneck AP, Hallak JC, Nakano E, Elkis H. Time to rehospitalization in patients with schizophrenia discharged on first generation antipsychotics, non-clozapine second generation antipsychotics, or clozapine. *Psychiatry Res.* 2011;188(3):315-319.

67. Williams R, Kopala L, Malla A, Smith G, Love L, Balshaw R. Medication decisions and clinical outcomes in the Canadian National Outcomes Measurement Study in Schizophrenia. *Acta Psychiatr Scand Suppl.* 2006(430):12-21.

68. Woo YS, Kim W, Chae JH, Yoon BH, Bahk WM. Blood pressure changes during clozapine or olanzapine treatment in Korean schizophrenic patients. *World J Biol Psychiatry.* 2009;10(4 Pt 2):420-425.