Supplementary material to:

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Quetiapine immediate release *v*. placebo for schizophrenia: systematic review, meta-analysis and reappraisal.
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Content of supplementary material

A. Protocol

Quetiapine immediate release versus placebo for people with a schizophrenia diagnosis: a systematic review and meta-analysis(1)
Paul Hutton, Peter Taylor, Lee Mulligan, Sarah Tully, Joanna Moncrieff.

Review question(s)
To review the efficacy and side-effect profile of quetiapine fumarate immediate release for people with a schizophrenia-spectrum diagnosis, compared to placebo only. To test hypothesis that low attrition double-blind RCTs (<50% and <25% attrition) will demonstrate superior efficacy for quetiapine IR over placebo compared to high-attrition studies (>50% attrition).

Searches
We will search through the Cochrane Trials Register (CENTRAL), the US Food and Drug Administration website, PubMed, most recent meta-analyses, the US online clinical trials register (clinicaltrials.gov), the European clinical trials register, the WHO clinical trials register, online clinical trials registers of top 12 pharmaceutical companies including AstraZeneca, relevant Cochrane reviews, a recent literature review by NICE and internal AstraZeneca documents released as part of a legal dispute in the US. We will limit our CENTRAL and PubMed search to the years 2006-2011, given the authors of the most recent meta-analysis completed their last search in 2006. We will search the abstract, title and keywords for the terms 'quetiapine', 'placebo' and 'schizophrenia' and 'quetiapine', 'placebo' and 'psychosis'. We will use the same terms for searching through the clinical trials registers, but the dates of the search will not be limited. We will also write to all major pharmaceutical companies asking them for details of unpublished studies where quetiapine IR is compared to placebo for treating schizophrenia.

Types of study to be included:
Double-blind randomised controlled trials, published and unpublished, meeting quality criteria A and B as outlined in the Cochrane Handbook will be included. Only data incorporating study end-point scores from 50% or more of those randomised will be included. A sensitivity analysis will explore the impact of including data from studies with >50% attrition, in order to test the hypothesis that effect sizes are lower in high-attrition studies.

Condition or domain being studied:
Schizophrenia-spectrum disorder/non-organic, non-affective psychosis

Participants/ population
Adults and adolescents with a schizophrenia-spectrum disorder diagnosis, or early psychosis. Children (12 or under) will be excluded.

Intervention(s), exposure(s)
Quetiapine immediate release >250mg arms only (oral)

Comparator(s)/ control
Placebo

Context
No limitation on settings.

Outcome(s):

Primary outcomes
Primary outcomes are (a) difference between treatment and control in mean change in PANSS or BPRS scores (b) difference in rates of clinically significant response (defined according to hierarchy outlined in meta-analysis by Leucht et al 2009). Positive and Negative Syndrome Scale/Brief Psychiatric Rating Scale data will be extracted. Any duration of study will be included.

Secondary outcomes
Relapse (author definition)
Positive symptoms, negative symptoms, depression (derived from PANSS/BPRS or authors definition)
Quality of life (as measured by authors)

Needing additional medication (antipsychotics, anxiolytics or sedatives).
Numbers leaving early for any reason.

For adverse effects, we again follow a similar protocol to Leucht et al 2009:
Use of antiparkinson medication
Mean scores on the Simpson Angus Scale of extrapyramidal side-effects (SAS) and the Extrapyramidal Symptoms Rating Scale (ESRS)
Drop-out due to adverse events
Sedation/somnolence.
Total number of adverse events
Insomnia
Weight-gain, where available.
Weight-loss, where available

Data extraction, (selection and coding)
All data extracted by PH. Independent extraction to be carried out by collaborators. Discrepancies resolved by discussion.

Risk of bias (quality) assessment
Risk of bias assessed by Cochrane Risk of Bias tool

Strategy for data synthesis
Summary data (means & proportions) will be meta-analysed using Revman. For continuous data the model will be random-effects looking at standardised mean differences, with a sensitivity analysis for fixed-effects. Mean differences will also be presented. For binary data, the analysis will be relative risk, with calculation of risk difference & NNT/NNH if significant effects. Random-effects will be model used, with a sensitivity analysis for fixed-effects. Most of the studies will use last-observation carried forward for imputation of missing data, so we expect to have to use this too. If we can use mixed-models, we will do so.

Analysis of subgroups or subsets
We plan to examine the impact on effect size of different degrees of overall attrition (25%, 50%, >50%). If possible, we will also carry out a sensitivity analysis of effect of using mixed-models imputation strategy vs last-observation carried forward.

Dissemination plans
Peer-review publications / conference presentations.

Contact details for further information
Paul Hutton
Greater Manchester West Mental Health NHS Foundation Trust
Bury New Road
Manchester
M253BL
paulhutton@nhs.net

Organisational affiliation of the review
Greater Manchester West Mental Health NHS Foundation Trust

Review team
Dr Paul Hutton, Greater Manchester West Mental Health NHS Foundation Trust
Dr Peter Taylor, University of Manchester
Dr Joanna Moncrieff, University College London
Mr Lee Mulligan, Greater Manchester West Mental Health NHS Foundation Trust
Miss Sarah Tully, Greater Manchester West Mental Health NHS Foundation Trust

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03 October 2011

Anticipated completion date

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None

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None known

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English

Country
England

Subject index terms status
Subject indexing assigned by CRD

Subject index terms
Antipsychotic Agents; Dibenzothiazepines; Humans; Schizophrenia

Any other information
Delayed due to disclosure of additional trial data by various trial sponsors.

Date of registration in PROSPERO
13 October 2011

Date of publication of this revision
20 June 2013

Stage of review at time of this submission: Started, but not completed
Preliminary searches: Started, but not completed
Piloting of the study selection process: Started, but not completed
Formal screening of search results against eligibility criteria: Started, but not completed
Data extraction: Started, but not completed
Risk of bias (quality) assessment: Started, but not completed
Data analysis: Started, but not completed
Prospective meta-analysis: Started, but not completed

B. Changes from protocol

The review protocol was registered in 2011 with PROSPERO (International Prospective Register of Systematic Reviews).(1) Subsequent changes, in addition to those detailed in the paper, reflect feedback from peer reviewers, as well as methodological advances relating to data synthesis and imputation strategies. Changes included converting BPRS to PANSS scores using recently published conversion tables,(2) using a different statistical package for meta-analysis, extracting and analysing data for functioning, need for hospital care and employment, and analysing data from the unpublished Study 15.(3) We also collected more data on adverse effects, including Barnes Akathisia Scale (BAS) and Abnormal Involuntary Movement Scale (AIMS) data, and examined number of people experiencing significant deterioration on measures of extrapyramidal effects as well as mean change. We also decided to use the GRADE approach to assess quality of outcomes.(4)

For our primary analysis we originally intended to only include study data if this incorporated end-point scores from 50% or more of those randomised to the included arms. However peer reviewers argued, and we agreed, that the better approach was to include the high attrition studies and conduct sensitivity analyses to explore the impact of excluding them. We used just-published guidelines to explore the robustness of the estimates to LOCF assumptions (5).

For important clinical response, we initially planned to use the same hierarchy as Leucht and colleagues(6) (50% of more reduction in PANSS/BPRS > Clinical Global Impression score of 'much improved' or better > authors definition, usually 20-30% reduction in PANSS/BPRS total scores). However, given this group's recently published concerns about the high risk of selective reporting bias in relation to antipsychotic response rates(7) we decided to use only ≥50% reduction in PANSS / BPRS scores,(8) imputing any missing estimates using the Furukawa method,(9) which also allowed us to use rescaled versions of the measures.(10, 11)

Since the majority of acute-treatment antipsychotic trials are 6 weeks long (and therefore the point where there would be most data),(6) we initially made this our primary endpoint. However, since this led to inclusion of data from only 3 trials,(12-14) peer reviewers argued, and we agreed, that pooling data across study endpoints would be more meaningful. We determined the upper and lower boundaries of this range by reference to clinical guidelines and empirical research on prescriber behaviour. PORT recommend a 2-6 week trial,(15) the World Federation of Biological Psychiatrists (WFBP) recommend a 2-8 week trial(16) whereas NICE guidelines endorse the British National Formulary (BNF) recommendations of a 4-6 week trial.(17) The recent Leucht analysis used 4-12 week data, although they also defined acute treatment as a 6-week period,(7) and included 2-week data in their 2009 analysis.(6) Empirical work suggests the average psychiatrist waits around 3 weeks before switching antipsychotics because of limited efficacy or adverse effects,(18) and no longer than 8 weeks. For these reasons, we decided to include endpoint data from all the trials, covering a treatment period of between 2 and 12 weeks, but conduct sensitivity analyses excluding the lower and upper end of this range. At the request of reviewers, we also conducted meta-regression to examine overall effect of study duration and publication year on total symptoms and clinically significant improvement.

C. Search strategy

We searched the Cochrane Group trials register (CENTRAL), the US Food and Drug Administration (FDA) website, Pubmed, EMBASE, previous reviews,(6, 19-22) and the online clinical trials registers of the US government, European Union, World Health Organisation and Current Controlled Trials Ltd. After searching their online trial registries, we sent written requests for unpublished studies to 12 of the main pharmaceutical companies. We also wrote to the Danish Medicines Agency and filed Freedom of Information requests with both the UK Medicines and Healthcare Regulatory Authority (MHRA) and the FDA. We unsuccessfully asked the latter to use their powers under the FDA Amendments Act (2007) to compel researchers to report the results of unpublished trials.(23) We searched the references of included trials for other eligible studies.

We limited our publication database searches to the years 2006-2013, given Leucht et al (6) completed their last search in 2006, but we searched all years in the trial registries. We searched the abstract, title and keywords for the terms ‘quetiapine’, ‘placebo’ and ‘schizophrenia’ and ‘quetiapine’, ‘placebo’ and ‘psychosis’. We did not limit the search by article type, language or duration. Once initial searches were complete, we used PubCrawler to run weekly PubMed searches for new studies mentioning ‘quetiapine’ and ‘placebo’ in the title or abstract, up until acceptance for publication.

D. Excluded studies

The following table details studies or reports excluded after inspection of the full-text report, or via correspondence with trial sponsor. Studies or reports excluded on basis of title or abstract alone are not detailed as these are too numerous and the vast majority were of different conditions or were otherwise unrelated to the review question.

Study	**Reason for exclusion**
Levkovitz 2010(24)	No QUE IR
Kane 2009 (25)	No placebo
Keefe 2008 (26)	No placebo
Blonde 2008(27)	No QUE IR
Bartko 2007(28)	Not RCT
Rupnow 2007(29)	Duplicate, secondary publication or not relevant
Zhong 2006(30)	No placebo
Ko 2006(31)	No placebo
Gharabawi 2006 (32)	Duplicate, secondary publication or not relevant
Honer 2012[10]	No placebo
Citrome 2012(33)	No QUE IR
Langguth 2008(34)	Not schizophrenia
Gentile 2011(35)	Not RCT
Scott 2010(36)	Not RCT
Peuskens 2007(37)	No QUE IR
Cohrs 2006(38)	No placebo
Bushe 2010(39)	No placebo
Cortese 2008(40)	No placebo
Deberdt 2008(41)	No placebo
Gaebel 2010(42)	No placebo
Gafoor 2010(43)	No placebo
Haro 2009(44)	Duplicate, secondary publication or not relevant
Kalali 2008(45)	Duplicate, secondary publication or not relevant
Meulien 2010(46)	Not RCT
Moller 2008(47)	No placebo
Riedel 2010(48)	Not RCT
Sacchetti 2008(49)	Not RCT
Schreiner 2009(50)	Not double-blind
Si 2009(51)	Not double-blind
Smeraldi 2009(52)	Not double-blind
Loebel 2013(53)	No QUE IR
Jones 2010(54)	Not RCT
Melnik 2010(55)	Not RCT
Isaac 2010(56)	Not RCT
Correll 2010(57)	Not RCT
D1444C00008[a]	No placebo
D1441C00023[a]	No placebo
BU-5077-0011[a]	No placebo
AU-SEA-0003[a]	No placebo
5077US/0043[a]	No placebo
5077IL/0054[a]	No placebo
5077IL/0053[a]	No placebo
5077IL/0050[a]	No placebo
5077IL/0031[a]	No placebo
5077IL/0015[a]	No placebo
D1443L00042[a]	No placebo
DC-990-0113[a]	Not schizophrenia
D1449C00012[a]	Not performed
D1449C00001[a]	Not double-blind

D1444C00145 [a]	No placebo
D1444C00003 [a]	Not double-blind
D1443L00077 [a]	Not performed
D1443L00041 [a]	Not performed
D1443L00024 [a]	Not performed
D1441L00034 [a]	Not RCT
D1441L00033 [a]	Not performed
D1441L00032 [a]	No placebo
D1441L00022 [a]	Not schizophrenia
D1441L00021 [a]	Not double-blind
D1441L00017 [a]	Not RCT
D1441L00009 [a]	Not double-blind
D1441C09906 [a]	Duplicate, secondary publication or not relevant
D1441C00131 [a]	Not performed
D1441C00130 [a]	Not double-blind
D1441C00027 [a]	Not double-blind
D1441C00021 [a]	Not schizophrenia
D1441C00020 [a]	Not double-blind
D1441C00005 [a]	Not schizophrenia
D1441C00004 [a]	Not double-blind
BU-5077-0015 [a]	No placebo
5077US/0047 [a]	No placebo
5077IL/0118 [a]	Not double-blind
5077IL/0116 [a]	Not double-blind
5077IL/0115 [a]	Not schizophrenia
5077IL/0114 [a]	No placebo
5077IL/0109 [a]	No QUE IR
5077IL/0014 [a]	No placebo
5077IL/0012 [a]	No placebo
5077GR/0001 [a]	Not RCT
5077CN/0012 [a]	Not double-blind
5077/9904 [a]	Not schizophrenia
5077/9902 [a]	Not schizophrenia
5077/9901 [a]	Not schizophrenia
5077/9064 [a]	Not double-blind
5077/9055 [a]	Not double-blind
5077/9043 [a]	Not schizophrenia
5077/9017 [a]	Not schizophrenia
5077/9014 [a]	Not double-blind
5077/9007 [a]	No placebo
NIS-NSI-SE R-2008/1 [a]	Not RCT
NL-401241 [a]	Not RCT
NIS-NRO-SER-2006-2 [a]	Not RCT
NIS-NHU-SER-2009/1 [a]	Not RCT
NIS-NBE-SER-2006/1 [a]	Not RCT
SRP-NB-SER-2006/1 [a]	Not RCT
NIS-NNL-SER/2005/1 [a]	Not RCT
NIS-NLV-SER/2008/1 [a]	Not RCT
NIS-NNL-SER-2008-1 [a]	Not RCT
D1443L00048 [a]	Not RCT
D1443L00074 [a]	Not double-blind
D1443L00009 [a]	Not double-blind
D1441C00028 [a]	Not double-blind
D1443L00031 [a]	No placebo
Fabre 1995(58)	Less than optimal dose

[a] filed under Seroquel in Astrazeneca clinical trial register, accessed 9th October 2011

E. Characteristics of included studies and baseline demographics

								Baseline demographics			
Trial	**Treatments**	**Dose, (mg/d)**	**Number of patients randomised**	**Duration of active medication (weeks)**	**Duration of wash-out (days)**	**Number of centres**	**Setting**	**Age, mean (SD)**	**Proportion female (%)**	**PANSS / BPRS, mean (SD)**	**Total number leaving early (N, [%])**
Arvanitis	Quetiapine IR	75mg	53	6	7 days	26	Inpatient	37 (10)	14 (26.4%)	No PANSS / 45.7 (7.2)*	36 (67.9%)
	Quetiapine IR	150mg	48	6	7 days	26	Inpatient	38 (9)	9 (18.8%)	No PANSS / 47.2 (6.9)*	27 (56.2%)
	Quetiapine IR	300mg	52	6	7 days	26	Inpatient	38 (9)	15 (28.8%)	No PANSS / 45.3 (7.1)*	28 (53.8%)
	Quetiapine IR	600mg	51	6	7 days	26	Inpatient	39 (8)	13 (25.5%)	No PANSS / 43.5 (7.1)*	24 (47.1%)
	Quetiapine IR	750mg	54	6	7 days	26	Inpatient	35 (10)	16 (29.6%)	No PANSS / 45.7 (6.8)*	28 (51.9%)
	Haloperidol	12mg	52	6	7 days	26	Inpatient	37 (10)	10 (19.2%)	No PANSS / 44.0 (7.2)*****	34 (65.4%)
	Placebo	-	51	6	7 days	26	Inpatient	36 (8)	10 (19.6%)	No PANSS / 45.3 (7.1)*****	35 (68.6%)
Small	Quetiapine IR (low dose)	250mg (max)	94	6	EU – >1 day US – >2 days	37	Inpatient	37 (9)	21 (22.3%)	25.5 (8.7) / 38.9 (9.8)	54 (57.4%)
	Quetiapine IR (high dose)	750mg (max)	96	6	EU – >1 day US – >2 days	37	Inpatient	36 (9)	30 (31.3%)	27.5 (9.4) / 41.0 (9.6)	48 (50%)
	Placebo	-	96	6	EU – >1 day US – >2 days	37	Inpatient	38 (10)	32 (33.3%)	24.4 (6.6) / 38.4 (9.7)	57 (59.4%)
Borison	Quetiapine IR	Mean daily dose 307mg (range, 58-526mg)	54	6	2-10 days	12	Inpatient	36 (9)	6 (11%)	No PANSS / 55.8 (8.3)	26 (48.1%)

								Baseline demographics			
Trial	**Treatments**	**Dose, (mg/d)**	**Number of patients randomised**	**Duration of active medication (weeks)**	**Duration of wash-out (days)**	**Number of centres**	**Setting**	**Age, mean (SD)**	**Proportion female (%)**	**PANSS / BPRS, mean (SD)**	**Total number leaving early (N, [%])**
	Placebo	-	55	6	2-10 days	12	Inpatient	37 (8)	5 (9%)	No PANSS / 54.1 (7)	33 (60%)
Kahn	Quetiapine IR	400mg	123	6	>2 days	39	Inpatient / outpatient	34.4 (10.2)	50 (42%)	96.5 (16.0) / No BPRS	27 (22%)
	Quetiapine XR	400mg	113	6	>2 days	39	Inpatient / outpatient	34.1 (9.6)	33 (29.7%)	95.8 (13.9) / No BPRS	30 (26.5%)
	Quetiapine XR	600mg	113	6	>2 days	39	Inpatient / outpatient	34.2 (9.9)	50 (45%)	96.8 (14.1) / No BPRS	21 (18.6%)
	Quetiapine XR	800mg	121	6	>2 days	39	Inpatient / outpatient	34.4 (10.3)	47 (40.2%)	97.3 (14.7) / No BPRS	31 (25.6%)
	Placebo	-	118	6	>2 days	39	Inpatient / outpatient	34.1 (12.1)	48 (41.7%)	96.2 (13.3) / No BPRS	33 (28%)
Canuso	Quetiapine IR	600-800mg	159	6	1 day	Multiple, not specified	Inpatient	36.9 (10.2)	50 (31.8%)	101.3 (13.3) / No BPRS	53 (33.35)
	Paliperidone XR	9-12mg	160	6	1 day	Multiple, not specified	Inpatient	35.7 (11.6)	52 (33.1%)	102.8 (13.1) / No BPRS	34 (21.3%)
	Placebo	-	80	6	1 day	Multiple, not specified	Inpatient	36.1 (10.4)	30 (37.5%)	103.8 (15.7) / No BPRS	29 (36.3%)
Potkin	Quetiapine IR	400-800mg	156	6	NS	30	Inpatient	34.2 (9.8)	56 (35.9%)	97.3 (19.1) / No BPRS	41 (26.3%)
	Risperidone	4-6mg	153	6	NS	30	Inpatient	34.7 (9.6)	48 (31.4%)	95.0 (18.0) / No BPRS	27 (17.6%)
	Placebo	-	73	6	NS	30	Inpatient	36.1 (9.8)	27 (37%)	94.3 (18.2) / No BPRS	28 (38.4%)
Chen	Quetiapine IR	400mg	89	52	4-6 weeks	1	Outpatient	23.5 (5.2)	50 (56.2%)	36.1 (4.6) / No BPRS	28 (31.5%)
	Placebo	-	89	52	4-6 weeks	1	Outpatient	24.9 (7.3)	48 (54%)	37.1 (6.4) / No BPRS	18 (20.2%)
Lindenmayer	Quetiapine IR	300mg	90	6	>2 days	55	Inpatient	39.8 (10.6)	21 (24.7%)	89.5 (15.7) / No BPRS	49 (54.4%)

								Baseline demographics			
Trial	**Treatments**	**Dose, (mg/d)**	**Number of patients randomised**	**Duration of active medication (weeks)**	**Duration of wash-out (days)**	**Number of centres**	**Setting**	**Age, mean (SD)**	**Proportion female (%)**	**PANSS / BPRS, mean (SD)**	**Total number leaving early (N, [%])**
	Quetiapine IR	600mg	86	6	>2 days	55	Inpatient	40.6 (9.7)	21 (26.2%)	88.6 (17.3) / No BPRS	53 (61.6%)
	Quetiapine XR	300mg	91	6	>2 days	55	Inpatient	39.1 (11.2)	24 (28.9%)	91.5 (19.2) / No BPRS	56 (61.5%)
	Quetiapine XR	600mg	92	6	>2 days	55	Inpatient	38.9 (9.5)	26 (29.9%)	92.4 (17.2) / No BPRS	52 (56.5%)
	Quetiapine XR	800mg	89	6	>2 days	55	Inpatient	37.8 (10.5)	16 (18.8%)	89.0 (14.9) / No BPRS	45 (50.6%)
	Placebo	-	84	6	>2 days	55	Inpatient	38.4 (10.1)	18 (23.1%)	91.1 (16.3) / No BPRS	55 (65.5%)
Cutler	Quetiapine IR	800mg	116	6	>2 days	40	Inpatient / outpatient	40.8 (10.4)	40 (36.7%)	93.0 (13.5) / No BPRS	54 (46.6%)
	Quetiapine XR	400mg	114	6	>2 days	40	Inpatient / outpatient	42.1 (10.1)	34 (30.1%)	91.1 (13.4) / No BPRS	40 (35.1%)
	Quetiapine XR	600mg	105	6	>2 days	40	Inpatient / outpatient	41.2 (10.8)	19 (18.8%)	93.1 (14.0) / No BPRS	44 (41.9%)
	Quetiapine XR	800mg	113	6	>2 days	40	Inpatient / outpatient	40.2 (9.1)	28 (25.5%)	92.6 (13.2) / No BPRS	45 (39.8%)
	Placebo	-	117	6	>2 days	40	Inpatient / outpatient	42.5 (10.8)	34 (30.6%)	90.8 (11.9) / No BPRS	49 (41.9%)
Findling	Quetiapine IR	400mg	73	6	1-28 days	43	Inpatient / outpatient	15.45 (1.25)	30 (41.1%)	96.2 (17.7) / No BPRS	17 (23.3%)
	Quetiapine IR	800mg	74	6	1-28 days	43	Inpatient / outpatient	15.45 (1.34)	30 (40.5%)	96.9 (15.3) / No BPRS	13 (17.6%)
	Placebo	-	75	6	1-28 days	43	Inpatient / outpatient	15.34 (1.39)	31 (42.5%)	96.7 (18.0) / No BPRS	28 (37.3%)

								Baseline demographics			
Trial	**Treatments**	**Dose, (mg/d)**	**Number of patients randomised**	**Duration of active medication (weeks)**	**Duration of wash-out (days)**	**Number of centres**	**Setting**	**Age, mean (SD)**	**Proportion female (%)**	**PANSS / BPRS, mean (SD)**	**Total number leaving early (N, [%])**
NCT00658645 (Study 11915A)	Quetiapine IR	600mg	76	12	21 day cross-titration	34	Inpatient / outpatient	NS (39 overall)	NS (46% overall)	No PANSS / 80.4 (12.9)	25 (33%)
	Bifeprunox	20mg	82	12	21 day cross-titration	34	Inpatient / outpatient	NS (39 overall)	NS (46% overall)	No PANSS /78.9 (12.4)	37 (45%)
	Placebo	-	68	12	21 day cross-titration	34	Inpatient / outpatient	NS (39 overall)	NS (46% overall)	No PANSS /79.9 (12.2)	30 (44%)
NCT00704509 (Study 11916A)	Quetiapine IR	600mg	116	12	21 day cross-titration	45	Inpatient / outpatient	NS (~38 overall)	NS (~46% overall)	No PANSS /80.1 (10.3)	52 (45%)
	Bifeprunox	20mg	110	12	21 day cross-titration	45	Inpatient / outpatient	NS (~38 overall)	NS (~46% overall)	No PANSS /78.8 (9.5)	58 (53%)
	Placebo	-	119	12	21 day cross-titration	45	Inpatient / outpatient	NS (~38 overall)	NS (~46% overall)	No PANSS /79 (9.3)	55 (46%)
Study 15	Quetiapine IR	75mg	85	52	7-28 days	34	NS	Mean across all groups: 38 (range 19 to 66)	Proportion female across all groups was 20%	NS	72 (85%)
	Quetiapine IR	300mg	88	52	7-28 days	34	NS	Mean across all groups: 38 (range 19 to 66)	Proportion female across all groups was 20%	NS	74 (84%)
	Quetiapine IR	600mg	87	52	7-28 days	34	NS	Mean across all groups: 38 (range 19 to 66)	Proportion female across all groups was 20%	NS	66 (76%)
	Haloperidol	12mg	41	52	7-28 days	34	NS	Mean across all groups: 38 (range 19 to 66)	Proportion female across all groups was 20%	NS	27 (66%)

								Baseline demographics			
Trial	**Treatments**	**Dose, (mg/d)**	**Number of patients randomised**	**Duration of active medication (weeks)**	**Duration of wash-out (days)**	**Number of centres**	**Setting**	**Age, mean (SD)**	**Proportion female (%)**	**PANSS / BPRS, mean (SD)**	**Total number leaving early (N, [%])**
Chapel	Quetiapine IR	375mg	37	2	5	6	NS ('stable')	39.6 (7.59)	10 (27%)	NS	10 (27%)
	Asenapine	5/10mg	38	2	5	6	NS ('stable')	42.4 (9.52)	5 (13.2%)	NS	11 (28.9%)
	Asenapine	10/20mg	38	2	5	6	NS ('stable')	43.6 (7.73)	12 (31.6%)	NS	9 (23.7%)
	Placebo	-	35	2	5	6	NS ('stable')	44.8 (8.39)	7 (20%)	NS	4 (11.4%)
Hough	Quetiapine IR	800mg	43	2	1-6	10	NS ('stable')	35 (8)	10 (23)	NS	5 (11.6%)
	Paliperidone	12/18mg	44	2	1-6	10	NS ('stable')	37 (9)	10 (23)	NS	8 (18.2%)
	Placebo	-	22	2	1-6	10	NS ('stable')	39 (8)	11 (50)	NS	2 (9.1%)

* Standard error reported, not standard deviation; NS, Not specified in report

F. Validation of Minimal Clinically Important Difference in PANSS scores

More details on method

Only two of the 11 short-term efficacy studies failed to report a power calculation.(59, 60) We calculated the MCID of both studies using their planned sample size estimates (adjusted for 15% attrition) and the median SD (22), alpha (0.05) and desired power (90%) of the other studies. For the two other studies that based their power calculations on minimally important standardised effect sizes,(61, 62) we again used median SDs to convert these estimates to PANSS scores. BPRS ratings from three older studies(63-65) were also converted to PANSS scores.(2)

G. Risk of bias assessment

Method
All assessments were conducted independently by two reviewers and any disagreements were resolved through discussion , or by consultation with a third author, and an overall rating decided on.

For random sequence generation and allocation concealment, we did not include any trials where allocation was described as not concealed or where the sequence generation was described as not random (e.g., sequential allocation). If no information was provided but the study was described as a randomised double-blind controlled trial, then we marked risk of bias as unclear. If, in addition to this, a clear description of independent, concealed and random allocation to groups was provided, then we described this as low risk.

With respect to performance and detection bias, we think a degree of unblinding due to sedative or other noticeable effects (e.g., weight-gain) is likely in placebo-controlled antipsychotic trials (66-69). Moreover, the double-blind design also does not protect against the risk of researchers adopting a high threshold for recording effects where the desired outcome is 'no difference' (70), particularly when there is no active control arm to provide assay sensitivity. The drug-placebo differential is larger in antipsychotic trials where participants and raters have a greater expectation of participants receiving placebo,(71, 72) which would be unlikely if blinding in these trials is successful. Nonetheless, we need more research examining whether unblinding occurs and, if it does, what effect it has. As such, we marked risk of performance bias for subjective outcomes as low if adequate methods were used to mask the appearance and taste of tablets, unclear if no description given, and high only if the methods described seemed inadequate. Open or single-blind trials were excluded.

If only sparse information was supplied in the prospectively registered protocol, or if no such protocol was available, then we classified risk of selective reporting bias as being at least unclear.(73) Efficacy studies without adequately detailed protocols were classified as being at high risk of selective reporting bias if they did not report usable data in relation to any of the following standard or essential outcomes: symptom change, global change, extra-pyramidal adverse effects and weight-gain. Adverse effect studies needed only to report usable adverse effect data. Usable data was defined as endpoint or mean change with an estimate of variance (SD, SE, p-value, t-value) and, for the same outcome, numbers with meaningful degree of improvement or deterioration, or number of events only where applicable.

Attrition bias was judged to be high if ≥25% of those randomised did not provide data at the pre-defined trial endpoint.(74) We did not include financial conflicts of interest in the 'other bias' section, but we did include factors such as stopping early for benefit.(75)

Overview
The risk of selection bias was low or unclear for most studies. The risk of selective reporting bias was generally high, due to inadequate information in published protocols and failure to report variance or individual response or deterioration. Attrition bias was high; eleven trials had less than 50% attrition at endpoint and four had ≥50% attrition. Almost all had over 25% attrition.

Other bias: Truncated trials
Two unpublished studies (11915A and 11916A)(59, 60) were originally designed with a 12-week acute treatment phase (quetiapine IR vs. bifeprunox vs. placebo) and 12-month maintenance phase (quetiapine IR vs. bifeprunox; both studies combined). An interim analysis suggesting bifeprunox would be unlikely to demonstrate non-inferiority to quetiapine meant both trials were terminated early. Although the summary reports state that 54%-62% of participants completed the 12-week acute treatment phase in each, the precise reasons for withdrawal at that time-point (e.g., adverse events, early termination) were not specified. Although these trials are 'truncated' whether this creates a risk of biased results, either for or against quetiapine IR, is unclear (Walters & Guyatt, personal communication).

Risk of bias ratings

Study	Rater	Sequence generation	Allocation concealment	Performance bias	Detection bias	Incomplete outcome data	Selective reporting	Other bias
Arvanitis	Rater 1	Unclear: Not reported	Unclear: Not reported	High: No description of tablets given and unblinding due to sedation likely.	High: Side-effects likely to unblind. Most efficacy measures are subjective and blinding does not prevent adoption of high threshold for adverse effects.	High: Over 50%	High: No pre-registered protocol; no reporting of SAEs; no variance for weight-gain or prolactin. 10% AE threshold used.	High: Seroquel study group did not publish other key trials or report all outcomes. Abrupt withdrawal can confound deterioration with withdrawal symptoms.
	Rater 2	Unclear: Not reported	Unclear: Not reported	Unclear: No description of tablets given. Unblinding likely but no clear evidence this biases results.	Unclear: Side-effects likely to unblind, but no clear evidence this can bias results.	High: Over 50%	Unclear: No pre-reg protocol. No overall SAEs but discussed for specific outcomes. Some reported incompletely.	High: Seroquel study group did not publish other key trials or report all outcomes. Abrupt withdrawal used.
	Overall	Unclear	Unclear	Unclear	Unclear	High	Unclear	High
	Leucht 2013 rating (7)	Low	Low	Low / unclear	Low / unclear	High	Low	Low
	Cochrane review rating (76)	Unclear	Unclear	Unclear	Unclear	Low	Low	High

Study	Rater	Sequence generation	Allocation concealment	Performance bias	Detection bias	Incomplete outcome data	Selective reporting	Other bias
Small	Rater 1	Low: "computer-generated randomisation scheme…"	Unclear: Not reported	High: No description of tablets given and unblinding due to sedation likely.	High: Side-effects likely to unblind. Most efficacy measures are subjective and blinding does not prevent adoption of high threshold for adverse effects.	High: Over 50%	High: No pre-reg protocol. Only binary figures given for EPS and weight-gain, and only continuous for prolactin. SAEs not defined or reported	High: Seroquel study group did not publish other key trials or report all outcomes. Abrupt withdrawal used.
	Rater 2	Low: "computer-generated randomisation scheme…"	Unclear: Not reported	Unclear: No description of tablets given. Unblinding likely but no clear evidence this biases results.	Unclear: Side-effects likely to unblind, but no clear evidence this can bias results.	High: Over 50%	Unclear: total SAEs not reported. No continuous EPS data but data skewed. Mean change in weight given without variance. No binary measure of prolactin.	High: Seroquel study group did not publish other key trials or report all outcomes. Abrupt withdrawal used.
	Overall	Low	Unclear	Unclear	Unclear	High	Unclear	High
	Leucht 2013 rating (7)	Low	Low	Low / unclear	Low / unclear	High	Low	Low
	Cochrane review rating (19)	Low	Low	-	-	-	-	-

Study	Rater	Sequence generation	Allocation concealment	Performance bias	Detection bias	Incomplete outcome data	Selective reporting	Other bias
Borison	Rater 1	Unclear: Not reported	Unclear: Not reported	Unclear: "matching placebo tablets". Unblinding due to sedation likely	High: Side-effects likely to unblind. Most efficacy measures are subjective and blinding does not prevent adoption of high threshold for adverse effects.	High: >50% drop-out	High: No pre-reg protocol. Missing outcomes include % change in BPRS scores and no binary figures for prolactin. No variance for weight gain.	High: Seroquel study group did not publish other key trials or report all outcomes. Abrupt withdrawal used. First author convicted of fraud.
	Rater 2	Unclear: Not reported	Unclear: Not reported	Unclear: "matching placebo tablets" Unblinding likely but no clear evidence this biases results.	Unclear: Side-effects likely to unblind, but no clear evidence this can bias results.	High: >50% drop-out	High: No pre-reg protocol. Missing outcomes include % change in BPRS scores and no binary figures for prolactin. No variance for weight gain.	Seroquel study group did not publish other key trials or report all outcomes. Abrupt withdrawal used. First author convicted of fraud.
	Overall	Unclear	Unclear	Unclear	Unclear	High	High	High
	Leucht 2013 rating (7)	Unclear	Unclear	Low	Low	High	Low	Low
	Cochrane review rating (19)	Unclear	Unclear	-	-	-	-	-

Study	Rater	Sequence generation	Allocation concealment	Performance bias	Detection bias	Incomplete outcome data	Selective reporting	Other bias
Kahn	Rater 1	Unclear: not reported	Unclear: not reported	Unclear: "dual-matched placebo" Unblinding due to sedation likely	High: Side-effects likely to unblind. Most efficacy measures are subjective and blinding does not prevent adoption of high threshold for adverse effects.	High: >25% attrition	High: little detail in protocol. N with sign. weight gain not reported; p-values given for main outcome, but not SEs or SDs.	Unclear: abrupt withdrawal used.
	Rater 2	Unclear: not reported	Unclear: not reported	Low: "dual-matched placebo" "matching in appearance" Unblinding likely but no clear evidence this biases results.	Unclear: Side-effects likely to unblind, but no clear evidence this can bias results.	High: >25% attrition	High: inadequately detailed protocol, but most usual outcomes reported. Binary data for weight-gain, 50% improvement in PANSS scores and variance for efficacy estimates not reported, although eventually obtained from sponsor.	Unclear: abrupt withdrawal used.
	Overall	Unclear	Unclear	Unclear	Unclear	High	High	Unclear
	Leucht 2013 rating (7)	Unclear	Unclear	Low	Low	Low	Low	Low

Study	Rater	Sequence generation	Allocation concealment	Performance bias	Detection bias	Incomplete outcome data	Selective reporting	Other bias
Canuso	Rater 1	Low: "interactive voice response system"	Low: "interactive voice response system" and identical capsules.	Unclear: "All medication was blinded and identically overencapsulated, including placebo." Unblinding due to sedation likely	Unclear: Side-effects likely to unblind. However, short trial duration may limit this possibility. Most efficacy measures are subjective and blinding does not prevent adoption of high threshold for adverse effects.	Low: <25% at 2 weeks	High: preregistered protocol available; "time to response" specified as secondary outcome but not looked at in study.	Unclear: abrupt withdrawal used.
	Rater 2	Unclear: not clear how sequence generated.	Low: "interactive voice response system"	Low: "All medication was blinded and identically overencapsulated, including placebo." Unblinding likely but no clear evidence this biases results.	Unclear: Side-effects likely to unblind, but no clear evidence this can bias results.	Low: <25% at 2 weeks	Low: preregistered protocol with better detail than usual. Analysis of time to response not supplied, but expected range of important outcomes supplied, and authors supplied extra data.	Unclear: abrupt withdrawal used.
	Overall	Low	Low	Unclear	Unclear	Low	Unclear	Unclear
	Cochrane review rating (77)	Low	Low	Low	Low	Low	High	High

Study	Rater	Sequence generation	Allocation concealment	Performance bias	Detection bias	Incomplete outcome data	Selective reporting	Other bias
Potkin	Rater 1	Low - the IVRS manages randomisation and concealment -	Low: “interactive voice response system”	Unclear: “Patients received visually matching, over-encapsulated, comparative dissolution-tested study medication.”	Unclear: Side-effects likely to unblind. However, short trial duration may limit this possibility.	Low: <25%	Unclear: Pre-registered protocol but little detail. Binary data on weight-gain and serious adverse events not reported. All other measures available.	Unclear: abrupt withdrawal probably used.
	Rater 2	Unclear: not clear how sequence generated.	Low: “interactive voice response system”	Low: “Patients received visually matching, over-encapsulated, comparative dissolution-tested study medication.” Unblinding likely but no clear evidence this biases results.	Unclear: “Due to concerns for potential unblinding of the active treatments, thyroid and prolactin tests results were not reported to the investigator after baseline.” Other side-effects likely to unblind, but no clear evidence this can bias results.	Low: <25%	High: Pre-registered protocol but little detail. Binary data on weight-gain and serious adverse events not reported.	Unclear: abrupt withdrawal probably used.
	Overall	Low	Low	Unclear	Unclear	Low	High	Unclear
	Cochrane review rating (78)	Unclear	Low	Low	Low	Low	Low	High

Study	Rater	Sequence generation	Allocation concealment	Performance bias	Detection bias	Incomplete outcome data	Selective reporting	Other bias
Chen	Rater 1	Low: "AstraZeneca generated a randomisation sequence by computer, with a fixed block size of four without stratification."	Low: "AstraZeneca prepared individually numbered sets of study drugs, packed them according to the randomisation sequence, and then shipped them to the study team in numbered but apparently identical sets. Study investigators assigned the study drug sets to participants consecutively according to the sequence of study entry. Investigators, patients, and all research staff were blind to the study drugs and the block size."	Unclear: "We randomised patients to maintenance with quetiapine (400 mg/day) or placebo of identical appearance" Unblinding due to sedation likely	High: Side-effects likely to unblind. Most efficacy measures are subjective and blinding does not prevent adoption of high threshold for adverse effects.	High: >25% drop-out	High: Protocol suggests QoL measured but not included, also neg symptoms not included but specified in protocol. Symptom change not reported although would be expected. No prolactin investigation.	High: Significantly more in quetiapine arm had received quetiapine prior to study entry. Gradual discontinuation used though.

Study	Rater	Sequence generation	Allocation concealment	Performance bias	Detection bias	Incomplete outcome data	Selective reporting	Other bias
	Rater 2	Low: "AstraZeneca generated a randomisation sequence by computer, with a fixed block size of four without stratification."	Low: "AstraZeneca prepared individually numbered sets of study drugs, packed them according to the randomisation sequence, and then shipped them to the study team in numbered but apparently identical sets. Study investigators assigned the study drug sets to participants consecutively according to the sequence of study entry. Investigators, patients, and all research staff were blind to the study drugs and the block size."	Low: "We randomised patients to maintenance with quetiapine (400 mg/day) or placebo of identical appearance" Unblinding likely but no clear evidence this biases results.	Unclear: "Investigators, patients, and all research staff were blind to the study drugs and the block size" Unblinding likely but no clear evidence this biases results.	High: >25% drop-out	High: No reporting of symptoms, QoL, cognitive functioning, despite being a priori secondary outcomes.	High: Significantly more in quetiapine arm had received quetiapine prior to study entry. Gradual discontinuation used though.
	Overall	Low	Low	Unclear	Unclear	High	High	High

Study	Rater	Sequence generation	Allocation concealment	Performance bias	Detection bias	Incomplete outcome data	Selective reporting	Other bias
	Leucht 2012 rating (79)	Low	Low	Unclear / low	Unclear / Low	High	Low	Low
Lindenmayer	Rater 1	Unclear: not reported	Unclear: not reported	Unclear: "tablets given to all patients for a given dose were identical in number and appearance" Unblinding due to sedation likely	High; Unblinding due to sedation likely	High: >50%	High; variance for efficacy poorly reported	Unclear: abrupt withdrawal used
	Rater 2	Unclear: not reported	Unclear: not reported	Low: "tablets given to all patients for a given dose were identical in number and appearance" "The study used a double-dummy technique to ensure blinding." Unblinding likely but no clear evidence this biases results.	Unclear: Unblinding likely but no clear evidence this biases results.	High: >50%	High; Could not trace protocol; variance for efficacy poorly reported	Unclear: abrupt withdrawal used
	Overall	Unclear	Unclear	Unclear	Unclear	High	High	Unclear
	Leucht 2013 rating (7)	Low	Low	Low	Low	High	Low	Low

Study	Rater	Sequence generation	Allocation concealment	Performance bias	Detection bias	Incomplete outcome data	Selective reporting	Other bias
Cutler	Rater 1	Unclear: not reported	Unclear: not reported	High: No description of tablets or blinding procedures and unblinding due to sedation likely.	High: Side-effects likely to unblind. Most efficacy measures are subjective and blinding does not prevent adoption of high threshold for adverse effects.	High >25%	High: Primary efficacy variables (PANSS and CGI) not presented in detail in paper.	Unclear: abrupt withdrawal used
	Rater 2	Unclear: not reported	Unclear: not reported	Unclear: No description of tablets or blinding procedures. Unblinding likely but no clear evidence this biases results.	Unclear: Side-effects likely to unblind, but no clear evidence this can bias results.	High: >25%	High: Primary efficacy variables (PANSS and CGI) not presented with variance in paper or trial synopsis, although provided in FDA report. Variance also not supplied for weight-gain. We obtained important data from sponsor that has not been published (e.g. 50% reduction in PANSS).	Unclear: abrupt withdrawal used
	Overall	Unclear	Unclear	Unclear	Unclear	High	High	Unclear
	Leucht 2013 rating	Unclear	Unclear	Unclear / low	Unclear / low	High	High	Low

Study	Rater	Sequence generation	Allocation concealment	Performance bias	Detection bias	Incomplete outcome data	Selective reporting	Other bias
Hough	Rater 1	Low: "A computerized randomization scheme was used, which was balanced using permuted blocks and implemented through a central call center."	Low: "A computerized randomization scheme was used, which was balanced using permuted blocks and implemented through a central call center."	Unclear: "All active medication and matching placebo tablets were overencapsulated" Equal number of tablets. Unblinding due to sedation likely.	High: Side-effects likely to unblind although short trial duration may limit this possibility. Most efficacy measures are subjective and blinding does not prevent adoption of high threshold for adverse effects.	Low <25%	High: poor reporting of weight-gain (no variance and no binary data)	Unclear: abrupt withdrawal used
	Rater 2	Low: "A computerized randomization scheme was used, which was balanced using permuted blocks and implemented through a central call center."	Low: "A computerized randomization scheme was used, which was balanced using permuted blocks and implemented through a central call center."	Low: "All active medication and matching placebo tablets were overencapsulated" Equal number of tablets. Unblinding likely but no clear evidence this biases results.	High: Side-effects likely to unblind, although not clear whether this leads to bias. Blinding does not prevent adoption of high threshold for adverse effects when goal is non-inferiority, as is the case here.	Low <25%	High: poor reporting of weight-gain (no variance and no binary data)	Unclear: abrupt withdrawal used
	Overall	Low	Low	Unclear	High	Low	High	Unclear

Study	Rater	Sequence generation	Allocation concealment	Performance bias	Detection bias	Incomplete outcome data	Selective reporting	Other bias
Chapel	Rater 1	Unclear: not reported	Unclear: not reported	Unclear: No description of tablets given.	High: Side-effects likely to unblind. However, short trial duration may limit this possibility. Blinding does not prevent adoption of high threshold for adverse effects when goal is non-inferiority, as is the case here	High: <25% overall but >25% in one group.	High: No other adverse effect information reported.	Unclear: abrupt withdrawal used
	Rater 2	Unclear: not reported	Unclear: not reported	Unclear: No description of tablets given. Unblinding likely but no clear evidence this biases results.	High: Side-effects likely to unblind, but no clear evidence this can bias results. Blinding does not prevent adoption of high threshold for adverse effects when goal is non-inferiority, as is the case here	Unclear: <25%. A group difference in attrition was observed but this is not sufficient for judgement of bias (80)	High: very little adverse effect information reported other than overall numbers.	Unclear: abrupt withdrawal used
	Overall	Unclear	Unclear	Unclear	High	Unclear	High	Unclear
Findling	Rater 1	Unclear	Unclear	Unclear: "The quetiapine and placebo tablets were identical in size and color in order to maintain blinding." Unblinding due to sedation likely.	High; Unblinding due to sedation likely	High: >25%	Low: All important outcomes reported.	Low: flexible washout used

Study	Rater	Sequence generation	Allocation concealment	Performance bias	Detection bias	Incomplete outcome data	Selective reporting	Other bias
	Rater 2	Low "Random assignment to treatment was achieved by a central randomization service, with stratification by gender."	Low "Random assignment to treatment was achieved by a central randomization service, with stratification by gender."	Low: "The quetiapine and placebo tablets were identical in size and color in order to maintain blinding." Unblinding likely but no clear evidence this biases results.	Unclear: Unblinding likely but no clear evidence this biases results.	High: >25%	Unclear: Little useful information in pre-registered protocol, but all important outcomes reported in satisfactory way. Additional analyses were performed but not reported in the original paper or synopsis.	Low: flexible washout used
	Overall	Low	Low	Unclear	Unclear	High	Low	Low
11915A	Rater 1	Unclear: not reported	Unclear: not reported	High: "encapsulated tablets". No more information provided. Unblinding due to sedation likely.	High; Unblinding due to sedation likely	High>25%	High: no response rates given for PANSS and no variance for weight change. Data on AIMS and BARS not available	High: trial stopped early due to futility of new compound.
	Rater 2	Unclear: not reported	Unclear: not reported	Unclear: "encapsulated tablets". No more information provided. Unblinding likely but no clear evidence this biases results.	Unclear: Unblinding likely but no clear evidence this biases results.	High>25%	High: several outcomes not fully reported (depression), and sponsor refused to supply more tables the synopsis references.	High: trial stopped early due to futility of new compound.
	Overall	Unclear	Unclear	Unclear	Unclear	High	High	High

Study	Rater	Sequence generation	Allocation concealment	Performance bias	Detection bias	Incomplete outcome data	Selective reporting	Other bias
11916A	Rater 1	Unclear: not reported	Unclear: not reported	High: "encapsulated tablets". No more information provided. Unblinding due to sedation likely.	High; Unblinding due to sedation likely	High>25%	High: no response rates given for PANSS and no variance for weight change. Data on AIMS and BARS not available	High: unpublished study. not peer-reviewed. trial stopped early due to futility of new compound.
	Rater 2	Unclear: not reported	Unclear: not reported	Unclear: "encapsulated tablets". No more information provided. Unblinding likely but no clear evidence this biases results.	Unclear: Unblinding likely but no clear evidence this biases results.	High>25%	High: several outcomes not fully reported (depression), and sponsor refused to supply more tables the synopsis references.	High: unpublished study. not yet peer-reviewed. trial stopped early due to futility of new compound.
	Overall	Unclear	Unclear	Unclear	Unclear	High	High	High
Study 15	Rater 1	Unclear: not reported	Unclear: not reported	Low: No expectation of placebo and unblinding in relation to dose unlikely. 'Matched placebo used to mask dose'	Low: No expectation of placebo and unblinding in relation to dose unlikely.	High:>25%	High: Multiple outcomes remain unpublished from this study, including quality of life. Overall figures never formally published.	High: Study completed in 1996 but remains unpublished. Trial stopped early. Seroquel study group did not publish other key trials or report all outcomes. A subtherapeutic dose may have a slight effect, which may slightly underestimate the effect of optimal dose.

Study	Rater	Sequence generation	Allocation concealment	Performance bias	Detection bias	Incomplete outcome data	Selective reporting	Other bias
	Rater 2	Unclear: not reported	Unclear: not reported	Low: No expectation of placebo and unblinding in relation to dose unlikely. 'matched placebo used to mask dose'	Low: No expectation of placebo and unblinding in relation to dose unlikely.	High:>25%	High: Multiple outcomes remain unpublished from this study, including quality of life. Overall figures never formally published.	High: Study completed in 1996 but remains unpublished. Trial stopped early. Seroquel study group did not publish other key trials or report all outcomes. A subtherapeutic dose may have a slight effect, which may slightly underestimate the effect of optimal dose.
	Overall	Unclear	Unclear	Low	Low	High	High	High

H. Primary and secondary efficacy outcomes

Outcome	Time-point (weeks)	No of included studies	Que N events / N	Pla N events / N	Hedges's g (95% CI)	Mean difference (95% CI)	Risk ratio (95% CI)	Absolute difference (95% CI)	NNTB/H (95% CI)	Heterogeneity for g or RR: I^2; Chi^2 (p-value)	Quality (GRADE)
Overall symptoms (mean change in PANSS total) based on LOCF or MMRM	2-12	11	1346	912	-0.33 (-0.44, -0.21)	-6.44 (-8.89, -4.00)	-	-	-	47%; 18.9 (p=0.040)	Moderate-high
Overall symptoms (mean change in PANSS total) using Strategy 1 imputations.	2-12	11	1373	931	-0.23 (-0.35, -0.11)	-4.25 (-6.46, -2.04)	-	-	-	52%; 20.7 (p=0.023)	
Overall symptoms (mean change in PANSS total) using Strategy 2 imputations	2-12	11	1373	931	-0.15 (-0.30, 0.01)	-2.66 (-5.46, 0.15)	-	-	-	70%; 32.9 (p<0.001)	
Significant improvement (≥50% reduction in PANSS / BPRS) based on LOCF	2-12	11	1126 / 1375	816 / 933	-	-	0.95 (0.91, 0.98)	-0.047 (-0.016, -0.016)	21B (13B, 63B)	43%; 17.5 (p=0.070)	Low - moderate
Relapse or exacerbation (vs. placebo or subtherapeutic dose; drop-outs ≠ relapse)	52	2	110 / 264	101 / 174	-	-	0.67 (0.36, 1.22)	-0.189 (-0.455, 0.076)	5B (2B, 13H)	87%; 7.8 (p=0.005)	Very low
Relapse or exacerbation (vs. placebo or subtherapeutic dose; drop-outs = relapse)	52	2	195 / 264	146 / 174	-	-	0.85 (0.67, 1.07)	-0.125 (-0.288, 0.038)	8B (3B, 26H)	78%; 4.5 (p=0.030)	
Need for hospital care (drop-outs not needing hospital care)	2-6	3	189 / 431	107 / 270	-	-	0.90 (0.74, 1.09)	-0.052 (-0.097, -0.007)	19B (10B, 143B)	27%; 2.7 (p=0.254)	Low
Need for hospital care (drop-outs needing hospital care)	2-6	3	246 / 431	163 / 270	-	-	0.91 (0.81, 1.03)	-0.052 (-0.127, 0.023)	19B (8B, 44H)	0%; 0.2 (p=0.892)	
Need for hospital care (drop-outs not needing hospital care)	52	1	4/89	12/89	-	-	0.33 (0.11, 0.99)	-0.090 (-0.173, -0.007)	11B (6B, 143B)	-	Very low

Outcome	Time-point (weeks)	No of included studies	Que N events / N	Pla N events / N	Hedges's g (95% CI)	Mean difference (95% CI)	Risk ratio (95% CI)	Absolute difference (95% CI)	NNTB/H (95% CI)	Heterogeneity for g or RR: I^2; Chi^2 (p-value)	Quality (GRADE)
Need for hospital care (drop-outs needing hospital care)	52	1	32 / 89	30/89	-	-	1.07 (0.71, 1.56)	0.022 (-0.117, 0.162)	50H (9B, 6H)	-	
Positive symptoms	2-12	11	1344	910	-0.32 (-0.44, -0.20)	-	-	-	-	49.5%; 19.8 (p=0.031)	Moderate
Negative symptoms	2-12	11	1305	879	-0.21 (-0.32, -0.10)	-	-	-	-	39%; 18.2 (p=0.079)	Moderate
Depression	2-6	7	906	581	-0.13 (-0.23, -0.02)	-	-	-	-	0%; 2.4 (p=0.880)	Low
Needing additional sedatives (drop-outs = unchanged outcome)	2-6	6	189 / 630	171 /475	-	-	0.86 (0.75, 0.99)	-0.029 (-0.077, 0.019)	34B (13B, 53H)	27%; 6.8 (p=0.235)	Low
Needing additional antipsychotics (drop-outs = unchanged outcome)	6	2	127 / 315	68 / 153	-	-	0.91 (0.72, 1.13)	-0.041 (-0.137, 0.054)	24B (7B, 19H)	0%; 0.4 (p=0.506)	Moderate
Quality of life (S-QoL based on OC data)	12	2	116	111	0.11 (-0.15, 0.36)	2.00 (-2.94, 6.94)	-	-		0%; 0 (p=1)	Very low
Quality of life (S-QoL; using Strategy 1 imputations)	12	2	192	187	0.06 (-0.14, 0.27)	1.21 (-2.57, 4.99)	-	-	-	0%; 0 (p=0.946)	
Functioning (CGAS, PSP; based on LOCF and OC data)	6-12	3	227	155	0.39 (0.18, 0.60)	-	-	-	-	0%; 1.6 (p=0.455)	Very low

Outcome	**Time-point (weeks)**	**No of included studies**	**Que N events / N**	**Pla N events / N**	**Hedges's g (95% CI)**	**Mean difference (95% CI)**	**Risk ratio (95% CI)**	**Absolute difference (95% CI)**	**NNTB/H (95% CI)**	**Heterogeneity for g or RR: I^2; Chi^2 (p-value)**	**Quality (GRADE)**
Functioning (CGAS, PSP; using Strategy 1 imputations)	6-12	3	301	230	0.28 (0.09, 0.46)	-	-	-	-	8.5%; 2.2 (p=0.335)	
Losing employment (missing = not lost employment or unemployed at baseline)	52	1	17/89	21/89	-	-	0.81 (0.46, 1.43)	-0.045 (-0.165, 0.075)	22B (6B,13H)	-	Very low
Early discontinuation (any reason)	2-6	11	424 /1258	318 / 802	-	-	0.85 (0.75, 0.96)	-0.048 (-0.098, 0.003)	21B (10B, 333H)	24%; 13.2 (p=0.215)	High

Shaded rows indicates result statistically significant at $p<0.05$; *indicates at least moderate heterogeneity ($I^2 \geq 40\%$); bold text indicates primary outcome

I. All safety outcomes

Outcome (definition, imputation strategy)	Time-point (weeks)	No of included studies	Que N events / N	Pla N events / N	Hedges's g (95% CI)	Mean difference (95% CI)	Risk ratio (95% CI)	Absolute difference (95% CI)	NNTB/H (95% CI)	Heterogeneity for g or RR: I^2; Chi^2 (p-value)	Quality (GRADE)
Serious adverse events	2-12	8	50/851	45/658	-	-	0.94 (0.64, 1.39)	-0.001 (-0.023, 0.021)	1000B (44B, 48H)	0%; 3.3 (p=0.885)	Very low
Serious adverse events (placebo or subtherapeutic dose)	52	2	31/264	10/174	-	-	1.05 (0.21, 5.23)	0.002 (-0.023, 0.026)	500H (44B, 39H)	0%; 0.0 (p=0.41)	Very low
Any adverse event	2-12	9	754/1112	438/756	-	-	1.14 (1.06, 1.22)	0.089 (0.045, 0.134)	11H (22H, 8H)	0%; 6.6 (p=0.583)	Low
Any adverse events (vs. subtherapeutic dose)	52	1	100/175	76/85	-	-	0.93 (0.85, 1.03)	-0.060 (-0.145, 0.026)	17B (7B, 38H)	-	Very low
Drug-attributable adverse effects	6	4	265/562	115/394	-	-	1.53 (1.18, 1.98)	0.156 (0.070, 0.243)	7H (4H, 14H)	50%; 6 (p=0.109)	Low
Simpson-Angus Scale (mean change)	2-6	6	835	523	-0.11 (-0.24, 0.02)	-0.27 (-0.60, 0.06)	-	-	-	25%; 6.7 (p=0.247)	Moderate
Simpson-Angus Scale (worsening)	6	7	128/869	83/596	-	-	0.97 (0.73, 1.29)	0.007 (-0.033, 0.047)	143H (30B, 21H)	15%; 7 (p=0.317)	Low
Simpson-Angus Scale (worsening)	52	1	1/89	4/89	-	-	0.25 (0.03, 2.19)	-0.034 (-0.082, 0.015)	29B (12B, 67H)	-	Very low
Abnormal Involuntary Movements Scale (mean change)	2-6	3	491	237	-0.01 (-0.17, 0.14)	0.00 (-0.43, 0.38)	-	-	-	0%; 0 (p=0.979)	Low

Outcome (definition, imputation strategy)	Time-point (weeks)	No of included studies	Que N events / N	Pla N events / N	Hedges's g (95% CI)	Mean difference (95% CI)	Risk ratio (95% CI)	Absolute difference (95% CI)	NNTB/H (95% CI)	Heterogeneity for g or RR: I^2; Chi^2 (p-value)	Quality (GRADE)
Abnormal Involuntary Movement Scale (worsening)	6	4	88/534	56/265	-	-	0.694 (0.521, 0.924)	-0.047 (-0.130, 0.037)	21B (8B, 27H)	0%; 2.6 (0.460)	Low
Abnormal Involuntary Movement Scale (worsening; placebo or subtherapeutic dose)	52	2	22/264	14/174	-	-	0.833 (0.440, 1.578	-0.021 (-0.056, 0.013)	48B (18B, 77H)	0%; 0.9 (p=0.344)	Very low
Dystonia / hypertonia	2-6	4	7/413	2/208	-	-	1.265 (0.287, 5.570)	0.003 (-0.017, 0.024)	333H (59B, 43H)	0%; 1.3 (p=0.512)	Very low
Barnes Akathesia Scale (mean change)	6	3	415	319	0.035 (-0.113, 0.182)	0.024 (-0.070, 0.118)	-	-	-	0%; 0.13 (p=0.939)	Low
Barnes Akathesia Scale (worsening)	2-6	7	67/973	49/643	-	-	0.866 (0.609, 1.234)	-0.005 (-0.030, 0.020)	200B (33B, 50H)	0%l 3.5 (p=0.745)	Low
Barnes Akathesia Scale (worsening)	52	1	4/89	2/89	-	-	2 (0.376, 10.643)	0.022 (-0.030, 0.075)	45H (33B, 13H)	-	Very low
Number with extra-pyramidal side-effects	6-12	5	44/619	28/429	-	-	0.886 (0.364, 2.158)	-0.004 (-0.057, 0.049)b	250B (18B, 21H)	67%; 12.0(p=0.017)	Very low
Needing medication for extra-pyramidal side-effects	2-6	9	97/1071	65/698	-	-	0.838 (0.597, 1.176)	0.004 (-0.025, 0.032)	250H (40B, 31H)	12%; 9.1 (p=0.334)	Moderate
Mean weight change	2-12	12	1410	948	0.640 (0.428, 0.852)	1.753kg (1.104, 2.402)	-	-	-	83%; 65.4 (p<0.001)	Very low

Outcome (definition, imputation strategy)	**Time-point (weeks)**	**No of included studies**	**Que N events / N**	**Pla N events / N**	**Hedges's g (95% CI)**	**Mean difference (95% CI)**	**Risk ratio (95% CI)**	**Absolute difference (95% CI)**	**NNTB/H (95% CI)**	**Heterogeneity for g or RR: I^2; Chi^2 (p-value)**	**Quality (GRADE)**
Mean weight change	52	1	89	89	0.35 (0.05, 0.64)	2.330kg (0.368, 4.292)	-	-	-	-	Very low
Significant weight-gain (≥7% or recorded as adverse effect)	2-12	10	140/1220	32/863	-	-	2.988 (2.048, 4.362)	0.076 (0.044, 0.109)	13H (23H, 9H)	0%; 6.9 (p=0.648)	Moderate
Significant weight-gain (≥7% or recorded as adverse effect)	52	1	9/89	9/89	-	-	1 (0.416, 2.401)	0.000 (-0.089, 0.089)	∞ (11B, 11H)	-	Very low
Weight loss (recorded as adverse effect)	12	2	3/192	16/187	-	-	0.21 (0.06, 0.77)	0.070 (0.027, 0.114)	14B (9B, 37B)	3%; 1.0 (p=0.309)	Very low
Weight loss (recorded as adverse effect)	52	1	9/89	23/89	-	-	0.39 (0.19, 0.80)	-0.157 (-0.047, -0.268)	6B (4B, 21B)	-	Very low
Sedation or somnolence	2-12	12	247/1419	57/958	-	-	2.818 (1.963, 4.047)	0.115 (0.078, 0.151)	9H (7H, 13H)	31%; 16.1 (p=0.138)	Moderate
Sedation or somnolence	52	1	62/89	44/89	-	-	1.409 (1.096, 1.811)	0.202 (0.061, 0.343)	5H (3H, 17H)	-	Very low
Insomnia	2-12	12	125/1419	148/958	-	-	0.585 (0.465, 0.736)	-0.064 (-0.090, -0.039)	16B (11B, 26B)	0%; 6.6 (p=0.831)	Moderate
Leaving early due to adverse effects	2-12	11	97/1263	74/885	-		1.009 (0.753, 1.351)	0.010 (-0.010, 0.031)	100H (100B, 32H)	0%; 9.4 (p=0.495)	Moderate

Outcome (definition, imputation strategy)	Time-point (weeks)	No of included studies	Que N events / N	Pla N events / N	Hedges's g (95% CI)	Mean difference (95% CI)	Risk ratio (95% CI)	Absolute difference (95% CI)	NNTB/H (95% CI)	Heterogeneity for g or RR: I^2; Chi^2 (p-value)	Quality (GRADE)
Leaving early due to adverse effects (placebo or subtherapeutic dose)	52	2	42/264	14/174	-	-	2.018 (1.134, 3.590)	0.080 (0.019, 0.141)	13H (7H, 53H)	0%; 0.16 (p=0.688)	Very low

Shaded rows indicates result statistically significant at p<0.05; *indicates at least moderate heterogeneity ($I^2 \geq 40\%$); bold text indicates primary outcome

J. GRADE Assessment of all outcomes

Method

All assessments were conducted independently by two reviewers and any disagreements were resolved through discussion, and an overall rating decided on. For assessment of outcome quality, we downgraded by 1 point if ≥50% studies contributing to an outcome had at least one 'high risk' rating according to the Cochrane Risk of Bias assessment we conducted (excluding the ratings of 'other bias'), and 2 points if ≥50% relevant studies had at least two ratings of 'high'. However we did not downgrade if the risk of bias did not affect that particular outcome. For example, if a study had significant missing data, or was at high risk of selective reporting bias, we only downgraded if the missing data and selective reporting directly affected the outcome in question. Indirectness ratings were informed by considerations of study population, treatment duration, and nature of control condition. We downgraded by 1 point for inconsistency if the I^2 statistic was ≥40% in the context of an unclear direction of effect or ≥75% in the context of a clear direction of effect. We downgraded by 2 points if the I^2 statistic was ≥75% in the context of an unclear direction of effect. We downgraded an outcome for imprecision if *"a recommendation or clinical course of action would differ if the upper versus the lower boundary of the CI represented the truth"* (81) and / or the number of events and sample size meant the optimal information size was not reached. For binary outcomes we based our judgements on absolute rather than relative estimates of effect. For the primary outcomes we considered statistical and clinical significance separately. We downgraded for publication bias when, for outcomes with at least 10 studies (82), funnel-plots suggested asymmetry and this was not better explained by selective reporting bias or some other factor.

J.1. GRADE assessment of efficacy outcomes

Questions and outcomes	Time	Rater	Quality	Inconsistency	Indirectness	Imprecision	Publication bias[1]	Other factors	Overall	Comments	Included studies
Is mean change in drug PANSS total score statistically superior to placebo?[2]	2-12 weeks	Rater 1	-1	0	0	0	0	0	Moderate	Missing data high. Imputation analyses suggests unlikely to have led to underestimate of effect, but may lead to overestimation of statistical significance. No evidence of selective reporting or publication bias.	(12-14, 59-65, 83)
		Rater 2	-1	0	0	0	0	0	Moderate	Efficacy data poorly reported in some studies, plus attrition high in most cases.	
		Overall	-1	0	0	0	0	0	Moderate		
Is mean change in drug PANSS total score clinically significant, compared to placebo?[2]	2-12 weeks	Rater 1	0	0	0	0	0	0	High	Missing data high but imputation analyses suggest unlikely to have led to underestimate of effect. Confidence intervals exclude clinically significant effects. No evidence of selective reporting or publication bias.	(12-14, 59-65, 83)
		Rater 2	0	0	0	0	0	0	High	Results reasonably robust to changes in assumptions concerning attrition	
		Overall	0	0	0	0	0	0	High		

Questions and outcomes	Time	Rater	Quality	Inconsistency	Indirectness	Imprecision	Publication bias[1]	Other factors	Overall	Comments	Included studies
Is there a significant difference in rates of 'much improvement' (≥50% reduction in PANSS / BPRS) with drug compared to placebo? [2]	2-12 weeks	Rater 1	-1	0	0	0	-1	0	Low	Selective reporting high but mitigated by imputation. Changing assumptions about outcomes for high rates of people leaving early may threaten statistical significance, and asymmetrical funnel-plot suggests possible publication bias.	(12-14, 59-65, 83)
		Rater 2	-1	0	0	0	-1	0	Low	Efficacy data poorly reported in some studies, plus attrition high in most cases. Evidence of publication bias.	
		Overall	-1	0	0	0	-1	0	Low		
Is there a significant difference in rates of relapse with drug compared to placebo or subtherapeutic dose?	52 weeks	Rater 1	-1	-1	-1	-1	0	0	Very low	Only two trials – only one with true placebo control. Inconsistent results. High drop-out. One trial limited by liberal definition of relapse. Differing populations.	(3, 84)

Questions and outcomes	Time	Rater	Quality	Inconsistency	Indirectness	Imprecision	Publication bias[1]	Other factors	Overall	Comments	Included studies
		Rater 2	-1	-1	-1	-1	n/a	0	Very low	CI vary from potential harm to potential benefit. Questionable definitions of relapse in both studies. One study no placebo. Attrition and selective reporting (unavailable data for some outcomes) an issue.	
		Overall	-1	-1	-1	-1	n/a	0	Very low		
Is there a significant difference in rates of needing hospital care with drug compared to placebo?	2-6 weeks	Rater 1	-2	0	0	0	0	0	Low	Only 3 trials. Although each well-powered and results consistent, the high drop-out and selective reporting suggests estimate inflated.	(14, 61, 62)
		Rater 2	-1	0	0	0	n/a	0	Moderate	One of three studies involves high risk of bias in multiple areas.	
		Overall	-2	0	0	0	n/a	0	Low	Agreed selective reporting a major concern for this outcome.	
Is there a significant difference in rates of needing hospital care with drug compared to placebo?	52 weeks	Rater 1	-2	0	0	-1	0	0	Very low	Only 1 out of 2 long-term trials reported data; high drop-out and small N suggests limited power and imprecise estimate. Significant imbalance in groups receiving quetiapine prior to randomisation	(84)

Questions and outcomes	Time	Rater	Quality	Inconsistency	Indirectness	Imprecision	Publication bias[1]	Other factors	Overall	Comments	Included studies
		Rater 2	-2	n/a (n=1)	0	-2	n/a	0	Very low	Only 1 study and few events (at least if dropout not needing hospital care) so high imprecision. Studies had high risk of bias in multiple areas. Assumptions concerning dropouts affect findings.	
		Overall	-2	n/a (n=1)	0	-2	n/a	0	Very low		
Is there a significant effect on positive symptoms? [2]	2-12 weeks	Rater 1	-1	0	0	0	0	0	Moderate	High drop-out suggests estimate inflated.	(12-14, 59-65, 83)
		Rater 2	-2	0	0	0	0	0	Low	Studies largely high risk of bias in multiple areas. Outcome not reported for a number of studies where would be expected.	
		Overall	-1	0	0	0	0	0	Moderate	Agreed selective reporting less of a concern for this outcome.	
Is there a significant effect on negative symptoms? [2]	2-12 weeks	Rater 1	-1	0	0	0	-1	0	Low	High drop-out suggests estimate inflated. Asymmetrical funnel-plot suggesting possible publication bias.	(12-14, 59-65, 83)

Questions and outcomes	Time	Rater	Quality	Inconsistency	Indirectness	Imprecision	Publication bias[1]	Other factors	Overall	Comments	Included studies
		Rater 2	-2	0	0	0	-1	0	Very low	Studies largely high risk of bias in multiple areas. Outcome not reported for a number of studies where would be expected.	
		Overall	-1	0	0	0	0	0	Moderate	Agreed selective reporting less of a concern on this outcome. Discussed publication bias and agreed unlikely if overall symptom scores do not demonstrate asymmetry in funnel-plots.	
Is there a significant effect on depression?	2-6 weeks	Rater 1	-2	0	0	0	0	0	Low	High drop-out and non-reporting by 2 x 6-week studies suggests estimate may be inflated. However 2 x 12-week trials found beneficial effects but failed to provide usable data.	(12-14, 61, 62, 65, 83)
		Rater 2	-2	0	0	0	n/a	0	Low	Outcome not reported in many studies. High attrition.	
		Overall	-2	0	0	0	n/a	0	Low		

Questions and outcomes	Time	Rater	Quality	Inconsistency	Indirectness	Imprecision	Publication bias[1]	Other factors	Overall	Comments	Included studies
Is there a significantly reduced need for additional sedatives with quetiapine IR?	2-6 weeks	Rater 1	-2	0	0	0	0	0	Low	High drop-out and non-reporting by 5/11 studies suggests estimate uncertain / inflated.	(12, 13, 61, 63-65)
		Rater 2	-1	0	0	0	n/a	0	Moderate	Two studies at high risk of bias in multiple areas. Reasonable proportion of events for precision.	
		Overall	-2	0	0	0	n/a	0	Low	Agreed selective reporting a concern for this outcome.	
Is there a significantly reduced need for additional antipsychotics with quetiapine IR?	6 weeks	Rater 1	-1	0	0	0	0	0	Moderate	High drop-out in only 2 trials suggests uncertainty over effect, although both trials well-powered, number of events high, and findings are consistent.	(61, 62)
		Rater 2	0	0	0	0	n/a	0	High	Only two studies but both limited risk of bias. Reasonable proportion of events.	
		Overall	-1	0	0	0	n/a	0	Moderate	Agreed drop-out a concern for this outcome.	

Questions and outcomes	Time	Rater	Quality	Inconsistency	Indirectness	Imprecision	Publication bias[1]	Other factors	Overall	Comments	Included studies
Is there a significant drug-attributable benefit on quality of life?	12 weeks	Rater 1	-1	0	0	-1	0	0	Low	Only 2 trials. Likely selective reporting suggesting inflated effect. High drop-out reduces power to detect small effects, but imputing data reduces effect estimates. Wide confidence intervals do not exclude small beneficial effect. Long-term data from 52-week trial not reported.	(59, 60)
		Rater 2	-2	0	-1	-1	n/a	0	Very low	Studies largely high risk of bias in multiple areas – high attrition and limited information available. CI vary from potential harm to potential benefit. Two studies halted early.	
		Overall	-2	0	-1	-1	n/a	0	Very low	Agreed that data-led approach to stopping trial likely to produce distorted results (direction unclear), thus limiting generalizability. Selective reporting a serious concern.	

Questions and outcomes	Time	Rater	Quality	Inconsistency	Indirectness	Imprecision	Publication bias[1]	Other factors	Overall	Comments	Included studies
Is there a significant drug-attributable benefit on functioning?	6-12 weeks	Rater 1	-1	0	0	-1	0	0	Low	Only 3 trials reported usable data. Likely selective reporting suggests inflated effect. High drop-out creates uncertainty about effects, and imputing data reduces effect estimates. Wide confidence intervals.	(12, 59, 60)
		Rater 2	-2	0	-1	0	n/a	0	Very low	Studies largely high risk of bias in multiple areas. Two studies halted early and another in adolescence only. Management of missing data effects findings.	
		Overall	-2	0	-1	0	n/a	0	Very low	Agreed that data-led approach to stopping trial likely to produce distorted results (direction unclear), thus limiting generalizability. Selective reporting a serious concern.	

Questions and outcomes	Time	Rater	Quality	Inconsistency	Indirectness	Imprecision	Publication bias[1]	Other factors	Overall	Comments	Included studies
Is there a significant drug-attributable effect on employment?	52 weeks	Rater 1	-2	0	0	-1	0	0	Very low	Only 1 out of 2 long-term trials reported data; high drop-out and small N suggests limited power and imprecise estimate. Imbalance in groups receiving quetiapine prior to randomisation	(84)
		Rater 2	-1	n/a (n = 1)	0	-2	n/a	0	Very low	Only one study and not that many events so high imprecision. High attrition.	
		Overall	-2	n/a (n = 1)	0	-2	n/a	0	Very low	Agreed selective reporting and imprecision both major problems.	
Is quetiapine IR associated with reduced early discontinuation, compared to placebo? [2]	2-6 weeks	Rater 1	0	0	0	0	0	0	High	Outcome reported by every trial. Minimal heterogeneity. Relatively narrow confidence intervals. Longer-term data not clearly usable due to early termination and relapse / exacerbation as researcher-defined exit criterion.	(12-14, 59-65, 83, 85, 86)
		Rater 2	0	0	0	0	-1	0	Moderate	Attrition not an issue for this outcome.	

Questions and outcomes	Time	Rater	Quality	Inconsistency	Indirectness	Imprecision	Publication bias[1]	Other factors	Overall	Comments	Included studies
		Overall	0	0	0	0	0	0	High	Agreed publication bias unlikely to be a serious issue for this outcome, as unlikely trial would remain unpublished only if drop-out favoured drug – particularly given absence of publication bias on primary outcome.	

[1]Only assessed if *k* studies ≥10; [2]*k* studies ≥10

J. 2. GRADE assessment of safety outcomes

Questions and outcomes	Time	Rater	Quality	Inconsistency	Indirectness	Imprecision	Publication bias[1]	Other factors	Overall	Comments	Included studies
Are there more serious adverse events with quetiapine IR than placebo?	2-12 weeks	Rater 1	-2	0	0	0	0	0	Low	High drop-out creates uncertainty over true effect, while 5/13 trials did not report usable or clear data on this outcome. Although a low number of events, the confidence intervals for the overall estimate do exclude high rates of harm or benefit, suggesting reasonable precision. Blind may not protect against use of high threshold for recording effects.	(12-14, 59, 60, 65, 83, 85)
		Rater 2	-2	0	0	-1	n/a	0	Very low	High attrition and several studies show poor reporting of adverse events. CI vary from potential harm to potential benefit.	

Questions and outcomes	Time	Rater	Quality	Inconsistency	Indirectness	Imprecision	Publication bias[1]	Other factors	Overall	Comments	Included studies
		Overall	-2	0	0	-1	n/a	0	Very low	Agreed estimate imprecise give low number of events.	
Are there more serious adverse events with optimal dose quetiapine IR than placebo or subtherapeutic dose?	52 weeks	Rater 1	-1	0	-1	-1	0	0	Very low	Only two trials – only one with true placebo control. High drop-out. Low number of events. Differing populations. Blind may not protect against use of high threshold for recording effects.	(3, 84)
		Rater 2	-2	0	-1	-2	n/a	0	Very low	High attrition and poor reporting of AE in some cases CI vary from potential harm to potential benefit. OIS not met. Few events and only two studies. One no placebo.	

Questions and outcomes	Time	Rater	Quality	Inconsistency	Indirectness	Imprecision	Publication bias[1]	Other factors	Overall	Comments	Included studies
		Overall	-1	0	-1	-1	n/a	0	Very low	Agreed selective reporting less of a concern and although estimate is very imprecise given low number of events, it is 'serious' not 'very serious'.	
Are there more adverse events of any degree of severity with quetiapine IR, than placebo?	2-12 weeks	Rater 1	-2	0	0	0	0	0	Low	High rates of missing data. Usable data not reported by 4 /13 studies. Adequate number of events and statistical power, suggesting reasonably precise estimate. Blind may not protect against use of high threshold for recording effects.	(12-14, 59-62, 83, 85)
		Rater 2	-1	0	0	0	n/a	0	Moderate	High attrition and poor reporting of AE in some cases.	
		Overall	-2	0	0	0	0	0	Low	Agreed selective reporting a greater concern on this outcome.	

Questions and outcomes	Time	Rater	Quality	Inconsistency	Indirectness	Imprecision	Publication bias[1]	Other factors	Overall	Comments	Included studies
Are there more adverse events of any degree of severity with optimal dose quetiapine IR, than subtherapeutic dose?	52 weeks	Rater 1	-2	0	-1	0	0	0	Very low	Only 1 of 2 long-term trials reported usable data. High drop-out and subtherapeutic dose used, not placebo. Blind may not protect against use of high threshold for recording effects.	(3)
		Rater 2	-2	n/a (n =1)	0	-1	n/a	0	Very low	Only single study, but OIS met. High attrition and generally poor reporting of AE	
		Overall	-2	0	-1	-1	0	0	Very low	Agreed indirectness and imprecision both serious concerns.	

Questions and outcomes	Time	Rater	Quality	Inconsistency	Indirectness	Imprecision	Publication bias[1]	Other factors	Overall	Comments	Included studies
Are there more drug-attributable adverse effects with quetiapine IR, than placebo?	6 weeks	Rater 1	-2	0	0	0	0	0	Low	Only 4 out of 13 trials reported usable data. High drop-out. Moderate heterogeneity relating to magnitude of effect, not direction. Blind may not protect against use of high threshold for recording effects.	(12-14, 83)
		Rater 2	-1	0	0	0	n/a	0	Moderate	High attrition and generally poor reporting of AE in some studies	
		Overall	-2	0	0	0	n/a	0	Low	Agreed 'low' because of serious risk of selective reporting bias on this outcome.	

Questions and outcomes	Time	Rater	Quality	Inconsistency	Indirectness	Imprecision	Publication bias[1]	Other factors	Overall	Comments	Included studies
Are Simpson-Angus Scale (mean change) scores higher with quetiapine IR?	2-6 weeks	Rater 1	-1	0	0	0	0	0	Moderate	High drop-out. Although only data from 6 trials, this may reflect skewed data or use of alternative measure in other trials. Blind may not protect against use of high threshold for recording effects.	(13, 14, 61, 62, 64, 83)
		Rater 2	-1	0	0	0	n/a	0	Moderate	Outcome missing in many studies.	
		Overall	-1	0	0	0	n/a	0	Moderate		
Is worsening on the Simpson-Angus Scale more likely with quetiapine IR?	2-6 weeks	Rater 1	-1	0	0	0	0	0	Moderate	High drop-out. Only usable data from 7 / 13 trials reported, although narrative descriptions from 2 x 12-week trials also indicate no group difference. Blind may not protect against use of high threshold for recording effects.	(12-14, 63-65, 83)

Questions and outcomes	Time	Rater	Quality	Inconsistency	Indirectness	Imprecision	Publication bias[1]	Other factors	Overall	Comments	Included studies
		Rater 2	-1	0	0	-1	n/a	0	Low	Outcome missing in many studies. High attrition. CI vary from potential harm to potential benefit.	
		Overall	-1	0	0	-1	n/a	0	Low	Agreed 'low' because of imprecise on in estimate.	
Is worsening on the Simpson-Angus Scale more likely with quetiapine IR?	52 weeks	Rater 1	-2	0	0	-1	0	0	Very low	Only 1 of 2 long-term trials reported usable data. High drop-out. Few events. Blind may not protect against use of high threshold for recording effects. Significant imbalance in groups receiving quetiapine prior to randomisation.	(84)
		Rater 2	-1	n/a (n = 1)	0	-2	n/a	0	Very low	Only k = 1 and few events. High attrition.	
		Overall	-2	n/a (n = 1)	0	-2	n/a	0	Very low		

Questions and outcomes	Time	Rater	Quality	Inconsistency	Indirectness	Imprecision	Publication bias[1]	Other factors	Overall	Comments	Included studies
Are Abnormal Involuntary Movements Scale (mean change) scores higher with quetiapine IR?	2-6 weeks	Rater 1	-2	0	0	0	0	0	Low	Estimate based on 2 trials lasting 2 weeks, and 1x 6-week trial with very high drop-out, meaning uncertainty around effect, unclear relevance to patients, and risk of selective reporting. However narrative description of unreported data from 2 x 12-week trials also suggests no difference. Blind may not protect against use of high threshold for recording effects.	(61, 62, 83)
		Rater 2	-1	0	0	0	0	0	Moderate	Outcome missing in many studies.	
		Overall	-2	0	0	0	n/a	0	Low	Agreed drop-out more of a concern on this outcome.	

Questions and outcomes	Time	Rater	Quality	Inconsistency	Indirectness	Imprecision	Publication bias[1]	Other factors	Overall	Comments	Included studies
Is worsening on the Abnormal Involuntary Movements Scale more likely with quetiapine IR?	6 weeks	Rater 1	-2	0	0	0	0	0	Low	Data from only 4 trials, suggesting risk of selective reporting. High drop-out.	(12, 64, 65, 83)
		Rater 2	-1	0	0	0	n/a	0	Moderate	Outcome missing in many studies.	
		Overall	-2	0	0	0	0	0	Low	Agreed drop-out more of a concern on this outcome.	
Is worsening on the Abnormal Involuntary Movement Scale more likely with quetiapine IR?	52 weeks	Rater 1	-1	0	-1	-1	0	0	Very low	Only two trials – only one with true placebo control. High drop-out. Few events. Differing populations. Blind may not protect against use of high threshold for recording effects.	(3, 84)
		Rater 2	-1	0	0	-2	n/a	0	Very low	Outcome missing in many studies. Poor reporting in one study. CI vary from potential harm to potential benefit. Few events.	
		Overall	-1	-1	0	-2	n/a	0	Very low		

Questions and outcomes	Time	Rater	Quality	Inconsistency	Indirectness	Imprecision	Publication bias[1]	Other factors	Overall	Comments	Included studies
Is dystonia / hypertonia more likely with quetiapine IR?	2-6 weeks	Rater 1	-2	0	0	-1	0	0	Very low	Only 4 trials reported data. High drop-out and low number of events. Blind may not protect against use of high threshold for recording effects.	(61, 64, 65, 85)
		Rater 2	0	0	0	-2	n/a	0	Low	Very few events. CI vary from potential harm to potential benefit.	
		Overall	-2	0	0	-2	n/a	0	Very low	Agreed imprecision, drop-out and selective reporting all serious concerns.	
Are Barnes Akathesia Scale (mean change) scores higher with quetiapine IR?	6 weeks	Rater 1	-2	0	0	0	0	0	Low	Only 3 trials reported data. High drop-out. Blind may not protect against use of high threshold for recording effects.	(13, 14, 83)
		Rater 2	-1	0	0	0	n/a	0	Moderate	Outcome missing in most studies. High attrition in many studies.	

Questions and outcomes	Time	Rater	Quality	Inconsistency	Indirectness	Imprecision	Publication bias[1]	Other factors	Overall	Comments	Included studies
		Overall	-2	0	0	0	n/a	0	Low	Agreed drop-out and selective reporting more of a concern on this outcome.	
Is worsening on the Barnes Akathesia Scale more likely with quetiapine IR?	2-6 weeks	Rater 1	-2	0	0	0	0	0	Low	Only 7 trials reported data. High drop-out. Blind may not protect against use of high threshold for recording effects.	(12-14, 61-63, 83)
		Rater 2	-1	0	0	-1	n/a	0	Low	Outcome missing in most studies. CI vary from potential harm to potential benefit. High attrition in many studies.	
		Overall	-2	0	0	0	n/a	0	Low		
Is worsening on the Barnes Akathesia Scale more likely with quetiapine IR?	52 weeks	Rater 1	-2	0	0	-1	0	0	Very low	Only 1 of 2 long-term trials reported usable data. High drop-out. Few events. Blind may not protect against use of high threshold for recording effects. Significant imbalance in groups receiving quetiapine prior to randomisation.	(84)

Questions and outcomes	Time	Rater	Quality	Inconsistency	Indirectness	Imprecision	Publication bias[1]	Other factors	Overall	Comments	Included studies
		Rater 2	-1	n/a (n = 1)	0	-2	n/a	0	Very low	Only k = 1 and few events. Outcome missing in most studies	
		Overall	-2	n/a (n = 1)	0	-1	n/a	0	Very low		
Are extra-pyramidal side-effects more likely with with quetiapine IR?	6-12 weeks	Rater 1	-2	-1	0	0	0	0	Very low	Only 5 trials reported data. High drop-out and considerable heterogeneity in context of unclear direction of effect. Blind may not protect against use of high threshold for recording effects.	(12-14, 59, 64)
		Rater 2	-1	-1	0	-2	n/a	0	Very low	Few events and CI vary from potential harm to potential benefit. High attrition	
		Overall	-2	-1	0	-2	n/a	0	Very low		
Is needing medication for extra-pyramidal side-effects more likely with quetiapine IR?	2-6 weeks	Rater 1	-1	0	0	0	0	0	Moderate	Nine trials reported data, but most had high drop-out. Little heterogeneity. Blind may not protect against use of high threshold for recording effects.	(12-14, 61, 63-65, 83, 85)
		Rater 2	-1	0	0	0	n/a	0	Moderate	High attrition	

Questions and outcomes	Time	Rater	Quality	Inconsistency	Indirectness	Imprecision	Publication bias[1]	Other factors	Overall	Comments	Included studies
		Overall	-1	0	0	0	n/a	0	Moderate		
Is mean weight-gain greater with quetiapine IR?[2]	2-12 weeks	Rater 1	-1	-1	0	0	0	0	Low	7/12 trials did not report variance parameter, meaning this had to be imputed from the other studies. High drop-out and inconsistency, albeit in context of clear direction of effect, limits conclusions about magnitude of effect.	(12-14, 59-65, 83, 85)
		Rater 2	-2	-1	0	0	0	0	Very low	Poor reporting in many cases and high attrition.	
		Overall	-2	-1	0	0	0	0	Very low	Agreed that poor reporting of variance parameters greatly reduced quality of estimate.	

Questions and outcomes	Time	Rater	Quality	Inconsistency	Indirectness	Imprecision	Publication bias[1]	Other factors	Overall	Comments	Included studies
Is mean weight-gain greater with quetiapine IR?	52 weeks	Rater 1	-2	0	0	-1	0	0	Very low	Only 1 of 2 long-term trials reported usable data. High drop-out, wide confidence intervals, small N and significant imbalance in groups receiving quetiapine prior to randomisation. Blind may not protect against use of high threshold for recording effects.	(84)
		Rater 2	-1	n/a (n = 1)	0	-1	n/a	0	Low	Only k =1 and small sample.	
		Overall	-2	0	0	-1	n/a	0	Very low	Agreed selective reporting and limited data more of a concern for this outcome.	

Questions and outcomes	Time	Rater	Quality	Inconsistency	Indirectness	Imprecision	Publication bias[1]	Other factors	Overall	Comments	Included studies
Is significant weight-gain more likely with quetiapine IR?[2]	2-12 weeks	Rater 1	-1	0	0	0	0	0	Moderate	Outcome reported by most trials (10/13), although some short-term estimates missing (3/13) High drop-out, but minimal heterogeneity. No evidence of publication bias and estimate relatively precise. Blind may not protect against use of high threshold for recording effects.	(12-14, 59-61, 63-65, 83)
		Rater 2	-2	0	0	-1	0	0	Very low	Few events, OIS not met. Poor reporting in many cases and high attrition.	
		Overall	-1	0	0	0	0	0	Moderate	Agreed selective reporting and imprecision less of a concern on this outcome.	

Questions and outcomes	Time	Rater	Quality	Inconsistency	Indirectness	Imprecision	Publication bias[1]	Other factors	Overall	Comments	Included studies
Is significant weight-gain more likely with quetiapine IR?	52 weeks	Rater 1	-2	0	0	-1	0	0	Very low	Only 1 of 2 long-term trials reported usable data. High drop-out. Few events. Blind may not protect against use of high threshold for recording effects. Significant imbalance in groups receiving quetiapine prior to randomisation.	(84)
		Rater 2	-1	n/a (n = 1)	0	-2	n/a	0	Very low	Only k = 1 and few events. High attrition	
		Overall	-2	0	0	-1	n/a	0	Very low		
Is significant weight-loss (recorded as adverse effect) more likely with quetiapine IR?	12 weeks	Rater 1	-2	0	0	-1	0	0	Very low	Data from only 2 trials (shorter trials did not report this outcome). High drop-out, wide confidence intervals, few events. Blind may not protect against use of high threshold for recording effects.	(59, 60)

Questions and outcomes	Time	Rater	Quality	Inconsistency	Indirectness	Imprecision	Publication bias[1]	Other factors	Overall	Comments	Included studies
		Rater 2	-2	0	0	-2	n/a	0	Very low	Generally poor reporting and high attrition. Few events and only two studies.	
		Overall	-2	0	0	-1	n/a	0	Very low		
Is significant weight-loss (recorded as adverse effect) more likely with quetiapine IR?	52 weeks	Rater 1	-2	0	0	-1	0	0	Very low	Only 1 of 2 long-term trials reported data. High drop-out. Few events. Blind may not protect against use of high threshold for recording effects. Significant imbalance in groups receiving quetiapine prior to randomisation.	(84)
		Rater 2	-1	n/a (n = 1)	0	-2	n/a	0	Very low	Only k = 1 and OIS not met. High attrition	
		Overall	-2	n/a (n = 1)	0	-2	n/a	0	Very low		

Questions and outcomes	Time	Rater	Quality	Inconsistency	Indirectness	Imprecision	Publication bias[1]	Other factors	Overall	Comments	Included studies
Is sedation or somnolence more likely with quetiapine IR?[2]	2-12 weeks	Rater 1	-1	0	0	0	0	0	Moderate	Data from almost all relevant trials. High drop-out but low heterogeneity, relatively narrow confidence intervals, and no evidence of publication bias. Blind may not protect against use of high threshold for recording effects.	(12-14, 59-65, 83, 85)
		Rater 2	-1	0	0	-1	-1	0	Very low	Proportionately few events so that OIS not met. Poor reporting of AE in many cases	
		Overall	-1	0	0	0	0	0	Moderate	Agreed publication bias and imprecision less of a concern on this outcome.	

Questions and outcomes	Time	Rater	Quality	Inconsistency	Indirectness	Imprecision	Publication bias[1]	Other factors	Overall	Comments	Included studies
Is sedation or somnolence more likely with quetiapine IR?	52 weeks	Rater 1	-2	0	0	-1	0	0	Very low	Only 1 of 2 long-term trials reported data. High drop-out. Blind may not protect against use of high threshold for recording effects. Significant imbalance in groups receiving quetiapine prior to randomisation.	(84)
		Rater 2	-1	n/a (n = 1)	0	-1	n/a	0	Low	Only single study. High attrition.	
		Overall	-2	n/a (n = 1)	0	-1	n/a	0	Very low	Agreed selective reporting more of a concern on this outcome.	

Questions and outcomes	Time	Rater	Quality	Inconsistency	Indirectness	Imprecision	Publication bias[1]	Other factors	Overall	Comments	Included studies
Is insomnia less likely with quetiapine IR?[2]	2-12 weeks	Rater 1	-1	0	0	0	0	0	Moderate	Data from almost all relevant trials. High drop-out, low heterogeneity, relatively narrow confidence intervals, and no evidence of publication bias. Blind may not protect against use of high threshold for recording effects. Longer-term data not reported.	(12-14, 59-65, 83, 85)
		Rater 2	-1	0	0	0	0	0	Moderate	Poor reporting of AE in many cases.	
		Overall	-1	0	0	0	0	0	Moderate		

Questions and outcomes	Time	Rater	Quality	Inconsistency	Indirectness	Imprecision	Publication bias[1]	Other factors	Overall	Comments	Included studies
Are more people likely to discontinue quetiapine IR treatment due to adverse effects?[2]	2-12 weeks	Rater 1	0	0	-1	0	0	0	Moderate	Usable data reported by almost every trial. Minimal heterogeneity, relatively narrow confidence intervals, and no evidence of publication bias. A reduction of 1 point was made under 'indirectness' due to recently expressed concerns that this outcome reflects a mixture of tolerability and efficacy effects.(7) Blind may not protect against use of high threshold for recording adverse effects as reason for leaving.	(12-14, 59-61, 63-65, 83, 85)
		Rater 2	0	0	0	-1	0	0	Moderate	CI vary from potential harm to potential benefit.	
		Overall	0	0	-1	0	0	0	Moderate		

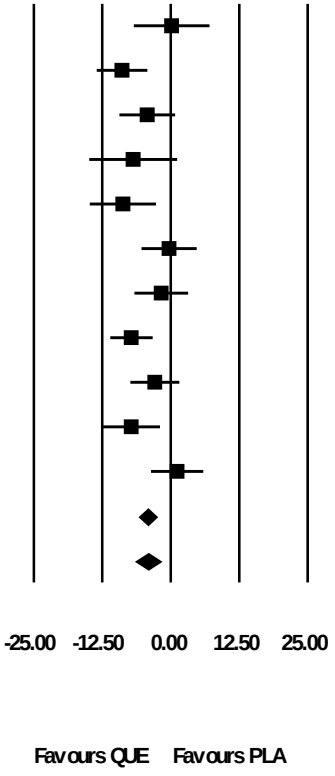
Questions and outcomes	Time	Rater	Quality	Inconsistency	Indirectness	Imprecision	Publication bias[1]	Other factors	Overall	Comments	Included studies
Leaving early due to adverse effects (placebo or subtherapeutic dose)	52 weeks	Rater 1	-1	0	-1	-1	0	0	Very low	Only two trials – only one with true placebo control. High drop-out. Low number of events. Differing populations. Concerns have recently been expressed that this outcome reflects a mixture of tolerability and efficacy effects.(7) Blind may not protect against use of high threshold for recording adverse effects as reason for leaving.	(3, 84)
		Rater 2	-1	0	-1	-2	n/a	0	Very low	Two studies and few events, OIS not met. One study no placebo. Outcome not reported in many studies	
		Overall	-1	0	-1	-2	n/a	0	Very low		

[1]Only assessed if *k* studies ≥10; [2]*k* studies ≥10

K. Additional forest-plots for various outcomes

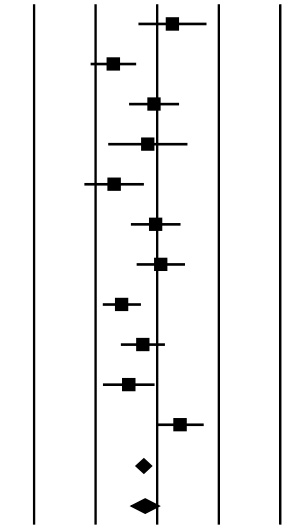
K.1. Mean change in PANSS total scores using Strategy 1 to impute missing data where possible (*indicates severe attrition, ≥50%)

Model	Study name	Statistics for each study				Sample size			Difference in means and 95% CI
		Difference in means	Lower limit	Upper limit	p-Value	Drug	Placebo	Total	
	Borison, 1996, 6 weeks, Strategy 1*	0.168	-6.811	7.146	0.962	54	55	109	
	11915A, 12 weeks	-8.900	-13.588	-4.212	0.000	76	68	144	
	Small, 1997, 6 weeks, Strategy 1*	-4.295	-9.445	0.854	0.102	96	96	192	
	Arvanitis, 1997, 6 weeks, Strategy 1*	-6.867	-14.967	1.232	0.097	157	51	208	
	Findling, 2012, 6 weeks	-8.730	-14.839	-2.622	0.005	147	73	220	
	Potkin, 2006, 2 weeks	-0.300	-5.397	4.797	0.908	156	71	227	
	Cutler, 2008, 6 weeks, Strategy 1	-1.737	-6.706	3.232	0.493	116	117	233	
	11916A, 12 weeks	-7.200	-11.129	-3.271	0.000	115	118	233	
	Canuso, 2009, 2 weeks	-2.900	-7.435	1.635	0.210	157	80	237	
	Kahn, 2007, 6 weeks, Strategy 1	-7.217	-12.533	-1.901	0.008	123	118	241	
	Lindenmayer, 2008, 6 weeks, Strategy 1*	1.166	-3.686	6.017	0.638	176	84	260	
Fixed		-4.320	-5.870	-2.770	0.000	1373	931	2304	
Random		-4.250	-6.460	-2.041	0.000	1373	931	2304	



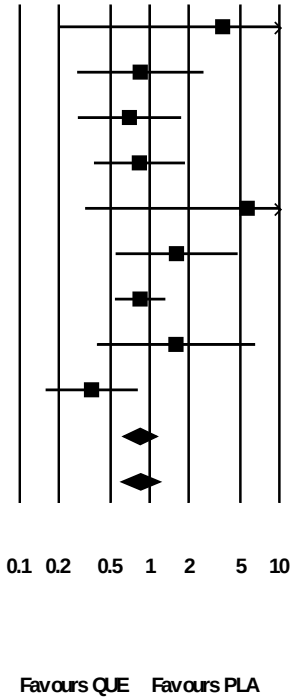
K.2. Mean change in PANSS total scores using Strategy 2 to impute missing data where possible (*indicates severe attrition, ≥50%)

Model	Study name	Statistics for each study				Sample size			Difference in means and 95% CI
		Difference in means	Lower limit	Upper limit	p-Value	Drug	Placebo	Total	
	Borison, 1996, 6 weeks, Strategy 2*	3.106	-3.872	10.084	0.383	54	55	109	
	11915A, 12 weeks	-8.900	-13.588	-4.212	0.000	76	68	144	
	Small, 1997, 6 weeks, Strategy 2*	-0.630	-5.780	4.519	0.810	96	96	192	
	Arvanitis, 1997, 6 weeks, Strategy 2*	-1.900	-10.000	6.199	0.646	157	51	208	
	Findling, 2012, 6 weeks	-8.730	-14.839	-2.622	0.005	147	73	220	
	Potkin, 2006, 2 weeks	-0.300	-5.397	4.797	0.908	156	71	227	
	Cutler, 2008, 6 weeks, Strategy 2	0.727	-4.242	5.697	0.774	116	117	233	
	11916A, 12 weeks	-7.200	-11.129	-3.271	0.000	115	118	233	
	Canuso, 2009, 2 weeks	-2.900	-7.435	1.635	0.210	157	80	237	
	Kahn, 2007, 6 weeks, Strategy 2	-5.780	-11.096	-0.464	0.033	123	118	241	
	Lindenmayer, 2008, 6 weeks, Strategy 2*	4.660	-0.191	9.511	0.060	176	84	260	
Fixed		-2.942	-4.492	-1.392	0.000	1373	931	2304	
Random		-2.658	-5.464	0.148	0.063	1373	931	2304	



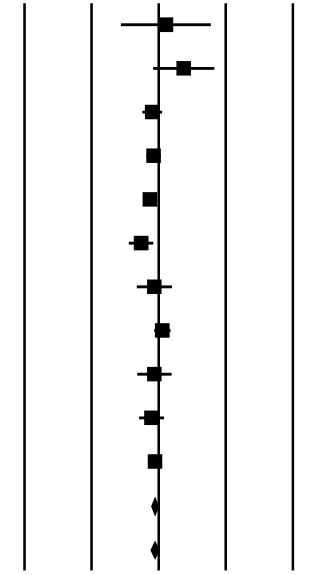
K.3.. Relative risk of using antiparkinson medication (*indicates severe attrition, ≥50%)

Model	Study name	Statistics for each study				Events			Sample size		
		Risk ratio	Lower limit	Upper limit	p-Value	Drug	Placebo	Total	Drug	Placebo	Total
	Hough, 2011, 2-WK	3.659	0.197	67.841	0.384	3	0	3	43	22	65
	Borison, 1996, 6-WK*	0.849	0.275	2.617	0.775	5	6	11	54	55	109
	Small, 1997, 6-WK*	0.700	0.278	1.763	0.449	7	10	17	96	96	192
	Arvanitis, 1997, 6-WK*	0.835	0.370	1.885	0.665	18	7	25	157	51	208
	Findling 2012, 6-WK	5.649	0.317	100.809	0.239	5	0	5	147	75	222
	Cutler, 2010, 6-WK	1.614	0.544	4.788	0.388	8	5	13	116	117	233
	Canuso 2009, 2-WK	0.846	0.537	1.333	0.471	37	22	59	159	80	239
	Kahn 2007, 6-WK	1.599	0.391	6.542	0.514	5	3	8	123	118	241
	Lindenmayer, 2008, 6-WK*	0.358	0.157	0.816	0.015	9	12	21	176	84	260
Fixed		0.829	0.616	1.115	0.214	97	65	162	1071	698	1769
Random		0.838	0.597	1.176	0.306	97	65	162	1071	698	1769



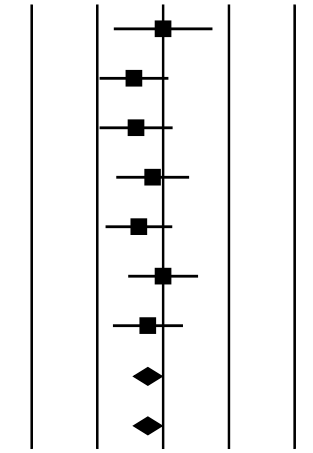
K.4. Leaving early for any reason

Model	Study name	Statistics for each study				Events			Sample size		
		Risk ratio	Lower limit	Upper limit	p-Value	Drug	Placebo	Total	Drug	Placebo	Total
	Hough, 2011, 2-WK	1.279	0.270	6.070	0.757	5	2	7	43	22	65
	Chapel, 2009, 2-WK	2.365	0.816	6.849	0.113	10	4	14	37	35	72
	Borison, 1996, 6-WK	0.802	0.565	1.140	0.219	26	33	59	54	55	109
	Small, 1997, 6-WK	0.842	0.650	1.092	0.194	48	57	105	96	96	192
	Arvanitis, 1997, 6-WK	0.742	0.584	0.945	0.015	80	35	115	157	51	208
	Findling, 2012, 6-WK	0.547	0.354	0.843	0.006	30	28	58	147	75	222
	Potkin 2006, 2-WK	0.864	0.467	1.598	0.641	24	13	37	156	73	229
	Cutler, 2010, 6-WK	1.135	0.847	1.519	0.396	54	48	102	116	117	233
	Canuso 2009, 2-WK	0.863	0.472	1.575	0.630	24	14	38	159	80	239
	Kahn 2007, 6-WK	0.785	0.505	1.221	0.282	27	33	60	123	118	241
	Lindenmayer, 2008, 6-WK	0.886	0.717	1.094	0.261	96	51	147	170	80	250
Fixed		0.848	0.764	0.941	0.002	424	318	742	1258	802	2060
Random		0.847	0.745	0.964	0.012	424	318	742	1258	802	2060

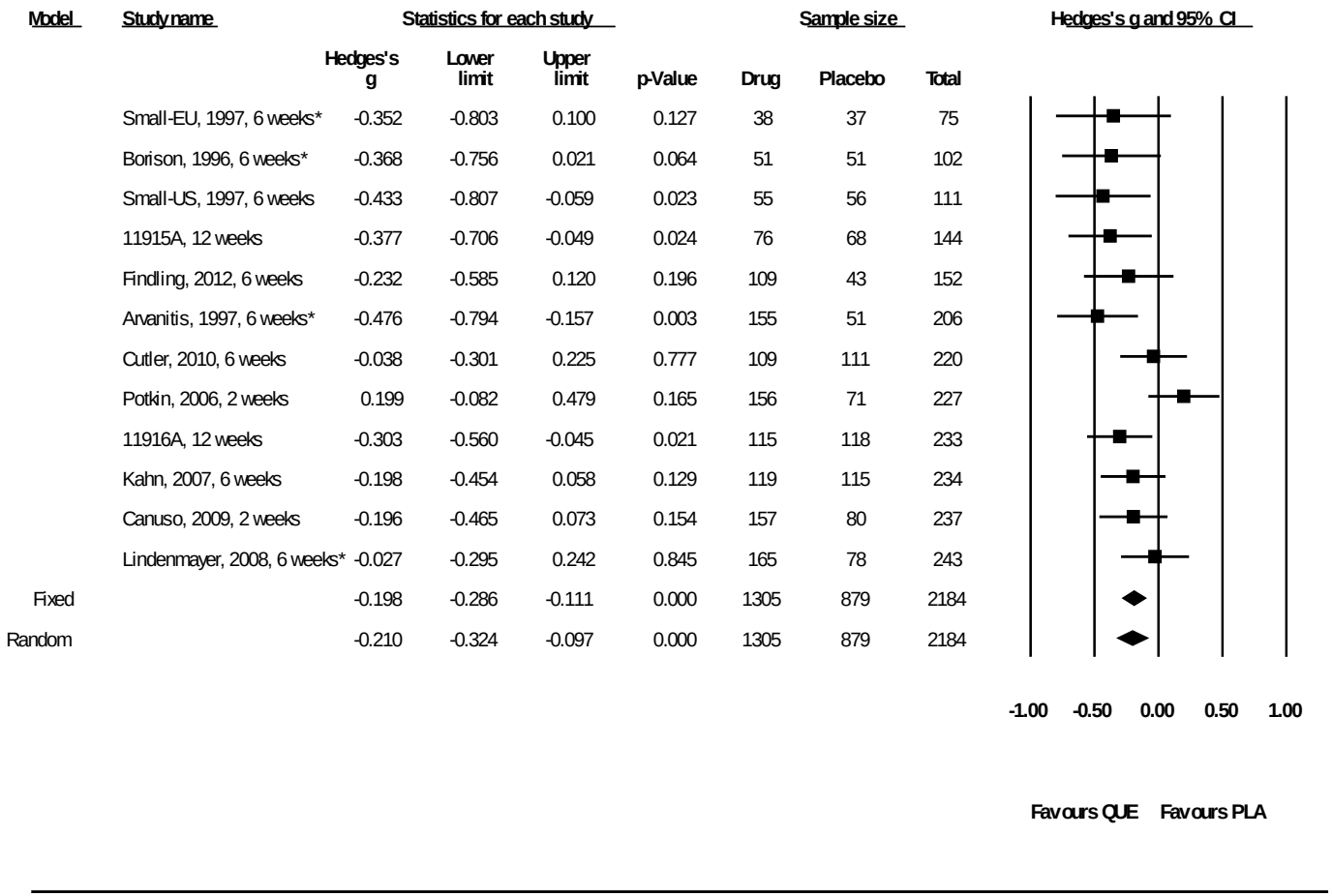


K.5. Standardised mean difference in depression ratings (Hedges's g), using mostly LOCF estimates to impute missing data (*indicates severe attrition, ≥50%)

Model	Study name	Statistics for each study				Sample size			Hedges's g and 95% CI
		Hedges's g	Lower limit	Upper limit	p-Value	Drug	Placebo	Total	
	Borison, 1992, 6 weeks*	0.000	-0.378	0.378	1.000	53	53	106	
	Cutler, 2008, 6 weeks	-0.222	-0.486	0.042	0.100	109	111	220	
	Findling, 2012, 6 weeks*	-0.205	-0.486	0.075	0.151	147	73	220	
	Potkin, 2006, 2 weeks	-0.079	-0.359	0.200	0.578	156	71	227	
	Kahn, 2007, 6 weeks	-0.184	-0.440	0.072	0.158	119	115	234	
	Canuso, 2009, 2 weeks	0.000	-0.268	0.268	1.000	157	80	237	
	Lindenmayer, 2008, 6 weeks*	-0.116	-0.384	0.153	0.399	165	78	243	
Fixed		-0.125	-0.230	-0.019	0.020	906	581	1487	
Random		-0.125	-0.230	-0.019	0.020	906	581	1487	



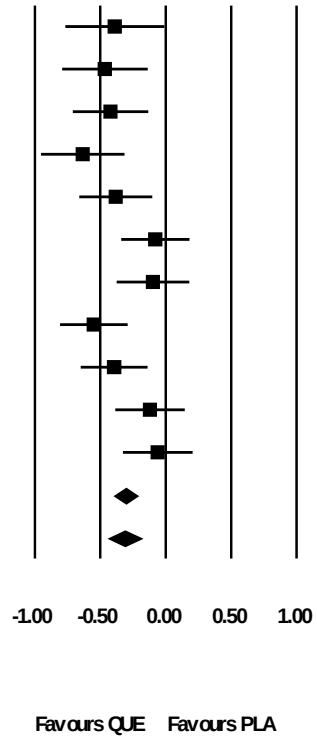
K.6.. Standardised mean difference in negative symptoms (Hedges's g), using mostly LOCF estimates to impute missing data (*indicates severe attrition, ≥50%)



Model	Study name	Statistics for each study				Sample size		
		Hedges's g	Lower limit	Upper limit	p-Value	Drug	Placebo	Total
	Small-EU, 1997, 6 weeks*	-0.352	-0.803	0.100	0.127	38	37	75
	Borison, 1996, 6 weeks*	-0.368	-0.756	0.021	0.064	51	51	102
	Small-US, 1997, 6 weeks	-0.433	-0.807	-0.059	0.023	55	56	111
	11915A, 12 weeks	-0.377	-0.706	-0.049	0.024	76	68	144
	Findling, 2012, 6 weeks	-0.232	-0.585	0.120	0.196	109	43	152
	Arvanitis, 1997, 6 weeks*	-0.476	-0.794	-0.157	0.003	155	51	206
	Cutler, 2010, 6 weeks	-0.038	-0.301	0.225	0.777	109	111	220
	Potkin, 2006, 2 weeks	0.199	-0.082	0.479	0.165	156	71	227
	11916A, 12 weeks	-0.303	-0.560	-0.045	0.021	115	118	233
	Kahn, 2007, 6 weeks	-0.198	-0.454	0.058	0.129	119	115	234
	Canuso, 2009, 2 weeks	-0.196	-0.465	0.073	0.154	157	80	237
	Lindenmayer, 2008, 6 weeks*	-0.027	-0.295	0.242	0.845	165	78	243
Fixed		-0.198	-0.286	-0.111	0.000	1305	879	2184
Random		-0.210	-0.324	-0.097	0.000	1305	879	2184

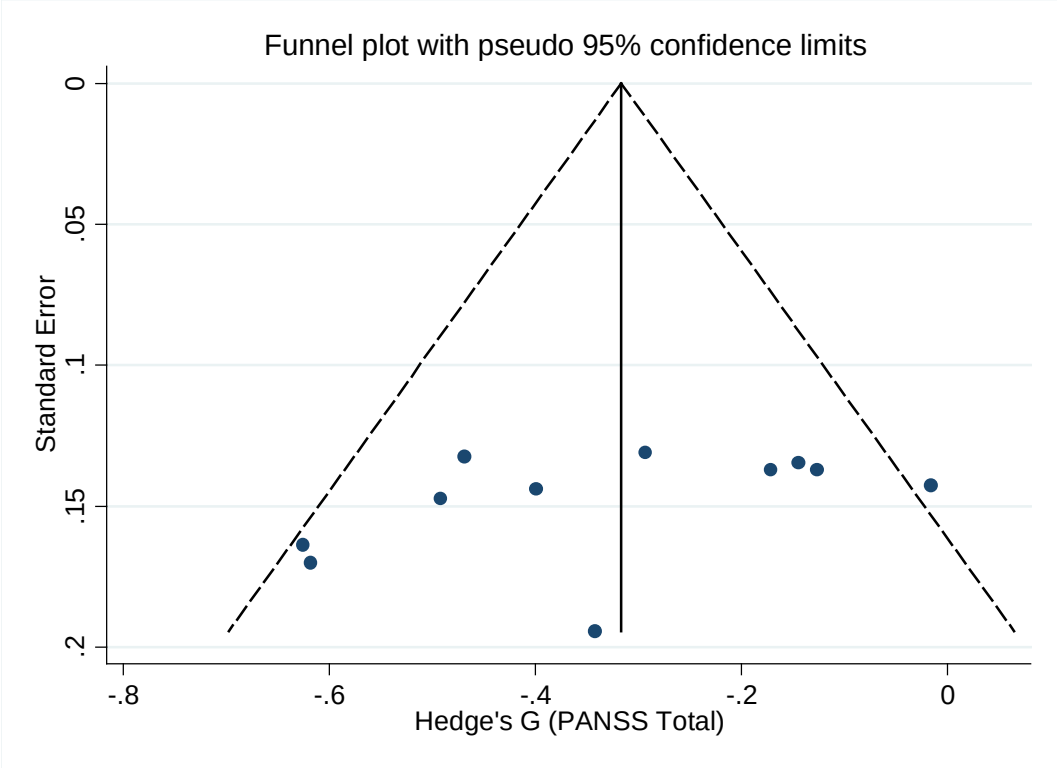
K.7. Standardised mean difference in positive symptoms (Hedges's g), using mostly LOCF estimates to impute missing data (*indicates severe attrition, ≥50%)

Model	Study name	Statistics for each study				Sample size		
		Hedges's g	Lower limit	Upper limit	p-Value	Drug	Placebo	Total
	Borison, 1996, 6 weeks*	-0.389	-0.771	-0.008	0.046	53	53	106
	11915A, 12 weeks	-0.465	-0.795	-0.135	0.006	76	68	144
	Small, 1997, 6 weeks*	-0.422	-0.713	-0.131	0.004	92	92	184
	Arvanitis, 1997, 6 weeks*	-0.634	-0.955	-0.313	0.000	155	51	206
	Findling, 2012, 6 weeks	-0.382	-0.664	-0.100	0.008	147	73	220
	Cutler 2010, 6 weeks	-0.079	-0.343	0.184	0.556	109	111	220
	Potkin 2006, 2 weeks	-0.097	-0.377	0.182	0.495	156	71	227
	11916A 12 weeks	-0.550	-0.811	-0.289	0.000	115	118	233
	Kahn 2007, 6 weeks	-0.395	-0.653	-0.137	0.003	119	115	234
	Canuso 2009, 2 weeks	-0.120	-0.388	0.149	0.382	157	80	237
	Lindenmayer 2008, 6 weeks*	-0.061	-0.330	0.207	0.654	165	78	243
Fixed		-0.310	-0.396	-0.224	0.000	1344	910	2254
Random		-0.317	-0.440	-0.195	0.000	1344	910	2254

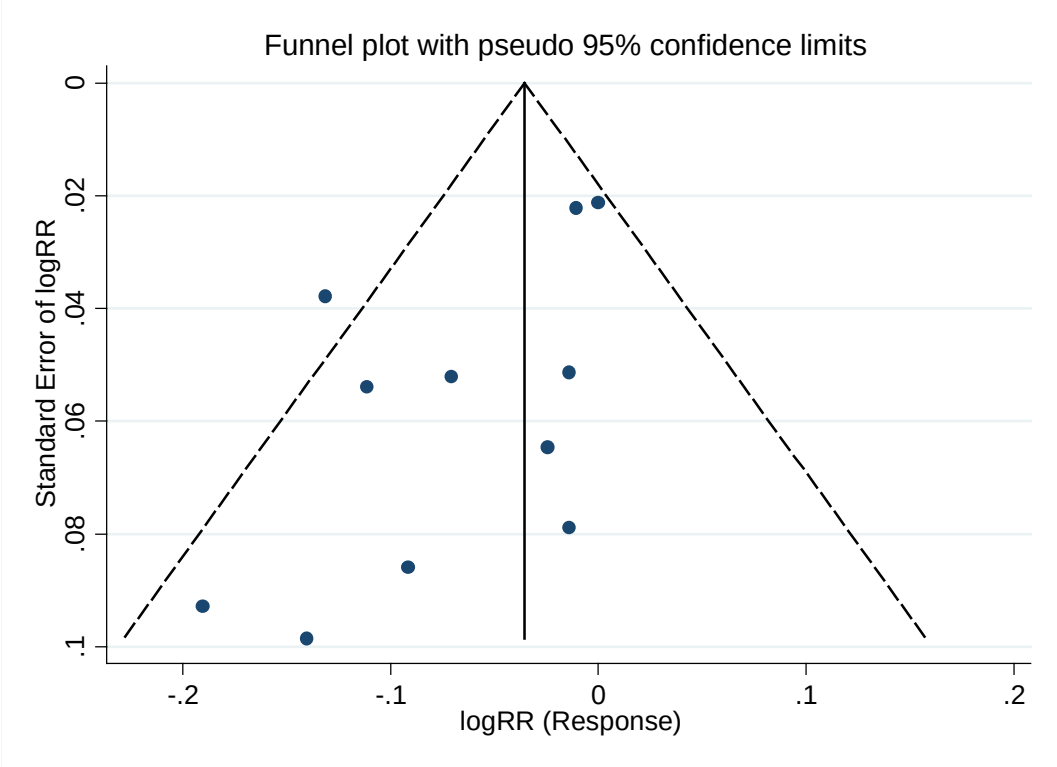


L. Publication bias funnel-plots

L.1: Funnel-plot of Standard Error by Hedges' g (total PANSS/BPRS scores)

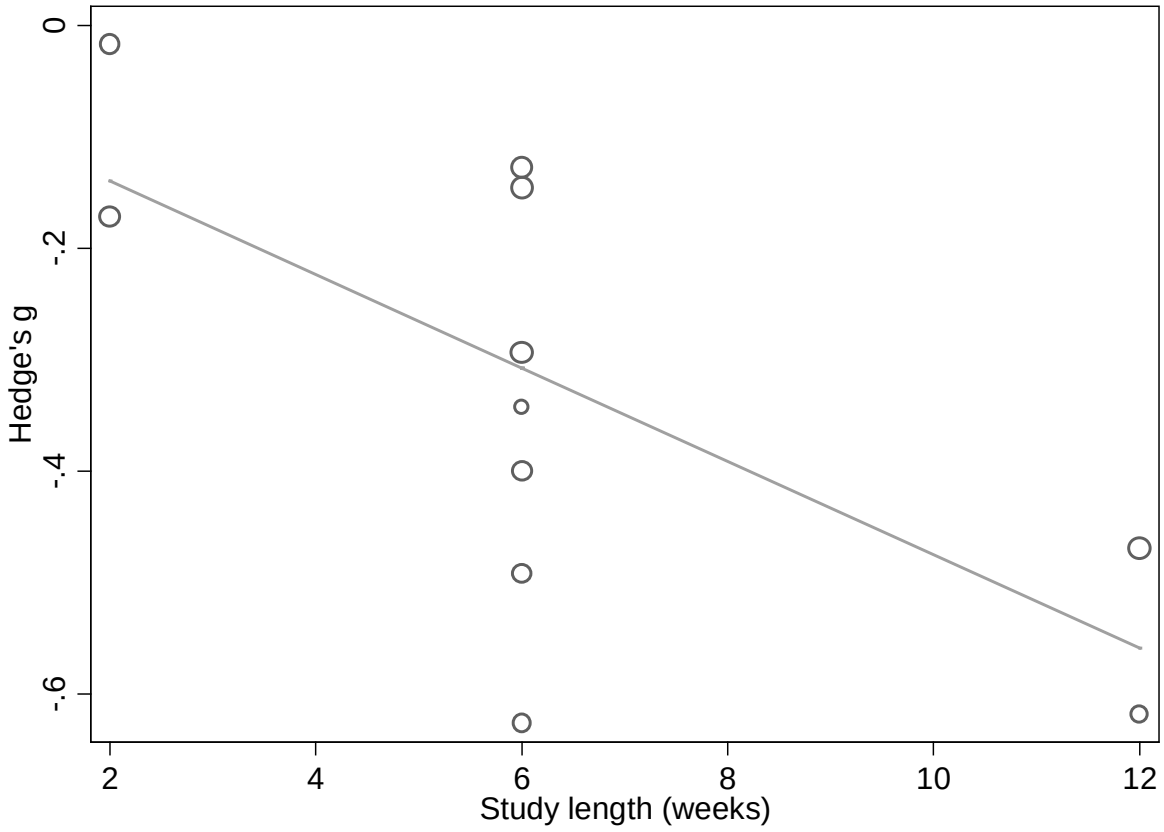


L.2: Funnel-plot of Standard Error by Clinically Significant Response (50% or more reduction in PANSS/BPRS scores)

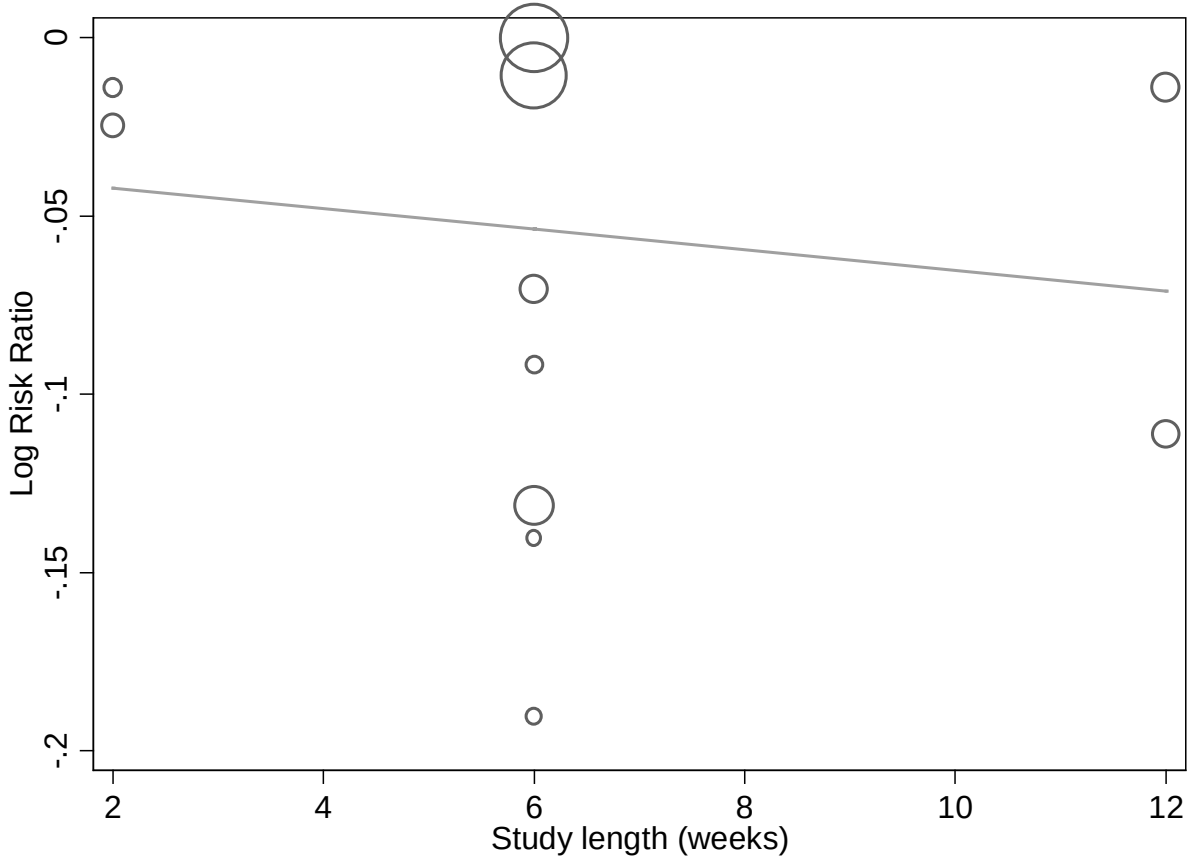


M. Bubble-plots for meta-regression

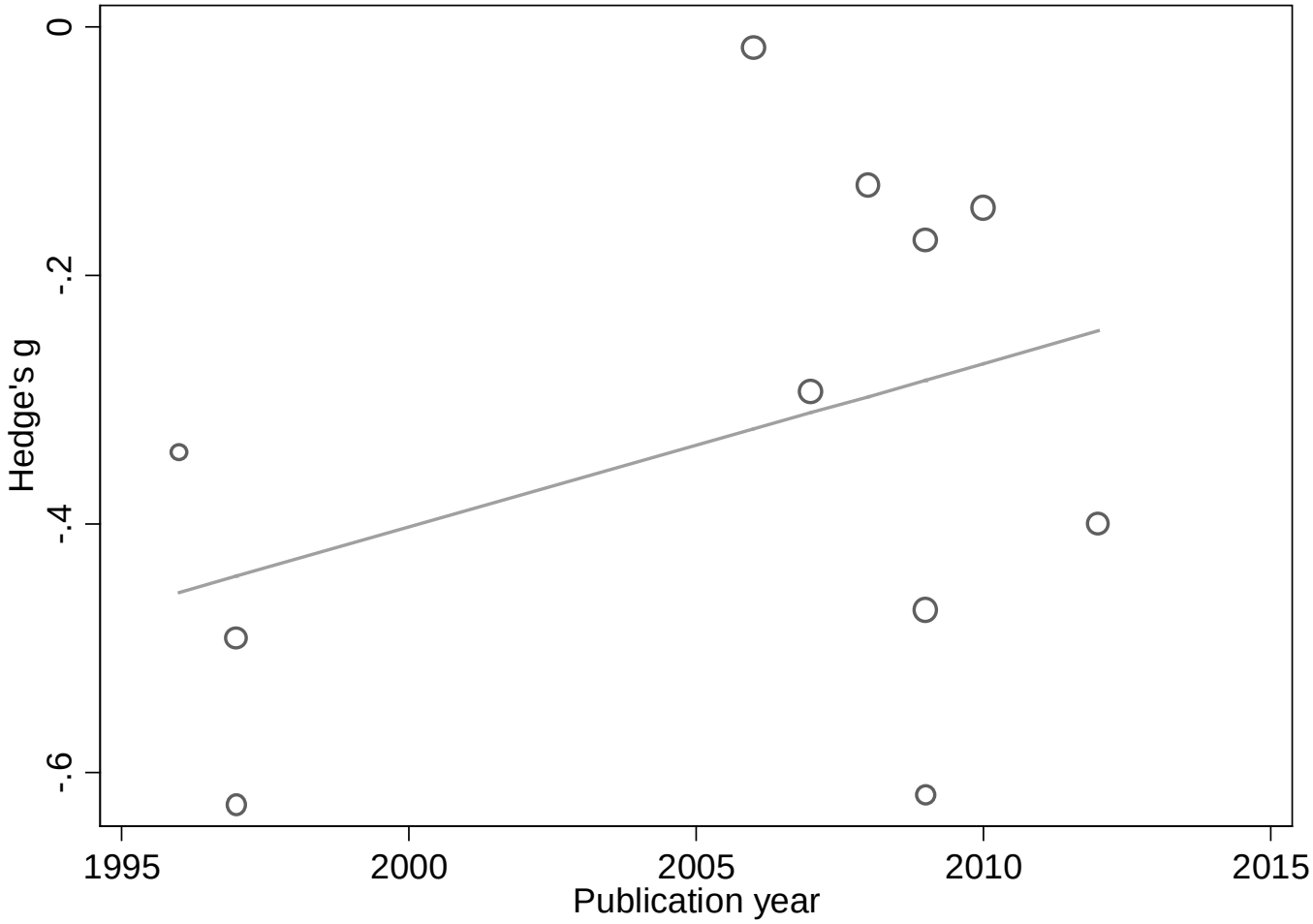
M.1: Bubble-plot of study duration by Hedges' g (total PANSS/BPRS scores)



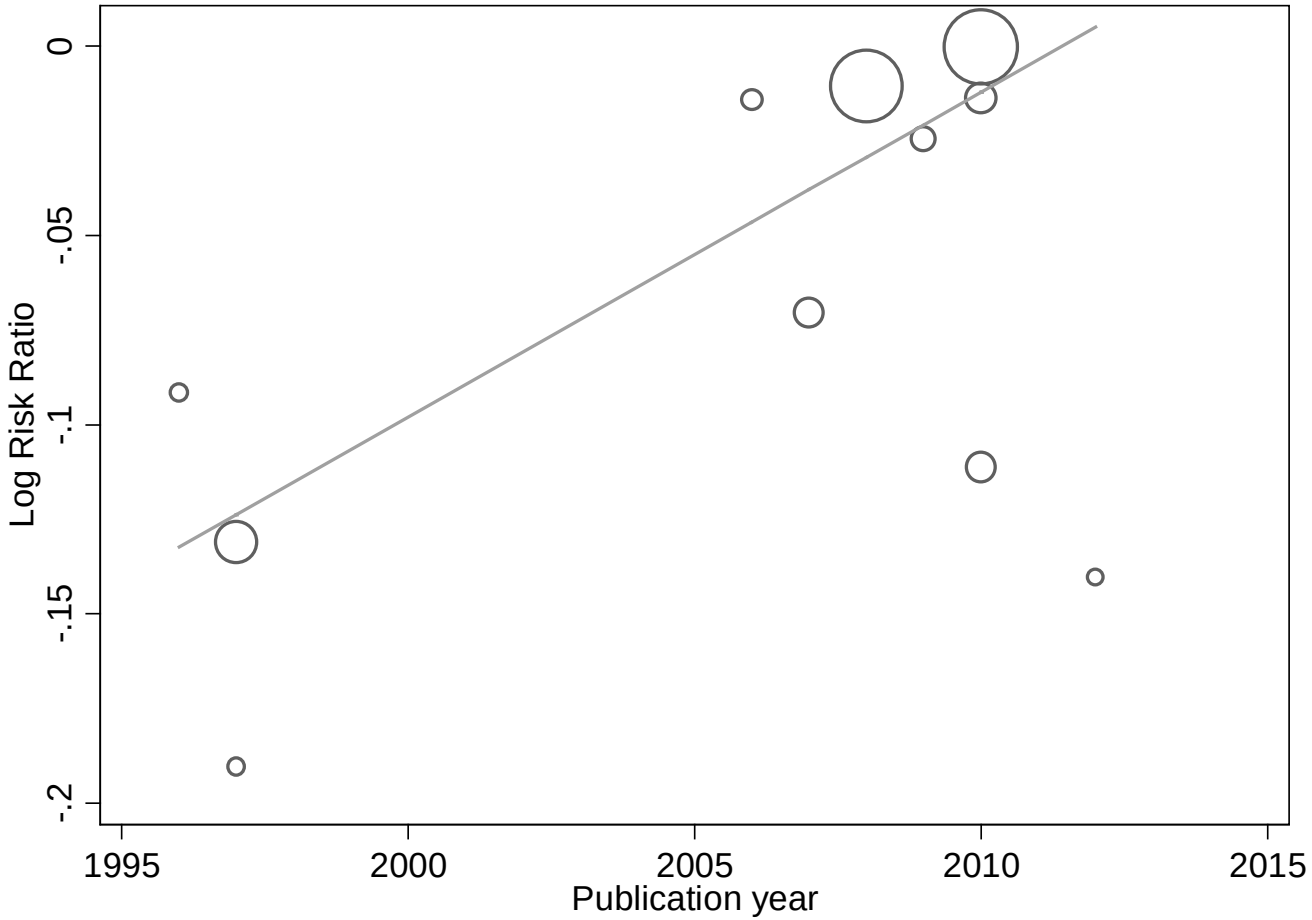
M.2: Bubble-plot of study duration by Clinically Significant Response (50% or more reduction in PANSS/BPRS scores)



M.3: Bubble-plot of publication year by Hedges' g (total PANSS/BPRS scores)



M.4: Bubble-plot of publication year by Clinically Significant Response (50% or more reduction in PANSS/BPRS scores)



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