

Content of supplemental material

Supplementary Table S1 – Search Strategy (page 2-11)

Supplementary Figure S1 – PRISMA diagram (page 12-13)

Supplementary Table S2 – Description of included studies (page 14-25)

Supplementary Figure S2 – Risk of bias assessment (page 26-30)

Supplementary Figure S3 – Sensitivity analyses (page 31-37)

Supplementary Table S1

Description of the search strategy

Search strategies for MEDLINE, Embase, PsycINFO, Cochrane Central Trials Register, BIOSIS, Clinicaltrials.gov, WHO trial register

**Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations,
Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present> 08-11-17**

1 Benperidol/ or Chlorpromazine/ or Clopenthixol/ or Clozapine/ or Flupenthixol/ or
Fluphenazine/ or Fluspirilene/ or Haloperidol/ or Methotrimeprazine/ or Loxapine/ or
Molindone/ or Penfluridol/ or Perazine/ or Perphenazine/ or Pimozide/ or Risperidone/ or
Sulpiride/ or Thioridazine/ or Thiothixene/ or Trifluoperazine/ or Clopenthixol/ (59220)
2 (Amisulpride or Aripiprazole or Asenapine or Benperidol or Brexpiprazole or Cariprazine
or Chlorpromazine or Clopenthixol or Clozapine or Flupenthixol or Fluphenazine or
Fluspirilene or Haloperidol or Iloperidone or Levomepromazine or Loxapine or Lurasidone or
Molindone or Olanzapine or Paliperidone or Quetiapine or Penfluridol or Perazine or
Perphenazine or Pimozide or Risperidone or Sertindole or Sulpiride or Thioridazine or
Thiothixene or Trifluoperazine or Ziprasidone or Zotepine or Zuclopenthixol).tw. (66930)
3 or/1-2 (85727)
4 exp schizophrenia/ (102222)
5 exp Paranoid Disorders/ (4115)
6 schizo\$.mp. (165120)
7 hebephreni\$.mp. (285)
8 oligophreni\$.mp. (1135)
9 psychotic\$.mp. (66059)
10 psychosis.mp. (34850)
11 psychoses.mp. (21241)
12 or/4-11 (222249)
13 exp clinical trial/ (859559)
14 exp randomized controlled trials/ (124530)
15 exp cross-over studies/ (45209)
16 randomized controlled trial.pt. (498672)
17 clinical trial.pt. (548437)
18 controlled clinical trial.pt. (99309)
19 (clinic\$ adj2 trial).mp. (719211)
20 (random\$ adj5 control\$ adj5 trial\$.mp. (686492)
21 (crossover or cross-over).mp. (91835)
22 ((singl\$ or double\$ or trebl\$ or tripl\$) adj (blind\$ or mask\$)).mp. (231374)
23 randomi\$.mp. (825577)
24 (random\$ adj5 (assign\$ or allocat\$ or assort\$ or reciev\$)).mp. (228557)
25 or/13-24 (1354690)
26 3 and 12 and 25 (6843)
27 limit 26 to ed=20161117-20171108 (142)

Embase <1974 to 2017 Week 45> 08-11-17

1 Amisulpride/ or Aripiprazole/ or Asenapine/ or Benperidol/ or Brexpiprazole/ or
Cariprazine/ or Chlorpromazine/ or Clopenthixol/ or Clozapine/ or Flupenthixol/ or
Fluphenazine/ or Fluspirilene/ or Haloperidol/ or Iloperidone/ or Levomepromazine/ or
Loxapine/ or Lurasidone/ or Molindone/ or Olanzapine/ or Paliperidone/ or Quetiapine/ or
Penfluridol/ or Perazine/ or Perphenazine/ or Pimozide/ or Risperidone/ or Sertindole/ or
Sulpiride/ or Thioridazine/ or Tiotixene/ or Trifluoperazine/ or Ziprasidone/ or Zotepine/ or
Zuclopenthixol/ (164376)
2 (Amisulpride or Aripiprazole or Asenapine or Benperidol or Brexpiprazole or Cariprazine
or Chlorpromazine or Clopenthixol or Clozapine or Flupenthixol or Fluphenazine or
Fluspirilene or Haloperidol or Iloperidone or Levomepromazine or Loxapine or Lurasidone or
Molindone or Olanzapine or Paliperidone or Quetiapine or Penfluridol or Perazine or
Perphenazine or Pimozide or Risperidone or Sertindole or Sulpiride or Thioridazine or
Thiothixene or Trifluoperazine or Ziprasidone or Zotepine or Zuclopenthixol).tw. (80449)

- 3 or/1-2 (170244)
- 4 exp schizophrenia/ (171035)
- 5 exp psychosis/ (261313)
- 6 schizo\$.mp. (213225)
- 7 hebephreni\$.mp. (942)
- 8 oligophreni\$.mp. (1550)
- 9 psychotic\$.mp. (48580)
- 10 psychosis.mp. (117286)
- 11 psychoses.mp. (12019)
- 12 or/4-11 (319625)
- 13 (clin\$ adj2 trial).mp. (1411147)
- 14 ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj (blind\$ or mask\$)).mp. (266600)
- 15 (random\$ adj5 (assign\$ or allocat\$)).mp. (159704)
- 16 randomi\$.mp. (1010534)
- 17 crossover.mp. (85681)
- 18 exp randomized-controlled-trial/ (480672)
- 19 exp crossover-procedure/ (54013)
- 20 exp randomization/ (76341)
- 21 or/13-20 (1984816)
- 22 3 and 12 and 21 (14661)

PsycINFO <1806 to October Week 5 2017> 08-11-17

- 1 Aripiprazole/ or Chlorpromazine/ or Clozapine/ or Fluphenazine/ or Haloperidol/ or Loxapine/ or Molindone/ or Olanzapine/ or Quetiapine/ or Perphenazine/ or Pimozide/ or Risperidone/ or Sulpiride/ or Thioridazine/ or Thiothixene/ or Trifluoperazine/ (18864)
- 2 (Amisulpride or Aripiprazole or Asenapine or Benperidol or Brexpiprazole or Cariprazine or Chlorpromazine or Clopenthixol or Clozapine or Flupenthixol or Fluphenazine or Fluspirilene or Haloperidol or Iloperidone or Levomepromazine or Loxapine or Lurasidone or Molindone or Olanzapine or Paliperidone or Quetiapine or Penfluridol or Perazine or Perphenazine or Pimozide or Risperidone or Sertindole or Sulpiride or Thioridazine or Thiothixene or Trifluoperazine or Ziprasidone or Zotepine or Zuclopenthixol).tw. (30668)
- 3 or/1-2 (30799)
- 4 exp schizophrenia/ (83402)
- 5 exp Schizoaffective Disorder/ (2896)
- 6 exp schizophreniform disorder/ (339)
- 7 schizo\$.mp. (126961)
- 8 exp psychosis/ (106639)
- 9 hebephreni\$.mp. (539)
- 10 oligophreni\$.mp. (521)
- 11 psychotic\$.mp. (43539)
- 12 psychosis.mp. (49799)
- 13 psychoses.mp. (15056)
- 14 or/4-13 (175047)
- 15 ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj (blind\$ or mask\$)).mp. (23680)
- 16 (random\$ adj5 (assign\$ or allocat\$)).mp. (38788)
- 17 randomi\$.mp. (70694)
- 18 crossover.mp. (6597)
- 19 or/15-18 (112844)
- 20 3 and 14 and 19 (2845)

Cochrane Library 08-11-17

- #1 MeSH descriptor: [Benperidol] this term only

- #2 MeSH descriptor: [Chlorpromazine] this term only
 #3 MeSH descriptor: [Clopenthixol] this term only
 #4 MeSH descriptor: [Clozapine] this term only
 #5 MeSH descriptor: [Flupenthixol] this term only
 #6 MeSH descriptor: [Fluphenazine] this term only
 #7 MeSH descriptor: [Fluspirilene] this term only
 #8 MeSH descriptor: [Haloperidol] this term only
 #9 MeSH descriptor: [Methotrimeprazine] this term only
 #10 MeSH descriptor: [Loxapine] this term only
 #11 MeSH descriptor: [Molindone] this term only
 #12 MeSH descriptor: [Penfluridol] this term only
 #13 MeSH descriptor: [Perazine] this term only
 #14 MeSH descriptor: [Perphenazine] this term only
 #15 MeSH descriptor: [Pimozide] this term only
 #16 MeSH descriptor: [Risperidone] this term only
 #17 MeSH descriptor: [Sulpiride] this term only
 #18 MeSH descriptor: [Thioridazine] this term only
 #19 MeSH descriptor: [Thiothixene] this term only
 #20 MeSH descriptor: [Trifluoperazine] this term only
 #21 (Amisulpride or Aripiprazole or Asenapine or Benperidol or Brexpiprazole or Cariprazine or Chlorpromazine or Clopenthixol or Clozapine or Flupenthixol or Fluphenazine or Fluspirilene or Haloperidol or Iloperidone or Levomepromazine or Loxapine or Lurasidone or Molindone or Olanzapine or Paliperidone or Quetiapine or Penfluridol or Perazine or Perphenazine or Pimozide or Risperidone or Sertindole or Sulpiride or Thioridazine or Thiothixene or Trifluoperazine or Ziprasidone or Zotepine or Zuclopenthixol):ti,ab,kw (Word variations have been searched)
 #22 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21
 #23 MeSH descriptor: [Schizophrenia] explode all trees
 #24 MeSH descriptor: [Paranoid Disorders] explode all trees
 #25 (schizo* or hebephrenic* or oligophreni* or psychotic* or psychosis or psychoses):ti,ab,kw (Word variations have been searched)
 #26 #23 or #24 or #25
 #27 #22 and #26 in Trials = 6132

Pubmed 08-11-17

- [#10](#) Search (#8 and #9) [146](#)
[#9](#) Search ("2016/11/17"[Date - Entrez] : "2017/11/08"[Date - Entrez]) [1087861](#)
[#8](#) Search ((#3 and #6 and #7)) [5365](#)
[#7](#) Search (((randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR clinical trials as topic[mesh:noexp] OR randomly[tiab] OR trial[ti] NOT (animals[mh] NOT humans [mh]))) [1033765](#)
[#6](#) Search ((#4 or #5)) [199259](#)
[#5](#) Search (((("Schizophrenia"[Mesh]) OR "Psychotic Disorders"[Mesh])) [131315](#)
[#4](#) Search (((schizo*[Title/Abstract] OR hebephrenic*[Title/Abstract] OR oligophreni*[Title/Abstract] OR psychotic*[Title/Abstract] OR psychosis[Title/Abstract] OR psychoses[Title/Abstract]))) [170390](#)
[#3](#) Search ((#1 or #2)) [81037](#)
[#2](#) Search (((Amisulpride[Title/Abstract] OR Aripiprazole[Title/Abstract] OR Asenapine[Title/Abstract] OR Benperidol[Title/Abstract] OR Brexpiprazole[Title/Abstract] OR Cariprazine[Title/Abstract] OR Chlorpromazine[Title/Abstract] OR Clopenthixol[Title/Abstract] OR Clozapine[Title/Abstract] OR Flupenthixol[Title/Abstract] OR Fluphenazine[Title/Abstract] OR Fluspirilene[Title/Abstract] OR Haloperidol[Title/Abstract]

OR Iloperidone[Title/Abstract] OR Levomepromazine[Title/Abstract] OR
Loxapine[Title/Abstract] OR Lurasidone[Title/Abstract] OR Molindone[Title/Abstract] OR
Olanzapine[Title/Abstract] OR Paliperidone[Title/Abstract] OR Quetiapine[Title/Abstract] OR
Penfluridol[Title/Abstract] OR Perazine[Title/Abstract] OR Perphenazine[Title/Abstract] OR
Pimozide[Title/Abstract] OR Risperidone[Title/Abstract] OR Sertindole[Title/Abstract] OR
Sulpiride[Title/Abstract] OR Thioridazine[Title/Abstract] OR Thiothixene[Title/Abstract] OR
Trifluoperazine[Title/Abstract] OR Ziprasidone[Title/Abstract] OR Zotepine[Title/Abstract]
OR Zuclopenthixol[Title/Abstract])) [65192](#)

[#1](#) Search (("Brexiprazole" [Supplementary Concept] or "sultopride" [Supplementary
Concept] or "aripiprazole" [Supplementary Concept] or "Asenapine" [Supplementary
Concept] or "Benperidol"[Mesh] or "cariprazine" [Supplementary Concept] or
"Chlorpromazine"[Mesh] or "Clopenthixol"[Mesh] or "Clozapine"[Mesh] or
"Flupenthixol"[Mesh] or "Fluphenazine"[Mesh] or "Fluspirilene"[Mesh] or
"Haloperidol"[Mesh] or "iloperidone" [Supplementary Concept] or
"Methotrimeprazine"[Mesh] or "Loxapine"[Mesh] or "lurasidone" [Supplementary Concept]
or "Molindone"[Mesh] or "olanzapine" [Supplementary Concept] or "paliperidone"
[Supplementary Concept] or "quetiapine" [Supplementary Concept] or "Penfluridol"[Mesh]
or "Perazine"[Mesh] or "Perphenazine"[Mesh] or "Pimozide"[Mesh] or "Risperidone"[Mesh]
or "sertindole" [Supplementary Concept] or "Sulpiride"[Mesh] or "Thioridazine"[Mesh] or
"Thiothixene"[Mesh] or "Trifluoperazine"[Mesh] or "ziprasidone" [Supplementary Concept]
or "zotepine" [Supplementary Concept] or "Clopenthixol"[Mesh])) [60649](#)

Biosis 08-11-17

12 [2,225](#) #11 AND #10 AND #9

Indexes=BCI Timespan=All years

11 [69,571](#) **TOPIC:** (Amisulpride or Aripiprazole or Asenapine or Benperidol or Brexpiprazole or
Cariprazine or Chlorpromazine or Clopenthixol or Clozapine or Flupenthixol or Fluphenazine or
Fluspirilene or Haloperidol or Iloperidone or Levomepromazine or Loxapine or Lurasidone or
Molindone or Olanzapine or Paliperidone or Quetiapine or Penfluridol or Perazine or Perphenazine
or Pimozide or Risperidone or Sertindole or Sulpiride or Thioridazine or Thiothixene or
Trifluoperazine or Ziprasidone or Zotepine or Zuclopenthixol)

Indexes=BCI Timespan=All years

10 [151,674](#) **TOPIC:** (schizo* or hebephrenic* OR oligophreni* OR psychotic* OR
psychosis OR psychoses)

Indexes=BCI Timespan=All years

9 [380,429](#) #8 OR #7 OR #6 OR #5 OR #2 OR #1

Indexes=BCI Timespan=All years

8 [39,548](#) **TOPIC:** (crossover*)

Indexes=BCI Timespan=All years

7 [462](#) **TOPIC:** (randomi* Near/1 assign*)

Indexes=BCI Timespan=All years

6 [79](#) **TOPIC:** (randomi* Near/1 allocate*)

Indexes=BCI Timespan=All years

5 [121,630](#) #4 AND #3

Indexes=BCI Timespan=All years

4 [223,836](#) **TOPIC:** (mask* OR blind*)

Indexes=BCI Timespan=All years

3 [2,240,458](#) **TOPIC:** (singl* OR Doubl* OR Tripl* OR Trebl*)

Indexes=BCI Timespan=All years

2 [313,760](#) **TOPIC:** (randomi*)

Indexes=BCI Timespan=All years

1 [163,861](#) TOPIC: (Randomized clinical trial*)
Indexes=BCI Timespan=All years

Clinicaltrials.gov 09-11-17

First posted 18/11/16-09/11/17

Intervention Amisulpride / Condition Schizophrenia / other terms Random = 0
Intervention Aripiprazole / Condition Schizophrenia / other terms Random = 3
Intervention Asenapine / Condition Schizophrenia / other terms Random = 0
Intervention Benperidol / Condition Schizophrenia / other terms Random = 0
Intervention Brexpiprazole / Condition Schizophrenia / other terms Random = 0
Intervention Cariprazine / Condition Schizophrenia / other terms Random = 0
Intervention Chlorpromazine / Condition Schizophrenia / other terms Random = 0
Intervention Clopenthixol / Condition Schizophrenia / other terms Random = 0
Intervention Clozapine / Condition Schizophrenia / other terms Random = 2
Intervention Flupenthixol / Condition Schizophrenia / other terms Random = 0
Intervention Fluphenazine / Condition Schizophrenia / other terms Random = 0
Intervention Fluspirilene / Condition Schizophrenia / other terms Random = 0
Intervention Haloperidol / Condition Schizophrenia / other terms Random = 1
Intervention Iloperidone / Condition Schizophrenia / other terms Random = 0
Intervention Levomepromazine / Condition Schizophrenia / other terms Random = 0
Intervention Loxapine / Condition Schizophrenia / other terms Random = 0
Intervention Lurasidone / Condition Schizophrenia / other terms Random = 1
Intervention Molindone / Condition Schizophrenia / other terms Random = 0
Intervention Olanzapine / Condition Schizophrenia / other terms Random = 3
Intervention Paliperidone / Condition Schizophrenia / other terms Random = 1
Intervention Quetiapine / Condition Schizophrenia / other terms Random = 0
Intervention Penfluridol / Condition Schizophrenia / other terms Random = 0
Intervention Perazine / Condition Schizophrenia / other terms Random = 0
Intervention Perphenazine / Condition Schizophrenia / other terms Random = 0
Intervention Pimozide / Condition Schizophrenia / other terms Random = 0
Intervention Risperidone / Condition Schizophrenia / other terms Random = 5
Intervention Sertindole / Condition Schizophrenia / other terms Random = 0
Intervention Sulpiride / Condition Schizophrenia / other terms Random = 0
Intervention Thioridazine / Condition Schizophrenia / other terms Random = 0
Intervention Thiothixene / Condition Schizophrenia / other terms Random = 0
Intervention Trifluoperazine / Condition Schizophrenia / other terms Random = 0
Intervention Ziprasidone / Condition Schizophrenia / other terms Random = 0
Intervention Zotepine / Condition Schizophrenia / other terms Random = 0
Intervention Zuclopenthixol / Condition Schizophrenia / other terms Random = 0
Intervention Amisulpride / Condition Schizophreniform / other terms Random = 0
Intervention Aripiprazole / Condition Schizophreniform / other terms Random = 0
Intervention Asenapine / Condition Schizophreniform / other terms Random = 0
Intervention Benperidol / Condition Schizophreniform / other terms Random = 0
Intervention Brexpiprazole / Condition Schizophreniform / other terms Random = 0
Intervention Cariprazine / Condition Schizophreniform / other terms Random = 0
Intervention Chlorpromazine / Condition Schizophreniform / other terms Random = 0
Intervention Clopenthixol / Condition Schizophreniform / other terms Random = 0
Intervention Clozapine / Condition Schizophreniform / other terms Random = 0
Intervention Flupenthixol / Condition Schizophreniform / other terms Random = 0
Intervention Fluphenazine / Condition Schizophreniform / other terms Random = 0

Intervention Fluspirilene / Condition Schizophreniform / other terms Random = 0
Intervention Haloperidol / Condition Schizophreniform / other terms Random = 0
Intervention Iloperidone / Condition Schizophreniform / other terms Random = 0
Intervention Levomepromazine / Condition Schizophreniform / other terms Random = 0
Intervention Loxapine / Condition Schizophreniform / other terms Random = 0
Intervention Lurasidone / Condition Schizophreniform / other terms Random = 0
Intervention Molindone / Condition Schizophreniform / other terms Random = 0
Intervention Olanzapine / Condition Schizophreniform / other terms Random = 1
Intervention Paliperidone / Condition Schizophreniform / other terms Random = 0
Intervention Quetiapine / Condition Schizophreniform / other terms Random = 0
Intervention Penfluridol / Condition Schizophreniform / other terms Random = 0
Intervention Perazine / Condition Schizophreniform / other terms Random = 0
Intervention Perphenazine / Condition Schizophreniform / other terms Random = 0
Intervention Pimozide / Condition Schizophreniform / other terms Random = 0
Intervention Risperidone / Condition Schizophreniform / other terms Random = 0
Intervention Sertindole / Condition Schizophreniform / other terms Random = 0
Intervention Sulpiride / Condition Schizophreniform / other terms Random = 0
Intervention Thioridazine / Condition Schizophreniform / other terms Random = 0
Intervention Thiothixene / Condition Schizophreniform / other terms Random = 0
Intervention Trifluoperazine / Condition Schizophreniform / other terms Random = 0
Intervention Ziprasidone / Condition Schizophreniform / other terms Random = 0
Intervention Zotepine / Condition Schizophreniform / other terms Random = 0
Intervention Zuclopenthixol / Condition Schizophreniform / other terms Random = 0
Intervention Amisulpride / Condition Schizoaffective / other terms Random = 0
Intervention Aripiprazole / Condition Schizoaffective / other terms Random = 0
Intervention Asenapine / Condition Schizoaffective / other terms Random = 0
Intervention Benperidol / Condition Schizoaffective / other terms Random = 0
Intervention Brexpiprazole / Condition Schizoaffective / other terms Random = 0
Intervention Cariprazine / Condition Schizoaffective / other terms Random = 0
Intervention Chlorpromazine / Condition Schizoaffective / other terms Random = 0
Intervention Clopenthixol / Condition Schizoaffective / other terms Random = 0
Intervention Clozapine / Condition Schizoaffective / other terms Random = 0
Intervention Flupenthixol / Condition Schizoaffective / other terms Random = 0
Intervention Fluphenazine / Condition Schizoaffective / other terms Random = 0
Intervention Fluspirilene / Condition Schizoaffective / other terms Random = 0
Intervention Haloperidol / Condition Schizoaffective / other terms Random = 0
Intervention Iloperidone / Condition Schizoaffective / other terms Random = 0
Intervention Levomepromazine / Condition Schizoaffective / other terms Random = 0
Intervention Loxapine / Condition Schizoaffective / other terms Random = 0
Intervention Lurasidone / Condition Schizoaffective / other terms Random = 0
Intervention Molindone / Condition Schizoaffective / other terms Random = 0
Intervention Olanzapine / Condition Schizoaffective / other terms Random = 0
Intervention Paliperidone / Condition Schizoaffective / other terms Random = 0
Intervention Quetiapine / Condition Schizoaffective / other terms Random = 0
Intervention Penfluridol / Condition Schizoaffective / other terms Random = 0
Intervention Perazine / Condition Schizoaffective / other terms Random = 0
Intervention Perphenazine / Condition Schizoaffective / other terms Random = 0
Intervention Pimozide / Condition Schizoaffective / other terms Random = 0
Intervention Risperidone / Condition Schizoaffective / other terms Random = 0
Intervention Sertindole / Condition Schizoaffective / other terms Random = 0
Intervention Sulpiride / Condition Schizoaffective / other terms Random = 0

Intervention Thioridazine / Condition Schizoaffective / other terms Random = 0
 Intervention Thiothixene / Condition Schizoaffective / other terms Random = 0
 Intervention Trifluoperazine / Condition Schizoaffective / other terms Random = 0
 Intervention Ziprasidone / Condition Schizoaffective / other terms Random = 0
 Intervention Zotepine / Condition Schizoaffective / other terms Random = 0
 Intervention Zuclopenthixol / Condition Schizoaffective / other terms Random = 0
 Intervention Amisulpride / Condition Psychosis / other terms Random = 0
 Intervention Aripiprazole / Condition Psychosis / other terms Random = 5
 Intervention Asenapine / Condition Psychosis / other terms Random = 0
 Intervention Benperidol / Condition Psychosis / other terms Random = 0
 Intervention Brexpiprazole / Condition Psychosis / other terms Random = 6
 Intervention Cariprazine / Condition Psychosis / other terms Random = 0
 Intervention Chlorpromazine / Condition Psychosis / other terms Random = 1
 Intervention Clopenthixol / Condition Psychosis / other terms Random = 0
 Intervention Clozapine / Condition Psychosis / other terms Random = 2
 Intervention Flupenthixol / Condition Psychosis / other terms Random = 0
 Intervention Fluphenazine / Condition Psychosis / other terms Random = 0
 Intervention Fluspirilene / Condition Psychosis / other terms Random = 0
 Intervention Haloperidol / Condition Psychosis / other terms Random = 5
 Intervention Iloperidone / Condition Psychosis / other terms Random = 0
 Intervention Levomepromazine / Condition Psychosis / other terms Random = 0
 Intervention Loxapine / Condition Psychosis / other terms Random = 0
 Intervention Lurasidone / Condition Psychosis / other terms Random = 2
 Intervention Molindone / Condition Psychosis / other terms Random = 0
 Intervention Olanzapine / Condition Psychosis / other terms Random = 4
 Intervention Paliperidone / Condition Psychosis / other terms Random = 1
 Intervention Quetiapine / Condition Psychosis / other terms Random = 3
 Intervention Penfluridol / Condition Psychosis / other terms Random = 0
 Intervention Perazine / Condition Psychosis / other terms Random = 0
 Intervention Perphenazine / Condition Psychosis / other terms Random = 0
 Intervention Pimozide / Condition Psychosis / other terms Random = 0
 Intervention Risperidone / Condition Psychosis / other terms Random = 6
 Intervention Sertindole / Condition Psychosis / other terms Random = 0
 Intervention Sulpiride / Condition Psychosis / other terms Random = 0
 Intervention Thioridazine / Condition Psychosis / other terms Random = 0
 Intervention Thiothixene / Condition Psychosis / other terms Random = 0
 Intervention Trifluoperazine / Condition Psychosis / other terms Random = 0
 Intervention Ziprasidone / Condition Psychosis / other terms Random = 0
 Intervention Zotepine / Condition Psychosis / other terms Random = 0
 Intervention Zuclopenthixol / Condition Psychosis / other terms Random = 0
 Total = 52

WHO ICTRP 09-11-17

Amisulpride and schizo* and random* = 0
 Aripiprazole and schizo* and random* = 4
 Asenapine and schizo* and random* = 0
 Benperidol and schizo* and random* = 0
 Brexpiprazole and schizo* and random* = 1
 Cariprazine and schizo* and random* = 0
 Chlorpromazine and schizo* and random* = 0

Clopentixol and schizo* and random* = 0
Clozapine and schizo* and random* = 4
Flupenthixol and schizo* and random* = 1
Fluphenazine and schizo* and random* = 1
Fluspirilene and schizo* and random* = 0
Haloperidol and schizo* and random* = 0
Iloperidone and schizo* and random* = 0
Levomepromazine and schizo* and random* = 0
Loxapine and schizo* and random* = 0
Lurasidone and schizo* and random* = 2
Molindone and schizo* and random* = 0
Olanzapine and schizo* and random* = 5
Paliperidone and schizo* and random* = 3
Quetiapine and schizo* and random* = 2
Penfluridol and schizo* and random* = 0
Perazine and schizo* and random* = 0
Perphenazine and schizo* and random* = 0
Pimozide and schizo* and random* = 0
Risperidone and schizo* and random* = 5
Sertindole and schizo* and random* = 0
Sulpiride and schizo* and random* = 0
Thioridazine and schizo* and random* = 0
Thiothixene and schizo* and random* = 0
Trifluoperazine and schizo* and random* = 0
Ziprasidone and schizo* and random* = 0
Zotepine and schizo* and random* = 0
Zucloperthixol and schizo* and random* = 1
Amisulpride and psycho* and random* = 0
Aripiprazole and psycho* and random* = 1
Asenapine and psycho* and random* = 0
Benperidol and psycho* and random* = 0
Brexipiprazole and psycho* and random* = 0
Cariprazine and psycho* and random* = 0
Chlorpromazine and psycho* and random* = 0
Clopentixol and psycho* and random* = 0
Clozapine and psycho* and random* = 0
Flupenthixol and psycho* and random* = 3
Fluphenazine and psycho* and random* = 1
Fluspirilene and psycho* and random* = 0
Haloperidol and psycho* and random* = 2
Iloperidone and psycho* and random* = 0
Levomepromazine and psycho* and random* = 0
Loxapine and psycho* and random* = 1
Lurasidone and psycho* and random* = 1
Molindone and psycho* and random* = 0
Olanzapine and psycho* and random* = 2
Paliperidone and psycho* and random* = 1
Quetiapine and psycho* and random* = 1
Penfluridol and psycho* and random* = 0
Perazine and psycho* and random* = 0
Perphenazine and psycho* and random* = 0

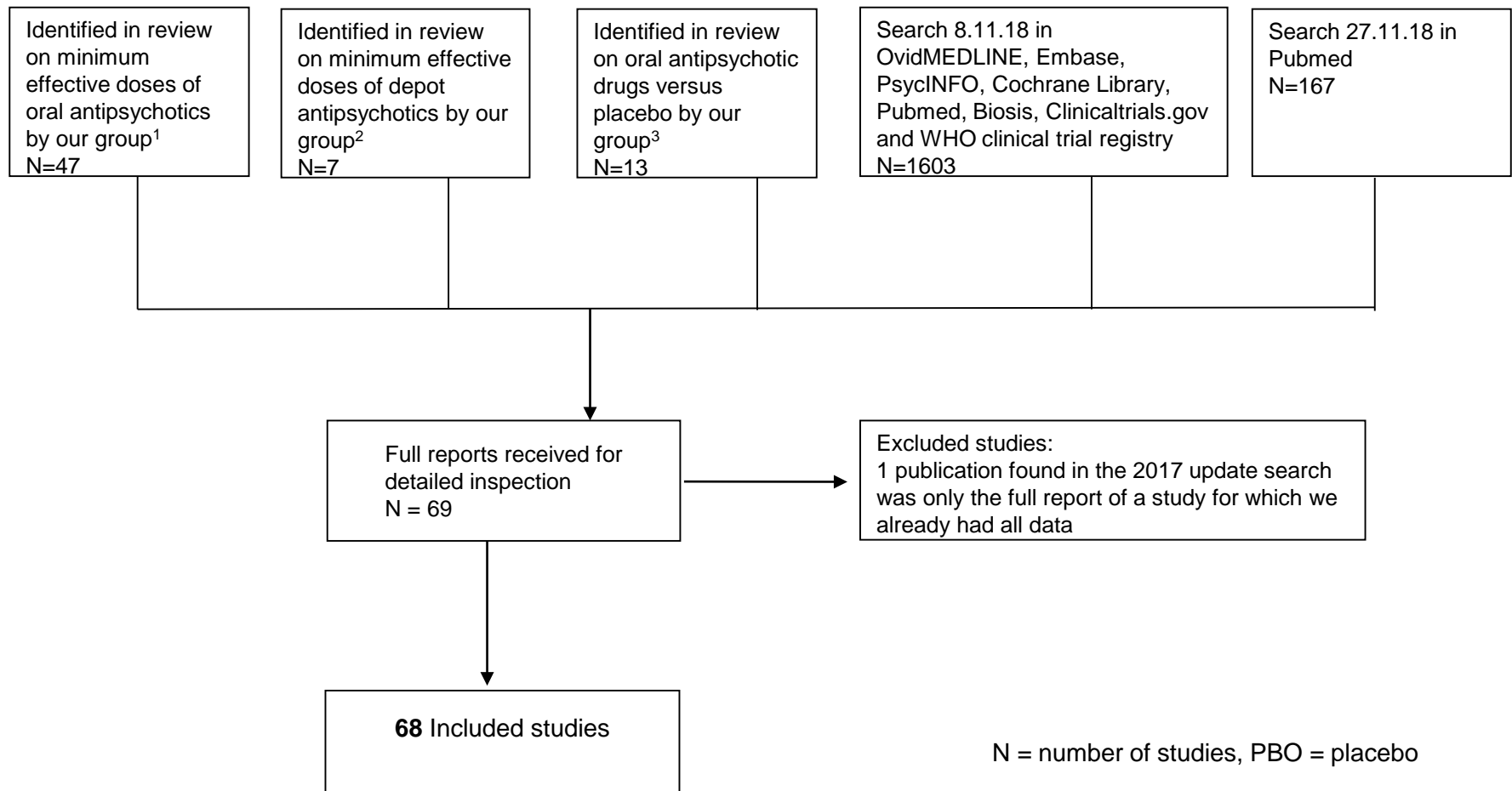
Pimozide and psycho* and random* = 0
Risperidone and psycho* and random* = 1
Sertindole and psycho* and random* = 0
Sulpiride and psycho* and random* = 0
Thioridazine and psycho* and random* = 0
Thiothixene and psycho* and random* = 0
Trifluoperazine and psycho* and random* = 0
Ziprasidone and psycho* and random* = 0
Zotepine and psycho* and random* = 0
Zuclopenthixol and psycho* and random* = 1
Total = 44

Pubmed update Nov 27th 2018

This update search used the same search terms as in 2017 (page 6-7) and it yielded 167 hits.

Supplementary Figure S1
PRISMA diagram of the search

PRISMA diagram of the search process



References

1. Leucht S, Samara M, Heres S, Patel MX, Woods SW, Davis JM. Dose equivalents for second-generation antipsychotics: the minimum effective dose method. *Schizophr Bull* 2014;40(2):314-3262.
2. Rothe PH, Heres S, Leucht S. Dose equivalents for second generation long-acting injectable antipsychotics: The minimum effective dose method. *Schizophr Res* Jul 21 2017.
3. Leucht S, Leucht C, Huhn M, et al. Sixty Years of Placebo-Controlled Antipsychotic Drug Trials in Acute Schizophrenia: Systematic Review, Bayesian Meta-Analysis, and Meta-Regression of Efficacy Predictors. *Am J Psychiatry* May 25 2017:appiajp2017161213584.

Supplementary Table S2

Description of included studies

Webappendix 3: Description of included studies

| Study | Antipsychotic dose groups | n | Duration in weeks | Mean duration of illness in years | Selected characteristics of patients |
|--|-----------------------------------|-------------------------|-------------------|-----------------------------------|--|
| AMISULPRIDE (patients with exacerbations of positive symptoms) | | | | | |
| Puech et al. 1998(1) | AMI 100; 400; 800; 1200 HAL 16 | 61;64; 65;65 64 | 4 | 10 | (Sub-) chronic schizophrenia, acute exacerbation of the disorganized, paranoid or undifferentiated type (DSM-III-R) |
| AMISULPRIDE (patients with predominant negative symptoms) | | | | | |
| Boyer et al. 1995(2) | AMI (100;300) PBO | (34;36) 34 | 6 | 11 | Schizophrenia, disorganised, catatonic, undifferentiated or residual type, patients had to comply with Andreasen´s criteria for “negative schizophrenia” (DSM-III) |
| Danion et al. 1999(3) | AMI (50; 100) PBO | 159 83 | 12 | ~10 | Patients with residual schizophrenia and predominantly negative symptoms (DSM-III-R) |
| ARIPIPRAZOLE | | | | | |
| Cutler et al. 2006(4) | ARI 2; 5; 10 PBO | 93;92;94 88 | 6 | n.i. | Hospitalized patients in acute relapse of schizophrenia (DSM-IV) |
| Kane et al. 2002(5) | ARI 15; 30 HAL 10 PBO | 102; 102 104 106 | 4 | 16.3 | Schizophrenia or schizoaffective disorder with acute relapse (DSM-IV) |
| McEvoy et al. 2007(6) | ARI 10; 15; 20 PBO | 106; 106; 100 108 | 6 | n.i. | Schizophrenia with acute relapse (DSM-IV) |
| Potkin et al. 2003(7) | ARI 20; 30 PBO RIS 6 | 101; 101 103 99 | 4 | n.i. | Schizophrenia or schizoaffective disorder with acute relapse (DSM-IV) |
| Study 94202(8) | ARI 2; 10; 30 HAL 10 PBO | 59;61; 60 63 64 | 4 | n.i. | Schizophrenia with acute relapse (DSM-IV) |
| ARIPIPRAZOLE long-acting injectable (lauroxil) | | | | | |
| Meltzer et al. 2015(9) | ARI 300; 400 PBO | 207; 208; 207 | 12 | | Schizophrenia, DSM-IV-TR; exacerbated |
| ASENAPINE | | | | | |
| Study 041-002(10) | ASE 0.4; 0.8;1.6 RIS 6 PBO | 60;60;60 60 61 | 6 | n.i. | Schizophrenia (DSM-IV) |
| Study 041-013(11) | ASE 3.2; 4.8 PBO | n.i. n.i. | 6 | n.i. | Schizophrenia (DSM-IV) |

| | | | | | |
|---|---|--------------------------------|----|------|--|
| Hera 041-021(12) | ASE 10; 20 OLA 15 PBO | 106; 102 103 106 | 6 | n.i. | Schizophrenia (DSM-IV) |
| Kane et al. 2010(13) | ASE 10; 20 HAL 8 PBO | 114;106 115 123 | 6 | n.i. | Schizophrenia and acute exacerbation (DSM-IV-TR) |
| NCT01098110 Kinoshita et al. 2016(14) | ASE 5;10 PBO | 176 182 174 | 6 | n.i. | Schizophrenia (DSM-IV-TR) |
| NCT01617187 Landbloom et al. 2017(15) | ASE 5;10 OLA 15 PBO | 98 ;113 46 103 | 6 | n.i. | Schizophrenia (DSM-IV-TR) |
| BREXPIPRAZOLE | | | | | |
| Kane et al. 2015(16) | BRE 1;2;4 PBO | 120;186; 184 184 | 6 | 12.9 | Schizophrenia (DSM-IV-TR) |
| Correll et al. 2015(17) | BRE 0.25;2;4 PBO | 90;182;180 184 | 6 | 12.7 | Schizophrenia (DSM-IV-TR) |
| Ishigooka et al. 2018 (18) | BRE 1, 2, 4 PBO | 115;115;113 116 | 6 | 16,5 | Schizophrenia (DSM-IV-TR) |
| NCT00905307 Correll et al. 2016(19) | BRE 0.25;1±0.5; 2.5±0.5;5±0.5 ARI 15 PBO | 42 ;89;90;93 50 95 | 6 | n.i. | Schizophrenia (DSM-IV-TR) |
| CARIPRAZINE | | | | | |
| Durgam et al. 2014(20) | CAR 1.5;3;4.5 RIS 4 PBO | 145;146;147 140 151 | 6 | 11.6 | Schizophrenia (DSM-IV-TR), all subtypes |
| NCT01104766 Durgam et al. 2015(21) | CAR 3;6 ARI 15 PBO | 155;157 152 153 | 6 | 12.5 | Schizophrenia (DSM-IV-TR), acute exacerbation |
| Study RGH-MD-03 Durgam et al. 2016(22) | CAR 1.5-4.5; 6-12 PBO | 128; 134 130 | 6 | 17.5 | Schizophrenia (DSM-IV-TR) |
| Study RGH-MD-05 Kane et al. 2015(23) | CAR 3-6; 6-9 PBO | 151; 148 147 | 6 | 11.5 | Schizophrenia (DSM-IV-TR) |
| CLOZAPINE | | | | | |
| Simpson et al. 1999(24) | CLO 100;300;600 | 14;17;17 | 48 | n.i. | Treatment refractory schizophrenia or schizoaffective disorder (DSM-III-R) |
| HALOPERIDOL | | | | | |
| Zimbroff et al. 1997(25) | SER 12; 20; 24 HAL 4; 8; 16 PBO | 76; 68; 72 71; 67; 70 73 | 8 | 16 | Schizophrenia, history of a previous response to antipsychotic drugs (DSM-III-R or DSM-IV) |
| ILOPERIDONE | | | | | |
| Study ILPB202(26) | ILO 4;8 PBO | 69 35 | 4 | n.i. | Schizophrenia (n.i.) |

| | | | | | |
|---|---|-----------------------------|------|------|--|
| Potkin 2008 study 3000(27) | ILO 4; 8; 12 HAL 15 PBO | 121; 125; 124 124 127 | 6 | 15.6 | Acute or subacute exacerbation of schizophrenia or schizoaffective disorder (DSM-IV) |
| Potkin 2008 study 3004(27) | ILO 4-8; 10-16 RIS 4-8 PBO | 153; 154 153 156 | 6 | n.i. | Acute or subacute exacerbation of schizophrenia or schizoaffective disorder (DSM-IV) |
| Potkin 2008 study 3005(27) | ILO 12-16; 20-24 RIS 6-8 PBO | 244; 145 157 160 | 6 | n.i. | Acute or subacute exacerbation of schizophrenia or schizoaffective disorder (DSM-IV) |
| LURASIDONE | | | | | |
| Ogasa et al. 2012(28) | LURA 40; 120 PBO | 50; 49 50 | 6 | n.i. | Schizophrenia (DSM-IV) |
| Study 049(29) | LURA 20;40; 80 HAL 10 PBO | 71; 69; 71 73 72 | 6 | n.i. | Schizophrenia (DSM-IV) |
| Nasrallah et al. 2013(30) | LURA 40; 80; 120 PBO | 125; 123; 124 128 | 6 | 14.2 | Schizophrenia (DSM-IV) |
| Meltzer et al. 2011(31) | LURA 40; 120 OLA 15 PBO | 120; 119 123 116 | 6 | 13.4 | Schizophrenia (DSM-IV) |
| Loebel et al. 2013(32) | LURA 80; 160 PBO QUE 600 | 125; 121 122 120 | 6 | 11.7 | Schizophrenia (DSM-IV) |
| Loebel et al. 2016(33) | LUR 20;96 PBO | 101;199 112 | 6 | 14.2 | Schizophrenia (DSM-IV-TR) |
| Study NCT00711269 (34) | LURA 40; 80 RIS 4 PBO | 440 (unpublished) | n.i. | n.i. | Schizophrenia (DSM-IV) |
| OLANZAPINE oral (patients with exacerbations of positive symptoms) | | | | | |
| Beasley et al. 1996a(35) | OLA 1; 10 PBO | 50; 52 50 | 6 | 16 | Schizophrenia with an acute exacerbation (DSM-III-R) |
| Beasley et al. 1996b(36) | OLA 5±2.5; 10±2.5; 15±2.5 HAL 15±5 PBO | 65; 64; 69 69 68 | 6 | 14 | Acute exacerbation of schizophrenia (DSM-III-R) |
| Beasley et al 1997(37) | OLA 1; 5±2.5; 10±2.5; 15±2.5 HAL 17.6 | 88; 87; 86; 89 81 | 6 | 12.2 | Acute exacerbation of schizophrenia (DSM-III-R) |
| OLANZAPINE oral (patients with predominant negative symptoms) | | | | | |
| Lecrubier et al. 2006(38) | AMI 150 OLA (5; 20) PBO | 70 (70; 70) 34 | 26 | n.i. | Schizophrenia with predominantly negative symptoms (criteria n.i.) |
| OLANZAPINE long-acting injectable (pamoate) | | | | | |

| | | | | | |
|--|--|-----------------------------------|----|------|---|
| Lauriello et al. 2008(39) | OLA 210/biweekly; 300/biweekly; 405/4-weekly PBO | 106; 100; 100; 98 | 8 | | Schizophrenia DSM-IV or DSM-IV-TR, moderate to high level of severity |
| PALIPERIDONE oral | | | | | |
| Davidson et al. 2007(40) | OLA 10 PAL 3; 9; 15 PBO | 128 127; 125; 115 123 | 6 | 11.9 | Acute episode of schizophrenia (DSM-IV) |
| Kane et al. 2007(41) | OLA 10 PAL 6; 9; 12 PBO | 128 123; 122; 130 127 | 6 | 10.1 | Acute episode of schizophrenia (DSM-IV) |
| Marder et al. 2007(42) | OLA 10 PAL 6; 12 PBO | 110 111; 111 110 | 6 | 16.4 | Acute episode of schizophrenia (DSM-IV) |
| Coppola et al. 2011(43) | PAL 1.5; 6 PBO | 66; 70 65 | 6 | n.i. | Acute episode of schizophrenia (DSM-IV) |
| Canuso et al. 2010(44) | PAL 6; 12 PBO | 109; 100 107 | 6 | 4.8 | Acute episode of schizoaffective disorder (DSM-IV) |
| PALIPERIDONE long-acting injectable (palmitate) | | | | | |
| Kramer et al. 2010(45) NCT00074477 | PAL 50 mg e.q.; 100 mg e.q.; all 4-weekly, open-label vs 4 oral doses, vs PBO in one arm | 79; 84; PBO 84 | 9 | | Schizophrenia, DSM-IV; acutely ill |
| Nasrallah et al. 2010(46) NCT00101634 | PAL 25 mg e.q.; 50 mg e.q.; 100 mg e.q. all 4-weekly, PBO | 131; 129; 131; 127 | 13 | | Schizophrenia, DSM-IV-TR; acutely ill |
| Gopal et al. 2010(47) NCT00210548 | PAL 50 mg e.q.; 100 mg e.q.; 150 mg e.q., all 4-weekly, PBO | 94; 97; 30; 135 | 13 | | Schizophrenia DSM-IV; acutely ill |
| Pandina et al. 2010(48) NCT00590577 | PAL 25 mg e.q.; 100 mg e.q.; 150 mg e.q., all 4-weekly PBO | 160; 165; 163; 160 | 13 | | Schizophrenia DSM-IV; acutely ill |
| QUETIAPINE | | | | | |
| Arvanitis et al. 1997(49) | QUE IR 75; IR 150; IR300; IR600; IR750 HAL 12 PBO | 50; 48; 52; 51; 54 52 51 | 6 | 15 | Acute exacerbation of (sub-) chronic schizophrenia (DSM-III-R) |

| | | | | | |
|--|--|-----------------------------|----|-------|--|
| Cutler et al. 2010(50) | QUE XR400; XR600; XR800; IR800 PBO | 114; 105;113; 116 117 | 6 | 17.7 | Acute exacerbation of schizophrenia (DSM-IV) |
| Kahn et al. 2007(51) | QUE IR400; XR400; XR600; XR800 PBO | 123; 113; 113; 121 118 | 6 | 8.3 | Acute schizophrenia (DSM-IV) |
| Lindenmayer et al. 2008(52) | QUE XR 300, 600; 800; IR 300, 600 PBO | 91; 92; 89; 90 ; 86 84 | 6 | 15.2 | Acute exacerbation of schizophrenia (DSM-IV) |
| RISPERIDONE oral | | | | | |
| Chouinard et al. 1993 (53) | RIS 2;6; 10;16 HAL 20 PBO | 24; 22; 22;24 21 22 | 8 | 16 | Chronic Schizophrenia (DSM-III-R) |
| Marder et al. 1994(54) | RIS 2;6; 10;16 HAL 20 PBO | 63;64; 65;64 66 66 | 8 | 16 | Chronic schizophrenia (DSM-III-R) |
| Peuskens et al. 1995(55) | RIS 1;4; 8;12; 16 HAL 10 | 229; 227; 230 ;226; 224 226 | 8 | 17 | Chronic schizophrenia (DSM-III-R) |
| Study RIS-USA-72 1996(56) | RIS 4; 8 PBO | 85; 78 83 | 4 | n.i. | Chronic or subchronic schizophrenia (DSM-III-R) |
| RISPERIDONE long-acting injectable (consta) | | | | | |
| Kane et al.2003(57) NCT00253136 | RIS 25; 50; 75; all 2-weekly, PBO | 99; 103, 100; 98 | 12 | | Schizophrenia, DSM-IV, PANSS 60-120, acutely ill |
| SERTINDOLE | | | | | |
| Hale et al. 2000(58) | SER 8;16; 20;24 HAL 10 | 372 120;127; 128; 117 125 | 8 | 8 | Hospitalized patients with schizophrenia (DSM-III-R) |
| Van Kammen et al. 1996(59) | SER 8; 12; 20 PBO | 52; 51; 54 48 | 6 | 14 | Schizophrenia, history of a previous response to antipsychotic drugs (DSM-III-R) |
| Zborowski et al. 1995(60) | SER 20; 24 HAL 16 PBO | 117; 113 115 116 | 8 | 15 | Schizophrenia (DSM-III-R or DSM-IV) |
| Zimbroff et al. 1997(25) | SER 12; 20; 24 HAL 4; 8; 16 PBO | 76; 68; 72 71; 67; 70 73 | 8 | 16 | Schizophrenia, history of a previous response to antipsychotic drugs (DSM-III-R or DSM-IV) |
| ZIPRASIDONE | | | | | |
| Daniel et al. 1999(61) | ZIP 80; 160 PBO | 106; 104 92 | 6 | 14 | Acute exacerbation of (sub-)chronic schizophrenia or schizoaffective disorder (DSM-III-R) |
| Goff et al. 1998(62) | ZIP 4;10;40; 160 HAL 15 | 19;17;17; 20 17 | 4 | 14-18 | Acute exacerbation of schizophrenia or schizoaffective disorder (DSM-III-R) |

| | | | | | |
|-------------------------|-----------------------------------|-----------------------|---|------|---|
| Keck et al. 1998(63) | ZIP 40; 120 PBO | 44; 47 48 | 4 | 16 | Acute exacerbation of schizophrenia or schizoaffective disorder (DSM-III-R) |
| Study 104 2000(64) | ZIP 20; 40; 80 PBO | 47; 55; 48 50 | 4 | | Acute exacerbation of schizophrenia or schizoaffective disorder (DSM-III-R) |
| Study 115 2000(64) | ZIP 40; 120; 200 HAL 15 PBO | 87;78; 86 85 83 | 6 | n.i. | Acute exacerbation of schizophrenia or schizoaffective disorder (DSM-III-R) |
| ZOTEPINE | | | | | |
| Knoll(65) | ZOT 75; 150; 300 PBO | n.i. | 6 | n.i. | Acute schizophrenia |

n= number of patients, AMI = Amisulpride, ARI = Aripiprazole, ASE = Asenapine, BRE = brexpiprazole, CAR = cariprazine, CLO = Clozapine, HAL = Haloperidol, ILO = Iloperidone, LUR = Lurasidone, OLA = Olanzapine, PAL = Paliperidone, QUE = Quetiapine, RIS = Risperidone, SER = Sertindole, ZIP = Ziprasidone, ZOT=Zotepine, PBO= Placebo, ICD 9/10 = International Classification of Diseases, 9th/10th Revision, DSM-III, -III-R, -IV = different versions of the Diagnostic and Statistical Manual of Mental Disorders, n.i. = not indicated, IR= immediate release, XR= extended release

References

1. Puech A, Fleurot O, Rein W. Amisulpride, an atypical antipsychotic, in the treatment of acute episodes of schizophrenia: a dose-ranging study vs. haloperidol. *Acta Psychiatr Scand*. 1998;98:65-72.
2. Boyer P, Lecrubier Y, Puech AJ, Dewailly J, Aubin F. Treatment of negative symptoms in schizophrenia with amisulpride. *Br J Psychiatry*. 1995;166:68-72.
3. Danion JM, Rein W, Fleurot O. Improvement of schizophrenic patients with primary negative symptoms treated with amisulpride. *Am J Psychiatry*. 1999;156:610-616.
4. Cutler AJ, Marcus RN, Hardy SA, O'Donnell A, Carson WH, McQuade RD. The efficacy and safety of lower doses of aripiprazole for the treatment of patients with acute exacerbation of schizophrenia. *CNS Spectr*. 2006;11:691-702.
5. Kane JM, Carson WH, Saha AR, McQuade RD, Ingenito GG, Zimbroff DL, Ali MW. Efficacy and safety of aripiprazole and haloperidol versus placebo in patients with schizophrenia and schizoaffective disorder. *J Clin Psychiatry*. 2002;63:763-771.
6. McEvoy JP, Daniel DG, Carson WH, Jr., McQuade RD, Marcus RN. A randomized, double-blind, placebo-controlled, study of the efficacy and safety of aripiprazole 10, 15 or 20 mg/day for the treatment of patients with acute exacerbations of schizophrenia. *J Psychiatr Res*. 2007;41:895-905.
7. Potkin SG, Saha AR, Kujawa MJ, Carson WH, Ali M, Stock E, Stringfellow J, Ingenito G, Marder SR. Aripiprazole, an antipsychotic with a novel mechanism of action, and risperidone vs placebo in patients with schizophrenia and schizoaffective disorder. *Arch Gen Psychiatry*. 2003;60:681-690.
8. 94202 S. Center for drug evaluation and research. Application number 21-436. Medical review(s). www.fda.gov. 2002.
9. Meltzer HY, Risinger R, Nasrallah HA, Du Y, Zummo J, Corey L, Bose A, Stankovic S, Silverman BL, Ehrlich EW. A randomized, double-blind, placebo-controlled trial of aripiprazole lauroxil in acute exacerbation of schizophrenia. *The Journal of clinical psychiatry*. 2015;76:1,478-1090.
10. 041-002 S. Center for drug evaluation and research. Application number 22-117. Medical review(s). <http://www.fda.gov>. 2009.
11. 041-013 S. Center for drug evaluation and research. Application number 200603. Medical review(s). <http://www.fda.gov>. 2009.
12. 041-021 SH. A multicenter, randomized, double-blind, fixed-dose, 6-week trial of the efficacy and safety of asenapine compared with placebo using olanzapine positive control in subjects with an acute exacerbation of schizophrenia. Center for drug evaluation and research Application number 22-117 Medical review(s) <http://www.fda.gov>. 2009.
13. Kane JM, Cohen M, Zhao J, Alphas L, Panagides J. Efficacy and safety of asenapine in a placebo- and haloperidol-controlled trial in patients with acute exacerbation of schizophrenia. *J Clin Psychopharmacol*. 2010;30:106-115.
14. Kinoshita T, Bai YM, Kim JH, Miyake M, Oshima N. Efficacy and safety of asenapine in Asian patients with an acute exacerbation of schizophrenia: a multicentre, randomized, double-blind, 6-week, placebo-controlled study. *Psychopharmacology*. 2016;233:2663-2674.
15. Landbloom R, Mackle M, Wu X, Kelly L, Snow-Adami L, McIntyre RS, Mathews M, Hundt C. Asenapine for the treatment of adults with an acute exacerbation of schizophrenia: results from

- a randomized, double-blind, fixed-dose, placebo-controlled trial with olanzapine as an active control. *CNS spectrums*. 2017;22:333-341.
16. Kane JM, Skuban A, Ouyang J, Hobart M, Pfister S, McQuade RD, Nyilas M, Carson WH, Sanchez R, Eriksson H. A multicenter, randomized, double-blind, controlled phase 3 trial of fixed-dose brexpiprazole for the treatment of adults with acute schizophrenia. *Schizophrenia research*. 2015;164:127-135.
 17. Correll CU, Skuban A, Ouyang J, Hobart M, Pfister S, McQuade RD, Nyilas M, Carson WH, Sanchez R, Eriksson H. Efficacy and Safety of Brexpiprazole for the Treatment of Acute Schizophrenia: A 6-Week Randomized, Double-Blind, Placebo-Controlled Trial. *The American journal of psychiatry*. 2015;172:870-880.
 18. Ishigooka J, Iwashita S, Tadori Y. Efficacy and safety of brexpiprazole for the treatment of acute schizophrenia in Japan: A 6-week, randomized, double-blind, placebo-controlled study. *Psychiatry and clinical neurosciences*. 2018;72:692-700.
 19. Correll CU, Skuban A, Hobart M, Ouyang J, Weiller E, Weiss C, Kane JM. Efficacy of brexpiprazole in patients with acute schizophrenia: Review of three randomized, double-blind, placebo-controlled studies. *Schizophrenia research*. 2016;174:82-92.
 20. Durgam S, Starace A, Li D, Migliore R, Ruth A, Nemeth G, Laszlovszky I. An evaluation of the safety and efficacy of cariprazine in patients with acute exacerbation of schizophrenia: a phase II, randomized clinical trial. *Schizophr Res*. 2014;152:450-457.
 21. Durgam S, Cutler AJ, Lu K, Migliore R, Ruth A, Laszlovszky I, Nemeth G, Meltzer HY. Cariprazine in acute exacerbation of schizophrenia: a fixed-dose, phase 3, randomized, double-blind, placebo- and active-controlled trial. *The Journal of clinical psychiatry*. 2015;76:e1574-1582.
 22. Durgam S, Litman RE, Papadakis K, Li D, Nemeth G, Laszlovszky I. Cariprazine in the treatment of schizophrenia: a proof-of-concept trial. *International clinical psychopharmacology*. 2016;31:61-68.
 23. Kane JM, Zukin S, Wang Y, Lu K, Ruth A, Nagy K, Laszlovszky I, Durgam S. Efficacy and Safety of Cariprazine in Acute Exacerbation of Schizophrenia: Results From an International, Phase III Clinical Trial. *Journal of clinical psychopharmacology*. 2015;35:367-373.
 24. Simpson GM, Josiassen RC, Stanilla JK, De Leon J, Nair C, Abraham G, Odom WA, Turner RM. Double-blind study of clozapine dose response in chronic schizophrenia. *AmJPsychiatry*. 1999;156:1744-1750.
 25. Zimbroff DL, Kane JM, Tamminga CA, Daniel DG, Mack RJ, Wozniak PJ, Sebree TB, Wallin BA, Kashkin KB, Adan F, Ainslie G, Allan E, Atri P, Baker R, Beitman B, Brown G, Canive J, Carman J, Dott S, Edwards J, Fenton W, Freidli J, Funderburg L, Ereshefsky L, Gladson M, Hamilton J, Haque S, Hartford J, Horne R, Houck C, Jampala C, Labelle A, Larson G, Liesem M, Liskow B, Makela E, Moore N, Morphy M, Posever T, Risch S, Rotrosen J, Sheehan D, Silverstone P, Swann A, Tapp A, Thomas M, Volavka J, Vora S. Controlled, dose response study of sertindole and haloperidol in the treatment of schizophrenia. *AmJPsychiatry*. 1997;154:782-791.
 26. FDA. Drug Approval Package. Fanapt (iloperidone) Tablets. 12 June 2009. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022192s000TOC.cfm. 2009.
 27. Potkin SG, Litman RE, Torres R, Wolfgang CD. Efficacy of iloperidone in the treatment of schizophrenia: initial phase 3 studies. *JClinPsychopharmacol*. 2008;28:S4-11.
 28. Ogasa M, Kimura T, Nakamura M, Guarino J. Lurasidone in the treatment of schizophrenia: a 6-week, placebo-controlled study. *Psychopharmacology (Berl)*. 2012.

29. 049 S. A 6-week, double-blind, randomized, fixed dose, parallel-group study of the efficacy and safety of three dose levels of SM-13496 (lurasidone) compared to placebo and haloperidol in patients with schizophrenia who are experiencing an acute exacerbation of symptoms. Center for drug evaluation and research Application number 200603 Medical review(s) <http://www.fda.gov>. 2010.
30. Nasrallah HA, Silva R, Phillips D, Cucchiaro J, Hsu J, Xu J, Loebel A. Lurasidone for the treatment of acutely psychotic patients with schizophrenia: a 6-week, randomized, placebo-controlled study. *J Psychiatr Res.* 2013;47:670-677.
31. Meltzer HY, Cucchiaro J, Silva R, Ogasa M, Phillips D, Xu J, Kalali AH, Schweizer E, Pikalov A, Loebel A. Lurasidone in the treatment of schizophrenia: a randomized, double-blind, placebo- and olanzapine-controlled study. *Am J Psychiatry.* 2011;168:957-967.
32. Loebel A, Cucchiaro J, Sarma K, Xu L, Hsu C, Kalali AH, Pikalov A, Potkin SG. Efficacy and safety of lurasidone 80 mg/day and 160 mg/day in the treatment of schizophrenia: a randomized, double-blind, placebo- and active-controlled trial. *Schizophr Res.* 2013;145:101-109.
33. Loebel A, Silva R, Goldman R, Watabe K, Cucchiaro J, Citrome L, Kane JM. Lurasidone Dose Escalation in Early Nonresponding Patients With Schizophrenia: A Randomized, Placebo-Controlled Study. *The Journal of clinical psychiatry.* 2016.
34. Pharma DS. Study NCT00711269. <http://clinicaltrials.gov/show/NCT00711269>. Last accessed 22.7.2013.
35. Beasley CM, Sanger T, Satterlee W. Olanzapine versus placebo: results of a double-blind fixed dose olanzapine trial. *Psychopharmacology.* 1996;124:159-167.
36. Beasley CM, Tollefson GD, Tran P, Satterlee W, Sanger T, Hamilton S, group. OHs. Olanzapine versus haloperidol and placebo. Acute phase results of the american double-blind olanzapine trial. *Neuropsychopharmacology.* 1996;14:111-123.
37. Beasley CM, Hamilton SH, Crawford AM, Dellva MA, Tollefson GD, Tran PV, Blin O, Beuzen J-N. Olanzapine versus haloperidol: acute phase results of the international double-blind olanzapine trial. *Eur Neuropsychopharmacol.* 1997;7:125-137.
38. Lecrubier Y, Quintin P, Bouhassira M, Perrin E, Lancrenon S. The treatment of negative symptoms and deficit states of chronic schizophrenia: olanzapine compared to amisulpride and placebo in a 6-month double-blind controlled clinical trial. *Acta Psychiatr Scand.* 2006;114:319-327.
39. Lauriello J, Lambert T, Andersen S, Lin D, Taylor CC, McDonnell D. An 8-week, double-blind, randomized, placebo-controlled study of olanzapine long-acting injection in acutely ill patients with schizophrenia. *The Journal of clinical psychiatry.* 2008;69:790-799.
40. Davidson M, Emsley R, Kramer M, Ford L, Pan G, Lim P, Eerdekens M. Efficacy, safety and early response of paliperidone extended-release tablets (paliperidone ER): results of a 6-week, randomized, placebo-controlled study. *Schizophr Res.* 2007;93:117-130.
41. Kane J, Canas F, Kramer M, Ford L, Gassmann-Mayer C, Lim P, Eerdekens M. Treatment of schizophrenia with paliperidone extended-release tablets: a 6-week placebo-controlled trial. *Schizophr Res.* 2007;90:147-161.
42. Marder SR, Kramer M, Ford L, Eerdekens E, Lim P, Eerdekens M, Lowy A. Efficacy and safety of paliperidone extended-release tablets: results of a 6-week, randomized, placebo-controlled study. *Biol Psychiatry.* 2007;62:1363-1370.
43. Coppola D, Melkote R, Lannie C, Singh J, Nuamah I, Gopal S, Hough D, Palumbo J. Efficacy and safety of paliperidone extended release 1.5 mg/day - a double-blind, placebo- and

- active-controlled, study in the treatment of patients with schizophrenia. *PsychopharmacolBull.* 2011;44:1-19.
44. Canuso CM, Lindenmayer JP, Kosik-Gonzalez C, Turkoz I, Carothers J, Bossie CA, Schooler NR. A randomized, double-blind, placebo-controlled study of 2 dose ranges of paliperidone extended-release in the treatment of subjects with schizoaffective disorder. *JClinPsychiatry.* 2010;71:587-598.
45. Kramer M, Litman R, Hough D, Lane R, Lim P, Liu Y, Eerdeken M. Paliperidone palmitate, a potential long-acting treatment for patients with schizophrenia. Results of a randomized, double-blind, placebo-controlled efficacy and safety study. *International Journal of Neuropsychopharmacology.* 2010;13:635-647.
46. Nasrallah HA, Gopal S, Gassmann-Mayer C, Quiroz JA, Lim P, Eerdeken M, Yuen E, Hough D. A controlled, evidence-based trial of paliperidone palmitate, a long-acting injectable antipsychotic, in schizophrenia. *Neuropsychopharmacology.* 2010;35:2072-2082.
47. Gopal S, Hough DW, Xu H, Lull JM, Gassmann-Mayer C, Remmerie BM, Eerdeken MH, Brown DW. Efficacy and safety of paliperidone palmitate in adult patients with acutely symptomatic schizophrenia: a randomized, double-blind, placebo-controlled, dose-response study. *International clinical psychopharmacology.* 2010;25:247-256.
48. Pandina GJ, Lindenmayer J-P, Lull J, Lim P, Gopal S, Herben V, Kusumakar V, Yuen E, Palumbo J. A randomized, placebo-controlled study to assess the efficacy and safety of 3 doses of paliperidone palmitate in adults with acutely exacerbated schizophrenia. *Journal of clinical psychopharmacology.* 2010;30:235-244.
49. Arvanitis LA, Miller BG, group Sts. Multiple fixed doses of "Seroquel" (quetiapine) in patients with acute exacerbation of schizophrenia: a comparison with haloperidol and placebo. *BiolPsychiatry.* 1997;42:233-246.
50. Cutler AJ, Tran-Johnson T, Kalali A, Astrom M, Brecher M, Meulien D. A failed 6-week, randomized, double-blind, placebo-controlled study of once-daily extended release quetiapine fumarate in patients with acute schizophrenia: lessons learned. *Psychopharmacol Bull.* 2010;43:37-69.
51. Kahn RS, Schulz SC, Palazov VD, Reyes EB, Brecher M, Svensson O, Andersson HM, Meulien D. Efficacy and tolerability of once-daily extended release quetiapine fumarate in acute schizophrenia: a randomized, double-blind, placebo-controlled study. *JClinPsychiatry.* 2007;68:832-842.
52. Lindenmayer JP, Brown D, Liu S, Brecher M, Meulien D. The efficacy and tolerability of once-daily extended release quetiapine fumarate in hospitalized patients with acute schizophrenia: a 6-week randomized, double-blind, placebo-controlled study. *PsychopharmacolBull.* 2008;41:11-35.
53. Chouinard G, Jones B, Remington G. Canadian placebo-controlled study of fixed doses of risperidone and haloperidol in the treatment of chronic schizophrenic patients. *JClinPsychopharmacol.* 1993;13:25-40.
54. Marder SR, Meibach RC. Risperidone in the treatment of schizophrenia. *AmJPsychiatry.* 1994;151:825-835.
55. Peuskens J, Group. RS. Risperidone in the treatment of patients with chronic schizophrenia: a multi-national, multi-centre, double-blind, parallel-group study versus haloperidol. *BrJPsychiatry.* 1995;166:712-726.
56. 1996 SR-U-. Office of Clinical pharmacology and biopharmacy review. NDA number: 20272. Janssen-Cilag, data on file. 1996.

57. Kane JM, Eerdeken M, Lindenmayer J-P, Keith SJ, Lesem M, Karcher K. Long-acting injectable risperidone: efficacy and safety of the first long-acting atypical antipsychotic. *American Journal of Psychiatry*. 2003.
58. Hale A, Azorin JM, Kasper S, Maier W, Syvalahti E, van der Burght M, Sloth-Nielsen M, Wehnert A. Sertindole improves both the positive and negative symptoms of schizophrenia: Results of a phase III trial. *IntJPsychClinPract*. 2000;4:55-62.
59. van Kammen DP. A randomized, controlled, dose-ranging trial of sertindole in patients with schizophrenia. *Psychopharmacology*. 1996;124:168-175.
60. Zborowski J, Schmitz P, Staser J, O'Neil J, Giles K, Wallin B, Sebree T, Tamminga C. Efficacy and safety of sertindole in a trial of schizophrenic patients. *BiolPsychiatry*. 1995;37:661-662.
61. Daniel DG, Zimbroff DL, Potkin SG, Reeves KR, Harrigan EP, Lakshminarayanan M. Ziprasidone 80 mg/day and 160 mg/day in the acute exacerbation of schizophrenia and schizoaffective disorder: A 6-week placebo-controlled trial. *Neuropsychopharmacology*. 1999;20:491-505.
62. Goff DC, Posever T, Herz L, Simmons J, Kletti N, Lapierre K, Wilner KD, Law CG, Ko GN. An exploratory haloperidol-controlled dose-finding study of ziprasidone in hospitalized patients with schizophrenia or schizoaffective disorder. *JClinPsychopharmacol*. 1998;18:296-304.
63. Keck P, Buffenstein A, Ferguson J, Feighner J, Jaffe W, Harrigan EP, Morrissey MR. Ziprasidone 40 and 120 mg/day in the acute exacerbation of schizophrenia and schizoaffective disorder: a 4-week placebo controlled trial. *Psychopharmacology*. 1998;140:173-184.
64. 2000 S. Center for drug evaluation and research approval package for application number 20-825. Medical review. <http://wwwfdagov>. 2000.
65. Pharmaceuticals K. A multicentre, double-blind, placebo-controlled, parallel-group, dose-ranging study to evaluate the efficacy, safety and tolerability of zotepine 75, 150 and 300mg daily doses in the treatment of acute schizophrenia. Study Reference No BPI 1201. 1996.

Supplementary Figure S2

**Assessment with the Cochrane risk of bias tool
(Risk of bias summary and risk of bias graph)**

Risk of bias summary: judgements about each bias item for each study

| | Random sequence generation (selection bias) | Allocation concealment (selection bias) | Blinding of participants and personnel (performance bias) | Blinding of outcome assessment (detection bias) | Incomplete outcome data (attrition bias) | Selective reporting (reporting bias) | Other bias |
|-----------------------|---|---|---|---|--|--------------------------------------|------------|
| Arvanitis et al. 1997 | ? | ? | ? | ? | + | + | + |
| Beasley et al. 1996a | + | + | + | + | + | + | + |
| Beasley et al. 1996b | + | + | ? | ? | + | + | + |
| Beasley et al. 1997 | + | + | + | + | + | + | + |
| Boyer et al. 1995 | + | + | ? | ? | - | - | + |
| Canuso et al. 2010 | ? | + | + | + | + | + | + |
| Chouinard et al. 1993 | ? | ? | + | + | + | + | + |
| Coppola et al. 2011 | + | + | + | + | + | + | + |
| Correll et al. 2015 | + | ? | ? | ? | + | + | + |
| Cutler et al. 2006 | ? | ? | + | + | + | + | + |
| Cutler et al. 2010 | ? | ? | + | + | + | + | + |
| Daniel et al. 1999 | + | ? | ? | ? | + | + | + |
| Danion et al. 1999 | ? | ? | ? | ? | + | + | + |
| Davidson et al. 2007 | + | + | + | + | + | + | + |
| Durgam et al. 2014 | ? | ? | ? | ? | + | + | + |
| Goff et al. 1998 | ? | ? | ? | ? | + | + | + |

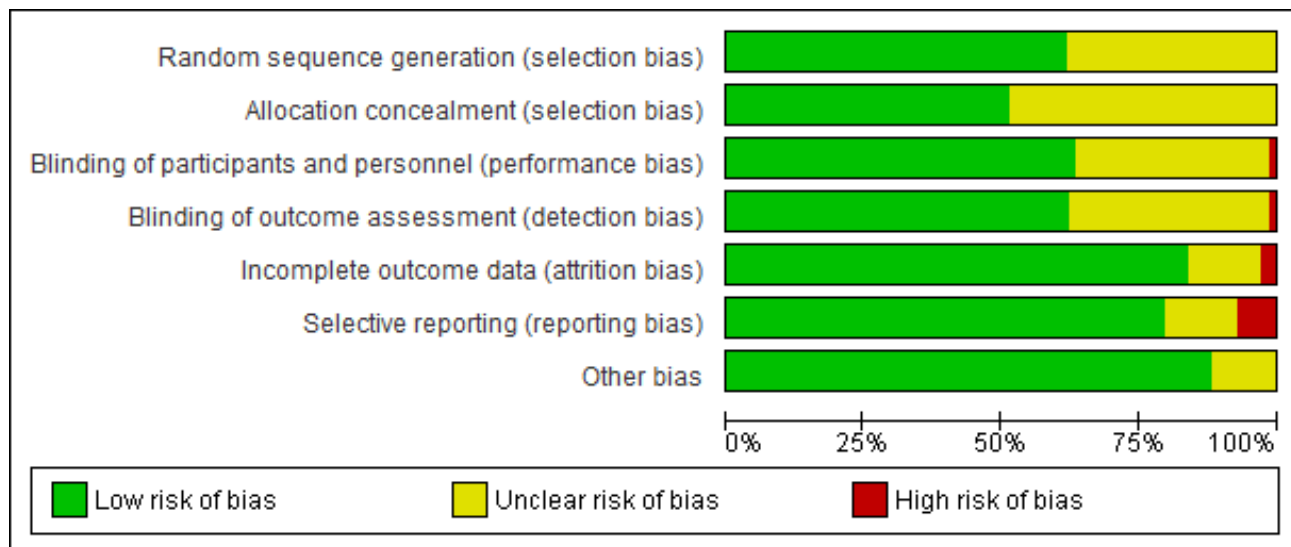
Risk of bias summary: judgements about each bias item for each study (cont.)

| | | | | | | | |
|-----------------------------------|---|---|---|---|---|---|---|
| Gopal et al. 2010 NCT00210548 | + | + | + | + | + | + | + |
| Hale et al. 2000 | + | + | + | + | + | + | + |
| Hera 041-021 | ? | ? | + | ? | ? | ? | ? |
| Ishigooka et al. 2018 | + | + | ? | ? | + | + | + |
| Kahn et al. 2007 | ? | ? | + | + | + | + | + |
| Kane et al. 2002 | ? | ? | ? | ? | + | + | + |
| Kane et al. 2003 NCT00253136 | + | + | + | + | + | + | + |
| Kane et al. 2007 | + | + | + | + | + | + | + |
| Kane et al. 2010 | ? | ? | + | + | ? | + | + |
| Kane et al. 2015 | + | + | + | + | + | + | + |
| Keck et al. 1998 | + | ? | ? | ? | + | + | + |
| Knoll | ? | ? | ? | ? | ? | ? | ? |
| Kramer et al. 2010 NCT00074477 | + | + | - | - | + | + | + |
| Lauriello et al. 2008 | + | + | ? | ? | + | + | + |
| Lecrubier et al. 2006 | + | + | + | + | - | - | ? |
| Lindenmayer et al. 2008 | + | + | + | + | + | + | + |
| Loebel et al. 2013 | + | + | + | + | + | + | + |
| Loebel et al. 2016 | + | + | + | + | + | + | + |
| Marder et al. 1994 | + | ? | + | + | + | + | + |
| Marder et al. 2007 | + | + | + | + | + | + | + |
| McEvoy et al. 2007 | + | + | + | + | + | + | + |
| Meltzer et al. 2011 | + | + | + | + | + | + | + |
| Meltzer et al. 2015 | ? | ? | + | + | + | + | + |
| Nasrallah et al. 2010 NCT00101634 | + | + | + | + | + | + | + |
| Nasrallah et al. 2013 | + | + | + | + | + | + | + |
| NCT00905307 Correll et al. 2016 | + | + | + | + | + | + | + |
| NCT01098110 Kinoshita et al. 2016 | + | ? | + | + | + | + | + |
| NCT01104766 Durgam et al. 2015 | ? | ? | ? | ? | + | + | + |

Risk of bias summary: judgements about each bias item for each study (cont.)

| | + | ? | + | + | + | + | + |
|------------------------------------|---|---|---|---|---|---|---|
| NCT01617187 Landbloom et al. 2017 | + | ? | + | + | + | + | + |
| Ogasa et al. 2012 | + | + | + | + | + | + | + |
| Pandina et al. 2010 NCT00590577 | + | + | + | + | ? | ? | + |
| Peuskens et al. 1995 | + | + | + | + | + | + | + |
| Potkin et al. 2003 | ? | ? | ? | ? | + | - | + |
| Potkin Study 3000 2008 | + | + | + | + | + | + | + |
| Potkin Study 3004 2008 | + | + | + | + | + | + | + |
| Potkin Study 3005 2008 | + | + | + | + | + | + | + |
| Puech et al. 1998 | + | + | + | + | + | + | + |
| Simpson et al. 1999 | ? | ? | + | + | ? | - | ? |
| Study 041-002 | ? | ? | + | + | + | + | + |
| Study 041-013 | ? | ? | ? | ? | ? | ? | ? |
| Study 049 | + | + | + | + | + | + | + |
| Study 104 2000 | ? | ? | ? | ? | ? | ? | ? |
| Study 115 2000 | + | ? | ? | ? | + | ? | + |
| Study 94202 2002 | ? | ? | + | + | + | + | + |
| Study ILPB202 | ? | ? | ? | ? | ? | ? | ? |
| Study NCT00711269 | ? | ? | ? | ? | ? | ? | ? |
| Study RGH-MD-03 Durgam et al. 2016 | ? | ? | ? | ? | + | ? | + |
| Study RGH-MD-05 Kane et al. 2015 | ? | ? | ? | ? | + | + | + |
| Study RIS-USA-72 1996 | ? | ? | + | + | + | + | + |
| van Kammen et al. 1996 | + | ? | ? | ? | + | + | + |
| Zborowski et al. 1995 | + | + | + | + | + | + | + |
| Zimbroff et al. 1997 | + | + | ? | ? | + | - | + |

Risk of bias graph: review authors' judgements (Low, Unclear and High) about each risk of bias item presented as percentages across all included studies.

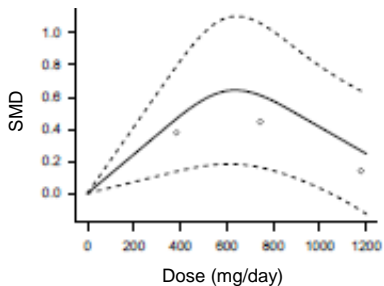


Supplementary Figure S3

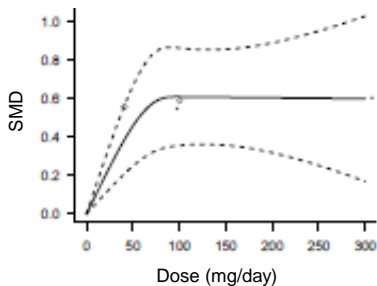
Sensitivity analyses

Sensitivity analysis 1: Including low-dose comparator groups. Drugs with new data are highlighted by bolt print

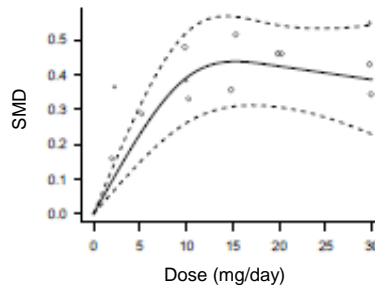
a) Amisulpride positive symptoms (N=1)



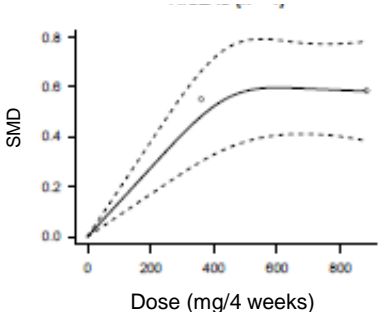
b) Amisulpride predominant negative symptoms (N=1)



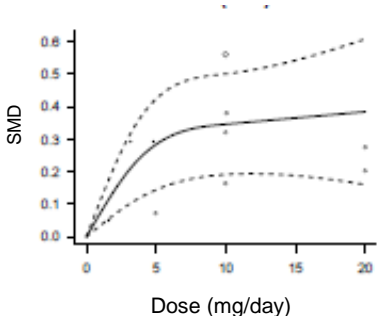
c) Aripiprazole oral (N=5)



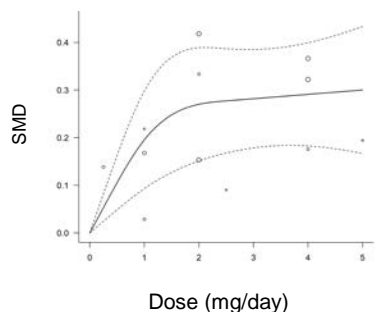
d) Aripiprazole LAI (lauroxil) (N=1)



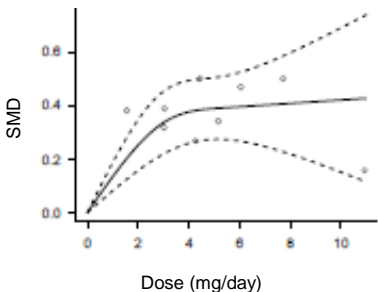
e) Asenapine (N=6)



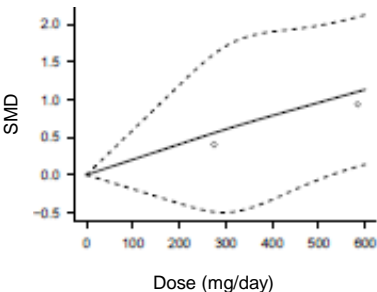
f) Brexpiprazole (N=4)



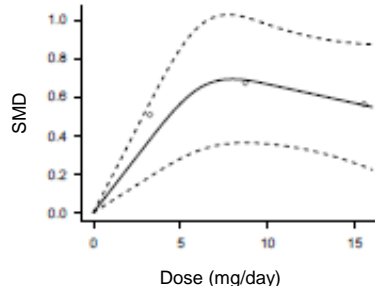
g) Cariprazine (N=4)



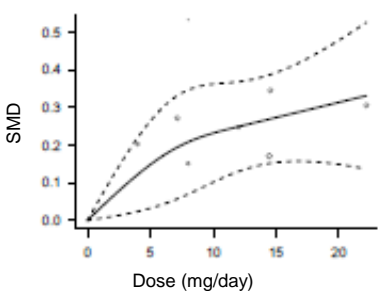
h) Clozapine (N=1)



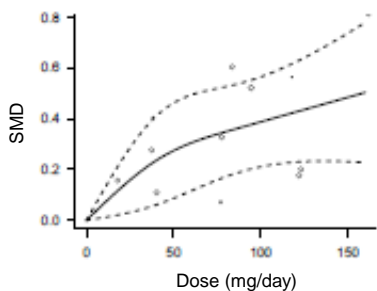
i) Haloperidol (N=1)



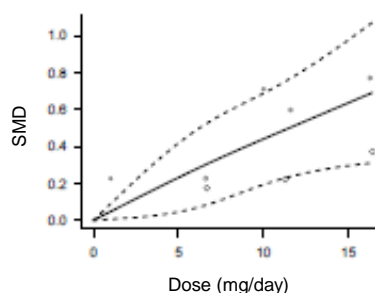
j) Iloperidone (N=4)



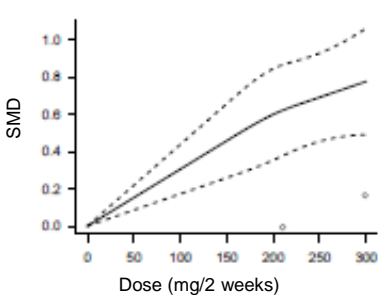
k) Lurasidone (N=6)



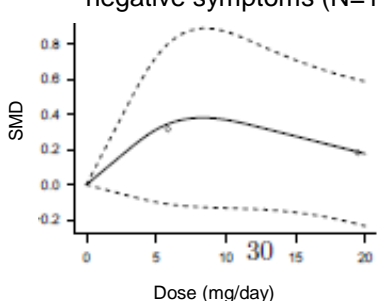
l) Olanzapine oral (N=3)



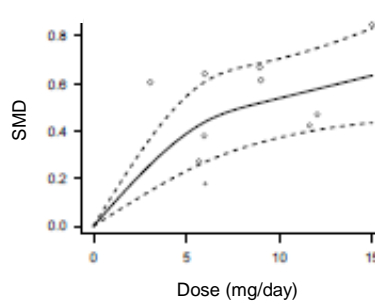
m) Olanzapine LAI (N=1)



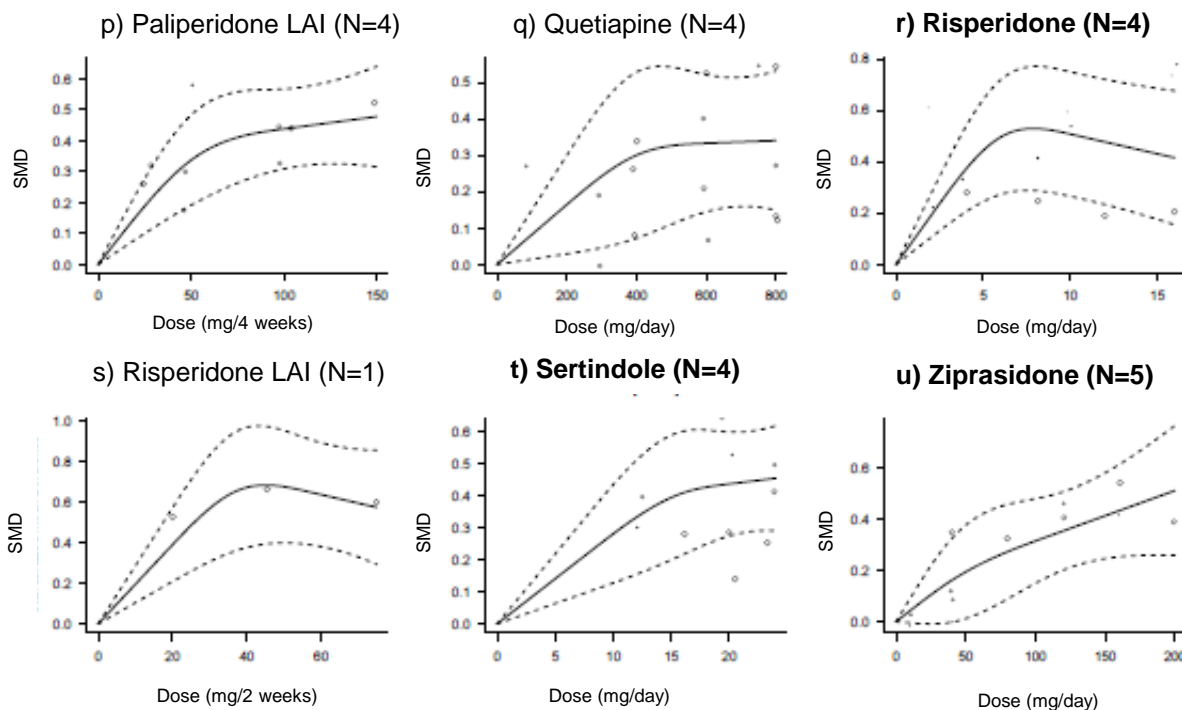
n) Olanzapine predominant negative symptoms (N=1)



o) Paliperidone oral (N=5)



Sensitivity analysis 1 (cont.): Including studies with low-dose comparator groups

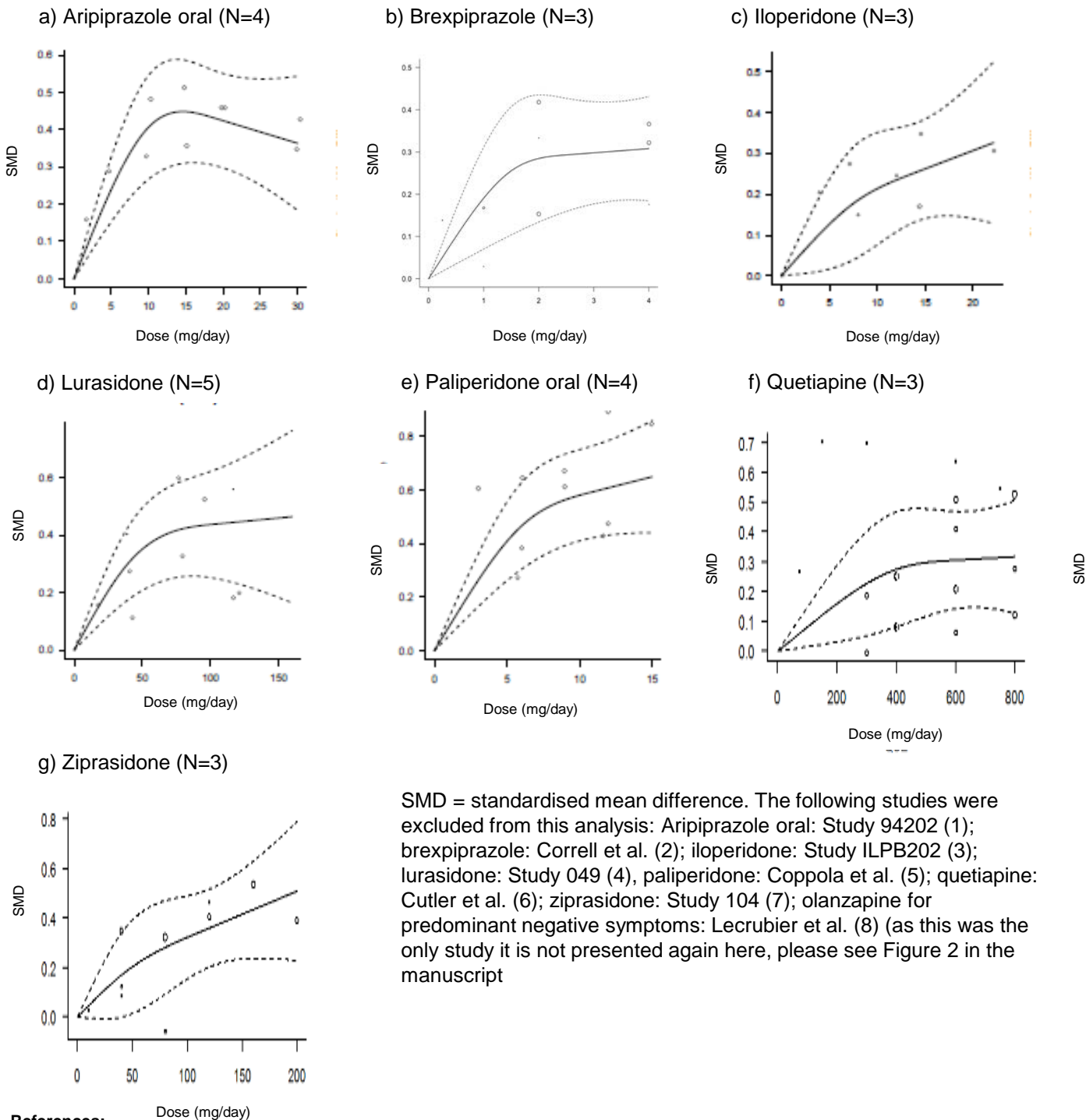


SMD = standardised mean difference. Drugs with additional studies available for this analysis are presented in bolt print. The additional studies are. For a) amisulpride in patients with positive symptoms Puech et al. (1) which used amisulpride 100mg/day as comparator, h) clozapine: Simpson et al. (2), which used clozapine 100mg/day as comparator l) olanzapine oral: Beasley et al. 1997 (3) which used olanzapine 1mg/day as comparator, t) sertindole: Hale et al. 2000 (4) which used sertindole 8mg/day as comparator, u) ziprasidone: Goff et al. (5) which used ziprasidone 4mg/day as comparator. For all other drugs no further studies could be identified

References

1. Puech A, Fleuret O, Rein W. Amisulpride, an atypical antipsychotic, in the treatment of acute episodes of schizophrenia: a dose-ranging study vs. haloperidol. *Acta Psychiatr Scand.* 1998;98:65-72.
2. Simpson GM, Josiassen RC, Stanilla JK, De Leon J, Nair C, Abraham G, Odom WA, Turner RM. Double-blind study of clozapine dose response in chronic schizophrenia. *AmJPsychiatry.* 1999;156:1744-1750.
3. Beasley CM, Hamilton SH, Crawford AM et al., Blin O, Beuzen J-N. Olanzapine versus haloperidol: acute phase results of the international double-blind olanzapine trial. *EurNeuropsychopharmacol.* 1997;7:125-137.
4. Hale A, Azorin JM, Kasper S, Maier W, Syvalahti E, van der Burght M, Sloth-Nielsen M, Wehnert A. Sertindole improves both the positive and negative symptoms of schizophrenia: Results of a phase III trial. *IntJPsychClinPract.* 2000;4:55-62.
5. Goff DC, Posever T, Herz L, Simmons J, Kletti N, Lapierre K, Wilner KD, Law CG, Ko GN. An exploratory haloperidol-controlled dose-finding study of ziprasidone in hospitalized patients with schizophrenia or schizoaffective disorder. *JClinPsychopharmacol.* 1998;18:296-304.

Sensitivity analysis 2: excluding failed studies



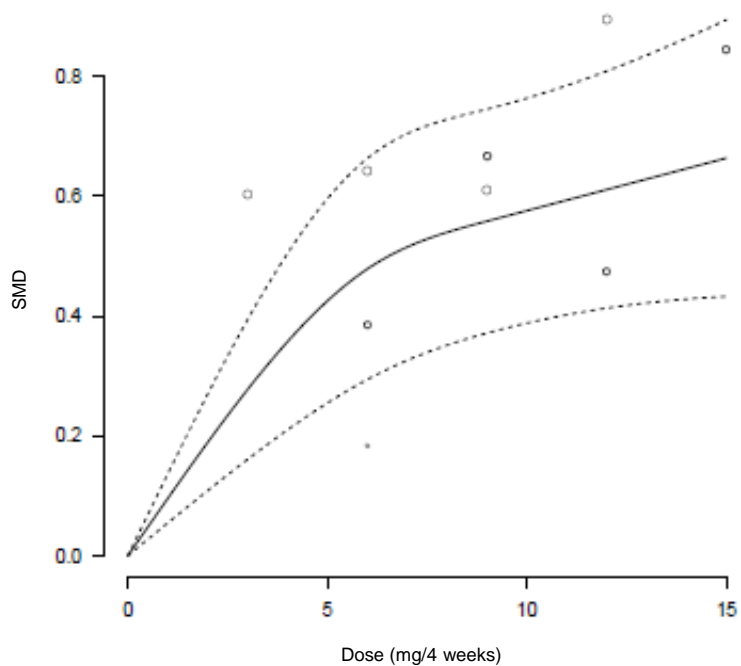
SMD = standardised mean difference. The following studies were excluded from this analysis: Aripiprazole oral: Study 94202 (1); brexpiprazole: Correll et al. (2); iloperidone: Study ILPB202 (3); lurasidone: Study 049 (4), paliperidone: Coppola et al. (5); quetiapine: Cutler et al. (6); ziprasidone: Study 104 (7); olanzapine for predominant negative symptoms: Lecrubier et al. (8) (as this was the only study it is not presented again here, please see Figure 2 in the manuscript)

References:

- 94202 S. Center for drug evaluation and research. Application number 21-436. Medical review(s). www.fda.gov. 2002.
- Correll CU, Skuban A, Hobart M et al. Efficacy of brexpiprazole in patients with acute schizophrenia: Review of three randomized, double-blind, placebo-controlled studies. *Schizophrenia research*. 2016;174:82-92.
- Study ILPB202 FDA. Drug Approval Package. Fanapt (iloperidone) Tablets. 12 June 2009.
- Study 049 S. A 6-week, double-blind, randomized, fixed dose, parallel-group study of the efficacy and safety of three dose levels of SM-13496 (lurasidone) compared to placebo and haloperidol in patients with schizophrenia who are experiencing an acute exacerbation of symptoms. Center for drug evaluation and research Application number 200603 Medical review(s) <http://www.fda.gov>. 2010.
- Coppola D, Melkote R, Lannie C et al.. Efficacy and safety of paliperidone extended release 1.5 mg/day - a double-blind, placebo- and active-controlled, study in the treatment of patients with schizophrenia. *Psychopharmacol Bull*. 2011;44:1-19.
- Cutler AJ, Tran-Johnson T, Kalali A, et al. A failed 6-week, randomized, double-blind, placebo-controlled study of once-daily extended release quetiapine fumarate in patients with acute schizophrenia: lessons learned. *Psychopharmacol Bull*. 2010;43:37-69.
- 104 S. Center for drug evaluation and research approval package for application number 20-825. Medical review. <http://www.fda.gov>. 1998.
- Lecrubier Y, Quintin P, Bouhassira M, et al. The treatment of negative symptoms and deficit states of chronic schizophrenia: olanzapine compared to amisulpride and placebo in a 6-month double-blind controlled clinical trial. *Acta psychiatrica Scandinavica*: 319-327

Sensitivity analysis 3: Excluding studies which were restricted to patients with schizoaffective disorder (this applied only to oral paliperidone)

Paliperidone oral (N=4)

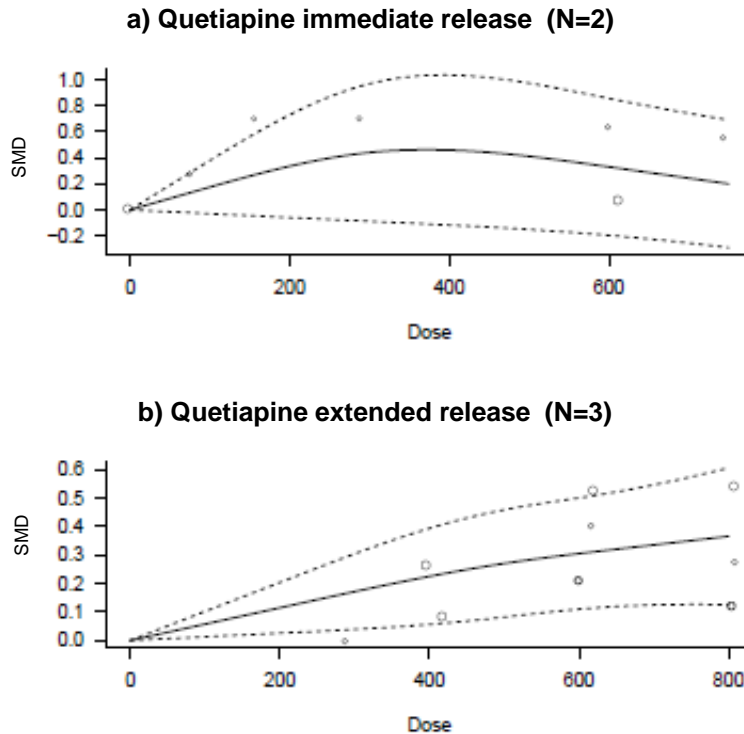


SMD = standardised mean difference. The following studies in patients with schizoaffective disorder were excluded from the analysis: Canuso et al. 2010 (1)

Reference:

1. Canuso CM, Lindenmayer JP, Kosik-Gonzalez Cet al. (1). A randomized, double-blind, placebo-controlled study of 2 dose ranges of paliperidone extended-release in the treatment of subjects with schizoaffective disorder. *J Clin Psychiatry*. 2010;71:587-598

Sensitivity analysis 4: Quetiapine immediate release and quetiapine extended release presented separately



The study included in the quetiapine immediate release analysis was: Arvanitis et al. (1), Lindenmayer et al. (2). Those included in the quetiapine extended release analyse were: Cutler et al. (3), Kahn et al. (4), Lindenmayer et al (2)

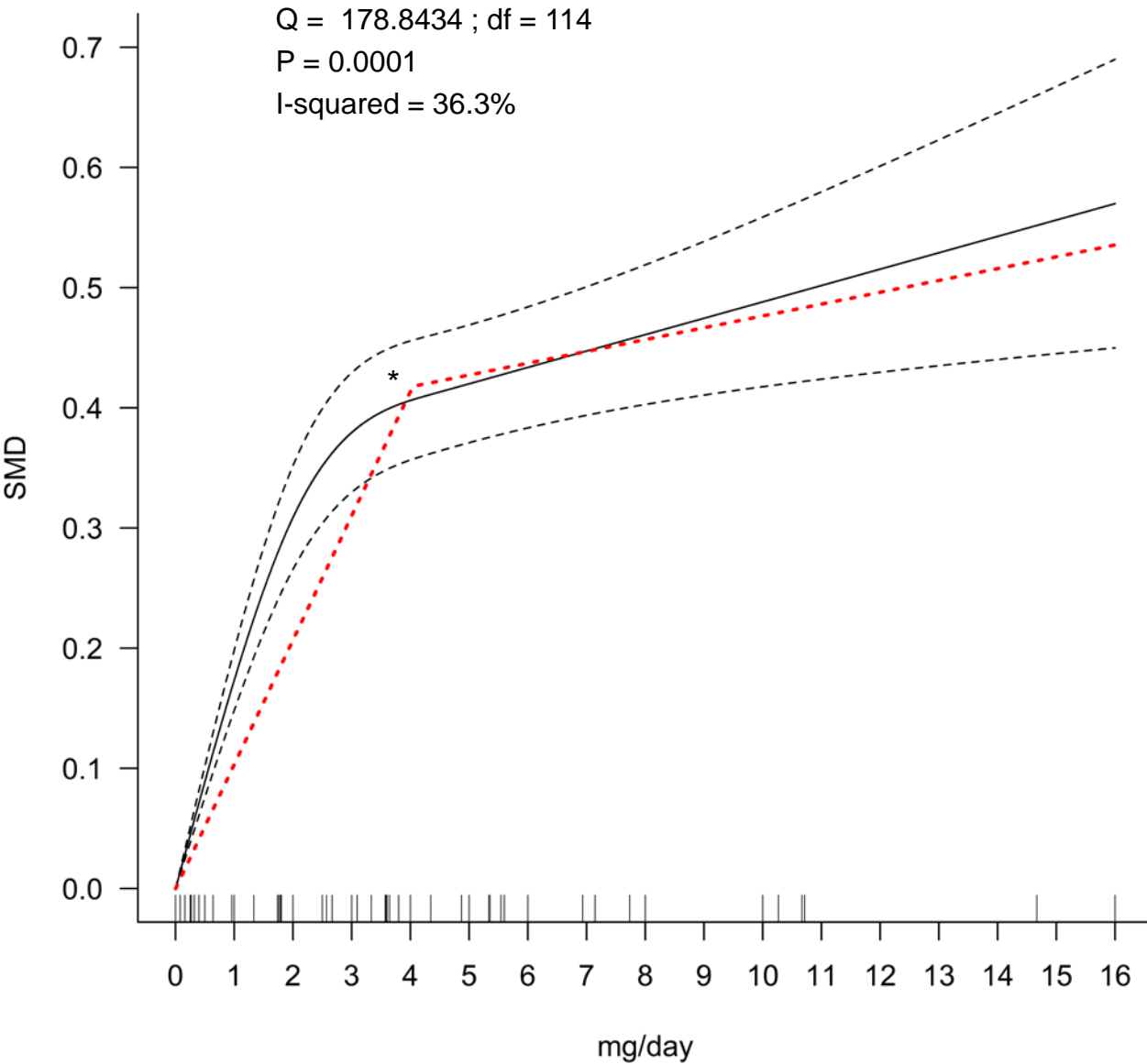
References

1. Arvanitis LA, Miller BG, group Sts. Multiple fixed doses of "Seroquel" (quetiapine) in patients with acute exacerbation of schizophrenia: a comparison with haloperidol and placebo. *BiolPsychiatry*. 1997;42:233-246
2. Lindenmayer JP, Brown D, Liu S, Brecher M, Meulien D. The efficacy and tolerability of once-daily extended release quetiapine fumarate in hospitalized patients with acute schizophrenia: a 6-week randomized, double-blind, placebo-controlled study. *Psychopharmacol Bull*. 2008;41:11-35.
3. Cutler AJ, Tran-Johnson T, Kalali A, Astrom M, Brecher M, Meulien D. A failed 6-week, randomized, double-blind, placebo-controlled study of once-daily extended release quetiapine fumarate in patients with acute schizophrenia: lessons learned. *Psychopharmacol Bull*. 2010;43:37-69
4. Kahn RS, Schulz SC, Palazov VD, Reyes EB, Brecher M, Svensson O, Andersson HM, Meulien D. Efficacy and tolerability of once-daily extended release quetiapine fumarate in acute schizophrenia: a randomized, double-blind, placebo-controlled study. *JClinPsychiatry*. 2007;68:832-842.

Sensitivity analysis 5: Dose-response curve across drugs with doses converted to risperidone equivalents based on the minimum effective dose method

ED50: 1.78
ED95: 13.90
Dose p = 0.1 : 4.04

Heterogeneity
Q = 178.8434 ; df = 114
P = 0.0001
I-squared = 36.3%



*The knot in the red dotted curve is the dose (4.0 mg risperidone/day) above which the slope was not longer significantly increasing ($p > 0.1$)