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APPENDICES ONLY

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A systematic review of atypical antipsychotic drugs in schizophrenia

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Health Technology Assessment
NHS R&D HTA Programme

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Appendix 1

Literature search strategy (including MeSH terms) used for identification of studies from electronic databases

Search of conference proceedings

The following conference proceedings and abstracts/posters were identified.

11th European College of Neuropsychopharmacology Congress: published in *Eur Neuropsychopharmacol* 1998;**8** Suppl 2. This journal issue was handsearched.

12th European College of Neuropsychopharmacology Congress: published in *Eur Neuropsychopharmacol* 1999;**9** Suppl 5. This journal issue was handsearched.

13th European College of Neuropsychopharmacology Congress: published in *Eur Neuropsychopharmacol* 2000;**10** Suppl 3, and searchable on the Internet. The Internet database was searched for each named drug at: http://ex2.excerptamedica.com/00ecnp

7th International Congress of Schizophrenia Research: published in *Schizophr Res* 1999;**36**(1/3) (indexed by several of the databases searched).

8th International Congress of Schizophrenia Research: published in *Schizophr Res* 2001;**49**(15) (indexed by several of the databases searched).

151st and 152nd Annual Meetings of the American Psychiatric Association: these were indexed by databases and the records retrieved. The proceedings/abstracts of the most recent meeting were available on CD-ROM and the Association's web master agreed to send us a copy: however, as yet, this has not arrived.

21st meeting of the Collegium Internationale Neuro-psychopharmacologicum: the abstracts were indexed by some of the large databases searched and published in *Int J Neuropsychopharmacol* 1998; **1** Suppl 1; posters were published in March 1999 issue of the journal.

22nd meeting of the Collegium Internationale Neuro-psychopharmacologicum: abstracts were available as an Internet database, which was searched using each drug name individually. Available from: http://ex2.excerptamedica.com/00cinp

9th Congress of the Association of European Psychiatrists: abstracts were published in *Eur Psychiatry* 1998;**13** Suppl 4 and indexed by several of the databases searched.

10th Congress of the Association of European Psychiatrists: abstracts were published in *Eur Psychiatry* 2000;**15** Suppl 2 and indexed by several of the databases searched.

Search of selected project registers

The National Research Register, Issue 2001/1, was searched on 18 April 2001 using the search strategy:

amisulp* or clozapine or olanzapine or quetiapine or risperidone or sertindole or ziprasidone or zotepine

The meta Register of Controlled Trials offered by Current Controlled Trials (available at: http://www.controlled-trials.com/) was searched on 7 June 2001. Apart from National Research Register projects that had been identified in the previous search, three American projects were found.

The main drug terms were searched individually, viz:

amisulpirid
amisulpiride
amisulpride
clozapine
olanzapine
quetiapine
risperidone
sertindole
ziprasidone
zotepine.

Search for RCTS

Cochrane Controlled Trials Register

Issue 2001/1 of the Cochrane Library was searched on 11 April 2001. The search was limited to publications with a date of 1998 or later and 420 records were retrieved.

1. (((((((AMISULPIRIDE or AMISULPRID) or AMISULPRIDE) or SOLIAN) or DENIBAN) OR (AMINO next SULTOPRIDE)) OR AST) OR DAN2163) OR SOCIAN) OR SULAMID)
2. (((CLOZAPINE or W108) or LX100129) or HF1854)
3. CLOZAPINE*:ME
4. ((OLANZAPINE or ZYPREX) or LANZAC)
5. ((QUETIAPINE or ICI204636) or SEROQUEL)
6. (((((RISPERIDONE or R64766) or RISPERDAL) or RISPOLIN) or BELIVON) or RISPERIN)
7. RISPERIDONE*:ME
8. (((SERTINDOLE or SERDOLECT) or SERLECT) or LU23174)
9. (((ZIPRASIDONE or BENZOTHIAZOLYLPIPERAZINE) or CP88059) or CP880591)
10. (((((((ZOTEPINE or DIBENZOTHIAPINE) or NIPOLEPT) or LODOPIN) or ZOLEPTIL) or SOPITE) or SETONS) or MAJORPIN)
11. (((((((((#1 or #2) or #3) or #4) or #5) or #6) or #7) or #8) or #9) or #10)
12. ((SCHIZOPHRENI* or PSYCHOTIC) or PSYCHOSIS)
13. ((HEBEPHRENI* or OLIGOPHRENI*) or PSYCHOSES)
14. (((CHRONIC next MENTAL) or (SEVERE next (MENTAL next ILL*))) OR (SEVERE NEXT (MENTAL NEXT DISORDER*)))
15. ((SEVERELY next (MENTAL* next ILL*)) or (SEVERELY next (MENTAL* next DISORDER*)))
16. SCHIZOPHRENIA-AND-DISORDERS-WITH-PSYCHOTIC-F*:ME
17. PSYCHOTIC-DISORDERS*:ME
18. SCHIZOPHRENIA*:ME
19. ((((((#12 or #13) or #14) or #15) or #16) or #17) or #18)
20. (#11 and #19)

Biological Abstracts (1988 onwards)

Searched 20 April 2001, using the EDINA telnet version of Biosis for the years 1998–2001, to the update of 11 April 2001.

1. title,desc1,desc2,abst(amisulpirid* or amisulpride or clozapine or olanzapine or quetiapine)
2. title,desc1,desc2,abst(risperidone or sertindole or ziprasidone or zotepine)
3. title,desc1,desc2,abst(schizophren* or psychosis or psychotic or psychoses or hebephrenic*)
4. 1 or 2
5. 3 and 4
6. title,desc1,desc2,abst(trial* or placebo* or control or controlled or controls)
7. title,desc1,desc2,abst(blind or blinded or study or random*)
8. 5 and (6 or 7)

MEDLINE

The SilverPlatter version of MEDLINE was searched on 11 April 2001. Records added to the database since the last update (1997) were searched (up to 2000/12) and 507 records were retrieved.

1. exact{RANDOMIZED-CONTROLLED-TRIAL} in PT
2. 'Random-Allocation'
3. 'Randomized-Controlled-Trials'/ all subheadings
4. 'Double-Blind-Method'
5. 'Single-Blind-Method'
6. explode 'Clinical-Trials'/ all subheadings
7. 'Placebos'/ all subheadings
8. 'Research-Design'/ all subheadings
9. explode 'Evaluation-Studies'/ all subheadings
10. 'Follow-Up-Studies'
11. 'Prospective-Studies'
12. #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11
13. exact{CLINICAL-TRIAL} in PT
14. clin* near (trial* in ti,ab)
15. (singl* or doubl* or trebl* or tripl*) near ((blind* or mask*) in ti,ab)
16. placebo* in ti,ab
17. random* in ti,ab
18. (control or controls or controlled) in ti,ab
19. (prospectiv* or allocat*) in ti,ab
20. #1 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19
21. (amisulpirid or amisulpiride or amisulpride or solian or deniban or amino sultopride or ast or dan2163 or socian or sulamid) in ti,ab
22. (clozapine or w108 or lx100129 or hf1854) in ti,ab
23. (olanzapine or zyprex or lanzac) in ti,ab
24. (quetiapine or ici204636 or seroquel) in ti,ab
25. (risperidone or R64766 or risperdal or rispolin or belivon or risperin) in ti,ab
26. (sertindole or serdolect or serlect or lu23174) in ti,ab

27. (ziprasidone or benzothiazolylpiperazine or cp88059 or cp880591) in ti,ab
28. (zotepine or dibenzothiapine or nipolept or lodopin or zoleptil or sopite or setons or majorpin) in ti,ab
29. 'Clozapine'/ all subheadings
30. 'Risperidone'/ all subheadings
31. #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30
32. #20 and #31
33. #32 and (UD > '199712')
34. explode 'Schizophrenia-and-Disorders-with-Psychotic-Features'/ all subheadings
35. (schizophren* or hebephreni* or oligophreni* or psychotic or psychosis or psychoses) in ti,ab
36. chronic mental illness
37. chronically mentally ill
38. chronic mentally ill
39. severe mental illness
40. severely mentally ill
41. #34 or #35 or #36 or #37 or #38 or #39 or #40
42. #33 and #41
43. exact{ANIMAL} in TG
44. exact{HUMAN} in TG
45. #43 not (#43 and #44)
46. #43 not #45

EMBASE

The SilverPlatter version of EMBASE was searched on 11 April 2001. The database was searched for all updates since 1998 and up to 2001/2; 1169 records were retrieved.

1. explode 'clinical-trial'/ all subheadings
2. 'double-blind-procedure'/ all subheadings
3. 'single-blind-procedure'/ all subheadings
4. 'crossover-procedure'/ all subheadings
5. 'evaluation'/ all subheadings
6. 'follow-up'/ all subheadings
7. 'prospective-study'/ all subheadings
8. 'clinical-article'/ all subheadings
9. 'major-clinical-study'/ all subheadings
10. 'prospective-study'/ all subheadings
11. 'placebo'/ all subheadings
12. 'randomization'/ all subheadings
13. #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12
14. explode 'comparative-study'/ all subheadings
15. 'meta-analysis'/ all subheadings
16. #14 or #15
17. ((intervention or clinical*) near (trial* or study or studies)) in ti,ab
18. (random* or placebo* or rct*) in ti,ab
19. ((singl* or doubl* or trebl* or tripl*) with (blind* or mask*)) in ti,ab
20. explode 'controlled-study'/ all subheadings
21. ((control or controls or controlled) with (trial* or study or studies)) in ti,ab
22. ((multi or multic*) with (trial* or study or studies)) in ti,ab
23. ((cross over or crossover or evaluation or prospectiv*) with (trial* or study or studies)) in ti,ab
24. ((follow or follow-up or followup) with (studies or study or trial*)) in ti,ab
25. #13 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24
26. 'amisulpride'/ all subheadings
27. 'clozapine'/ all subheadings
28. 'olanzapine'/ all subheadings
29. 'quetiapine'/ all subheadings
30. 'risperidone'/ all subheadings
31. 'sertindole'/ all subheadings
32. 'ziprasidone'/ all subheadings
33. 'zotepine'/ all subheadings
34. #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33
35. (amisulp* or solian or deniban or amino sultopride or ast or dan2163 or socian or sulamid) in ti,ab
36. (clozapine or w108 or lx100129 or hf1854) in ti,ab
37. (olanzapine or zyprex or lanzac) in ti,ab
38. (quetiapine or ici204636 or seroquel) in ti,ab
39. (risperidone or R64766 or risperdal or rispolin or belivon or risperin) in ti,ab
40. (sertindole or serdolect or serlect or lu23174) in ti,ab
41. (ziprasidone or benzothiazolylpiperazine or cp88059 or cp880591) in ti,ab
42. (zotepine or dibenzothiapine or nipolept or lodopin or zoleptil or sopite or setons or majorpin) in ti,ab
43. (schizophren* or hebephreni* or oligophreni* or psychotic or psychosis or psychoses) in ti,ab
44. chronic mental illness
45. chronically mentally ill
46. chronic mentally ill
47. severe mental illness
48. severely mentally ill
49. explode 'schizophrenia'/ all subheadings
50. explode 'paranoid-psychosis'/ all subheadings
51. 'acute-psychosis'/ all subheadings
52. 'schizoaffective-psychosis'/ all subheadings
53. #49 or #50 or #51 or #52
54. #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42
55. #43 or #44 or #45 or #46 or #47 or #48 or #49 or #53
56. #25 and #54 and #55
57. exact{HUMAN}
58. exact{animal}

59. #58 not (#57 and #58)
60. #56 not #59

Dialog Onesearch

Dialog was searched on 17 April 2001 using the Onesearch option to search a range of databases. Results were de-duplicated against MEDLINE using Onesearch. Records were restricted to those added to the databases in updates during 1999, 2000 and 2001.

The following databases were searched, using the strategy described below.

MEDLINE® 1999–2001/Apr W3
Mental Health Abstracts 1999–2000/Jun
(this file is now closed)
ExtraMED™ 1999–2000/Dec
Pascal 1999–2001/Apr W3
CAB HEALTH 1999–2001/Feb
Conference Papers Index 1999–2001/Mar
Int.Pharm.Abs. 1999–2001/Mar
JICST-EPlus 1999–2001/Apr W1
NTIS 1999–2001/Apr W5
Derwent Drug File 1999–2001/Apr W5

Set	Items	Description
S1	138,987	DT=RANDOMIZED CONTROLLED TRIAL
S2	17,625	RANDOMIZED CONTROLLED TRIALS/DE
S3	41,819	RANDOM ALLOCATION/DE
S4	62,925	DOUBLE-BLIND METHOD/DE
S5	5,572	SINGLE-BLIND METHOD/DE
S6	298,363	DT=CLINICAL TRIAL
S7	90,282	CLINICAL TRIALS!/DE
S8	886,154	TRIAL OR TRIALS OR TRIALIST? OR PLACEBO
S9	204,213	(SINGL? OR DOUBL? OR TREBL? OR TRIPL?) (4W) (BLIND? OR MASK?)
S10	587,316	RANDOM?
S11	54,909	DT=CONTROLLED CLINICAL TRIAL
S12	67,859	CROSSOVER OR CROSSOVERS OR RCT OR RCTS
S13	1,391,172	S1:S12
S14	94,490	SCHIZOPHRENIA!/DE
S15	2,708	PARANOID DISORDERS!/DE
S16	170,865	SCHIZO? OR HEBEPHRENI? OR OLIGOPHRENI? OR PSYCHOTIC?
S17	84,912	PSYCHOSIS OR PSYCHOSES
S18	205,976	S14:S17
S19	557	SERTINDOLE OR SERDOLECT OR SERLECT
S20	834	ZIPRASIDONE OR BENZOTHIAZOLYLPIPERAZINE OR ZOTEPINE OR DIBENZOTHIAPINE OR NIPOLEPT
S21	7	LODOPIN OR ZOLEPTIL
S22	520	AMISULPIRIDE OR AMISULPRIDE OR SOLIAN OR DENIBAN
S23	15,414	OLANZAPINE OR RISPERIDONE OR CLOZAPINE
S24	10	LU23174 OR SERDOLECT
S25	0	CP88059 OR CP880591
S26	5,886	AMINO SULTOPRIDE OR AST OR DAN2163 OR SOCIAN OR DENIBAN OR SOLIAN OR SULAMID
S27	7	W108 OR LX100129 OR HF1854
S28	1	ZYPREX OR LANZAC
S29	103	R64766 OR RISPERDAL OR RISPOLIN OR BELIVON OR RISPERIN
S30	795	QUETIAPINE OR ICI204636 OR SEROQUEL
S31	22,490	S19:S30
S32	2681	S13 AND S18 AND S31
S33	2,975,828	UD=1999? OR UD=200?
S34	819	S32 AND S33
S35	617	RD S34 (unique items)

Datastar searches

The following databases on the Datastar service were searched on 19 April 2001 for publications from 1998 onwards.

ADIS Inpharma (21 records)
ADIS LMS Drug alerts (708 records)
IDIS Drug file (58 records)
Pharmline (42 records)
Pharma marketing (1 record)
British Library Inside Conferences (9 records)

The search strategy used in each database was the same:

1. SCHIZOPHREN$ OR PARANOIA OR PARANOID OR PSYCHOSIS OR PSYCHOTIC OR PSYCHOSES
2. TRIAL$ OR RCT$ OR RANDOM$ OR PLACEBO
3. (DOUBL$ OR SINGL$ OR TREBL$ OR TRIPL$) WITH BLIND$
4. CONTROL OR CONTROLS OR CONTROLLED
5. SERTINDOLE OR LU23174 OR SERDOLECT OR SERLECT
6. ZIPRASIDONE OR CP88059 OR CP88059-1
7. ZOTEPINE OR NIPOLEPT OR LODOPIN OR ZOLEPTIL OR ZOPITE OR SETONS OR MAJORPIN

8. AMISULPRIDE OR AMISULPIRIDE OR AMINO SULTOPRIDE OR AST OR DAN2163 OR SOCIAN OR DENIBAN OR SOLIAN OR SULAMID
9. CLOZAPINE OR W108 OR LX100129 OR HF1854
10. OLANZAPINE OR ZYPREX OR LANZAC
11. RISPERIDONE OR R64766 OR RISPERDAL OR RISPOLIN OR BELIVON OR RISPERIN
12. QUETIAPINE OR ICI204636 OR SEROQUEL
13. 2 OR 3 OR 4
14. 1 AND 13
15. 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12
16. 14 AND 15
17. LIMIT 16 PY GT 1997

PsycINFO

The BIDS WebSPIRS version of PsycINFO was searched on 11 April 2001. Updates to the database from 1 January 1998 to 28 March 2001 were searched and 1136 records retrieved.

(((amisulpiride or amisulprid or amisulpride or solian or deniban or amino sultopride or ast or dan2163 or socian or sulamid) or (clozapine or w108 or lx100129 or hf1854) or (olanzapine or zyprex or lanzac) or (quetiapine or ici204636 or seroquel) or (risperidone or r64766 or risperdal or rispolin or belivon or risperin) or (sertindole or serdolect or serlect or lu23174) or (ziprasidone or benzothiazolylpiperazine or cp88059 or cp880591) or (zotepine or dibenzothiapine or nipolept or lodopin or zoleptil or sopite or setons or majorpin))

and

(((CLINICAL-TRIAL in PT:PY) or (EMPIRICAL-STUDY in PT:PY) or (FOLLOWUP-STUDY in PT:PY) or (LITERATURE-REVIEW-RESEARCH-REVIEW in PT:PY) or (LONGITUDINAL-STUDY in PT:PY) or (META-ANALYSIS in PT:PY) or (PROGRAM-EVALUATION in PT:PY) or (PROSPECTIVE-STUDY in PT:PY) or (TREATMENT-OUTCOME-STUDY in PT:PY)) or (trial* in ti,ab) or ((random* or control or controls or controlled) in ti,ab) or (placebo* in ti,ab) or ((singl* or doubl* or tripl* or trebl*) with ((mask* or blind*) in ti,ab))))

and

((explode 'Psychosis-' in DE) or ((schizo* or psychosis or psychotic or psychoses) in ti,ab) or ((hebephreni* or oligophreni*) in ti,ab) or (chronic mental ill* in ti,ab) or (chronically mentally ill in ti,ab) or (chronic mental disorder* in ti,ab) or (severely mentally ill in ti,ab) or (severe mental illness in ti,ab))

and

(UD=19980101-20010328)

Economics studies

MEDLINE

MEDLINE is searched regularly for records to be added to the NHS Economic Evaluation Database with the sensitive search strategy shown below. The records so identified were searched for the named neuroleptic drugs and restricted to publications dated 1998 and later.

1. economics.sh.
2. exp 'costs and cost analysis'/
3. economic value of life.sh.
4. exp 'economics, dental'/
5. exp 'economics, hospital'/
6. exp 'economics, medical'/
7. exp 'economics, nursing'/
8. economics, pharmaceutical.sh.
9. exp 'fees and charges'/
10. exp 'budgets'/
11. (cost or costs or costed or costly or costing).ab,ti,kw,kp.
12. (economic$ or pharmacoeconomic$ or price$ or pricing).ab,ti,kw,kp.
13. or/1-12
14. letter.pt.
15. editorial.pt.
16. historical article.pt.
17. 14 or 15 or 16
18. 13 not 17
19. 'animal'/
20. 'human'/
21. 19 not (19 and 20)
22. 18 not 21

Dialog Onesearch

Dialog was searched on 2 May 2001 using the Onesearch option to search a range of databases. Results were de-duplicated against MEDLINE using Onesearch. Records were restricted to those published from 1998 onwards.

The following databases were searched, using the strategy described below.

MEDLINE® 1999–2001/Apr W3
Mental Health Abstracts 1999–2000/Jun
(this file is now closed)

ExtraMED(tm) 1999–2000/Dec
Pascal 1999–2001/Apr W3
CAB HEALTH 1999–2001/Feb
Conference Papers Index 1999–2001/Mar
Int.Pharm.Abs. 1999–2001/Mar
JICST-EPlus 1999–2001/Apr W1
NTIS 1999–2001/Apr W5
Derwent Drug File 1999–2001/Apr W5

1. s dt=randomized controlled trial
2. s randomized controlled trials/de
3. s random allocation/de
4. s double-blind method/de
5. s single-blind method/de
6. s dt=clinical trial
7. s clinical trials!/de
8. s trial or trials or trialist? Or placebo
9. S (singl? Or doubl? Or trebl? Or tripl?)(4w)(blind? Or mask?)
10. s random?
11. s dt=controlled clinical trial
12. s crossover or crossovers or rct or rcts
13. s s1:s12
14. s schizophrenia!/de
15. s paranoid disorders!/de
16. s schizo? Or hebephreni? Or oligophreni? Or psychotic?
17. S psychosis or psychoses
18. s s14:s17
19. s Sertindole OR serdolect or serlect
20. s Ziprasidone OR benzothiazolylpiperazine or Zotepine OR dibenzothiapine or nipolept
21. s lodopin or zoleptil
22. s Amisulpiride or amisulpride OR solian OR deniban
23. s olanzapine or risperidone or clozapine
24. s Lu23174 or serdolect
25. s CP88059 or CP880591
26. s amino sultopride or AST or Dan2163 or Socian or Deniban or Solian or Sulamid
27. s W108 or LX100129 or HF1854
28. s zyprex or Lanzac
29. s R64766 or Risperdal or Rispolin or Belivon or Risperin
30. s Quetiapine or ICI204636 or Seroquel
31. s cost(w)effect? or economic(w)evaluation?
32. S pharmacoeconomic? ? or cost(w)benefit
33. S cost(w)utility or qaly? ? or quality(w)adjusted(w)life
34. S s19:s30
35. S s31:33
36. S s13 and s18 and s34
37. S s18 and s34 and s35
38. S s37 not s36
39. S s38/1998-2001
40. RD s39

Datastar

The IDIS Drug File (IOWA) database on the Datastar service was searched on 2 May 2001 for records published since 1998 (inclusive).

1. SCHIZOPHREN$ OR PARANOIA OR PARANOID
2. TRIAL$ OR RCT$ OR RANDOM$ OR PLACEBO
3. (DOUBL$ OR SINGL$ OR TREBL$ OR TRIPL$) WITH BLIND$
4. CONTROL OR CONTROLS OR CONTROLLED
5. SERTINDOLE OR LU23174 OR SERDOLECT OR SERLECT
6. ZIPRASIDONE OR CP88059 OR CP88059-1
7. ZOTEPINE OR NIPOLEPT OR LODOPIN OR ZOLEPTIL OR ZOPITE OR SETONS OR MAJORPIN
8. AMISULPRIDE OR AMISULPIRIDE OR AMINO SULTOPRIDE OR AST OR DAN2163 OR SOCIAN OR DENIBAN OR SOLIAN OR SULAMID
9. CLOZAPINE OR W108 OR LX100129 OR HF1854
10. OLANZAPINE OR ZYPREX OR LANZAC
11. RISPERIDONE OR R64766 OR RISPERDAL OR RISPOLIN OR BELIVON OR RISPERIN
12. QUETIAPINE OR ICI204636 OR SEROQUEL
13. COST ADJ EFFECT$ OR ECONOMIC ADJ EVALUATION$
14. PHARMACOECONOMIC$ OR COST ADJ BENEFIT
15. COST ADJ UTILITY OR QALY$ OR QUALITY ADJ ADJUSTED ADJ LIFE
16. 1 OR 2 OR 3 OR 4
17. 2 or 3 or 4
18. 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
19. 13 or 14 or 15
20. 1 and 17 and 18
21. 1 and 18 and 19
22. 21 not 20
23. limit 22 year gt 1997

EMBASE

EMBASE in the WinSPIRS implementation was searched on 27 April 2001 over issues 1998–2001/2. The following strategy searches for economic evaluation studies that have not already been identified by the RCT search; 72 additional records were identified.

1. explode 'clinical-trial'/ all subheadings
2. 'double-blind-procedure'/ all subheadings
3. 'single-blind-procedure'/ all subheadings
4. 'crossover-procedure'/ all subheadings
5. 'evaluation'/ all subheadings

6. 'follow-up'/ all subheadings
7. 'prospective-study'/ all subheadings
8. 'clinical-article'/ all subheadings
9. 'major-clinical-study'/ all subheadings
10. 'prospective-study'/ all subheadings
11. 'placebo'/ all subheadings
12. 'randomization'/ all subheadings
13. #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12
14. explode 'comparative-study'/ all subheadings
15. 'meta-analysis'/ all subheadings
16. #14 or #15
17. ((intervention or clinical*) near (trial* or study or studies)) in ti,ab
18. (random* or placebo* or rct*) in ti,ab
19. ((singl* or doubl* or trebl* or tripl*) with (blind* or mask*)) in ti,ab
20. explode 'controlled-study'/ all subheadings
21. ((control or controls or controlled) with (trial* or study or studies)) in ti,ab
22. ((multi or multic*) with (trial* or study or studies)) in ti,ab
23. ((cross over or crossover or evaluation or prospectiv*) with (trial* or study or studies)) in ti,ab
24. ((follow or follow-up or followup) with (studies or study or trial*)) in ti,ab
25. #13 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24
26. 'amisulpride'/ all subheadings
27. 'clozapine'/ all subheadings
28. 'olanzapine'/ all subheadings
29. 'quetiapine'/ all subheadings
30. 'risperidone'/ all subheadings
31. 'sertindole'/ all subheadings
32. 'ziprasidone'/ all subheadings
33. 'zotepine'/ all subheadings
34. #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33
35. (amisulp* or solian or deniban or amino sultopride or ast or dan2163 or socian or sulamid) in ti,ab
36. (clozapine or w108 or lx100129 or hf1854) in ti,ab
37. (olanzapine or zyprex or lanzac) in ti,ab
38. (quetiapine or ici204636 or seroquel) in ti,ab
39. (risperidone or R64766 or risperdal or rispolin or belivon or risperin) in ti,ab
40. (sertindole or serdolect or serlect or lu23174) in ti,ab
41. (ziprasidone or benzothiazolylpiperazine or cp88059 or cp880591) in ti,ab
42. (zotepine or dibenzothiapine or nipolept or lodopin or zoleptil or sopite or setons or majorpin) in ti,ab
43. (schizophren* or hebephreni* or oligophreni* or psychotic or psychosis or psychoses) in ti,ab
44. chronic mental illness
45. chronically mentally ill
46. chronic mentally ill
47. severe mental illness
48. severely mentally ill
49. explode 'schizophrenia'/ all subheadings
50. explode 'paranoid-psychosis'/ all subheadings
51. 'acute-psychosis'/ all subheadings
52. 'schizoaffective-psychosis'/ all subheadings
53. #49 or #50 or #51 or #52
54. #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42
55. #43 or #44 or #45 or #46 or #47 or #48 or #49 or #53
56. #25 and #54 and #55
57. exact{HUMAN}
58. exact{animal}
59. #58 not (#57 and #58)
60. #56 not #59
61. explode 'health-economics'/ all subheadings
62. (pharmacoeconomic* or economic evaluation* or technology assessment*) in ti, ab
63. (cost effectiv* or cost benefit* or cost util*) in ti, ab
64. #61 or #62 or #63
65. #54 and #55
66. #65 not #59
67. #64 and #66
68. #67 not #60

PsycINFO

The BIDS WebSPIRS version of PsycINFO was searched on 27 April 2001 over the updates added to the database from 1 January 1998 to 28 March 2001. Only records not retrieved by the RCT search were retrieved and 24 additional records were identified.

(((amisulpiride or amisulprid or amisulpride or solian or deniban or amino sultopride or ast or dan2163 or socian or sulamid) or (clozapine or w108 or lx100129 or hf1854) or (olanzapine or zyprex or lanzac) or (quetiapine or ici204636 or seroquel) or (risperidone or r64766 or risperdal or rispolin or belivon or risperin) or (sertindole or serdolect or serlect or lu23174) or (ziprasidone or benzothiazolylpiperazine or cp88059 or cp880591) or (zotepine or dibenzothiapine or nipolept or lodopin or zoleptil or sopite or setons or majorpin))

and

((explode 'Psychosis-' in DE) or ((schizo* or psychosis or psychotic or psychoses) in ti,ab) or ((hebephreni* or oligophreni*) in ti,ab) or

(chronic mental ill* in ti,ab) or (chronically mentally ill in ti,ab) or (chronic mental disorder* in ti,ab) or (severely mentally ill in ti,ab) or (severe mental illness in ti,ab))

and

cost utility or cost benefit or cost effective* or economic evaluation* or pharmaceoeconomic* or explode 'Costs-and-Cost-Analysis' in DE or 'Economics-' in DE (828 records)

NOT

(((amisulpiride or amisulprid or amisulpride or solian or deniban or amino sultopride or ast or dan2163 or socian or sulamid) or (clozapine or w108 or lx100129 or hf1854) or (olanzapine or zyprex or lanzac) or (quetiapine or ici204636 or seroquel) or (risperidone or r64766 or risperdal or rispolin or belivon or risperin) or (sertindole or serdolect or serlect or lu23174) or (ziprasidone or benzothiazolylpiperazine or cp88059 or cp880591) or (zotepine or dibenzothiapine or nipolept or lodopin or zoleptil or sopite or setons or majorpin))

AND

(((CLINICAL-TRIAL in PT:PY) or (EMPIRICAL-STUDY in PT:PY) or (FOLLOWUP-STUDY in PT:PY) or (LITERATURE-REVIEW-RESEARCH-REVIEW in PT:PY) or (LONGITUDINAL-STUDY in PT:PY) or (META-ANALYSIS in PT:PY) or (PROGRAM-EVALUATION in PT:PY) or (PROSPECTIVE-STUDY in PT:PY) or (TREATMENT-OUTCOME-STUDY in PT:PY)) or (trial* in ti,ab) or ((random* or control or controls or controlled) in ti,ab) or (placebo* in ti,ab) or ((singl* or doubl* or tripl* or trebl*) with ((mask* or blind*) in ti,ab))))

and

((explode 'Psychosis-' in DE) or ((schizo* or psychosis or psychotic or psychoses) in ti,ab) or ((hebephreni* or oligophreni*) in ti,ab) or (chronic mental ill* in ti,ab) or (chronically mentally ill in ti,ab) or (chronic mental disorder* in ti,ab) or (severely mentally ill in ti,ab) or (severe mental illness in ti,ab))

HEED

The April 2001 issue of HEED was searched on 1 May 2001 for economic evaluations. Searches were restricted to records published later than 1997.

1. AX=AMISULPIR* OR AX=AMISULPRID*
2. AX=SOLIAN OR AX=DENIBAN OR AX='AMINO SULTOPRIDE' OR AX=AST OR AX=DAN2163
3. AX=SOCIAN OR AX=SULAMID OR AX=CLOZAPINE
4. AX=W108 OR AX=LX100129 OR AX=HF1854
5. AX=OLANZAPINE OR AX=ZYPREX OR AX=LANZAC
6. AX=QUETIAPINE OR AX=ICI204636 OR AX=SEROQUEL
7. AX=RISPERIDONE OR AX=R64766 OR AX=RISPERDAL OR AX=RISPOLIN
8. AX=BELIVON OR AX=RISPERIN OR AX=SERTINDOLE OR AX=SERDOLECT
9. AX=SERLECT OR AX=LU23174
10. AX=ZIPRASIDONE OR AX=BENZOTHIALZOLYLPIPERAZINE
11. AX=CP88059 OR AX=CP880591
12. AX=ZOTEPINE OR AX=DIBENZOTHIAPINE OR AX=NIPOLEPT
13. AX=LODOPIN OR AX=ZOLEPTIL OR AX=SOPITE OR AX=SETONS OR AX=MAJORPIN
14. CS=1 OR CS=2 OR CS=3 OR CS=4 OR CS=5 OR CS=6 OR CS=7 OR CS=8
15. CS=9 OR CS=10 OR CS=11 OR CS=12 OR CS=13
16. CS=14 OR CS=15
17. JD =1998 OR JD=1999 OR JD=2000 OR JD=2001
18. BD =1998 OR BD=1999 OR BD=2000 OR BD=2001
19. CS=17 OR CS=18
20. CS=16 AND CS=19

NHS EED

The administration database containing all candidate documents considered for the public NHS EED database was searched on 2 May 2001 for material published in the years 1998–2001. The administration database contains the results of highly sensitive searches of MEDLINE, CINAHL and Current Contents Clinical Medicine, as well as material found by searching a range of journals.

1. s AMISULPIRIDE or AMISULPRID or AMISULPRIDE or SOLIAN or DENIBAN OR AMINO(w)SULTOPRIDE OR AST OR DAN2163 OR SOCIAN OR SULAMID
2. s CLOZAPINE or W108 or LX100129 or HF1854
3. s OLANZAPINE or ZYPREX or LANZAC
4. s QUETIAPINE or ICI204636 or SEROQUEL
5. s RISPERIDONE or R64766 or RISPERDAL or RISPOLIN or BELIVON or RISPERIN

6. s SERTINDOLE or SERDOLECT or SERLECT or LU23174
7. s ZIPRASIDONE or BENZOTHIAZOLYLPIPERAZINE or CP88059 or CP880591
8. s ZOTEPINE or DIBENZOTHIAPINE or NIPOLEPT or LODOPIN or ZOLEPTIL or SOPITE or SETONS or MAJORPIN
9. s s1 or s2 or s3 or s4 or s5 or s6 or s7 or s8
10. s 1998/dat
11. s 1999/dat
12. s 2000/dat
13. s 2001/dat
14. s s10 or s11 or s12 or s13
15. s s9 and s14

Side-effects/adverse effects

A specific search for side-effects and adverse effects of atypical antipsychotic drugs was not conducted in the earlier review. The following searches were developed for this report and were designed to capture the major long-term side-effects that had been identified as arising from the use of atypical antipsychotic drugs. The time pressures surrounding this work meant that a pragmatic approach to searching was adopted. This can be seen in the use of MeSH subheadings (such as 'adverse effects' linked to drug names, and 'chemically-induced' linked to specific side-effects) when searching MEDLINE and EMTREE subheadings (such as side-effect linked to specific side-effects) when searching EMBASE. This search approach enhances the precision of a search but has an unknown effect on its sensitivity. If more time had been available, it would have been desirable to search without limiting it to the subheadings in EMBASE and MEDLINE.

MEDLINE

The SilverPlatter version of MEDLINE was searched on 18 May 2001. Searches were conducted from 1966 to 2000/12) and 1443 records were retrieved.

1. exact{RANDOMIZED-CONTROLLED-TRIAL} in PT
2. 'Random-Allocation'
3. 'Randomized-Controlled-Trials'/ all subheadings
4. 'Double-Blind-Method'
5. 'Single-Blind-Method'
6. explode 'Clinical-Trials'/ all subheadings
7. 'Placebos'/ all subheadings
8. 'Research-Design'/ all subheadings
9. explode 'Evaluation-Studies'/ all subheadings
10. 'Follow-Up-Studies'
11. 'Prospective-Studies'
12. #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11
13. exact{CLINICAL-TRIAL} in PT
14. clin* near (trial* in ti,ab)
15. (singl* or doubl* or trebl* or tripl*) near ((blind* or mask*) in ti,ab)
16. placebo* in ti,ab
17. random* in ti,ab
18. (control or controls or controlled) in ti,ab
19. (prospectiv* or allocat*) in ti,ab
20. #1 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19
21. (amisulprid or amisulpiride or amisulpride or solian or deniban or amino sultopride or ast or dan2163 or socian or sulamid) in ti,ab
22. (clozapine or w108 or lx100129 or hf1854) in ti,ab
23. (olanzapine or zyprex or lanzac) in ti,ab
24. (quetiapine or ici204636 or seroquel) in ti,ab
25. (risperidone or R64766 or risperdal or rispolin or belivon or risperin) in ti,ab
26. (sertindole or serdolect or serlect or lu23174) in ti,ab
27. (ziprasidone or benzothiazolylpiperazine or cp88059 or cp880591) in ti,ab
28. (zotepine or dibenzothiapine or nipolept or lodopin or zoleptil or sopite or setons or majorpin) in ti,ab
29. 'Clozapine'/ all subheadings
30. 'Risperidone'/ all subheadings
31. #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30
32. #20 and #31
33. #33 and (UD > '199712')
34. explode 'Schizophrenia-and-Disorders-with-Psychotic-Features'/ all subheadings
35. (schizophren* or hebephreni* or oligophreni* or psychotic or psychosis or psychoses) in ti,ab
36. chronic mental illness
37. chronically mentally ill
38. chronic mentally ill
39. severe mental illness
40. severely mentally ill
41. #34 or #35 or #36 or #37 or #38 or #39 or #40
42. #33 and #41
43. exact{ANIMAL} in TG
44. exact{HUMAN} in TG
45. #43 not (#43 and #44)
46. #42 not #45
47. 'Clozapine'/ adverse-effects
48. 'Risperidone'/ adverse-effects
49. 'Suicide'/ all subheadings
50. 'Suicide-Attempted'/ all subheadings
51. 'Mortality'/ all subheadings

52. 'Dyskinesia-Drug-Induced'/ all subheadings
53. 'Neuroleptic-Malignant-Syndrome'/ all subheadings
54. explode 'Liver-Diseases'/ chemically-induced
55. explode 'Heart-diseases'/ chemically-induced
56. 'arrythmia'/ chemically-induced
57. 'Death-Sudden'/ all subheadings
58. 'Death-Sudden,-Cardiac'/ all subheadings
59. 'Cardiomyopathy-Congestive'/ chemically-induced
60. 'Myocarditis'/ chemically-induced
61. explode 'Tachycardia'/ chemically-induced
62. 'Bradycardia'/ chemically-induced
63. 'Pulmonary-Embolism'/ chemically-induced
64. 'Long-QT-Syndrome'/ chemically-induced
65. 'Torsades-de-Pointes'/ chemically-induced
66. 'Hyperprolactinemia'/ chemically-induced
67. 'Weight-Gain'/ drug-effects
68. explode 'Menstruation-Disturbances'/ chemically-induced
69. 'Galactorrhea'/ chemically-induced
70. explode 'Impotence'/ chemically-induced
71. 'Gynecomastia'/ chemically-induced
72. explode 'Intestinal-Obstruction'/ chemically-induced
73. explode 'Seizures'/ chemically-induced
74. explode 'Substance-Related-Disorders'/ chemically-induced
75. explode 'Crime'/ chemically-induced
76. 'Leukopenia'/ chemically-induced
77. explode 'Agranulocytosis'/ chemically-induced
78. 'Pancreatitis'/ chemically-induced
79. explode 'Syncope'/ chemically-induced
80. explode 'Diabetes-Mellitus'/ chemically-induced
82. explode 'Urinary-Incontinence'/ chemically-induced
83. 'Urinary-Retention'/ chemically-induced
84. 'Priapism'/ chemically-induced
85. #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57
86. #58 or #59 or #60 or #61 or #62 or #63 or #64 or #65 or #66 or #67 or #68 or #69
87. #70 or #71 or #72 or #73 or #74 or #75 or #76 or #77 or #78 or #79 or #80 or #81 or #82 or #83
88. #84 or #85 or #86
89. #31 and #87
90. #88 not #46
91. #89 not #45
92. exact{CASES} in PT
93. #90 not #91

EMBASE

The SilverPlatter version of EMBASE was searched on 18/5/01. The database was searched for the period 1980–2001/2 and 1674 records were retrieved.

1. explode 'clinical-trial'/ all subheadings
2. 'double-blind-procedure'/ all subheadings
3. 'single-blind-procedure'/ all subheadings
4. 'crossover-procedure'/ all subheadings
5. 'evaluation'/ all subheadings
6. 'follow-up'/ all subheadings
7. 'prospective-study'/ all subheadings
8. 'clinical-article'/ all subheadings
9. 'major-clinical-study'/ all subheadings
10. 'prospective-study'/ all subheadings
11. 'placebo'/ all subheadings
12. 'randomization'/ all subheadings
13. #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12
14. explode 'comparative-study'/ all subheadings
15. 'meta-analysis'/ all subheadings
16. #14 or #15
17. ((intervention or clinical*) near (trial* or study or studies)) in ti,ab
18. (random* or placebo* or rct*) in ti,ab
19. ((singl* or doubl* or trebl* or tripl*) with (blind* or mask*)) in ti,ab
20. explode 'controlled-study'/ all subheadings
21. ((control or controls or controlled) with (trial* or study or studies)) in ti,ab
22. ((multi or multic*) with (trial* or study or studies)) in ti,ab
23. ((cross over or crossover or evaluation or prospectiv*) with (trial* or study or studies)) in ti,ab
24. ((follow or follow-up or followup) with (studies or study or trial*)) in ti,ab
25. #13 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24
26. 'amisulpride'/ all subheadings
27. 'clozapine'/ all subheadings
28. 'olanzapine'/ all subheadings
29. 'quetiapine'/ all subheadings
30. 'risperidone'/ all subheadings
31. 'sertindole'/ all subheadings
32. 'ziprasidone'/ all subheadings
33. 'zotepine'/ all subheadings
34. #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33
35. (amisulpiride or amisulpirid or amisulpride or solian or deniban or amino sultopride or ast or dan2163 or socian or sulamid) in ti,ab
36. (clozapine or w108 or lx100129 or hf1854) in ti,ab
37. (olanzapine or zyprex or lanzac) in ti,ab
38. (quetiapine or ici204636 or seroquel) in ti,ab
39. (risperidone or R64766 or risperdal or rispolin or belivon or risperin) in ti,ab
40. (sertindole or serdolect or serlect or lu23174) in ti,ab
41. (ziprasidone or benzothiazolylpiperazine or cp88059 or cp880591) in ti,ab

42. (zotepine or dibenzothiapine or nipolept or lodopin or zoleptil or sopite or setons or majorpin) in ti,ab
43. (schizophren* or hebephreni* or oligophreni* or psychotic or psychosis or psychoses) in ti,ab
44. chronic mental illness
45. chronically mentally ill
46. chronic mentally ill
47. severe mental illness
48. severely mentally ill
49. explode 'schizophrenia'/ all subheadings
50. explode 'paranoid-psychosis'/ all subheadings
51. 'acute-psychosis'/ all subheadings
52. 'schizoaffective-psychosis'/ all subheadings
53. #49 or #50 or #51 or #52
54. #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42
55. #43 or #44 or #45 or #46 or #47 or #48 or #49 or #53
56. #25 and #54 and #55
57. exact{HUMAN}
58. exact{animal}
59. #58 not (#57 and #58)
60. #56 not #59
61. 'amisulpride'/ side-effect, drug-toxicity
62. 'clozapine'/ adverse-drug-reaction, side-effect, drug-toxicity
63. 'quetiapine'/ adverse-drug-reaction, side-effect, drug-toxicity
64. 'risperidone'/ adverse-drug-reaction, side-effect, drug-toxicity
65. 'sertindole'/ adverse-drug-reaction, side-effect, drug-toxicity
66. 'ziprasidone'/ adverse-drug-reaction, side-effect, drug-toxicity
67. 'zotepine'/ adverse-drug-reaction, side-effect, drug-toxicity
68. 'amisulpride'/ adverse-drug-reaction
69. 'suicide'/ side-effect
70. explode 'suicidal-behavior'/ side-effect
71. 'death'/ all subheadings
72. 'sudden-death'/ all subheadings
73. 'dyskinesia'/ side-effect, drug-toxicity
74. 'neuroleptic-malignant-syndrome'/ side-effect
75. explode 'adverse-drug-reaction'/ all subheadings
76. explode 'side-effect'/ all subheadings
77. explode 'liver-disease'/ side-effect
78. explode 'heart-disease'/ side-effect
79. 'congestive-cardiomyopathy'/ side-effect
80. explode 'myocarditis'/ side-effect
81. explode 'tachycardia'/ side-effect
82. explode 'bradycardia'/ side-effect
83. 'lung-embolism'/ side-effect
84. 'long-QT-syndrome'/ side-effect
85. 'torsade-des-pointes'/ side-effect
86. 'hyperprolactinemia'/ side-effect
87. explode 'amenorrhea-and-oligomenorrhea'/ side-effect
88. explode 'galactorrhea'/ side-effect
89. 'impotence'/ side-effect
90. 'gynecomastia'/ side-effect
91. explode 'intestine-obstruction'/ side-effect
92. 'seizure'/ side-effect
93. explode 'drug-dependence'/ side-effect
94. explode 'leukopenia'/ side-effect
95. 'agranulocytosis'/ side-effect
96. explode 'pancreatitis'/ side-effect
97. 'syncope'/ side-effect
98. 'diabetes-mellitus'/ side-effect
99. 'insulin-dependent-diabetes-mellitus'/ side-effect
100. 'maturity-onset-diabetes-mellitus'/ side-effect
101. 'non-insulin-dependent-diabetes-mellitus'/ side-effect
102. 'ketoacidosis'/ side-effect
103. 'urine-incontinence'/ side-effect
104. 'urine-retention'/ side-effect
105. 'priapism'/ side-effect
106. 'weight-gain'/ all subheadings
107. explode 'crime'/ all subheadings
108. 'case-report'/ all subheadings
109. #61 or #62 or #63 or #64 or #65 or #66 or #67 or #68
110. #69 or #70 or #71 or #72 or #73 or #74 or #75 or #76 or #77 or #78 or #79
111. #80 or #81 or #82 or #83 or #84 or #85 or #86 or #87 or #88 or #89 or #90 or #91
112. #92 or #93 or #94 or #95 or #96 or #97 or #98 or #99 or #100 or #101 or #102 or #103 or #104 or #105 or #106 or #107
113. #110 or #111 or #112
114. #54 and #113
115. #109 or #114
116. #115 not #60
117. #116 not #59
118. #117 not #108

PsycINFO

The BIDS WebSPIRS version of PsycINFO was searched on 18 May 2001, from 1887 to 2001,05 week 2, and 722 records were retrieved.

#1 explode 'Side-Effects-Drug' in DE (2632 records)
#2 ('Attempted-Suicide' in DE) or ('Suicide-' in DE) (1141 records)
#3 'Mortality-Rate' in DE (259 records)
#4 explode 'Dyskinesia-' in DE (140 records)
#5 'Neuroleptic-Malignant-Syndrome' in DE (58 records)
#6 explode 'Liver-Disorders' in DE (109 records)

#7 explode 'Heart-Disorders' in DE (399 records)
#8 'Body-Weight' in DE (428 records)
#9 'Menstruation-' in DE (17 records)
#10 'Impotence-' in DE (24 records)
#11 'Intestines-' in DE (8 records)
#12 'Convulsions-' in DE (208 records)
#13 explode 'Drug-Abuse' in DE (3069 records)
#14 'Pancreas-' in DE (20 records)
#15 'Syncope-' in DE (12 records)
#16 explode 'Diabetes-' in DE (317 records)
#17 'Urinary-Incontinence' in DE (70 records)
#18 'Urinary-Function-Disorders' in DE (18 records)
#19 sudden death or myocarditis or pulmonary embolism (45 records)
#20 long qt or torsades or hyperprolactinemia or galactorrhea or
#21 intestinal obstruction* or leukopenia or agranulocytosis or priapism
#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 amisulpiride or amisulprid or amisulpride or solian or deniban or amino sultopride or ast or dan2163 or socian or sulamid
#24 clozapine or w108 or lx100129 or hf1854
#25 olanzapine or zyprex or lanzac
#26 quetiapine or ici204636 or seroquel
#27 risperidone or r64766 or risperdal or rispolin or belivon or risperin
#28 sertindole or serdolect or serlect or lu23174
#29 ziprasidone or benzothiazolylpiperazine or cp88059 or cp880591
#30 zotepine or dibenzothiapine or nipolept or lodopin or zoleptil or sopite or setons or majorpin
#31 #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30
#32 (CLINICAL-TRIAL in PT:PY) or (EMPIRICAL-STUDY in PT:PY) or (FOLLOWUP-STUDY in PT:PY) or (LITERATURE-REVIEW-RESEARCH-REVIEW in PT:PY) or (LONGITUDINAL-STUDY in PT:PY) or (META-ANALYSIS in PT:PY) or (PROGRAM-EVALUATION in PT:PY) or (PROSPECTIVE-STUDY in PT:PY) or (TREATMENT-OUTCOME-STUDY in PT:PY)
#33 trial* in ti,ab
#34 (random* or control or controls or controlled) in ti,ab
#35 placebo* in ti,ab
#36 (singl* or doubl* or tripl* or trebl*) with ((mask* or blind*) in ti,ab
#37 #32 or #33 or #34 or #35 or #36
#38 #31 and #37
#39 explode 'Psychosis-' in DE
#40 (schizo* or psychosis or psychotic or psychoses) in ti,ab
#41 (hebephreni* or oligophreni*) in ti,ab
#42 chronic mental ill* in ti,ab
#43 chronically mentally ill in ti,ab
#44 chronic mental disorder* in ti,ab
#45 severely mentally ill in ti,ab
#46 severe mental illness in ti,ab
#47 #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46
#48 #47 and #38
#49 #47 and #38
#50 #49 and (UD=19980101-20010328)
#51 #22 and #31
#52 #51 not #50
#53 'Case-Report' in DE
#54 #52 not #53
#55 explode 'Mammals-' in DE
#56 #54 not #55

TOXLINE

TOXLINE (Toxicology Literature online (http://toxnet.nlm.nih.gov/cgi-bin/sis/search) was searched via the Internet on 31 May 2001 and 1064 references were retrieved. The following search terms were entered individually.

Amisulpride
Clozapine
Olanzapine
Quetiapine
Risperidone
Sertindole
Ziprasidone
Zotepine

SEDBASE

SEDBASE was searched via the Dialog Datastar service on 18 May 2001. It has been a closed file since 1996. 134 records were retrieved.

1. AMISULPRIDE
2. CLOZAPINE
3. OLANZAPINE
4. QUETIAPINE
5. RISPERIDONE
6. SERTINDOLE
7. ZIPRASIDONE
8. ZOTEPINE
9. 1 2 3 4 5 6 7 8

Appendix 2

Data extraction sheets for new RCTs

Amisulpride RCTs

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Muller 1998[41]	**Intervention:** amisulpride **Dose:** 600–1000 mg daily; oral **Control:** flupentixol **Dose:** 15–25 mg daily; oral **Duration:** 6 weeks **Washout:** none stated **Concomitant medications:** not stated **Comments:** analysis focused on efficacy of high-dose amisulpride versus flupentixol on depressive and negative symptoms in acute schizophrenia	**Age:** not stated **Sex:** not stated **Illness:** schizophrenia **Diagnosis:** DSM-III-R ***N*:** 126 **Duration of illness:** not stated **Special characteristics:** latent structure of negative and depressive symptomatology analysed by confirmatory factor analysis using baseline data of 126 patients **Inclusion/exclusion criteria:** none stated **Further details:** no further comments	**Intervention group:** not stated **Control group:** not stated	None reported	**Authors' conclusions** Analysis of latent structures of acute schizophrenic symptomatology revealed three distinguishable components of depressive and negative symptoms in acute schizophrenia (depression, anhedonia/apathy and negative symptoms) and indicated a specific beneficial effect of high-dose amisulpride on 'depressive' dimension compared with flupentixol, independent of effects on positive, negative and extrapyramidal symptoms
Results – general comments Substantial treatment differences on positive symptomatology not found. No substantial treatment differences found with respect to negative and anhedonia/apathy dimensions, whereas significant difference emerged with respect to depressive symptoms. Decrease in depressive symptoms: amisulpride 51%; flupentixol 26% (p = 0.014). Depressive factor improved in 93.8% of amisulpride patients and 71.2% of flupentixol patients					
SOFA, Social Functioning Assessment					

Amisulpride RCTs *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Lecrubier 2000[43]	**Intervention:** amisulpride ***N*:** 152 **Dose:** initial 600 mg daily, adjusted 400–1000 mg daily **Control:** risperidone ***N*:** 158 **Dose:** initial 6 mg daily, adjusted 4–10 mg daily **Duration:** 6 months (possible extension to 12 months)	**Age:** mean: 38.4 years **Sex:** 55% male (171/310) **Illness:** schizophrenia **Diagnosis:** DSM-IV ***N*:** 310 **Duration of illness:** mean: 11.8 years **Special characteristics:** mainly paranoid type: 73% (226/310) **Inclusion/exclusion criteria:** not stated	Not reported	Neither treatment provoked increase in extrapyramidal symptoms as measured by SAS, BAS and AIMS	**Authors' conclusions** Amisulpride showed comparable efficacy profile to risperidone with some trends to superior improvement in several measures during medium-term treatment of schizophrenic patients

Results

General comments:	Outcome 1	Outcome 2	Outcome 3	Outcome 4
	Outcome: change scores: PANSS total; negative **Intervention:** –32.2, 23.9; –5.1, 5.1 **Control:** –31.4, 21.0, $p < 0.001$; –3.9, 6.1, $p = 0.09$	**Outcome:** BPRS change scores **Intervention:** –19.8, 15.0 **Control:** –19.6, 12.6	**Outcome:** PANSS and BPRS (at least 50% improvement) **Intervention:** 65% and 72% **Control:** 52% and 58%, $p < 0.05$ for both	**Outcome:** CGI (very much/ much improved); Social Functioning Assessment scale (50% improvement); subjective response to treatment (Van Putten scale) **Intervention:** 77%; 33%; 7% **Control:** 65%, $p < 0.05$; 23%, $p < 0.10$; 17%, $p = 0.015$

Amisulpride RCTs *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Wetzel 1998[45]	**Intervention:** amisulpride ***N*:** 70 **Dose:** initial: 1000 mg daily; mean (SD): 956 (105) mg daily **Control:** flupentixol ***N*:** 62 **Dose:** initial: 25 mg daily; mean (SD): 22.6 (3.4) mg daily **Duration:** 6 weeks **Washout:** 1–9 days (placebo) **Concomitant medications:** biperiden (up to 12 mg daily) and diazepam (up to 40 mg daily, during washout) **Comments:** mean (SD) duration of washout: amisulpride 3.23 (2.28) days; flupentixol 3.18 (2.05) days. Study drugs given on twice daily regimen. Dose adjustable in case of side-effects to minimum of 600 and 15 mg daily, respectively. Dose decreased 35/70 amisulpride and 31/62 flupentixol patients	**Age:** mean (SD): amisulpride 35 (11) years; flupentixol 33 (9) years **Sex:** amisulpride 36/70 male; flupentixol 38/62 male **Illness:** schizophrenia **Diagnosis:** DSM-III-R ***N*:** 132 **Duration of illness:** not stated **Special characteristics:** schizophrenic subtypes – paranoid: amisulpride 37/70; flupentixol 35/62; undifferentiated: amisulpride 33/70; flupentixol 27/62 **Inclusion/exclusion criteria:** aged 18–65 years; diagnosis of schizophrenia, paranoid or undifferentiated type; score at least 36 points on BPRS (item score 1–7); use of adequate contraception by women Excluded: diagnosis of schizoaffective disorder or other axis I disorder, like dementia or organic brain disorder; prevailing negative schizophrenic symptomatology as assessed by SANS composite score above 55 points; history of alcohol or substance dependence/abuse; suicidal ideations; Parkinson's disease; epilepsy; narrow-angle glaucoma; prostate hypertrophy; urinary retention; severe hypotonia or arteriosclerosis; severe liver or kidney dysfunction; other serious somatic co-morbid disorders; significant laboratory, ECG or EEG abnormality; pregnancy or lactation; necessity of psychotropic medication; participation in another clinical trial with any investigational drug within last 30 days; and depot neuroleptic medication within period of 3 months prior to study inclusion **Further details:** amisulpride group presented with significantly higher BPRS and SANS scores ($p < 0.05$)	**Intervention group:** 19/70 withdrew – 5 insufficient response, 4 adverse events (2 serious), 6 lack of co-operation, 2 complete remission, 2 other **Control group:** 25/62 withdrew – 8 insufficient response, 11 adverse event (0 serious), 4 lack of cooperation, 1 complete remission, 1 other	Significant difference between treatment groups ($p = 0.030$) in favour of amisulpride. In all extrapyramidal outcome parameters (SAS, AIMS and BAS), amisulpride caused significantly fewer motor side-effects ($p < 0.01$). UKU scale: 70% amisulpride and 79% flupentixol rated to suffer from EPS of any degree of severity at least once during treatment. Fewer in amisulpride group needed biperiden co-medication (43%:61%); average daily dose: amisulpride 3.0 (2.2) mg daily; flupentixol 5.4 (4.3) mg daily, average duration: amisulpride 22.3 days; flupentixol 27.3 days **Adverse events:** sedation, amisulpride 45.7%, flupentixol 54.8%; inner unrest, amisulpride 27.8%, flupentixol 29.0%; concentration difficulty, amisulpride 24.3%, flupentixol 24.2; increased sleep duration, amisulpride 22.9%, flupentixol 38.7% ($p < 0.05$); weight gain, amisulpride 21.4%; flupentixol 22.6%; headache, amisulpride 20.0%, flupentixol 8.1%; emotional indifference, amisulpride 18.6%, flupentixol 27.4%; accommodation disturbance, amisulpride 18.6%, flupentixol 27.4%; increased salivation, amisulpride 17.1%, flupentixol 22.6%; constipation, amisulpride 17.1%, flupentixol 9.7%; increased sweating, amisulpride 14.3%, flupentixol 9.7%; orthostaic dizziness, amisulpride 12.9%, flupentixol 17.7%; menorrhagia, amisulpride 14.7%, flupentixol 14.2%; galactorrhoea, amisulpride 5.7%, flupentixol 4.8%; gynecomastia, amisulpride 2.9%, flupentixol 3.2%; ejaculatory dysfunction, amisulpride 5.5%, flupentixol 5.3%; erectile dysfunction, amisulpride 2.5%, flupentixol 13.2%; any adverse event, amisulpride 87%, flupentixol 92%	**Authors' conclusions** Compared with mixed D1/D2-like antagonist flupentixol, the selective D2-like antagonist amisulpride proved equipotent with regard to overall antipsychotic efficacy and onset of response. In dose range chosen, amisulpride caused significantly fewer extrapyramidal side-effects. Hence, amisulpride appears to be effective antipsychotic agent with favourable extrapyramidal side-effect profile

continued

Amisulpride RCTs *contd*

Wetzel 1998[45] *contd*

Results

General comments: dose effects on outcome parameters cannot be entirely ruled out	**Outcome 1**	**Outcome 2**	**Outcome 3**	**Outcome 4**
	Outcome: BPRS total scores **Intervention:** 32.4, 15.4 ANCOVA (BPRS baseline and dosage reduction), 5.6 points in favour of amisulpride (95% CI, 0.55 to 10.65) **Control:** 33.3, 15.6; no difference in efficacy; ANCOVA, $p = 0.059$, trend in favour of amisulpride	**Outcome:** reduction ≥ 40% BPRS total score; CGI final improvement score 'very much/much better' **Intervention:** 39%; 62% **Control:** 30%; 62% Cox proportional hazard regression analysis (time needed to reach 40% reduction BPRS total score) showed no difference between groups	**Outcome:** BPRS change in subscores (anxiety/depression; anergia; thought disturbance; activation; hostile suspiciousness); CGI-S; GAS scores **Intervention:** –5.6, 3.7; –2.5, 3.3; –8.1, 4.5; –4.2, 3.7; –2.6; 3.8; –2.5, 1.5; 28.7, 14.7 **Control:** –3.6, 4.6; –1.0; 3.4; –5.9, 4.8; –3.1, 3.6; –2.6, 3.9; –2.0, 1.6; 26.5, 20.4	**Outcome:** SAPS score; SANS score **Intervention:** 14.7, 23.4; 22.8, 19.4 **Control:** 20.1, 31.1; 22.3, 22.0 ANCOVA, $p = 0.069$ in favour of amisulpride; no significant difference on ANCOVA

Amisulpride RCTs *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Carriere 2000[47]	**Intervention:** amisulpride ***N*:** 94 **Dose:** 400–1200 mg daily oral **Control:** haloperidol ***N*:** 105 **Dose:** 10–30 mg daily oral **Duration:** 4 months **Washout:** none **Concomitant medications:** as required: anxiolytics, hypnotics, drugs to control incapacitating extrapyramidal symptoms, drugs for somatic disorders **Comments:** initial dose haloperidol, 20 mg daily; amisulpride, 800 mg daily; adjustable thereafter according to patient's condition	**Age:** mean (SD): 30.9 (8.6) years **Sex:** 68% (*n* = 136) male **Illness:** combined diagnoses **Diagnosis:** DSM-IV ***N*:** 199 **Inclusion/exclusion criteria:** patients of either sex with paranoid schizophrenia or schizophreniform disorder Excluded: requirement for mood regulators or antidepressants; concomitant serious diseases; alcohol or drug addiction; agitation due to organic, toxic or iatrogenic causes; sensitivity to haloperidol or benzamides **Further details:** majority (82%) classified as having schizophrenia of paranoid type according to DSM-IV criteria and duration of illness; others suffered from schizophreniform disorders	**Intervention group:** 24 (26%) withdrew, 4 due to adverse events (4%), 8 uncooperative (9%), 6 lack of efficacy (6%), 2 lost to follow-up (2%), 0 recovery (0%), 4 other (4%) **Control group:** 46 (44%) withdrew, 22 due to adverse events (21%), 9 uncooperative (9%), 9 lack of efficacy (9%), 3 lost to follow-up (3%), 1 recovered (1%) and 2 other (2%)	Amisulpride (*n* = 94): extrapyramidal disorder 22 (23%); depression 1 (1%); hypertonia 6 (6%); tremor 2 (2%); somnolence 1 (1%); dry mouth 1 (1%); hyperkinesia 2 (2%); weight increase 7 (7%) Haloperidol (*n* = 105): extrapyramidal disorder 49 (47%); depression 11 (10%); hypertonia 10 (10%); tremor 8 (8%); somnolence 6 (6%); dry mouth 6 (6%); dyskinesia 6 (6%); hyperkinesia 5 (5%); suicide attempt 5 (5%)	**Authors' conclusions** Amisulpride globally superior to haloperidol in treatment of acute exacerbations of schizophrenia and significantly improves patients' quality of life and social adjustment

Results

General comments:	Outcome 1	Outcome 2	Outcome 3	Outcome 4
	Outcome: BPRS total (anxiety/depression; anergia; thought disturbance; activation; hostile-suspiciousness; productive factor) **Intervention:** (*n* = 91) 37.6 (ITT), 37.1 (PP28) (8.4; 8.7; 8.6; 6.5; 5.4; 8.9) **Control:** (*n* = 103) 43.6 (ITT), 41.1 (PP28) (10.1, 10.6, 9.1, 7.4, 6.4, 9.9)	**Outcome:** PANSS (positive; negative subscales) **Intervention:** ITT: 13.7; 18.2 PANSS positive 28: 13.3; 18.1 **Control:** ITT: 14.9; 21.5 PANSS positive 28: 13.6; 21.4	**Outcome:** CGI (global improvement scale: 'much' or 'very much' improved; severity of illness score: 'normal', 'borderline' or 'mildly' ill) **Intervention:** *n* = 65, 71%; *n* = 36, 40% **Control:** *n* = 49, 47%, *n* = 26, 25%	**Outcome:** FSQ psychological function subscale; FSQ number of friends or relatives; QLS mean score **Intervention:** change from baseline: +21.0; +1.6; +1.0 **Control:** change from baseline: +12.4; –0.3; +0.6

continued

Amisulpride RCTs *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Colonna 2000[361] Rein 1999[50]	**Intervention:** amisulpride ***N*:** 370 **Dose:** 200–800 mg daily; maximum in acute episode 1200 mg; oral **Control:** haloperidol ***N*:** 118 **Dose:** 5–20 mg daily; maximum in acute episode 30 mg; oral **Duration:** 12 months **Washout:** not stated **Concomitant medications:** other neuroleptic and psychotropic drugs not permitted during study. Diazepam and anti-parkinsonism drugs allowed for relief of insomnia, anxiety and EPS as required	**Age:** 37.5 (SD 11.1) years **Sex:** 327/488 (67% male) **Illness:** schizophrenia **Diagnosis:** DSM-III-R ***N*:** 488 **Duration of illness:** 12 (SD 8.5) years **Special characteristics:** patients with chronic or sub-chronic schizophrenia **Inclusion/exclusion criteria:** Inclusion: minimum score of 4 on 7-point scale on at least 2 BPRS positive items Excluded: standard criteria, plus patients with positive symptoms not corresponding to schizophrenia criteria, severe cardiovascular disease, Parkinson's disease or phaeochromacytoma. Also excluded: schizophreniform or schizoaffective disorder **Further details:** statistically significant differences between treatment groups for age (36.8 (SD 10.9) versus 39.6 (SD 11.2) years); duration of illness (12 (SD 8.4) versus 13 (SD 8.7) years); AIMS total score at baseline (2.3 (SD 4.6) versus 2.9 (SD 5.2))	**Intervention group:** total, 167; 10 lost to follow-up; 79 uncooperative; 33 lack of efficacy; 30 adverse events; 1 recovery; 14 other **Control group:** total, 62; 6 lost to follow-up; 17 uncooperative; 20 lack of efficacy; 12 adverse events; 0 recovery; 7 other	Results given as number of patients (amisulpride versus haloperidol) Total participants 370:118; any adverse event 254:82; any EPS 96:48; any endocrine disorder 15:3; any serious aderse event 38:8; insomnia 50:15; anxiety 42:17; psychosis 22:4; agitation 15:6; EPS 48:33; hyperkinesia 33:11; tremor 19:7; dyskinesia 9:6; weight increase 40:4; amenorrhoea 7:0; discontinuation due to adverse events 30:12 SAS scores showed maximal aggravation and change in intensity from baseline of EPS statistically significantly greater in haloperidol group (p = 0.0001), with change in baseline score of –0.22 with haloperidol versus 0.11 with amisulpride; 336/370 patients free from akathisia with amisulpride versus 92/118 with haloperidol (p = 0.0001). Changes in AIMS mean scores from baseline to end of study 0.6 versus –0.2 (p = 0.014)	**Authors' conclusions** Amisulpride safe and well-tolerated during long-term administration and led to significant improvement in quality of life and social functioning of patients with chronic schizophrenia

continued

Amisulpride RCTs *contd*

Colonna 2000;[361] Rein 1999[50] *contd*

Results

General comments:
Results calculated using last observation carried forward

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome: total BPRS **Intervention:** 38.9 (SD 16.1) Change from baseline 17.0 (SD 15.8) $p = 0.01$ versus haloperidol **Control:** 44.4 (SD 17.2) Change from baseline 12.8 (SD 15.5)	**Outcome:** positive PANSS **Intervention:** 15.6 (SD 8.1) Change from baseline 8.8 (SD 8.7) (not significant versus haloperidol) **Control:** 17.6 (8.8) Change from baseline 8.3 (SD 8.4)	**Outcome:** negative PANSS **Intervention:** 18.1 (SD 7.9) Change from baseline 7.1 (SD 7.7) $p = 0.0001$ versus haloperidol **Control:** 21.3 (SD 8.1). Change from baseline 3.7 (SD 7.4)	**Outcome:** CGI-2 index; quality-of-life change score (QLS); number of patients requiring benzodiazepines; GAF change scores **Intervention:** very much improved 55% ($n = 200$) ($p = 0.057$ versus haloperidol); –0.64 ($p = 0.02$ versus haloperidol); 210 (57%); –20.1 ($p = 0.09$ versus haloperidol) **Control:** 44% ($n = 52$); –0.30; 69 (58%); –13.6

Outcome 5 (from Rein 1999)
Outcome: overall incidence of emergent tardive dyskinesia (last two visits) **Intervention:** 39 patients not free of tardive dyskinesia at baseline **Endpoint:** 11/331 (5/331) **Control:** 12 patients not free of tardive dyskinesia at baseline **Endpoint:** 9/106, $p = 0.034$ (6/106, $p = 0.028$)

continued

Amisulpride RCTs *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Lecrubier 1999[42]	**Intervention:** olanzapine ***N*:** 140 **Dose:** 5 mg daily (70); 20 mg daily (70); oral **Intervention 2:** amisulpride ***N*:** 70 **Dose:** 150 mg daily; oral **Control:** placebo ***N*:** 34 **Dose:** oral **Duration:** 6 months **Washout:** not stated **Concomitant medications:** not stated	**Age:** not stated **Sex:** not stated **Illness:** schizophrenia **Diagnosis:** not stated ***N*:** 244 **Duration of illness:** not stated **Special characteristics:** primarily negative symptoms **Inclusion/exclusion criteria:** minimum score 10 on SANS summary score (excluding attention subscore); no score > 4 on hallucination and delusion items of PANSS (normalised, score 0–6)	**Intervention group** ***n*:** not stated	Efficacy on both negative and overall symptomatology observed in context of very good safety and tolerance profile, specifically on EPS as measured by BAS and SAS	**Authors' conclusions** Olanzapine is effective and safe in treating negative, positive and overall symptoms in predominantly negative schizophrenic patients

Results

General comments	Outcome 1	Outcome 2	Outcome 3
General comments: data from all olanzapine patients showed statistically greater improvement in this subscore compared with amisulpride patients (p = 0.044)	**Outcome:** SANS summary change scores **Intervention:** olanzapine, 5 mg, –5.6 (5.0); olanzapine, 20 mg, –4.0 (5.2); amisulpride, –4.5 (4.9) **Control:** placebo, –3.4 (4.9) (p = 0.046 compared with olanzapine, 5 mg)	**Outcome:** positive clinical response* **Intervention:** olanzapine, 5 mg, 75.4%; olanzapine, 20 mg, 48.4%; amisulpride, 56.5% **Control:** 48.1% (p = 0.013 compared with olanzapine, 5 mg)	**Outcome:** PANSS total change score; positive subscore (change) **Intervention:** olanzapine, 5 mg, –23.4 (24.4); –1.8 (6.8); amisulpride not reported **Control:** –12.6 (24.0), p = 0.05 compared with olanzapine, 5 mg; +1.9 (6.8), p = 0.021

* *Defined as patients having > 4 weeks of treatment; improvement from baseline in endpoint SANS summary score of ≥ 20% and improvement from baseline in endpoint PANSS total score of ≥ 10%*

continued

Amisulpride RCTs *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Ziegler 1989[44]	**Intervention:** amisulpride ***N*:** 20 **Dose:** 600 mg daily (10); 300–750 mg daily (10); oral **Control:** haloperidol ***N*:** 20 **Dose:** 12 mg daily (10); 2.5–22.5 mg daily (10); oral **Duration:** 4 weeks **Washout:** 3 days **Concomitant medications:** not stated	**Age:** mean 35.5 years **Sex:** not stated **Illness:** schizophrenia **Diagnosis:** ICD-9 ***N*:** 40 **Duration of illness:** not stated **Special characteristics:** paranoid and/or delusional disorders. First episode and chronic schizophrenia, positive and negative symptoms **Inclusion/exclusion criteria:** schizophrenic patients suffering from restlessness requiring heavy doses of neuroleptic drugs included provided acute symptoms had decreased and after washout period Excluded: organid brain disorder, intellectual disability, acute somatic disease, participants treated with delayed effect neuroleptic drugs during previous 2 weeks	One participant receiving haloperidol withdrew early	Webster scale score (incidence of EPS): amisulpride 4/20; haloperidol 11/20 ($p < 0.05$)	**Authors' conclusions** Not stated (data taken from manufacturer's submission, full report not obtainable)

Results		
General comments:	**Outcome 1**	**Outcome 2**
	Outcome: BPRS change scores **Intervention:** –19.3 (31%) **Control:** –15.9 (26%) *p* not significant	**Outcome:** AMDP scores **Intervention:** amisulpride and haloperidol both effective at treating paranoid and depressive symptoms

continued

Amisulpride RCTs *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Pfizer 128-305 (2001)[46] **Trial ID:** 128-305	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed
Results: commercial-in-confidence: data removed					

continued

Clozapine RCTs

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Covington 2000[69]	**Intervention:** clozapine ***N*:** 40 **Dose:** not stated; oral **Control:** haloperidol ***N*:** 42 **Dose:** not stated; oral **Duration:** 2 years **Washout:** not stated **Concomitant medications:** not stated	**Age:** mean (SD) – clozapine 25.3 (5.7) years; haloperidol 24.1 (5.1) years **Sex:** 61 male, 21 female **Illness:** combined diagnoses **Diagnosis:** DSM-III-R ***N*:** 82 **Duration of illness:** ≤ 5 years **Special characteristics:** schizophrenia or schizoaffective disorder **Inclusion/exclusion criteria:** not stated **Further details:** all 'relatively young'	**Intervention group *n*:** not stated **Control group *n*:** not stated	Not reported	**Authors' conclusions** Clozapine-treated men maintained greater interest and activity than clozapine-treated women and haloperidol-treated mne and women. When sexual function defined as 'ability to maintain mature intimate relationships and satisfying sexual activity' women, regardless of treatment, were superior to men with clozapine women maintaining grossly superior improvement at 24 months

Results		
General comments: men had documented increased sexual interest and activity; however, females had greater interest in maintaining relationships	**Outcome 1**	**Outcome 2**
	Outcome: SANS measure 'sexual interest and activity' at 2 years **Intervention:** 0.62 **Control:** 1.14	**Outcome:** quality-of-life measure 'the ability to maintain mature intimate relationships and satisfying sexual activity' at 2 years **Intervention:** 1.71 **Control:** 1.48

continued

Clozapine RCTs *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Fleming 1998[70]	**Intervention:** olanzapine ***N*:** 9 **Dose:** 20 mg daily **Control:** clozapine ***N*:** 9 **Dose:** 200–600 mg daily **Duration:** 6 weeks **Washout:** mean of 9.3 days **Concomitant medications:** not stated **Comments:** crossover design; no information about washout period between treatment phases	**Age:** not stated **Sex:** not stated **Illness:** schizophrenia **Diagnosis:** not stated ***N*:** 18 **Duration of illness:** not stated **Special characteristics:** stable outpatients	Not stated	Not presented	**Authors' conclusions** Although findings must be viewed with caution as sample size small, they highlight possibility that olanzapine and clozapine may be differentially effective at treating clinical and neurocognitive aspects of schizophrenia

Results

General comments: no data presented

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome: PANSS total score compared with placebo washout period (baseline)	**Outcome:** PANSS negative symptoms only (compared with placebo washout (baseline))	**Outcome:** cognition (motor speed) compared with placebo washout (baseline)	**Outcome:** immediate memory and attention (compared with placebo washout)
Intervention: $p < 0.002$	**Intervention:** not significant	**Intervention:** $p < 0.04$	**Intervention:** immediate memory: $p < 0.03$ (also $p < 0.03$ compared with clozapine) Attention: $p < 0.05$ (and versus clozapine $p < 0.01$); not significant
Control: $p < 0.008$	**Control:** $p < 0.002$	**Control:** $p < 0.08$	

continued

Clozapine RCTs *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Tollefson 2001[76] **Trial ID:** Beuzen 1998 with some additional data (see appendix 3)	**Intervention:** olanzapine ***N*:** 90 **Dose:** 15 mg daily, after first 2 weeks 15–25 mg daily **Control:** clozapine ***N*:** 90 **Dose:** Fixed dose escalation from 25 to 200 mg daily during days 1–8 of therapy; after first 2 weeks, 200–600 mg daily **Duration:** 18 weeks **Washout:** 2–9 days **Concomitant medications:** benzodiazepine (up to 40 mg daily diazepam equivalent or 8 mg lorazepam equivalent) for agitation, choral hydrate for insomnia, and biperiden or benztropine mesylate (up to 4 mg daily) for EPS permitted. **Comments:** with either drug, blinded titration was permitted. Investigators had opportunity to increase or decrease dose by either olanzapine, 2.5 or 5 mg, or clozapine, 50 or 100 mg, per visit interval. 44/83 clozapine-treated participants received maximum daily dose of 400–600 mg, mean (SD) dose 303.6 (108.7) mg daily. 59/88 olanzapine-treated participants received maximum dose of 25 mg, mean (SD) dose 20.5 (2.8) mg daily	**Age:** Mean (SD): 38.6 (10.6) years **Sex:** 115/180 male **Illness:** schizophrenia **Diagnosis:** DSM-IV ***N*:** 180 **Duration of illness:** not stated **Special characteristics:** schizophrenia subtypes: catatonic 3/180; disorganised 34/180; paranoid 101/180; undifferentiated 34/180; residual 8/180 Schizophrenia course: residual symptoms 81/180; no residual symptoms 3/180; continuous 92/180; in partial remission 2/180; other pattern 2/180 **Inclusion/exclusion criteria:** aged 18–70 years; in- or outpatients; minimum BPRS score, extracted from PANSS, at least 45 with score of 4 or more on at least two items of the PANSS positive symptom subscale (items 1–7); clinically resistant to previous antipsychotic treatments (lack of satisfactory clinical response to at least two previous oral neuroleptic treatments, each of different chemical class, duration ≥ 6 weeks, appropriate dose equivalent to chlorpromazine, at least 500 mg, or to maximum daily dose when intolerable side-effects were documented Excluded: previous treatment with olanzapine, olanzapine or clozapine nonresponders, with known intolerance to either drug; pregnant or lactating women; patients with serious medical illnesses in which pharmacotherapy posed risk	**Intervention group:** 60.0% participants completed study (lack of efficacy 13.3%; patient decision 10.0%; lost to follow-up 2.2%; other 10.1%; adverse event 4.4%) **Control group:** 58.9% participants completed study (lack of efficacy 10.0%; patient decision 4.4%; lost to follow-up 2.2%; other 10.1%; adverse event 14.4%, $p = 0.22$)	Olzanzapine: somnolence 12/90; agitation 10/90; headache 10/90; insomnia 7/90; constipation 6/90; weight gain 6/90; anxiety 5/90; rhinitis 5/90; dry mouth 4/90 ($p = 0.043$); vomiting 4/90; influenza syndrome 3/90; asthenia 2/90; increased salivation 2/90, sweating 2/90; dizziness 1/90; fever 1/90; leucopenia 1/90; nausea 1/90 Clozapine: somnolence 22/90; agitation 4/90; headache 5/90; insomnia 3/90; constipation 17/90 ($p = 0.014$); weight gain 6/90; anxiety 5/90; rhinitis 3/90; vomiting 5/90; influenza syndrome 5/90; asthenia 6/90; increased salivation 26/90 ($p < 0.001$); sweating 5/90; dizziness 8/90 ($p = 0.017$); fever 5/90; leucopenia 5/90; nausea 10/90 ($p = 0.005$); tooth disorder 4/90 ($p = 0.043$) AMDP-5 solicited adverse events scale (statisically significant): *olanzapine*: drowsiness 23/89; hypersalivation 13/89; dry mouth 24/89 ($p = 0.019$) dizziness 6/89; increased perspiration 8/89; hypotonia 2/89; tardive dykinesia 5/89 ($p = 0.026$); *clozapine*: drowsiness 41/86 ($p = 0.003$) hypersalivation 54/86 ($p < 0.001$); dry mouth 11/86; dizziness 26/86 ($p = 0.001$); increased perspiration 19/89 ($p = 0.016$); hypotonia 9/86 ($p = 0.025$); tardive dykinesia 0/86 Mean weight change (SD): olanzapine 1.8 (5.0) kg; clozapine 2.3 (4.9) kg – no significant difference Mean decrease in orthostatic blood pressure (SD): olanzapine 0.5 (14.5) mmHg; 3.7 (18.1) mmHg – no significant difference	**Authors' conclusions** Olanzapine demonstrated to be non-inferior to clozapine and better tolerated among patients with treatment-resistant illness eligible for treatment with clozapine

continued

Clozapine RCTs *contd*

Tollefson 2001[76] *contd*

Results

	Outcome 1	Outcome 2	Outcome 3	Outcome 4
General comments: Using 'absolute' observed group mean changes from baseline, difference in means was 3.5 units in favour of olanzapine, and one-sided lower 95% confidence limit, –2.2, indicating no clinical difference between treatments. Using 'adjusted' group mean changes from baseline, difference in means was 3.8 units in favour of olanzapine and one-sided lower 95% confidence limit, –1.9. *Post-hoc* ANCOVA: adjusted endpoint least squares means, 80.3 olanzapine; 83.4 clozapine, with one-sided CI of –3.7	**Outcome:** PANSS total (postive; negative subscales). Final equals change from baseline **Intervention:** (*n* = 89) –25.6, 25.5 (–6.8, 7.6; –7.1, 7.4) **Control:** (*n* = 87) –22.1, 23.1, *p* = 0.888 (–6.4, 7.2; –5.6, 6.9)	**Outcome:** CGI-S; BPRS total. Final equals change from baseline **Intervention:** (*n* = 89) –1.1, 1.2; –15.2, 15.3 **Control:** (*n* = 87) –0.9, 1.1; –14.0, 13.3	**Outcome:** BPRS+ CGI-S; PANSS total score (≥ 20%; ≥ 30%; ≥ 40%; ≥ 50% improvement; no improvement) **Intervention:** (*n* = 89) 34/89; 53/89; 41/89; 24/89; 9/89; 11/89 **Control:** (*n* = 87) 30/87; 47/87; 28/87; 14/87; 9/87; 14/87	**Outcome:** EPS rating scales: SAS total; AIMS non-global total; BAS global score. Final equals change from baseline **Intervention:** (*n* = 88) –3.2, 4.8; –0.8, 2.2; –0.3, 0.9 **Control:** (*n* = 84) –1.4, 3.3 (*p* = 0.006); –0.7, 2.5; –0.4, 1.0

Clozapine RCTs *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
HGCF (2001)[201]	**Intervention:** olanzapine ***N*:** not stated **Dose:** not stated **Control:** clozapine ***N*:** not stated **Dose:** not stated **Duration:** not stated	**Age:** not stated **Sex:** not stated **Illness:** schizophrenia **Diagnosis:** not stated **Duration of illness:** not stated **Special characteristics:** patients with treatment-resistant illness **Inclusion/exclusion criteria:** not stated	Not stated	Not reported	**Authors' conclusions** Not stated

Results

General comments:	Outcome 1	Outcome 2	Outcome 3
	Outcome: mean improvement in total PANSS score	**Outcome:** response rates, improvement in PANSS score > 20% and > 50%	**Outcome:** response rates, improvement in PANSS score > 30%; > 40%
	Intervention: equivalent efficacy to clozapine: WMD, –3.50, p = 0.3	**Intervention:** not stated	**Intervention:** trend in favour of olanzapine; risk difference 14%, p = 0.06; risk difference 11%, p = 0.08

Clozapine RCTs *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Chowdhury 1999[71]	**Intervention:** clozapine ***N*:** 30 **Dose:** initial dose, 50 mg daily, increased by 50 mg to 150 mg daily by week 2. By week 3, dose range 250–300 mg daily **Control:** risperidone ***N*:** 30 **Dose:** 1 mg twice daily starting dose, then 2 mg twice daily from day 2 onwards. After week 1, 6 mg daily up to maximum 8 mg daily **Duration:** 16 weeks **Washout:** 7 days **Concomitant medications:** none reported **Comments:** mean (SD) maximum dose, clozapine, 342.86 (84.21) mg daily; risperidone, 5.8 (1.33) mg daily	**Age:** mean (SD): clozapine 30.3 (8.78) years; risperidone 32.43 (9.79) years **Sex:** clozapine 22/30 male; risperidone 23/30 male **Illness:** schizophrenia **Diagnosis:** ICD10 ***N*:** 60 **Duration of illness:** mean (SD): clozapine 6.92 (5.07) years; risperidone 18 (4.38) years **Special characteristics:** paranoid subtype, clozapine 56.67%; risperidone 60%; other subtypes included hebephrenia, residual and undifferentiated **Inclusion/exclusion criteria:** aged 15–60 years; duration of illness > 6 months and received at least one full course of treatment with conventional antipsychotic drugs (either chlorpromazine, 600–800 mg daily, haloperidol or trifluoperazine in equivalent doses) without adequate response; patients intolerant to traditional neuroleptic drugs because of intractable neurological and non-neurological side-effects, necessitating withdrawal of drug or inadequate dosing **Further details:** 72 participants satisfied inclusion criteria for study, nine did not enter trial; of 63 remaining, three dropped out during washout period	**Intervention group:** 6 dropouts: 4 side-effects; 1 refusal to do blood test; 1 lost to follow-up **Control group:** 8 dropouts: 3 severe akathisia; 3 inadequate response; 2 lost to follow-up	Clozapine: tachycardia 76.66%; hypersalivation 60%; sedation 60%; weight gain 43.33%; constipation 30%; leucocytosis 26.66%. (1 patient suffered an episode of seizure) Risperidone: constipation 50%; dry mouth 46.66%; weight gain 43.33%; akathisia 36.67%; insomnia 33.33%; tachycardia 30%; impotence 26.66%	**Authors' conclusions** Both clozapine and risperidone effective and well tolerated at standard doses in Indian patients with chronic schizophrenia who were resistant to or intolerant of conventional neuroleptic drugs

Results

General comments: results of statistical analyses reported in paper very unclear

Outcome 1

Outcome: PANSS scores total (postive, negative, general subscales)

Intervention: (*n* = 30) 93.16 (SD 9.57) (22.0, SD 6.74; 23.67, SD 6.46; 47.53, SD 7.18) (*n* = 30) 92.97, SD 14.80 (21.67, SD 5.92; 23.73, SD 8.66; 47.57, SD 8.72)

Control: (*n* = 24) 50.0, SD 17.80 (10.08, SD 3.06; 14.08, SD 6.66; 25.83, SD 8.74) (*n* = 22) 50.45, SD 20.74 (10.04, SD 3.26; 14.55, SD 8.33; 25.86, SD 9.98)

Outcome 2

Outcome: treatment success rate (> 20% reduction from baseline on PANSS) total; positive; negative; general subscales

Intervention: 80%; 80%; 73.33%; 80% 66.7%; 66.7%; 63.33%; 66.7%

Clozapine RCTs *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Salganik 1998[72]	**Intervention:** clozapine ***N*:** 17 **Dose:** not stated **Control:** haloperidol ***N*:** 17 **Dose:** not stated **Duration:** 10 weeks on each treatment **Washout:** 7 days x 2 **Concomitant medications:** none administered **Comments:** crossover design study; prior to washout, patients underwent 14 days of gradual reduction of current medication. After 10 weeks patients blindly switched to other study drug, again following gradual dose reduction and further washout period. Doses adjusted according to clinical response	**Age:** Mean (SD): 66.6 (5.08) years **Sex:** 10/17 female **Illness:** schizophrenia **Diagnosis:** DSM-III-R ***N*:** 17 **Duration of illness:** not stated **Special characteristics:** all patients aged 60–78 years and hospitalised in closed psychogeriatric ward **Inclusion/exclusion criteria:** Excluded: history of granulocytopenia or myelo-proliferative disorders or alcoholic or toxic psychosis, drug intoxication, or hepatic or renal disease **Further details:** elderly patients with chronic schizophrenia	**Intervention group *n*:** 5 participants dropped out while on clozapine (1 urinary tract infection, 2 ataxia, 1 electro-cardiographic changes, 1 lack of efficacy) **Control group *n*:** 2 participants dropped out while on halo-peridol (1 leuko-cytopenia, 1 lack of compliance)	No significant differences noted between clozapine and haloperidol for weekly blood pressure or weight gain, fewer extrapyramidal symptoms, somnolence and ataxia with clozapine, but did not reach statistical significance	**Authors' conclusions** Present study shows that clozapine and haloperidol do not have significantly different effect in elderly patients with chronic schizophrenia
Results					
General comments: ANOVA, with repeated measures of average total scores of all rating scales at end of each period of drugs use for ten patients who completed study, showed no significant difference in effect between clozapine and haloperidol; no significant difference in findings for men and women. However, when each symptom analysed separately, results significant for exaggerated self-esteem ($F = 2.15$, $df = 9$, $p = < 0.05$) and motor retardation ($F = 2.58$, $df = 9$, $p < 0.01$) on BPRS. Effect of clozapine on those symptoms noted after first week of intake, whereas haloperidol induced change to similar levels only after 7 weeks. Paired *t*-test and ANCOVA of total scores of last 2 weeks with baseline score as covariate yielded no significant results for any of psychometric measures. Patients with severe depression (depression scores > 15) improved significantly ($p < 0.0.5$) with clozapine				

Clozapine RCTs *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Chow 2000[73]	**Intervention:** clozapine **N:** 12 **Dose:** not stated **Control:** usual antipsychotic medication **N:** 13 **Dose:** not stated **Duration:** 12 weeks **Washout:** possibly 2 weeks (not clear) **Concomitant medications:** not stated	**Age:** Not stated **Sex:** 17/25 male **Illness:** combined diagnoses **Diagnosis:** DSM-IV **N:** 25 **Duration of illness:** not stated **Special characteristics:** 21 schizophrenia, 2 schizoaffective disorder, psychotic disorder due to general medical condition; aggressive psychotic patients **Inclusion/exclusion criteria:** not stated	**Intervention group *n*:** not stated **Control group *n*:** not stated	Not reported	**Authors' conclusions** Although sample size small and duration of study relatively short, results of study provide further evidence for anti-aggressive effect of clozapine
Results					
General comments: two study groups did not differ in age, duration of illness, PANSS nor MOAS scores at baseline. On repeated measures ANOVA over time, mean total MOAS scores were significantly different between two groups ($F = 5.24$, $df = 1$; $p = 0.03$). Analysis of subscales of MOAS indicated that reduction in total MOAS score came mainly from decrease in verbal aggression. Time spent in seclusion also significantly decreased in clozapine group ($F = 2.69$, $df = 6$; $p = 0.02$), although no difference in use of restraints				

MOAS, Modified Overt Agression Scale

Clozapine RCTs *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Bitter 1999[74]	**Intervention:** olanzapine ***N*:** not stated **Dose:** 10 mg daily **Control:** clozapine ***N*:** not stated **Dose:** 25 mg daily, titrated in a fixed manner from 25 mg daily to 150 mg daily over 7 days **Duration:** 18 weeks **Washout:** 2–9 days **Concomitant medications:** not stated **Comments:** numbers in each group not given	**Age:** most > 30 years **Sex:** 59.3% male **Illness:** schizophrenia **Diagnosis:** DSM-IV ***N*:** 150 **Duration of illness:** not stated **Special characteristics:** treatment-resistant or -intolerant **Inclusion/exclusion criteria:** patients must have failed to respond adequately to standard acceptable antipsychotic medication, because of either ineffectiveness or intolerable side-effects caused by medication	Not stated	Patients treated with olanzapine reported statistically more back pain; those treated with clozapine reported statistically more somnolence and dizziness. Tachycardia occurred numerically more often in clozapine- than olanzapine-treated patients. In terms of extrapyramidal symptoms, no statistically significant differences found in parkinsonism (measured by SAS), akathisia (Hillside akathisia scale) and dykinesia (AIMS). No statistically significant difference in weight change between clozapine- and olanzapine-treated patients	**Authors' conclusions** Olanzapine demonstrated similar efficacy and safety to clozapine in patients with treatment-resistant schizophrenia

Results		
General comments:	**Outcome 1**	**Outcome 2**
	Outcome: BPRS total (positive; negative)	**Outcome:** PANSS total (positive; negative; general subscales)
	Intervention: –24.0, 1.7 (–7.2, 4.7; –3.6, 2.8)	**Intervention:** –37.7, 23.1(–11.7, 7.3; –7.6, 6.0; –18.4, 11.7)
	Control: –23.7, 14.2 (–7.4, 3.4; –3.6, 2.8) no significant difference	**Control:** –37.9, 23.4 (–11.8, 7.9; –7.7, 6.1; –18.4, 11.5) no significant difference

Clozapine RCTs *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Cosar 1999[75]	**Intervention:** clozapine ***N*:** 40 **Dose:** average 463 mg daily; oral **Control 1:** sulpiride ***N*:** 40 **Dose:** average 696 mg daily; oral **Control 2:** haloperidol ***N*:** 40 **Dose:** average 35 mg daily; oral **Control 3:** chlorpromazine ***N*:** 40 **Dose:** average 454 mg daily; oral **Duration:** 90 days **Washout:** not stated **Concomitant medications:** none stated	**Age:** not stated **Sex:** not stated **Illness:** schizophrenia **Diagnosis:** DSM-IV ***N*:** 160 **Duration of illness:** not stated **Inclusion/exclusion criteria:** not stated **Further details:** abstract states *N* = 120 but 40 participants in each of 4 groups = 160	**Intervention group *n*:** not stated **Control group *n*:** not stated	None reported	**Authors' conclusions** Clozapine and sulpiride are antipsychotic drugs that show different mechanism of action than chlorpromazine and haloperidol. This generally causes them to be more effective than classical antipsychotic drugs in treatment of schizophrenic symptoms

Results

General comments: not clear what is meant by efficiency

Outcome 1

Outcome: BPRS

Intervention: comparing groups, most efficient results obtained in clozapine group, sulpiride group second and chlorpromazine and haloperidol had equal antipsychotic effects ($p < 0.01$, Sheffe analysis)

Olanzapine RCTs

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Breier 2001[160]	**Intervention:** olanzapine ***N*:** not stated **Dose:** up to three injections within 24 hours of 2.5, 5 7.5 or 10 mg intramuscularly **Control:** haloperidol ***N*:** not stated **Dose:** up to three injections within 24 hours of 7.5 mg; intramuscularly **Control 2:** placebo ***N*:** not stated **Dose:** up to three injections within 24 hours intramuscularly **Duration:** 24 hours **Washout:** none **Concomitant medications:** anticholinergic and benzodiazepine use recorded	**Age:** not stated **Sex:** not stated **Illness:** schizophrenia **Diagnosis:** not stated ***N*:** 270 **Duration of illness:** not stated **Special characteristics:** acutely agitated patients with schizophrenia for whom oral therapy could not be instituted **Inclusion/exclusion criteria:** not stated	**Intervention group *n*:** none stated	Anticholinergics rarely used; benzodiazepine use most common in placebo group. Hypotension, dizziness and tremor most frequently reported adverse events. EPS improved in olanzapine and placebo groups but worsened in haloperidol group ($p < 0.05$ versus haloperidol)	**Authors' conclusions** Study suggests that intramuscular olanzapine (2.5–10 mg) provides rapid, sustained, safe alleviation of acute agitation in patients with schizophrenia
Results					
General comments: olanzapine therapy showed dose-related alleviation of agitation across all treatment groups ($p < 0.001$). Onset of action rapid, with olanzapine, 5, 7.5 and 10 mg, groups showing significant improvement versus placebo as early as 30 minutes after first injection. All olanzapine and haloperidol groups showed significant improvement versus placebo at 2 hours and olanzapine, 5, 7.5 and 10 mg, groups significantly improved at all measured time-points versus placebo. Olanzapine, 2.5 mg, and haloperidol groups significantly different from placebo at 60 minutes. Response rates higher in all olanzapine and haloperidol groups. Alleviation of acute agitation by olanzapine but not haloperidol sustained at 24 hours ($p < 0.05$)			**Outcome 1** Reduction in agitation (PANSS excited component) at 2 hours post first injection	

Olanzapine RCTs *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Naukkarinen 1999[147]	**Intervention:** olanzapine ***N*:** 23 **Dose:** 5–20 mg daily **Control:** perphenazine ***N*:** 23 **Dose:** 8–32 mg daily **Duration:** not stated	**Age:** not stated **Sex:** not stated **Illness:** schizophrenia **Diagnosis:** DSM-IV ***N*:** 46 **Duration of illness:** not stated **Inclusion/exclusion criteria:** at least moderately ill (CGI 4); aged 18–70 years	**Intervention group *n*:** not reported **Control group *n*:** not reported	Not reported	**Authors' conclusions** On basis of results, it can be concluded that olanzapine and perphenazine exhibited very similar pattern of treatment efficacy and safety in re-entry patients with schizophrenia with acute symptoms

Results

General comments: no significant differences between groups with regard to treatment efficacy, treatment-emergent extrapyramidal symptoms or other adverse effects; no statistical differences between groups with regard to premature discontinuation of treatment, or amount of cocomitant medication. No clinical differences noticed in vital signs or weight gain

Outcome 1

Outcome: PANSS, BPRS and CGI total scores

Intervention: both groups declined significantly

Control: both groups declined

Olanzapine RCTs *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Gureje 1998[186]	**Intervention:** olanzapine ***N*:** not stated **Dose:** 10–20 mg once daily (started at 15 mg daily) **Control:** risperidone ***N*:** not stated **Dose:** 4–8 mg daily (started at 1 mg twice daily) **Duration:** 30 weeks with washout period of not more than 9 days	**Age:** not stated **Sex:** not stated **Illness:** schizophrenia, schizophreniform disorder or schizoaffective disorder **Diagnosis:** DSM-IV ***N*:** not stated **Duration of illness:** not stated **Inclusion/exclusion criteria:** BPRS total score > 36 (extracted from PANSS, items 1–7)	**Intervention group *n*:** not reported **Control group *n*:** not reported	Trend for olanzapine-treated patients to evidence fewer treatment-emergent adverse effects	**Authors' conclusions** Not stated
Results					
General comments: compared with those treated with risperidone, olanzapine-treated patients showed greater reduction in BPRS total score for weeks 22–30. Greater proportion also achieved reduction of 20% or more on PANSS total score at week 30. At week 30, olanzapine-treated patients had better profile of quality of life as assessed by SF-36 and disease-specific Quality of Life in Schizophrenia scale. Trend for olanzapine-treated patients to evidence fewer treatment-emergent adverse effects				

Olanzapine RCTs *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Fleming 1998[70]	**Intervention:** olanzapine ***N*:** 9 **Dose:** 20 mg daily **Control:** clozapine ***N*:** 9 **Dose:** 200–600 mg daily **Duration:** 6 weeks **Washout:** mean of 9.3 days **Concomitant medications:** not stated **Comments:** crossover design; no information about washout period between treatment phases	**Age:** not stated **Sex:** not stated **Illness:** schizophrenia **Diagnosis:** not stated ***N*:** 18 **Duration of illness:** not stated **Special characteristics:** stable outpatients **Inclusion/exclusion criteria:** stable outpatients	Not stated	Not presented	**Authors' conclusions** Although findings must be viewed with caution as sample size small, they highlight possibility that olanzapine and clozapine may be differentially effective at treating clinical and neurocognitive aspects of schizophrenia

Results

General comments: no data presented

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome: PANSS total score compared with placebo washout period (baseline)	**Outcome:** PANSS negative symptoms only, compared with placebo washout (baseline)	**Outcome:** cognition (motor speed) compared with placebo washout (baseline)	**Outcome:** immediate memory and attention, compared with placebo washout
Intervention: $p < 0.002$	**Intervention:** not significant	**Intervention:** $p < 0.04$	**Intervention:** immediate memory: $p < 0.03$ (also $p < 0.03$ compared with clozapine); attention: $p < 0.05$ (and versus clozapine $p < 0.01$); not significant
Control: $p < 0.008$	**Control:** $p < 0.002$	**Control:** $p < 0.08$	

Olanzapine RCTs *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Reams 1998[149] Kuntz 1998[362]	**Intervention:** olanzapine ***N*:** not stated **Dose:** 5–20 mg daily **Control:** haloperidol ***N*:** not stated **Dose:** 5–20 mg daily **Duration:** 6 weeks	**Age:** 59 years or older **Sex:** not stated **Illness:** combined diagnoses **Diagnosis:** not stated ***N*:** 59 **Duration of illness:** not stated **Special characteristics:** elderly **Inclusion/exclusion criteria:** schizophrenia, schizophreniform or schizoaffective disorder	Not stated	Treatment-emergent adverse events reported by more than 10% patients in olanzapine group: insomnia, somnolence, accidental injury. Those reported statistically significantly more often in haloperidol group: back pain, tremor, akathisia, rhinitis. None reported statistically significantly more often in olanzapine compared with haloperidol group. BAS improved on olanzapine but worsened on haloperidol; treatment difference statistically significant	**Authors' conclusions** Results suggest that olanzapine, 5–20 mg daily, is safe and effective treatment for schizophrenia and related psychotic disorders in elderly patients
Results					
General comments: probably other outcomes not reported	**Outcome 1** **Outcome:** BPRS total, PANSS total and negative, MADRS total **Intervention:** greater improvement compared with haloperidol; not statistically significant				

Olanzapine RCTs *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Gomez 2001[150]	**Intervention:** olanzapine ***N*:** 1112 **Dose:** 5 mg daily increasing after 1 week as necessary in increments of 5 mg weekly to maximum of 20 mg daily. Dose reductions permitted during study (minimum dose 5 mg daily); oral **Control:** haloperidol ***N*:** 546 **Dose:** 5 mg daily increasing after 1 week as necessary in increments of 5 mg weekly to maximum of 20 mg daily. Dose reductions permitted during study (minimum dose 5 mg daily); oral **Duration:** 6 week, acute phase **Washout:** 2–9 days, placebo controlled **Concomitant medications:** not stated	**Age:** 38.62 (SD 11.41) **Sex:** 1132/1658 male **Illness:** schizophrenia (sub-group of larger study) **Diagnosis:** DSM-III-R ***N*:** 1658 **Duration of illness:** not stated **Special characteristics:** 1658 diagnosed with schizophrenia of total study population of 1996 with schizophrenia or schizophreniform or schizoaffective disorder **Inclusion/exclusion criteria:** see Tollefson 1997[164]	**Intervention group *n*:** 1096/1112 included in analysis (had baseline plus at least one postbaseline measurement) **Control group *n*:** 526/546 included in analysis	Not reported	**Authors' conclusions** Olanzapine more effective than haloperidol in treating varied spectrum of patients with schizophrenia, including those with positive, negative, or mixed symptom profiles, and either chronic or sub-chronic course of illness

Results

General comments:	**Outcome 1**	**Outcome 2**
detailed breakdown by further subgroups produced findings that were generally suppportive of overall findings. These subgroups of subgroups not presented	**Outcome:** BPRS total; positive; negative (mean) **Intervention:** change from baseline (mean, SD): –10.80, 12.76; –3.38, 4.23; –2.04, 2.88 **Control:** change from baseline (mean, SD): –8.31,12.55 ($p < 0.001$); –2.92, 3.95 ($p = 0.022$); –1.34, 2.92 ($p < 0.001$)	**Outcome:** PANSS total, positive, negative (mean) **Intervention:** change from baseline (mean, SD): –17.53, 21.65; –4.69, 6.72; –4.48, 6.32 **Control:** change from baseline (mean, SD): –14.04, 21.16 ($p < 0.001$); –3.97, 6.36 ($p = 0.023$); –3.37, 6.19 ($p < 0.001$)

Olanzapine RCTs *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Tollefson 2001[76] **Trial ID:** same as Beuzen 1998 but with some additional data (see appendix 3)	**Intervention:** olanzapine ***N*:** 90 **Dose:** 15 mg daily, after first 2 weeks 15–25 mg daily **Control:** clozapine ***N*:** 90 **Dose:** fixed dose escalation, 25–200 mg daily during first 8 days of therapy, after first 2 weeks 200–600 mg daily **Duration:** 18 weeks **Washout:** 2–9 days **Concomitant medications:** Benzodiazepine (up to 40 mg daily diazepam equivalent or 8 mg lorazepam equivalent) for agitation, choral hydrate for insomnia, and biperiden or benztropine mesylate (up to 4 mg daily) for EPS permitted **Comments:** with either drug, blinded titration permitted; investigators had opportunity to increase or decrease dose by either olanzapine, 2.5 or 5 mg, or clozapine, 50 or 100 mg, per visit interval. 44/83 clozapine-treated patients received maximum daily dose, 400–600 mg, mean (SD) dose, 303.6 (108.7) mg daily. 59/88 olanzapine-treated patients received maximum dose, 25 mg, mean (SD) dose, 20.5 (2.8) mg daily	**Age:** mean (SD): 38.6 (10.6) years **Sex:** 115/180 male **Illness:** schizophrenia **Diagnosis:** DSM-IV ***N*:** 180 **Duration of illness:** not stated **Special characteristics:** schizophrenia subtypes: catatonic 3/180; disorganised 34/180; paranoid 101/180; undifferentiated 34/180; residual 8/180. Schizophrenia course: residual symptoms 81/180; no residual symptoms 3/180; continuous 92/180; in partial remission 2/180; other pattern 2/180 **Inclusion/exclusion criteria:** aged 18–70 years; in- or outpatient; minimum BPRS score, extracted from PANSS, at least 45 and score of 4 or more on at least two items of PANSS positive symptom subscale (items 1–7); clinically resistant to previous antipsychotic treatments (lack of satisfactory clinical response to ≥ 2 previous oral neuroleptic treatments, each of different chemical class, duration ≥ 6 weeks, appropriate dose equivalent to ≥ 500 mg chlorpromazine, or to maximum daily dosage when intolerable side-effects were documented Excluded: previous treatment with olanzapine, olanzapine or clozapine nonresponders or with known intolerance to either drug; pregnant or lactating women; patients with serious medical illnesses in which pharmacotherapy posed risk	**Intervention group *n*:** 60.0% participants completed study (lack of efficacy 13.3%; patient decision 10.0%; lost to follow-up 2.2%; other 10.1%; adverse event 4.4%) **Control group *n*:** 58.9% participants completed study (lack of efficacy 10.0%; patient decision 4.4%; lost to follow-up 2.2%; other 10.1%; adverse event 14.4%, $p = 0.22$)	Olzanzapine: somnolence 12/90; agitation 10/90; headache 10/90; insomnia 7/90; constipation 6/90; weight gain 6/90; anxiety 5/90; rhinitis 5/90; dry mouth 4/90 ($p = 0.043$); vomiting 4/90; flu syndrome 3/90; asthenia 2/90; increased salivation 2/90, sweating 2/90; dizziness 1/90; fever 1/90; leucopenia 1/90; nausea 1/90. Clozapine: somnolence 22/90; agitation 4/90; headache 5/90; insomnia 3/90; constipation 17/90 ($p = 0.014$); weight gain 6/90; anxiety 5/90; rhinitis 3/90; vomiting 5/90; flu syndrome 5/90; asthenia 6/90; increased salivation 26/90 ($p < 0.001$); sweating 5/90; dizziness 8/90 ($p = 0.017$); fever 5/90; leucopenia 5/90; nausea 10/90 ($p = 0.005$); tooth disorder 4/90 ($p = 0.043$) AMDP-5 Solicited Adverse Events Scale (statistically significant): *olanzapine*: drowsiness 23/89; hypersalivation 13/89; dry mouth 24/89 ($p = 0.019$) dizziness 6/89; increased perspiration 8/89; hypotonia 2/89; tardive dyskinesia 5/89 ($p = 0.026$) *clozapine*: drowsiness 41/86 ($p = 0.003$); hypersalivation 54/86 ($p < 0.001$); dry mouth 11/86; dizziness 26/86 ($p = 0.001$); increased perspiration 19/89 ($p = 0.016$); hypotonia 9/86 ($p = 0.025$); tardive dyskinesia 0/86 Mean weight change (SD): olanzapine 1.8 (5.0) kg; clozapine 2.3 (4.9) kg; no significant difference Mean decrease in orthostatic blood pressure (SD): olanzapine 0.5 (14.5) mmHg; 3.7 (18.1) mmHg; no significant difference	**Authors' conclusions** Olanzapine demonstrated to be non-inferior to clozapine and better tolerated in schizophrenic patients with treatment-resistant illness eligible for treatment with clozapine

continued

Olanzapine RCTs *contd*

Tollefson 2001[76] *contd*

Results

	Outcome 1	Outcome 2	Outcome 3	Outcome 4
General comments: using 'absolute' observed group mean changes from baseline, difference in means was 3.5 units in favour of olanzapine, and one-sided lower 95% confidence limit was –2.2, indicating no clinical difference between treatments. Using 'adjusted' group mean changes from baseline, difference in means was 3.8 units in favour of olanzapine and one-sided lower 95% confidence limit was –1.9. *Post-hoc* ANCOVA: adjusted endpoint least squares means, 80.3 olanzapine, 83.4 clozapine, with one-sided CI of –3.7	**Outcome:** PANSS total (positive; negative subscales); final equals change from baseline **Intervention:** (*n* = 89) –25.6, 25.5 (–6.8, 7.6; –7.1, 7.4) **Control:** (*n* = 87) –22.1, 23.1, *p* = 0.888 (–6.4, 7.2; –5.6, 6.9)	**Outcome:** CGI-S; BPRS total; final equals change from baseline **Intervention:** (*n* = 89) –1.1, 1.2; –15.2, 15.3 **Control:** (*n* = 87) –0.9, 1.1; –14.0, 13.3	**Outcome:** BPRS + CGI-S; PANSS total score (≥ 20%; ≥ 30%; ≥ 40%; ≥ 50% improvement; no improvement) **Intervention:** (*n* = 89) 34/89; 53/89; 41/89; 24/89; 9/89; 11/89 **Control:** (*n* = 87) 30/87; 47/87; 28/87; 14/87; 9/87; 14/87	**Outcome:** EPS rating scales: SAS total; AIMS non-global total; BAS global score; final equals change from baseline **Intervention:** (*n* = 88) –3.2, 4.8; –0.8, 2.2; –0.3, 0.9 **Control:** (*n* = 84) –1.4, 3.3 (*p* = 0.006); –0.7, 2.5; –0.4, 1.0

Olanzapine RCTs *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Wright 2000[151]	**Intervention:** olanzapine ***N*:** not stated **Dose:** 10 mg x 3 in 24 hours; intramuscular injection **Control:** haloperidol ***N*:** not stated **Dose:** 7.5 mg x 3 in 24 hours; intramuscular injection **Control 2:** placebo; intramuscular injection ***N*:** not stated **Duration:** 2 hours **Washout:** not stated **Concomitant medications:** not stated **Comments:** numbers in each group not stated; randomised olanzapine: haloperidol: placebo 2:2:1	**Age:** not stated **Sex:** not stated **Illness:** schizophrenia **Diagnosis:** not stated ***N*:** 311 **Duration of illness:** not stated **Inclusion/exclusion criteria:** patients with schizophrenia who refused antipsychotic therapy or were acutely agitated	Not reported	Significantly fewer olanzapine- and placebo-treated patients required concomitant anticholinergic therapy during 24-hour period compared with haloperidol-treated patients (4.6%: 3.7%: 20.6%; $p < 0.001$ and $p = 0.003$, respectively). Significantly fewer olanzapine- and haloperidol-treated patients required concomitant benzodiazepine therapy compared with placebo-treated patients (16.0%: 19.8%: 38.9%; $p = 0.002$ and $p = 0.009$, respectively). Statistically significantly greater incidence of treatment-emergent adverse events shown for haloperidol- compared with olanzapine-treated patients for EPS (5.6% versus 0.8%, $p = 0.033$) and dystonia (7.1% versus 0%, $p = 0.001$). Olanzapine- and placebo-treated patients experienced improvement in symptoms of parkinsonism, as measured by SAS, while haloperidol-treated patients worsened ($p < 0.001$ in both cases). Olanzapine-treated patients experienced improvement in akathisia symptoms, measured by BAS global score, while haloperidol-treated patients worsened ($p = 0.002$)	**Authors' conclusions** Study provides evidence that short-acting intramuscular olanzapine rapidly and effectively provides sustained and safe alleviation of acute agitation in patients with schizophrenia

Results		
General comments:	**Outcome 1**	**Outcome 2**
	Outcome: PANSS excited component change from baseline	**Outcome:** sustained alleviation of acute agitation at 24 hours
	Intervention: –7.74	**Intervention:** significant compared with placebo ($p < 0.001$)
	Control: –7.63 (0.11 difference compared with olanzapine, one-sided 97.5% CI = –1.2)	**Control:** significant compared with placebo ($p < 0.001$)
	Control 2: –3.55, significant difference	

Olanzapine RCTs *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Kolff 2000[152]	**Intervention:** risperidone ***N*:** 23 **Dose:** not stated; oral **Control:** olanzapine ***N*:** 27 **Dose:** not stated; oral **Duration:** 6 weeks **Washout:** not stated **Concomitant medications:** not stated	**Age:** not stated **Sex:** not stated **Illness:** schizophrenia **Diagnosis:** not stated ***N*:** 50 **Duration of illness:** not stated **Special characteristics:** not specified that patients' illnesses were treatment-resistant, or refractory or that they were treatment-intolerant **Inclusion/exclusion criteria:** not stated	**Intervention group *n*:** not stated **Control group *n*:** not stated	Not reported	**Authors' conclusions** Risperidone and olanzapine were generally comparable both with respect to their clinical properties and their cognitive effects. Indication obtained that risperidone may act more on positive and olanzapine more on negative symptoms of schizophrenia

Results

General comments	Outcome 1	Outcome 2	Outcome 3
General comments: only conference abstract so little information presented. Because of small sample size, reported trend for olanzapine to affect negative and risperidone positive symptoms should be disregarded	**Outcome:** clinical symptoms (PANSS) **Intervention:** in both groups, general improvement established on PANSS score between baseline and final assessment on both positive and negative symptoms; no significant differences found between drugs although olanzapine tended to have larger effect on negative symptoms and risperidone on positive symptoms	**Outcome:** psychometric tests (continuous performance test for sustained attention, verbal learning and memory test, Stroop interference test and WAIS) **Intervention:** no general differences between drugs found on all measured cognitive functions; however, participants treated with olanzapine scored significantly better on Stroop interference test	**Outcome:** psychomotor speed (finger-tapping and trail-making tests) **Intervention:** no differences between drugs found

Olanzapine RCTs *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Malyarov 1999[153]	**Intervention 1:** olanzapine ***N*:** 15 **Dose:** 5–15 mg daily **Intervention 2:** risperidone ***N*:** 10 **Dose:** 3–6 mg daily **Control:** haloperidol ***N*:** 18 **Dose:** 5–20 mg daily **Duration:** 6 months	**Age:** average: 24.5 years **Sex:** 28/43 male **Illness:** schizophrenia **Diagnosis:** ICD10 ***N*:** 43 **Duration of illness:** < 3 years **Special characteristics:** patients with diagnosis of schizophrenia with acute psychotic states; hospitalised **Inclusion/exclusion criteria:** not stated	**Intervention 1 group:** 0 dropouts **Intervention 2 group:** 2 dropouts **Control group:** 3 dropouts	Not reported	**Authors' conclusions** Changes in atypical antipsychotic-treated patients directly related to social functioning may be useful explanantion of striking differences between two groups in GAF scores

Results

General comments: most prominent changes in patients treated with atypical antipsychotic drugs observed in symptoms directly related to social functioning, e.g. emotional withdrawal, poor rapport, abstract thinking, impulse control, disturbance of volition, lack of judgement, poor insight

Outcome 1	Outcome 2	Outcome 3
Outcome: PANSS total scores **Intervention:** scores did not vary significantly	**Outcome:** GAF mean scores **Intervention:** 55–70 (both groups) **Control:** 45–60, $p < 0.05$	**Outcome:** mean difference PANSS (postive; negative; general subscales) **Intervention:** 1.4%, no significant difference; 11%, $p < 0.01$; 13.5%, $p < 0.01$)

Olanzapine RCTs *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Gregor 1999[163]	**Intervention:** olanzapine ***N*:** 520 **Dose:** not stated **Control:** haloperidol ***N*:** 258 **Dose:** not stated **Duration:** 6 weeks acute phase, then 46 weeks maintenance phase for responders **Washout:** not stated **Concomitant medications:** not stated **Comments:** maintenance phase double-blind; predefined level of response	**Age:** not stated **Sex:** not stated **Illness:** schizophrenia **Diagnosis:** not stated ***N*:** 778 **Duration of illness:** not stated **Inclusion/exclusion criteria:** not stated	**Intervention group *n*:** 69.4% completed acute phase, 52.0% completed maintenance phase **Control group *n*:** 53.9% completed acute phase ($p < 0.001$), 35.6% completed maintenance phase ($p = 0.005$)	None reported	**Authors' conclusions** Findings suggest that olanzapine's clinical profile leads to reduced hospitalisation and improvements in social and vocational functioning superior to that achieved with haloperidol treatment

Results

General comments:

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome: BPRS total **Intervention:** olanzapine participants' improvements superior to haloperidol participants ($p = 0.041$)	**Outcome:** PANSS negative **Intervention:** olanzapine participants' improvements superior to haloperidol participants ($p = 0.042$)	**Outcome:** QLS total score ≥ 20% improvement **Intervention:** acute 50.0%, maintenance 69.5% **Control:** acute 31.0% ($p = 0.046$), maintenance 41.7% ($p = 0.003$)	**Outcome:** hospitalised; working part or full time; participating in useful work ≥ 75% of time **Intervention:** hospitalisation less likely ($p = 0.001$); 15.1%; 21.0% **Control:** hospitalisation more likely ($p = 0.001$); 5.3%, $p = 0.021$; 10.5%, $I = 0.048$

Olanzapine RCTs *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Szafranski 1999[155]	**Intervention:** olanzapine ***N*:** not stated **Dose:** 5–20 mg **Control:** perphenazine ***N*:** not stated **Dose:** 8–40 mg **Duration:** 18 weeks **Comments:** numbers in groups not stated	**Age:** not stated **Sex:** not stated **Illness:** schizophrenia **Diagnosis:** DSM-IV ***N*:** 95 **Duration of illness:** not stated **Inclusion/exclusion criteria:** not stated	**Intervention group *n*:** 56 patients completed DAI-30 at end of study: 30 from olanzapine and 26 from perphenazine group **Control group *n*:** patients not completing protocol had more negative symptoms at baseline and after first week ($p < 0.05$); DAI-30 scores also differed (more negative attitude) after first week of treatment ($p < 0.05$)	Not stated	**Authors' conclusions** Substantial improvement of subjective attitude to pharmacotherapy found in group of patients treated with olanzapine and non-significant improvement in those treated with perphenazine

Results		
General comments: findings must be interpreted with caution due to small sample size and lack of DAI-30 scores for those who dropped out of study	**Outcome 1**	**Outcome 2**
	Outcome: DAI-30 score: mean (SD) **Intervention:** 18.6 (8.6) **Control:** 17.2 (9.9) ($p < 0.005$, ANOVA)	**Outcome:** SAS and BAS **Intervention:** motor side-effects significantly less pronounced in olanzapine group ($p < 0.05$ and $p < 0.01$, respectively)

Olanzapine RCTs *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Zhang 1999[156,157]	**Intervention:** olanzapine ***N*:** not stated **Dose:** not stated **Control:** haloperidol ***N*:** not stated **Dose:** not stated **Duration:** 6 weeks **Washout:** not stated **Concomitant medications:** not stated **Comments:** numbers in each group not given	**Age:** not stated **Sex:** not stated **Illness:** schizoaffective disorder **Diagnosis:** not stated ***N*:** 177 **Duration of illness:** not stated **Special characteristics:** schizoaffective disorder, bipolar type: currently manic *n* = 28, currently mixed *n* = 47, currently depressed *n* = 53, euthymic *n* = 49 **Inclusion/exclusion criteria:** not stated **Further details:** subsample of large, multicentre double-blind study	**Intervention group *n*:** not stated **Control group *n*:** not stated	None reported	**Authors' conclusions** None stated

Results

General comments	Outcome 1	Outcome 2	Outcome 3	Outcome 4
General comments: repeated measures analysis of PANSS cognitive component score by each diagnostic subtype showed that patients with schizoaffective disorder, bipolar type, currently manic randomised to olanzapine had average score reduction of 1.09/week on therapy compared with 0.22 for haloperidol group ($p = 0.050$), patients with currently depressed status randomised to olanzapine had average reduction of 0.86 compared with increase of 0.37 for haloperidol group ($p = 0.002$). No significant treatment differences present in other subgroups Relative to haloperidol, olanzapine produced greater reduction of manic symptoms in patients with schizoaffective disorder, bipolar type, currently manic or currently depressed, and a greater reduction of depressive symptoms in those with schizoaffective disorder, bipolar type, currently depressed. Results indicate olanzapine appears to have mood stabilising properties in this patient population	**Outcome:** PANSS cognitive component score mean change **Intervention:** –4.08 **Control:** –2.16 ($p = 0.052$)	**Outcome:** PANSS cognitive component score ≥ 40% improvement **Intervention:** 20.0% **Control:** 7.1% ($p = 0.043$)	**Outcome:** repeated measures analysis BPRS mania score (manic; depressed groups) **Intervention:** –1.13, –0.57 **Control:** –0.53 ($p = 0.075$), 0.11 ($p = 0.028$)	**Outcome:** MADRS score (mean change from baseline) **Intervention:** depressed: –8.57 **Control:** depressed: 6.63 ($p = 0.0001$)

Olanzapine RCTs *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Oliemeulen 2000[109]	**Intervention:** olanzapine ***N*:** 21 **Dose:** not stated **Control:** clozapine ***N*:** 15 **Dose:** not stated **Duration:** 8 weeks	**Age:** not stated **Sex:** not stated **Illness:** combined diagnoses **Diagnosis:** DSM-IV ***N*:** 36 **Duration of illness:** not stated **Inclusion/exclusion criteria:** therapy-resistant; schizophrenia or other psychotic disorders	Not stated	None reported	**Authors' conclusions** These first results show that instrument appears more sensitive than classical scales and shows differences in frontal lobe functioning of two medication groups

Results

General comments	Outcome 1	Outcome 2	Outcome 3	Outcome 4
General comments: study already in clozapine part of earlier review but not olanzapine part	**Outcome:** PANSS **Control:** showed greater improvement on positive symptoms $p < 0.01$	**Outcome:** psychomotor tests **Intervention:** significant difference from baseline **Control:** significant difference from baseline. No significant difference compared with olanzapine	**Outcome:** matching time of computerised SD score **Intervention:** significant difference in favour of clozapine	**Outcome:** Fitt's Aiming Task **Intervention:** significant difference in favour of olanzapine

Olanzapine RCTs *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
HGCF 2001[201]	**Intervention:** olanzapine ***N*:** not stated **Dose:** not stated **Control:** clozapine ***N*:** not stated **Dose:** not stated **Duration:** not stated	**Age:** not stated **Sex:** not stated **Illness:** schizophrenia **Diagnosis:** not stated ***N*:** not stated **Duration of illness:** not stated **Special characteristics:** those with treatment-resistant illness **Inclusion/exclusion criteria:** not stated	Not stated	Not reported	

Results

General comments:

Outcome 1	Outcome 2	Outcome 3
Outcome: mean improvement in total PANSS score	**Outcome:** responses rates, improvement in PANSS score > 20% and > 50%	**Outcome:** responses rates, improvement in PANSS score > 30%; > 40%
Intervention: equivalent efficacy to clozapine: WMD –3.50, p = 0.3	**Intervention:** not significant	**Intervention:** trend in favour of olanzapine; risk difference 14%, p = 0.06; risk difference 11%, p = 0.08

Olanzapine RCTs *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Tollefson 1999[164] **Trial ID:** Tollefson 1997,[163] extra data (see appendix 3)	**Intervention:** olanzapine ***N*:** 1312 **Dose:** 5–20 mg daily **Control:** haloperidol ***N*:** 636 **Dose:** 5–20 mg daily **Duration:** 6 weeks **Washout:** Not stated **Concomitant medications:** as required: benztropine mesylate (maximum 6 mg daily) or lorazepam (maximum 12 mg daily) **Comments:** after first week and at discretion of investigator, study drugs could be titrated up to maximum of 20 mg daily	**Age:** Not reported **Sex:** Not reported **Illness:** combined diagnoses **Diagnosis:** DSM-III-R ***N*:** 1948 **Duration of illness:** not reported **Inclusion/exclusion criteria:** score of 18 or more on BPRS, rated on scale of 0–6, and/or intolerant to last antipsychotic medication Excluded: other primary axis I diagnosis **Further details:** for more detailed discussion of trial, see Tollefson 1997	**Intervention group *n*:** none reported **Control group *n*:** none reported	Not reported	**Authors' conclusions** Novel pharmacology of olanzapine delivered greater therapeutic activity in anxious and depressive symptoms accompanying schizophrenia than haloperidol

Results

General comments:	Outcome 1	Outcome 2	Outcome 3
	Outcome: BPRS anxiety–depression score greater than or equal to 9 (less than nine) **Intervention:** 37% (*n* = 485/1312); acute improvement: –4.49, 3.93 (–1.70, 3.02) **Control:** 39.6% (*n* = 252/636); acute improvement: –3.87, 4.01 (–0.64, 3.04)	**Outcome:** BPRS total (anxiety/depression) **Intervention:** 22.16 (4.7) **Control:** 26.16 (5.81)	**Outcome:** path analysis **Intervention:** subgroup data presented (see paper for full details)

Olanzapine RCTs *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Tollefson 1998[167] **Trial ID:** Beasley 1996a,[168] with extra data (see appendix 3)	**Intervention:** olanzapine ***N*:** 198 **Dose:** low: 2.5, 5, or 7.5 mg daily (*n* = 65) medium: 7.5, 10, or 12.5 mg daily (*n* = 64) high:12.5, 15, or 17.5 mg daily (*n* = 69) **Control:** haloperidol ***N*:** 69 **Dose:** 10, 15, or 20 mg daily **Control 2:** placebo ***N*:** 68 **Duration:** 6 weeks **Washout:** 4–7 days **Concomitant medications:** as required: lorazepam and/or benztropine mesylate **Comments:** patients began therapy with middle dose within assigned dose range; on basis of investigator's clinical judgement, dose could subsequently be decreased or increased to optimal dosage in permitted range	**Age:** mean (SD): 35 (8)–37 (10) years **Sex:** 78.3–92.3% male **Illness:** schizophrenia **Diagnosis:** DSM-III-R ***N*:** 335 **Duration of illness:** not stated. **Special characteristics:** by subtype paranoid: placebo 60.3%; olanzapine low 55.4%; medium 64.1%; high 58.0%; haloperidol 59.4% disorganised: placebo 7.4%; olanzapine low 4.6%; medium 4.7%; high 7.2%; haloperidol 5.8% undifferentiated: placebo 32.4%; olanzapine low 40.0%; medium 31.3%; high 34.8%; haloperidol 34.8% **Course:** subchronic, acute exacerbation: placebo 10.3%; olanzapine low 6.2%; medium 7.8%; high 8.7%; haloperidol 8.7% chronic, acute exacerbation: placebo 88.2%; olanzapine low 92.3%; medium 90.6%; high 91.3%; haloperidol 91.3% unspecified: placebo 1.5%; olanzapine low 1.5%; medium 1.6%; high 0.0%; haloperidol 0.0% **Inclusion/exclusion criteria:** minimum 18-item BPRS total score of at least 24 and CGI severity of illness score ≥ 4; 18–65 years old Excluded: diagnosis of DSM-III-R organic mental disorder or substance-use disorder active within 3 months of study entry or serious suicidal risk; those with serious and unstable medical conditions **Further details:** required to be hospitalised for at least 2 weeks at beginning of study	**Intervention group *n*:** olanzapine low: 0 medium: 2 high: 4 **Control group *n*:** haloperidol 1 placebo 5	No data presented (see Beasley 1996a)	**Authors' conclusions** Contributions from more selective mesolimbic dopaminergic profile may explain differential benefit seen with olanzapine in treatment of comorbid anxious and depressive symptoms in schizophrenia

Results

General comments:

Outcome 1	Outcome 2
Outcome: BPRS anxiety–depression factor **Intervention:** olanzapine low: 7.00, 5.05; medium: 5.47, 4.30; high: 6.26, 4.56 **Control:** 6.47, 4.56 **Control 2:** 7.29, 5.42 Both olanzapine medium and high arms achieved significantly greater improvement than placebo	**Outcome:** path-analytic comparison **Intervention:** olanzapine high versus haloperidol: 65% direct treatment advantage in mood improvement. Secondary contribution from improvement in negative symptoms (47%); olanzapine high versus placebo: secondary contributions from postive symptom (51%) advantages and negative symptom (28%) advantages. 21% direct treatment effect

Olanzapine RCTs *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Hamilton 2000[162] **Trial ID:** Tollefson 1997,[164] extra data (see appendix 3)	**Intervention:** olanzapine ***N*:** 520 **Dose:** 5–20 mg daily **Control:** haloperidol ***N*:** 258 **Dose:** 5–20 mg daily **Duration:** 6-week acute phase followed by 46-week maintenance phase **Washout:** yes but length not stated **Concomitant medications:** only benzodiazepines for sedation and biperiden or benztropine mesylate for EPS **Comments:** initial 5 mg daily dose was increased weekly for patients whose CGI severity score was > 1; decreases in dose could occur at any time	**Age:** mean (SD): 38 (12) years **Sex:** 61.1% male **Illness:** combined diagnoses **Diagnosis:** DSM-III-R ***N*:** 778 **Duration of illness:** mean (SD): 13.4 (10.8) years **Inclusion/exclusion criteria:** at least 18 years old and either had BPRS total score of ≥ 18 and/or no longer tolerating current neuroleptic (excluding haloperidol) therapy Excluded: documented treatment-resistance to neuroleptic agents, DSM-III-R organic mental disorder or substance-use disorder, and/or serious, unstable medical illness **Further details:** after completing acute phase, patients showing CGI-S score of 3 or less or decrease in score ≥ 3; CGI-S (adverse event) score of 3 or more; and clinician judgement that continued treatment was warranted eligible for continued double-blind therapy in 46-week maintenance phase	**Intervention group *n*:** 319/520 patients continued to maintence phase Acute phase completion rate: 69.4%; reasons: lack of efficacy (17.9%); adverse event (3.7%); patient decision (3.5%) Maintenance phase completion rate: 52.0%; reasons: adverse events (12.9%); patient decision (10.7%); lack of efficacy (12.5%) **Control group *n*:** 104/258 patients continued to maintenance phase Acute phase completion rate: 53.9% ($p < 0.001$); reasons: lack of efficacy (23.3%, $p = 0.085$); adverse event (8.9%, $p = 0.004$); patient decision (7.8%, $p = 0.013$) Maintenance phase completion rate: 35.6%, $p = 0.005$; reasons: adverse events (26.0%, $p = 0.003$); patient decision (19.2%, $p = 0.08$); lack of efficacy (10.6%, $p = 0.729$)	Not reported	**Authors' conclusions** Findings suggest that olanzapine's clinical profile leads to reduced hospitilisation and improvements in work and social functioning superior to that achieved with haloperidol **Comments** BPRS total (PANSS positive; PANSS negative) efficacy response rates (*n*, %) Olanzapine: acute phase: 265, 53.5 (182, 36.8; 110, 22.3); maintenance phase: 200, 64.9 (150, 48.7; 1.6, 34.4); haloperidol: acute phase: 88, 35.1 (64, 25.5; 29, 11.6); maintenance phase: 57, 55.9 (45, 44.1; 27, 26.5)

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4	Outcome 5
Outcome: BPRS total (PANSS positive; PANSS negative) change scores **Intervention:** acute phase: –12.7, 14.3 (–5.7, 7.3; 5.4, 6.7); maintenance phase: –16.5, 14.4 (–7.5, 7.8; –7.2, 7.3) **Control:** acute phase: –9.8, 13.4 (–4.7, 6.5; –4.0, 6.8); maintenance phase: –14.7, 16.3 (–6.5, 7.7; –6.8, 8.0)	**Outcome:** QLS scores total (intrapsychic foundations; interpersonal relations; instrumental role category; common objects and activites) mean change from baseline **Intervention:** acute phase: 10.3, 15.8 (3.8, 6.4; 4.2, 6.5; 1.2, 4.7; 1.1, 2.0); maintenance phase: 19.1, 18.7 (6.4, 7.4; 7.0, 7.7; 4.0, 5.3; 1.7, 2.4) **Control:** acute phase: 5.4, 17.4 (1.8, 6.4; 1.7, 7.5; 1.7, 4.1; 0.2, 2.1); maintenance phase: 7.6, 20.6 (1.7, 7.2; 3.7, 8.9; 1.5, 5.6; 0.7, 2.4)	**Outcome:** QLS response (greater than 20% improvement) rates total (intrapsychic foundations; interpersonal relations; instrumental role category; common objects and activites) (*n*, %) **Intervention:** acute phase: 65, 50.0 (55, 42.6; 69, 53.1; 44, 38.3; 48, 37.8); maintenance phase: 73, 69.5% (68, 65.4%; 75, 71.4%; 56, 60.9%; 61, 59.2%) **Control:** acute phase: 18, 31.0 (21, 36.2; 19, 32.8; 15, 31.3; 17, 29.3); maintenance phase: 15, 41.7% (12, 33.3%; 13, 36.1%; 15, 48.4%; 17, 47.2%)	**Outcome:** vocational/social functioning (work full/part-time; useful work 75–100%; socialise > 1/month; independent living) **Intervention:** (*n*, %) 46, 15.1; 64, 21.0; 164, 53.8; 102, 33.4 **Control:** 5, 5.3; 10, 10.5; 36, 37.9; 27, 28.4	**Outcome:** BPRS total (PANSS positive; PANSS negative) efficacy response rates (*n*, %) **Intervention:** acute phase: 265, 53.5 (182, 36.8; 110, 22.3) maintenance phase: 200, 64.9 (150, 48.7; 1.6, 34.4) **Control:** acute phase: 88, 35.1 (64, 25.5; 29, 11.6) maintenance phase: 57, 55.9 (45, 44.1; 27, 26.5)

Olanzapine RCTs *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Ljubin 2000[158]	**Intervention:** olanzapine ***N*:** not stated **Dose:** 5–20 mg daily **Control:** fluphenazine ***N*:** not stated **Dose:** 6–21 mg daily **Duration:** 22 week **Washout:** 2–9 days (placebo) **Comments:** before entering study, patients were on low dose of conventional antipsychotic drug	**Age:** average: 37 years (range 25–61 years) **Sex:** 12/18 male **Illness:** schizophrenia **Diagnosis:** DSM-IV ***N*:** 18 **Duration of illness:** not stated **Inclusion/exclusion criteria:** CGI-S score ≥ 4; women must be using contraception; each participant must have sufficient level of understanding to communicate intelligently with investigators and nurses; must be reliable and understand nature of study Excluded: diagnosis of DSM-IV organic mental disorder or substance-use disorder active within 3 months of entering study; patients at serious suicidal risk; women who were either preganant or lactating; serious unstable illness including hepatic, renal, gasterenterologic, respiratory, cardiovascular, endocrinologic, neurologic, immunologic or haematological disease such that hospitalisation for disease was expected within 3 months or death within 3 years; uncorrected hypo- or hyperthyroidism; myasthenia gravis; narrow angle glaucoma; chronic urinary retention; 1+ seizures without clear or resolved aetiology; leucopenia; previous exposure to olanzapine or fluoxetine within 4 weeks; remoxipride within 6 months; treatment with non-reversible monoamine oxidase inhibitor, reserpine, guanthidine or guanadrel within 1 week **Further details:** numbers randomised in each intervention group not stated; final numbers: olanzapine group 10; fluphenazine 8	**Intervention group *n*:** not reported **Control group *n*:** not reported	Not reported	**Authors' conclusions** Results indicate that a benefit in cognitive functioning related to olanzapine treatment is worth studying further

Results

General comments: olanzapine showed statistically significant benefit in comparison to fluphenazine treatment but only in increased conceptual level responses ($p = 0.031$); main limitation of study lies in small number of participants

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome: WAIS overall performance functioning (object assembly; 2-D construction test; digit symbol; picture completion; similarities) (mean, SD) **Intervention:** 80.9, 22.71 (6.9, 4.71; 6.4, 4.58; 5.2, 3.55; 6.0, 3.62; 8.9, 3.44) **Control:** 81.6, 13.18 (6.3, 4.83; 7.9, 3.00; 5.5, 2.56; 5.8, 3.15; 8.4, 4.83)	**Outcome:** Stroop colour task (number of words,errors) (mean, SD) **Intervention:** 218.6, 48.32; 1.4, 3.10 **Control:** 214.1, 50.58; 1.0, 2.14	**Outcome:** Stroop colour-word task (mean, SD) **Intervention:** 75.3, 44.99; 3.7, 4.69 **Control:** 82.1, 19.10; 1.9, 1.81	**Outcome:** Wisconsin card sorting test total number correct (% perservative; % nonperservative; % conceptual level errors) (mean, SD) **Intervention:** 0.9, 29.68 (11.8, 7.35; 20.4, 14.65; 52.2, 26.02) **Control:** 57.4, 28.64 (10.3, 5.39; 17.1, 12.40; 48.5, 25.03)

Olanzapine RCTs *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Bitter 1999[74]	**Intervention:** olanzapine ***N*:** not stated **Dose:** 10 mg daily **Control:** clozapine ***N*:** not stated **Dose:** 25 mg daily, titrated in a fixed manner from 25 mg daily to 150 mg daily over 7 days **Duration:** 18 weeks **Washout:** 2–9 days **Comments:** numbers in each group not given	**Age:** most > 30 **Sex:** 59.3% male **Illness:** schizophrenia **Diagnosis:** DSM-IV ***N*:** 150 **Duration of illness:** not stated. **Special characteristics:** treatment-resistant or treatment-intolerant **Inclusion/exclusion criteria:** patients must have failed to respond adequately to standard acceptable antipsychotic medication, because of either ineffectiveness or intolerable side-effects caused by medication	Not stated	Patients treated with olanzapine reported statistically more back pain and those treated with clozapine reported statistically more somnolence and dizziness. Tachycardia occurred numerically more often in clozapine- than olanzapine-treated patients. In terms of extrapyramidal symptoms, no statistically significant differences found in parkinsonism (SAS), akathisia (Hillside akathisia scale) and dykinesia (AIMS); no statistically significant difference in weight change between clozapine- and olanzapine-treated patients	**Authors' conclusions** Olanzapine demonstrated similar efficacy and safety to clozapine among patients with treatment-resistant schizophrenia

Results		
General comments:	**Outcome 1**	**Outcome 2**
	Outcome: BPRS total (positive; negative)	**Outcome:** PANSS total (positive; negative; general subscales)
	Intervention: –24.0, 1.7 (–7.2, 4.7; –3.6, 2.8)	**Intervention:** –37.7, 23.1 (–11.7, 7.3; –7.6, 6.0; –18.4, 11.7)
	Control: –23.7, 14.2 (–7.4, 3.4; –3.6, 2.8) no significant difference	**Control:** –37.9, 23.4 (–11.8, 7.9; –7.7, 6.1; –18.4, 11.5) no significant difference

Olanzapine RCTs *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Breier 2000[159]	**Intervention:** olanzapine ***N*:** not stated **Dose:** mean (SD): 11.1 (3.4) mg daily **Control:** haloperidol ***N*:** not stated **Dose:** mean (SD): 10.0 (3.6) mg daily **Duration:** 6 weeks	**Age:** not stated **Sex:** not stated **Illness:** schizophrenia **Diagnosis:** not stated ***N*:** 526 **Duration of illness:** not stated **Special characteristics:** subpopulation of participants with treatment-resistant illness **Inclusion/exclusion criteria:** not stated	Not stated	Not reported	**Authors' conclusions** Olanzapine superior to haloperidol for key symptom domains and parkinsonian adverse events. Implications of these data for therapeutics of this severely ill subgroup discussed
Results					
General comments: olanzapine demonstrated significantly greater mean improvement from baseline on PANSS negative symptoms, comorbid depressive symptoms (MADRS), akathisia (BAS rating) with last observation carried forward analysis; olanzapine significantly superior to haloperidol for BPRS total (p = 0.006), PANSS total (p = 0.005) and PANSS positive (p = 0.017) in completers. Significantly greater response rates observed in olanzapine (47%) than haloperidol group (35%) (p = 0.008) in last observation carried forward analysis				

Olanzapine RCTs *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Lecrubier 1999[42]	**Intervention:** olanzapine ***N*:** 140 **Dose:** 5 mg daily (70); 20 mg daily (70); oral **Intervention 2:** amisulpride ***N*:** 70 **Dose:** 150 mg daily; oral **Control:** placebo ***N*:** 34 **Dose:** oral **Duration:** 6 months **Washout:** not stated **Concomitant medications:** not stated	**Age:** not stated **Sex:** not stated **Illness:** schizophrenia **Diagnosis:** not stated ***N*:** 244 **Duration of illness:** not stated **Special characteristics:** primarily negative symptoms **Inclusion/exclusion criteria:** minimum score of 10 on SANS summary score (excluding attention subscore); no score > 4 on hallucination and delusion items of PANSS (normalised, score 0–6)	**Intervention group *n*:** not stated	Efficacy on both negative and overall symptomatology was observed in context of very good safety and tolerance profile, specifically on EPS as measured by the BAS and SAS	**Authors' conclusions** Olanzapine effective and safe in treating negative, positive and overall symptoms in predominantly negative schizophrenic patients

Results

General comments: data from all olanzapine patients showed statistically greater improvement in this subscore compared with amisulpride patients ($p = 0.044$)

* Defined as patients having > 4 weeks of treatment; improvement from baseline in endpoint SANS summary score of ≥ 20% and improvement from baseline in endpoint PANSS total score of ≥ 10%

Outcome 1	Outcome 2	Outcome 3
Outcome: SANS summary change scores	**Outcome:** positive clinical response*	**Outcome:** PANSS total change score; positive subscore (change)
Intervention: olanzapine, 5 mg, –5.6 (5.0); 20 mg, –4.0 (5.2); amisulpride, –4.5 (4.9)	**Intervention:** olanzapine, 5 mg, 75.4%; 20 mg, 48.4%; amisulpride, 56.5%	**Intervention:** olanzapine, 5 mg, –23.4 (24.4); 20 mg,–1.8 (6.8); amisulpride, not reported
Control: placebo, –3.4 (4.9); $p = 0.046$ compared with olanzapine, 5 mg	**Control:** 48.1% ($p = 0.013$ compared with olanzapine, 5 mg)	**Control:** –12.6 (24.0), $p = 0.05$ compared with olanzapine, 5 mg; +1.9 (6.8), $p = 0.021$

Olanzapine RCTs *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Conley 2001[161]	**Intervention:** risperidone ***N*:** 188 **Dose:** 2–6 mg daily (flexible dose); oral **Control:** olanzapine ***N*:** 189 **Dose:** 5–20 mg daily; oral **Duration:** 8 weeks **Washout:** 1 week gradual discontinuation **Concomitant medications:** not stated **Comments:** both drugs given once daily according to following regimes: days 1–2, 2 mg risperidone or 10 mg olanzapine; days 3–7, 2–4 mg risperidone or 5–10 mg olanzapine; days 8–14, 2–6 mg risperidone or 5–15 mg olanzapine; days 15–56, 2–6 mg risperidone or 5–20 mg olanzapine	**Age:** mean risperidone 41.0 (11.0) years, olanzapine 38.9 (10.5) years **Sex:** 274 male, 103 female **Illness:** combined diagnoses **Diagnosis:** DSM-IV ***N*:** 377 **Duration of illness:** mean risperidone 16.5 (10.5) years, olanzapine 15.4 (10.6) years **Special characteristics:** schizophrenia (n = 325) or schizoaffective disorder (n = 52) **Inclusion/exclusion criteria:** baseline PANSS score, 60–120, aged 18–64 years; out- or inpatients hospitalised ≤ 4 weeks Excluded: another axis I diagnosis, substance abuse in 3 months before trial, CNS disease, use of concomitant mood stabilisers or antidepressants, history of clozapine treatment for > 4 weeks, being known by investigator to be sensitive or unresponsive to risperidone or olanzapine **Further details:** 79% were outpatients	**Intervention group *n*:** 53/188 (adverse event 22/188) **Control group *n*:** 43/189 (adverse event 17/189)	All risperidone versus olanzapine Serious adverse events: 15/188 versus 22/189; psychosis: 8/188 versus 8/189; suicide attempt: 2/188 versus 5/189; agitation: 3/188 versus 3/189; depression: 3/188 versus 3/189; insomnia: 3/188 versus 2/189; hallucinations: 2 versus 3; drug abuse: 0 versus 3; cardiovascular symptoms: 0 versus 3; gastrointestinal disorders: 0 versus 3; other: 14 versus 21 Weight gain: 3.4 lb (SD 7.8) versus 7.2 lb (SD 11.2); increase in body weight of ≥ 7%: 18/155 versus 44/161 Less serious adverse events: somnolence: 69/188 versus 73/189; insomnia: 45 versus 35; headache: 41 versus 32; agitation: 29 versus 40; dry mouth: 21 versus 42; rhinitis: 30 versus 31; dizziness: 26 versus 27; anxiety: 20 versus 23; vision abnormalities: 12 versus 19 Extrapyramidal symptoms: 45/188 versus 38/189 Patients using antiparkinsonian medication: 61/188 versus 53/189	**Authors' conclusions** Both risperidone and olanzapine generally well tolerated and efficacious in treatment of patients with schizophrenia and schizoaffective disorder. The frequency and severity of extra-pyramidal symptoms similar in both treatment groups. PANSS scores on two factors – positive symptoms and anxiety/depression – better with risperidone than olanzapine among participants who completed 8-week trial. Weight gain associated with olanzapine treatment may constitute meaningful health hazard

Results

General comments:	Outcome 1	Outcome 2	Outcome 3	Outcome 4
	Outcome: change scores: PANSS total; PANSS positive; PANSS negative; PANSS disorganised thoughts; PANSS uncontrolled hostility; PANSS anxiety/depression **Intervention:** (n = 134) –16.0 (16.6); –5.6 (6.4); –3.5 (6.0); –2.9 (4.6); –1.4 (2.8); –2.5 (3.6) **Control:** (n = 144) –15.4 (16.8); –4.8 (6.4); –3.3 (5.7); –3.5 (4.7); –1.7 (2.7); –2.2 (3.4)	**Outcome:** response: ≥ 20% reduction in PANSS; 40% reduction in PANSS; CGI-I much or very much improved **Intervention:** 69/188; 34/188; 60/188 (data not available for all participants) **Control:** 68/189; 23/189; 58/189 (data not available for all participants)	**Outcome:** CGI-S **Intervention:** (n = 133) not ill/very mild/mild, n = 67, moderate/marked n = 62, severe/extremely severe n = 4 **Control:** (n = 145) not ill/very mild/mild n = 69, moderate/marked n = 75, severe/extremely severe n = 1	**Outcome:** change scores: ESRS total, questionnaire, parkinsonism, akathisia, and dyskinesia **Intervention:** (n = 133) –1.3 (4.6); –0.6 (2.4); –0.8 (3.4); –0.2 (1.0); –0.4 (2.4) **Control:** (n = 145) –1.6 (4.1); –0.5 (2.4); –1.0 (3.3); –0.2 (0.8); –0.5 (2.2)

Olanzapine RCTs *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Edgell 2000[170] **Trial ID:** Subset of Tran 1997[171] (see appendix 3)	**Intervention:** risperidone ***N*:** 75 **Dose:** 4–12 mg daily; oral **Control:** olanzapine ***N*:** 75 **Dose:** 10–20 mg daily **Duration:** 28 weeks (maximum) **Washout:** 2–9 days **Concomitant medications:** see Tran 1997	See Tran 1997	Not stated	Not reported	**Authors' conclusions** Olanzapine-treated patients experienced clinical improvements that translated into savings in costs of care for both in- and outpatient services. These savings offset difference in medication acquisition cost between olanzapine and risperidone

Results

General comments:	Outcome 1	Outcome 2	Outcome 3	Outcome 4
	Outcome: response (≥ 20% on PANSS total scores; 30%; 40%; 50%) – olanzapine: 44/75; 38/75; 21/75; 7/75; risperidone: 47/75; 31/75; 15/75; 5/75 Olanzapine-treated participants more likely to maintain response than those on risperidone (p = 0.048)	**Outcome:** required anticholinergic therapy: risperidone: 34/75 (45.3%); olanzapine: 19/75 (25.3%); p = 0.016 versus risperidone	**Outcome:** Costs: total per patient medical costs over study interval were $US2843 (1997 values, 36%) lower in olanzapine than in risperidone treatment group (p = 0.342) Medication costs significantly higher for olanzapine-treated patients ($US2513 versus $US1581, p < 0.001) but difference offset by reduction of $US3774 (52%) in in-/outpatient service costs	**Outcome:** treatment-emergent EPS (SAS; BAS; AIMS): risperidone: 8/75; 18/76; 9/75; olanzapine: 5/75; 17/75; 2/75

Olanzapine RCTs *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Littrell 1999[154]	**Intervention:** risperidone ***N*:** 12 **Dose:** mean dose 5.2 mg daily; oral **Control:** olanzapine ***N*:** 12 **Dose:** mean dose 19.2 mg daily; oral **Duration:** 1 year **Washout:** not stated **Concomitant medications:** not stated **Comments:** medication compliance quantitatively verified by monthly plasma drug levels	**Age:** not stated **Sex:** not stated **Illness:** schizophrenia **Diagnosis:** not stated ***N*:** 24 **Duration of illness:** not stated **Special characteristics:** switched from depot antipsychotic to atypical medication **Inclusion/exclusion criteria:** not stated	**Intervention group *n*:** 1/12 dropped out; reasons not stated **Control group *n*:** 2/12 dropped out; reasons not stated	Risperidone: changes in severity of extrapyramidal symptoms (SAS) not significant Olanzapine: severity of extrapyramidal symptoms not changed	**Authors' conclusions** Both risperidone and olanzapine well tolerated in patients switched from depot to oral antipsychotic drugs but superior efficacy seen with risperidone

Results

General comments: within-group comparisons only, no between-group *p*-values, no data suitable to include in meta-analysis other than attrition. Superior efficacy of risperidone not demonstrated

Outcome 1

Outcome: PANSS total; subscales

Intervention: significant reductions at 6 months in positive symptoms ($p < 0.01$), negative symptoms ($p < 0.05$) and general psychopathology ($p < 0.01$); significant reduction in positive symptoms at 1 year ($p < 0.001$)

Control: mean positive symptom scores reduced at 1 year (not significant) but no reductions seen in total scores, negative symptoms or general psychopathology

Olanzapine RCTs *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Tohen 1999[172] **Trial ID:** subgroup of larger trial, possibly Tollefson 1997[164] (see appendix 3)	**Intervention:** olanzapine ***N*:** not stated **Dose:** not stated; oral **Control:** haloperidol ***N*:** not stated **Dose:** not stated; oral **Duration:** 6 weeks **Washout:** not stated **Concomitant medications:** not stated	**Age:** not stated **Sex:** not stated **Illness:** schizoaffective disorder **Diagnosis:** not stated ***N*:** 177 **Duration of illness:** not stated **Special characteristics:** schizoaffective disorder, bipolar type. Currently manic (n = 28), currently mixed (n = 47), currently depressed (n = 53), currently euthymic (n = 49) **Inclusion/exclusion criteria:** not stated **Further details:** subgroup of large multicentre trial (reference to trial not given), data not to be pooled	Not stated	Not reported	**Authors' conclusions** Compared with haloperidol, olanzapine produced greater reduction of manic symptoms (BPRS mania score) in patients with schizoaffective disorder, bipolar type, currently manic or currently depressed, and greater reduction of depressive symptoms (MADRS) in patients with schizoaffective disorder, bipolar type, currently depressed. Overall, results indicate that olanzapine appears to have mood-stabilising properties in this patient population

Results

General comments	Outcome 1	Outcome 2
General comments: subgroup of larger trial but only people with schizoaffective disorder; hence, results cannot be pooled in meta-analysis. No SDs for change scores	**Outcome:** BPRS mania score **Intervention:** currently manic average –1.13 per week; currently depressed –0.57 per week **Control:** currently manic –0.53 per week (p = 0.075 versus olanzapine); currently depressed +0.11 per week (p = 0.028 versus olanzapine)	**Outcome:** MADRS change scores **Intervention:** –8.57 **Control:** +6.63 (p = 0.0001 versus olanzapine)

Olanzapine RCTs *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Johnstone 1998[148]	**Intervention:** olanzapine ***N*:** not stated **Dose:** not stated; oral **Control:** haloperidol ***N*:** not stated **Dose:** not stated; oral **Duration:** 1 year **Washout:** not stated **Concomitant medications:** not stated	**Age:** not stated **Sex:** not stated **Illness:** schizophrenia **Diagnosis:** not stated ***N*:** 814 **Duration of illness:** not stated **Special characteristics:** patients from USA **Inclusion/exclusion criteria:** not stated	Not stated	None reported	**Authors' conclusions** Olanzapine displayed significant cost and effectiveness advantages for treatment of schizophrenia in comparison with haloperidol over 1 year from ITT perspective

Results		
General comments: abstract only, many details missing	**Outcome 1**	**Outcome 2**
	Outcome: BPRS-based symptom-free days	**Outcome:** annual cost per patient
	Intervention: 17.72 more than haloperidol group (p = 0.05)	**Intervention:** $US10,179 less than with haloperidol; ICER, –$US575 per symptom-free day

Olanzapine RCTs *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Sanger 1998[173–175] **Trial ID:** subgroup of Tollefson 1997[164] (see appendix 3)	**Intervention:** olanzapine ***N*:** 59 **Dose:** 5–20 mg daily; oral **Control:** haloperidol ***N*:** 24 **Dose:** 5–20 mg daily; oral **Duration:** 6 weeks **Washout:** not stated **Concomitant medications:** not stated	**Age:** not stated **Sex:** not stated **Illness:** combined diagnoses **Diagnosis:** DSM-III-R ***N*:** 83 **Duration of illness:** > 5 years **Special characteristics:** schizophrenia, schizophreniform disorder or schizoaffective disorder, first-episode schizophrenia **Inclusion/exclusion criteria:** > 45 years of age at onset of symptoms **Further details:** subgroup from Tollefson 1997, hence data cannot be pooled	Not stated	Olanzapine-treated patients showed statistically significant improvements on SAS and BAS scores, while haloperidol-treated patients showed worsening on both measures	**Authors' conclusions** In patients experiencing first-episode psychosis, olanzapine showed significantly superior risk–benefit profile than haloperidol. Results suggest that novel antipsychotic agents, such as olanzapine, should be considered as preferred option in first-episode psychosis, based on both safety and efficacy advantages

Results

General comments:	Outcome 1	Outcome 2
compared with olanzapine-treated multi-episode patients in parent study, olanzapine-treated first-episode patients achieved statistically significantly higher response. Haloperidol-treated first-episode patients experienced statistically significantly more extrapyramidal symptoms than haloperidol-treated multi-episode patients	**Outcome:** BPRS total; BPRS negative; PANSS total; PANSS positive **Intervention versus control:** compared with haloperidol, olanzapine showed statistically significantly greated reductions on all measures	**Outcome:** response (40% improvement in BPRS total score) **Intervention:** 67.2% (40/59 or 38/57) **Control:** 29.2% (7/24 or 8/26)

Olanzapine RCTs *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Kinon 2000[166] **Trial ID:** Tollefson 1997[164] (see appendix 3)	**Intervention:** olanzapine ***N*:** 1336 **Dose:** 5–20 mg daily; oral **Control:** haloperidol ***N*:** 660 **Dose:** 5–20 mg daily; oral **Duration:** 6 weeks **Washout:** not stated **Concomitant medications:** not stated	**Age:** not stated **Sex:** not stated **Illness:** combined diagnoses **Diagnosis:** not stated ***N*:** 1996 **Duration of illness:** not stated **Special characteristics:** schizophrenia, schizoaffective disorder or schizophreniform disorder **Inclusion/exclusion criteria:** not stated	Not stated	Not reported	**Authors' conclusions** Results supportive of beneficial effects of olanzapine in controlling behavioural agitation and positive psychotic symptoms associated with schizophrenic decompensation. Comparative data indicate that olanzapine may be considered as first-line treatment for patient in acute episode of schizophrenia

Results

General comments	Outcome 1	Outcome 2
BPRS agitation subscore formed by combining five non-psychosis items of BPRS scale: anxiety, tension, hostility, uncooperativeness and excitement. BPRS positive symptom score assessed in subpopulation of patients who demonstrated predominantly positive psychotic symptoms at baseline. Results used last observation carried forward	**Outcome:** BPRS agitation score **Intervention versus control:** olanzapine-treated participants experienced significantly greater improvement in behavioural agitation than did haloperidol-treated participants (p = 0.0002)	**Outcome:** BPRS positive symptom score (n = 382) **Intervention versus control:** significantly greater improvement with olanzapine than haloperidol (p = 0.013)

Olanzapine RCTs *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Pfizer 2001[283] **Trial ID:** R-0548	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed
Results					
Commercial-in-confidence: data removed					

Quetiapine RCTs

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Mullen 1999[208]	**Intervention:** quetiapine ***N*:** 554 **Dose:** mean dose at completion: 253.9 mg daily; oral **Control:** risperidone ***N*:** 175 **Dose:** mean dose at completion: 4.4 mg daily; oral **Duration:** 4 months	**Age:** mean: quetiapine 45.1 years; risperidone 46.2 **Sex:** quetiapine 277/554 male; ripseridone 95/175 male **Illness:** psychosis **Diagnosis:** DSM-IV ***N*:** 751 **Duration of illness:** not stated **Special characteristics:** included those > 65 years **Diagnosis:** (quetiapine; risperidone) – bipolar: 83/554; 20/175 major depressive disorder: 75/554; 26/175 schizoaffective: 158/554; 57/175 schizophrenia: 218/554; 67/175 all non-mood diagnoses: 316/554; 103/175 all mood diagnoses: 238/554; 72/175 **Inclusion/exclusion criteria:** excluded: evidence of medically significant disorders; current treatment with clozapine or history of nonresponsiveness to clozapine; history of drug-induced agranulocytosis; majority = mood disorders	Not stated	Not reported	**Authors' conclusions** Quetiapine less likely than risperidone to require dose adjustment for EPS or concurrent anti-EPS medication; more effective than risperidone in improving depressive symptoms; as effective as risperidone in treating positive and negative symptoms of outpatients with psychosis. Quetiapine produced statistically significantly greater effect in patients with higher initial on Hamilton Rating Scale (depression) scores than risperidone

Results

General comments: extrapyramidal events (EPS checklist) declined in both groups, with no significant differences between groups in overall occurrence of EPS. Odds of risperidone-treated patient having treatment-emergent EPS that required adjustment of or anti-EPS medication 5.6 times greater than odds of quetiapine-treated patient having similar event ($p < 0.001$). Extrapyramidal symptoms rated as 'at least moderate' (EPS checklist) occurred more frequently at each visit in risperidone-treated participants

Quetiapine group had significantly ($p = 0.028$) greater improvement on Hamilton Rating Scale (depression) than risperidone group. Greater % of quetiapine group than risperidone group had improvement in CGI at each visit. No statistically significant differences between groups in PANSS scale

Outcome 1

Outcome: Percentage change from baseline score on Hamilton Rating Scale (depression) (schizoaffective; schizophrenia)

Intervention: –41.6%; –41.6%

Control: –34.6%; –31.4% (no significant difference between groups)

Quetiapine RCTs *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Purdon 2001[211] **Trial ID:** Canada 1999	**Intervention:** quetiapine ***N*:** 13 **Dose:** 300–600 mg daily (flexible dose); oral **Control:** haloperidol ***N*:** 12 **Dose:** 10–20 mg daily (flexible dose); oral **Duration:** 6 months **Washout:** 2 days oral, 1 interval depot **Concomitant medications:** not stated	**Age:** mean 33.9 years (7.3) **Sex:** 20 males; 5 females **Illness:** schizophrenia **Diagnosis:** DSM-III-R ***N*:** 25 **Duration of illness:** mean 12.1 years (7.7) **Special characteristics:** paranoid 13, undifferentiated 12 **Inclusion/exclusion criteria:** no history of serious medical disease or neurological disorder; no active substance abuse in past 30 days	**Intervention group *n*:** 3/13 reasons not clear **Control group *n*:** 9/12 reasons not clear	Quetiapine versus haloperidol: weight gain 3/13: 1/12; irritability 2: 1; impotency 2: 0; dry mouth 1: 0; hypersalivation 1: 0; involuntary jaw movement 1: 0; fatigue 1: 0; somnolence 1: 1; drowsiness 1: 0; fine tremors 1: 0; twitch in extremities 1: 0; menstrual problems 1/3: 0/2; cold flushes 1: 0; nausea/vomiting 0: 1; restlessness 0: 1; increased appetite 0: 1; EPS 0: 1; akathisia 0: 1; headache 0: 1; blurred vision 0: 1; insomnia 0: 1; sedation 0: 1; stiffness 0: 1; dry skin/rash 0: 1	**Authors' conclusions** These preliminary results support potential value of quetiapine for improving cognitive impairment in patients with schizophrenia, and emphasise importance of further research with this promising atypical antipsychotic drug

Results

General comments:	Outcome 1	Outcome 2	Outcome 3	Outcome 4
	Outcome: CGI; PANSS total; PANSS general; positive; negative **Intervention:** 2.9 (0.8); 55.7 (7.8); 27.4 (5.9); 13.6 (3.6); 14.7 (4.8) **Control:** 3.4 (0.5); 57.9 (14.8); 25.0 (5.3); 14.3 (4.9); 18.6 (7.7)	**Outcome:** mood: BDI; CDS **Intervention:** 13.9 (10.5); 2.7 (3.6) **Control:** 9.3 (4.6); 0.7 (1.3)	**Outcome:** cognition: general; motor speed and dexterity; attention span; verbal reasoning and fluency; visuospatial fluency and construction; executive skills and visuomotor tracking; immediate recall **Intervention:** –1.0 (1.0); –0.6 (1.6); –0.6 (1.1); –0.6 (0.8); –1.6 (1.6); –1.3 (1.7); –1.3 (1.1) **Control:** –1.5 (0.9); –1.5 (2.1); –1.0 (0.8); –1.1 (0.6); –1.3 (1.1); –1.9 (1.2); –2.1 (1.1)	**Outcome:** movement: AIMS; SAS **Intervention:** 1.1 (1.5); 11.8 (2.6) **Control:** 2.4 (3.5); 12.7 (4.8)

Quetiapine RCTs *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Reinstein 1999[209] **Trial ID:** QUEST	**Intervention:** quetiapine ***N*:** not stated **Dose:** flexible (mean dose 253.9 mg daily); oral **Control:** risperidone ***N*:** not stated **Dose:** flexible (mean dose 4.4 mg daily); oral **Duration:** 4 months **Washout:** not stated **Concomitant medications:** not stated	**Age:** not stated **Sex:** not stated **Illness:** psychosis **Diagnosis:** not stated ***N*:** 751 **Duration of illness:** not stated **Special characteristics:** adult outpatients with psychotic disorders **Inclusion/exclusion criteria:** not stated	Not stated	EPS checklist: extrapyramidal events in both treatment groups declined over treatment period, with no significant differences between groups in overall occurrence. Those in risperidone group more likely to have extrapyramidal event and more likely ($p < 0.001$) to have one that required adjustment of study medication or adjunctive medication than participants in quetiapine group	**Authors' conclusions** Quetiapine less likely than risperidone to require dose adjustment for EPS or concurrent anti-EPS medication, more effective than risperidone in treating depressive symptoms and as effective as risperidone in treating positive and negative symptoms of out-patients with psychosis

Results

General comments	Outcome 1	Outcome 2
General comments: abstract only, many details missing	**Outcome:** CGI; PANSS; DAI-10 Quetiapine and risperidone groups had improvements in all efficacy measures (not significant). Higher percentage of those in quetiapine group relative to risperidone group had improvement in CGI at each visit	Outcome: Hamilton Rating Scale (depression); quetiapine group had significantly greater improvement than risperidone group ($p = 0.028$)

Quetiapine RCTs *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
AstraZeneca 2000[207] **Trial ID:** QUEST	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed	Commercial-in confidence: data removed	Commercial-in-confidence: data removed
Results					
Commercial-in-confidence: data removed					

Quetiapine RCTs *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Murasaki 2000[213] **Trial ID:** Japan 1999b	**Intervention:** quetiapine ***N*:** 100 **Dose:** mean (SD): 226 (122.5) mg daily **Control:** haloperidol ***N*:** 97 **Dose:** mean (SD): 6.7 (3.6) mg daily **Duration:** 8 weeks **Comments:** during week 1, dosages titrated up to quetiapine, 150 mg daily, and haloperidol, 4.5 mg daily, (up to maximum quetiapine, 600 mg daily, and haloperidol, 18 mg daily)	Quetiapine: haloperidol **Age:** mean (SD): 46 (12) years: 44 (13) years **Sex:** 129/197 male **Illness:** schizophrenia **Diagnosis:** ICD10 ***N*:** 197 **Duration of illness:** mean (SD): 17.5 (13.6) years: 16.9 (12.4) years **Special characteristics:** predominantly negative symptoms hospitalised 171/197 (86/100: 85/97); outpatients 22/197 (12/100: 10/97); in/outpatients 4/197 (2/100: 2/97) **Inclusion/exclusion criteria:** hospitalised patients and outpatients; aged 18–65 years Excluded: significant deterioration of personality; receiving high-dose antisychotic therapy; severe endocrinological disease; epilepsy or convulsive disorders, Parkinson's disease; organic cerebral disorder	**Intervention group *n*:** 34/100 participants withdrew – adverse events 11%, aggravation of symptoms 21%, others 2% **Control group *n*:** 43/97 participants withdrew – adverse events 26%, aggravation of symptoms 6%, others 11%	Number of adverse drug reactions reported by quetiapine group was 248 compared with 412 for haloperidol group. Number/ proportion of participants reporting adverse drug reactions was significantly lower ($p < 0.05$) in quetiapine group (67%) than in haloperidol group (83%). Quetiapine group had lower incidence of EPS (63) compared with haloperidol group (188). Significantly fewer ($p < 0.001$) in quetiapine group (29%) exhibited extrapyramidal symptoms compared with haloperidol group (64%)	

Results

General comments: reported in earlier review as Murasaki 1999/Japan 1999b (see appendix 3). New data on BPRS and PANSS reported here

Outcome 1	Outcome 2
Outcome: PANSS total score (negative; positive; general subscales)	**Outcome:** BPRS total score
Intervention: 78.5, 26.5 (23.0, 8.2; 15.9, 8.2; 39.6, 14.2)	**Intervention:** 42, 16
Control: 78.3, 25.7 (22.6, 7.8; 15.5, 7.2; 40.3, 14.7)	**Control:** 42, 16

Quetiapine RCTs *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Velligan 1999[210]	**Intervention:** quetiapine ***N*:** 17 **Dose:** 300 mg daily **Intervention 2:** quetiapine ***N*:** 26 **Dose:** 600 mg daily **Control:** haloperidol ***N*:** 15 **Dose:** 12 mg daily **Duration:** 24 weeks **Comments:** cognitive assessments conducted prior to randomisation when patients receiving haloperidol, ≤ 30 mg daily or equivalent (mean: 9.2 mg daily) and again after 24 weeks' treatment	**Age:** reported graphically **Sex:** reported graphically **Illness:** schizophrenia **Diagnosis:** DSM-III-R ***N*:** 58 **Duration of illness:** reported graphically **Inclusion/exclusion criteria:** currently treated with standard neuroleptic doses equivalent to haloperidol, ≤ 30 mg daily; full or partial remission; scores of ≤ 3 on all psychosis items on BPRS (0–6 scale); scores of moderately ill or less on CGI **Further details:** subgroup of patients from multicentre trial (Arvanitis?) – stable outpatients	Not reported	Not reported	**Authors' conclusions** In addition to effectiveness of quetiapine in treatment of symptoms of schizophrenia, it also appears to have positive impact on important domains of cognitive performance that have been found to predict role function and community outcomes in patients with schizophrenia

Results

General comments: treatment group differences not solely due to anticholinergic use, medication side-effects, or improvements in symptomatology

Difference between treatments remained significant when controlling for changes in positive and negative symptoms and side-effects, but not use of anticholinergic medication (benztropine); 50% haloperidol group versus 8% quetiapine group used benztropine. Significant differences found between quetiapine, 600 mg daily, and haloperidol groups for two cognitive tests, verbal fluency (ANCOVA, $p < 0.03$) and paragraph recall (ANCOVA, $p < 0.01$)

Outcome 1

Outcome: overall cognitive function; executive function (verbal fluency); verbal memory (paragraph recall)

Intervention: improved to greater extent: $p < 0.03$; $p < 0.05$; $p < 0.01$

Outcome 2

Outcome: cognitive summary score (stroop colour-word; verbal learning; symbol-digit sub.; trails b-a; paragraph recall; verbal fluency)

Intervention: –0.13, 4.38 (45.81, 13.02; 20.82, 5.55; 37.47, 12.60; 3.78, 1.20; 1.62, 1.07; 4.44, 0.67)

Intervention 2: 0.51, 4.15 (48.92, 14.02; 21.04, 5.63; 37.65, 12.71; 3.72, 0.96; 1.95, 0.71, $p < 0.04$ (within group); 4.44, 0.71)

Control: –1.17, 4.69, (45.13, 20.08; 19.40, 7.93; 38.73, 15.55; 3.96, 0.72; 1.57, 1.01, $p < 0.03$ (within group); 4.30, 0.66, $p < 0.03$ (between group)

ANCOVA on cognition summary score with baseline summary score (covariate) between quetiapine, 600 mg daily, and haloperidol; $p < 0.04$

Risperidone RCTs

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Gureje 1998[186]	**Intervention:** olanzapine ***N*:** not stated **Dose:** 10–20 mg once daily (started at 15 mg daily) **Control:** risperidone ***N*:** not stated **Dose:** 4–8 mg daily (started at 1 mg twice daily) **Duration:** 30 weeks with washout period of not longer than 9 days	**Age:** not stated **Sex:** not stated **Illness:** schizophrenia, schizophreniform disorder or schizoaffective disorder **Diagnosis:** DSM-IV ***N*:** not stated **Duration of illness:** not stated **Inclusion/exclusion criteria:** BPRS total score > 36 (extracted from PANSS, items 1–7)	**Intervention group *n*:** not reported **Control group *n*:** not reported	Trend for olanzapine-treated patients to evidence fewer treatment-emergent adverse effects	**Authors' conclusions** Not stated
Results					
General comments: compared with risperidone-treated patients, olanzapine-treated patients showed greater reduction in BPRS total score at week 22 through 30. Greater proportion also achieved reduction of 20% or more on PANSS total score at week 30. At week 30, olanzapine-treated patients had better profile of quality of life (SF-36 and disease-specific Quality of Life in Schizophrenia scale)					

Risperidone RCTs *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Tys 1999[232]	**Intervention:** risperidone ***N*:** 10 **Dose:** 0.5 mg twice daily, increased after 3 days to 1 mg twice daily; oral **Control:** haloperidol ***N*:** 10 **Dose:** 15–20 mg daily; oral **Duration:** 2 months	**Age:** not stated **Sex:** not stated **Illness:** schizophrenia **Diagnosis:** not stated ***N*:** 20 **Duration of illness:** not stated **Special characteristics:** chronically institutionalised patients with prominent emotional and vocational defects. Before treatment, total PANSS score was 80–110 **Inclusion/exclusion criteria:** not stated	Not stated	No side-effects to compare with haloperidol group	**Authors' conclusions** None stated
Results					
General comments: negative score improvement more prominent in risperidone group (no data presented); number of hospital days reduced in risperidone group (no data reported)		**Outcome 1** **Outcome:** mean PANSS score **Intervention:** 91.7 **Control:** 91.1			

Risperidone RCTs *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Heck 2000[233]	**Intervention:** risperidone ***N*:** 40 **Dose:** flexible dose (maximum 16 mg); oral **Control:** haloperidol ***N*:** 37 **Dose:** flexible dose (maximum 24 mg); oral **Duration:** 6 weeks + 1 week dose-rising phase **Washout:** none **Concomitant medications:** all antiparkinsonian drugs and psychotropic drugs except benzodiazepines stopped. If patient developed EPS during trial, antiparkinsonian drugs permitted. Psychotropic drugs, except benzodiazepines, not allowed **Comments:** dose rising phase was 1 week: day 1, one tablet; day 2, 2 tablets; days 3–7, 3 tablets	**Age:** mean, risperidone 40 years, haloperidol 44.5 years (range 23–68) **Sex:** 38 male, 39 female **Illness:** combined diagnoses **Diagnosis:** DSM-III-R ***N*:** 77 **Duration of illness:** ?14 years **Special characteristics:** schizophrenia (subchronic or chronic course) or other psychotic conditions. Patients with disturbing EPS during previous neuroleptic treatment **Inclusion/exclusion criteria:** 18–70 years, clinically stable on current antipsychotic medication, score of ≥ 5 on parkinsonism subscale of ESRS, or using antiparkinsonian medication **Further details:** hospitalised, average duration 7 years	**Intervention group *n*:** 15/40 withdrew (reasons not stated) **Control group *n*:** 15/37 withdrew (reasons not stated)	Overall frequency of adverse events similar in both treatment groups. Most frequent in risperidone group: headache (4/40), oculogyric crisis (3/40) and hypersalivation (3/40); most frequent in haloperidol group: sleep disorders (4/37), tremor (4/37) and vomiting (3/37). Five patients in risperidone and six in haloperidol group stopped medication because of adverse events	**Authors' conclusions** In this group of schizophrenic patients with disturbing EPS during previous neuroleptic treatment, risperidone caused greater reduction in parkinsonism than haloperidol at comparatively effective antipsychotic doses

Results

General comments: between-group *p*-values not presented except for outcome 'hyperkinesia (akathisia and tremor)' for which both groups were statistically significantly different in favour of risperidone after 1, 3 and 5 weeks of treatment, and tended to be different at endpoint ($p = 0.055$). SDs not presented for scale data

Outcome 1	Outcome 2	Outcome 3
Outcome: use of antiparkinson medication	**Outcome:** BPRS total score; CGI	**Outcome:** ESRS parkinsonism; CGI-S parkinsonism (total scores)
Intervention: 18/40 (baseline); 11/40 (end of trial)	**Intervention:** 39.7; 3.2 (baseline); 38.6 (end of trial); no significant improvement	**Intervention:** 12.3; 3.4 (baseline); 9.7; 2.4 (end of trial)
Control: 16/37 (baseline); 10/37 (end of trial)	**Control:** 40.9; 3.4 (baseline); 39.1 (end of trial); no significant improvement	**Control:** 10.9; 3.0 (baseline); 9.6; 2.6 (end of trial)

Risperidone RCTs *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Reinstein 1999[209] **Trial ID:** QUEST	**Intervention:** quetiapine ***N*:** not stated **Dose:** flexible (mean 253.9 mg daily); oral **Control:** risperidone ***N*:** not stated **Dose:** flexible (mean 4.4 mg daily); oral **Duration:** 4 months **Washout:** not stated **Concomitant medications:** not stated	**Age:** not stated **Sex:** not stated **Illness:** psychosis **Diagnosis:** not stated ***N*:** 751 **Duration of illness:** not stated **Special characteristics:** adult outpatients with psychotic disorders **Inclusion/exclusion criteria:** not stated	Not stated	EPS checklist: extrapyramidal events in both groups declined over treatment period, with no significant differences between groups in overall occurrence; risperidone group more likely to have extrapyramidal event and more likely ($p < 0.001$) to be one requiring adjustment of study medication or adjunctive medication than quetiapine group	**Authors' conclusions** Quetiapine less likely than risperidone to require dose adjustment for EPS or concurrent anti-EPS medication; more effective than risperidone in treating depressive symptoms; as effective as risperidone in treating positive and negative symptoms of outpatients with psychosis

Results

General comments: abstract only, many details missing

Outcome 1	Outcome 2
Outcome: CGI; PANSS; DAI-10 Both groups had improvements in all efficacy measures (not significant). Higher percentage from quetiapine group had improvement in the CGI at each visit compared with risperidone group	**Outcome:** Hamilton Rating Scale (depression) – quetiapine group had significantly greater improvement than risperidone group ($p = 0.028$)

Risperidone RCTs *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Kolff 2000[152]	**Intervention:** risperidone ***N*:** 23 **Dose:** not stated; oral **Control:** olanzapine ***N*:** 27 **Dose:** not stated; oral **Duration:** 6 weeks **Washout:** not stated **Concomitant medications:** not stated	**Age:** not stated **Sex:** not stated **Illness:** schizophrenia **Diagnosis:** not stated ***N*:** 50 **Duration of illness:** not stated **Special characteristics:** not stated whether illness was treatment-resistant, -refractory or patients were intolerant **Inclusion/exclusion criteria:** not stated	**Intervention group *n*:** not stated **Control group *n*:** not stated	Not reported	**Authors' conclusions** Risperidone and olanzapine generally comparable with respect to clinical properties and cognitive effects. Indication obtained that risperidone may act more on positive and olanzapine more on negative symptoms of schizophrenia

Results

General comments	Outcome 1	Outcome 2	Outcome 3
General comments: conference abstract so little information presented; small sample size means reported trend for olanzapine to affect negative and risperidone positive symptoms should be disregarded	**Outcome:** clinical symptoms (PANSS) **Intervention:** in both groups, general improvement established on PANSS score between baseline and final assessment for both positive and negative symptoms **Control:** no significant differences were found between drugs, although olanzapine tended to have larger effect on negative symptoms and risperidone on positive symptoms	**Outcome:** psychometric tests (continuous performance test for sustained attention, verbal learning and memory test, Stroop interference test and WAIS for intelligence **Intervention:** no general differences between drugs discovered on all measured cognitive functions; however, those treated with olanzapine scored significantly better on Stroop interference test	**Outcome:** psychomotor speed (finger tapping test and trail making test) **Intervention:** no differences between drugs were found

Risperidone RCTs *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Malyarov 1999[153]	**Intervention:** olanzapine ***N*:** 15 **Dose:** 5–15 mg daily **Intervention 2:** risperidone ***N*:** 10 **Dose:** 3–6 mg daily **Control:** haloperidol ***N*:** 18 **Dose:** 5–20 mg daily **Duration:** 6 months	**Age:** average 24.5 years **Sex:** 28/43 male **Illness:** schizophrenia **Diagnosis:** ICD10 ***N*:** 43 **Duration of illness:** < 3 years **Special characteristics:** patients with diagnosis of schizophrenia with acute psychotic states; hospitalised **Inclusion/exclusion criteria:** not stated	**Intervention:** none **Intervention 2:** 2 dropouts **Control group:** 3 dropouts	Not reported	**Authors' conclusions** Changes in atypical antipsychotic-treated patients directly related to social functioning may be useful for explaning striking differences between groups in GAF scores

Results

	Outcome 1	Outcome 2	Outcome 3
Comments: most prominent changes in atypical antipsychotic-treated patients observed with symptoms directly related to social functioning, such as emotional withdrawal, poor rapport, abstract thinking, impulse control, disturbance of volition, lack of judgement and poor insight	**Outcome:** PANSS total scores **Intervention:** scores did not vary significantly	**Outcome:** GAF mean scores **Intervention:** 55–70 (both groups) **Control:** 45–60, $p < 0.05$	**Outcome:** mean difference PANSS (positive; negative; general subscales) **Intervention:** 1.4%, no significant difference; 11%, $p < 0.01$; 13.5%, $p < 0.01$)

Risperidone RCTs *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Mullen 1999[208]	**Intervention:** quetiapine ***N*:** 554 **Dose:** mean at completion: 253.9 mg daily; oral **Control:** risperidone ***N*:** 175 **Dose:** mean at completion: 4.4 mg daily; oral **Duration:** 4 months	Quietipine: risperidone **Age:** mean: 45.1: 46.2 years **Sex:** 277/554: 95/175 male **Illness:** psychosis **Diagnosis:** DSM-IV ***N*:** 751 **Duration of illness:** not stated **Special characteristics:** included those > 65 years **Diagnosis:** bipolar: 83/554; 20/175 major depressive disorder: 75/554; 26/175 schizoaffective: 158/554; 57/175 schizophrenia: 218/554; 67/175 all non-mood diagnoses: 316/554; 103/175 all mood diagnoses: 238/554; 72/175 **Inclusion/exclusion criteria:** Exclude: evidence of medically significant disorders; current treatment with clozapine/history of nonresponsiveness to clozapine; history of drug-induced agranulocytosis. Majority = mood disorders	Not stated	Not reported	**Authors' conclusions** Quetiapine less likely than risperidone to require dose adjustment for EPS or concurrent anti-EPS medication; more effective than risperidone in improving depressive symptoms; as effective as risperidone in treating positive and negative symptoms of outpatients with psychosis. Quetiapine produced statistically significant greater effect in patients with higher initial scores than risperidone on Hamilton Rating Scale (depression)

Results

Comments: extrapyramidal events (EPS checklist) declined in both groups; no significant differences between groups in overall occurrence. Odds of risperidone-treated patient having treatment-emergent EPS requiring adjustment of medication or anti-EPS medication 5.6 times greater than odds of quetiapine-treated patient having similar event ($p < 0.001$). Extrapyramidal symptoms rated as 'at least moderate' (EPS checklist) occurred more frequently at each visit in risperidone participants. Quetiapine group had significantly ($p = 0.028$) greater improvement on Hamilton Rating Scale (depression) than risperidone group. Higher percentage in quetiapine group had improvement in CGI at each visit compared with risperidone group. No statistically significant differences between groups in PANSS scale

Outcome 1

Outcome: % change from baseline Hamilton Rating Scale (depression) scores (schizoaffective; schizophrenia)

Intervention: –41.6%; –41.6%

Control: –34.6%; –31.4% (no significant difference between groups)

Risperidone RCTs *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Purdon 2001[211] **Trial ID:** Canada 1999	**Intervention:** quetiapine ***N*:** 13 **Dose:** 300–600 mg daily (flexible dose); oral **Control:** haloperidol ***N*:** 12 **Dose:** 10–20 mg daily (flexible dose); oral **Duration:** 6 months **Washout:** 2 days oral, 1 interval depot **Concomitant medications:** not stated	**Age:** mean 33.9 years (7.3) **Sex:** male 20 **Illness:** schizophrenia **Diagnosis:** DSM-III-R ***N*:** 25 **Duration of illness:** mean 12.1 years (7.7) **Special characteristics:** paranoid 13, undifferentiated 12 **Inclusion/exclusion criteria:** no history of serious medical disease or neurological disorder; no active substance abuse in past 30 days	**Intervention group *n*:** 3/13 reasons not clear **Control group *n*:** 9/12 reasons not clear	Quetiapine, haloperidol Weight gain 3/13, 1/12; irritability 2, 1; impotency 2, 0; dry mouth 1, 0; hypersalivation 1, 0; involuntary jaw movement 1, 0; fatigue 1, 0; somnolence 1, 1; drowsiness 1, 0; fine tremors 1, 0; twitch in extremities 1, 0; menstrual problems 1/3, 0/2; cold flashes 1, 0; nausea/vomiting 0, 1; restlessness 0, 1; increased appetite 0, 1; EPS 0, 1; akathisia 0, 1; headache 0, 1; blurred vision 0, 1; insomnia 0, 1; sedation 0, 1; stiffness 0, 1; dry skin/rash 0, 1	**Authors' conclusions** Preliminary results support potential value of quetiapine for improving cognitive impairment in patients with schizophrenia and emphasise importance of further research with this promising atypical antipsychotic drug

Results

General comments:	Outcome 1	Outcome 2	Outcome 3	Outcome 4
	Outcome: CGI; PANSS total; PANSS general; positive; negative **Intervention:** 2.9 (0.8); 55.7 (7.8); 27.4 (5.9); 13.6 (3.6); 14.7 (4.8) **Control:** 3.4 (0.5); 57.9 (14.8); 25.0 (5.3); 14.3 (4.9); 18.6 (7.7)	**Outcome:** mood: BDI; CDS **Intervention:** 13.9 (10.5); 2.7 (3.6) **Control:** 9.3 (4.6); 0.7 (1.3)	**Outcome:** cognition: general, motor speed and dexterity, attention span, verbal reasoning and fluency, visuospatial fluency and construction, executive skills and visuomotor tracking, immediate recall **Intervention:** –1.0 (1.0); –0.6 (1.6); –0.6 (1.1); –0.6 (0.8); –1.6 (1.6); –1.3 (1.7); –1.3 (1.1) **Control:** –1.5 (0.9); –1.5 (2.1); –1.0 (0.8); –1.1 (0.6); –1.3 (1.1); –1.9 (1.2); –2.1 (1.1)	**Outcome:** movement: AIMS; SAS **Intervention:** 1.1 (1.5); 11.8 (2.6) **Control:** 2.4 (3.5); 12.7 (4.8)

Risperidone RCTs *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Lecrubier 2000[43]	**Intervention:** amisulpride ***N*:** 152 **Dose:** initial 600 mg daily, adjusted to 400–1000 mg daily **Control:** risperidone ***N*:** 158 **Dose:** initial 6 mg daily, adjusted to 4–10 mg daily **Duration:** 6 months (possible extension to 12 months)	**Age:** mean: 38.4 years **Sex:** 55% male (171/310) **Illness:** schizophrenia **Diagnosis:** DSM-IV ***N*:** 310 **Duration of illness:** mean: 11.8 years **Special characteristics:** mainly paranoid type: 73% (226/310) **Inclusion/exclusion criteria:** not stated	Not reported	Both treatments did not provoke increase in extrapyramidal symptoms as measured by SAS, BAS and AIMS	**Authors' conclusions** Amisulpride showed efficacy profile comparable to risperidone with some trends to superior improvement in several measures during medium-term treatment of schizophrenic patients

Results

General comments:	Outcome 1	Outcome 2	Outcome 3	Outcome 4
	Outcome: change scores: PANSS total; negative **Intervention:** –32.2, 23.9; –5.1, 5.1 **Control:** –31.4, 21.0, $p < 0.001$; –3.9, 6.1, $p = 0.09$	**Outcome:** BPRS change scores **Intervention:** –19.8, 15.0 **Control:** –19.6, 12.6	**Outcome:** PANSS and BPRS (at least 50% improvement) **Intervention:** 65% and 72% **Control:** 52% and 58%, $p < 0.05$ for both	**Outcome:** CGI (very much/much improved); Social Functioning Scale (50% improvement); subjective response to treatment (Van Putten scale) **Intervention:** 77%; 33%; 7% **Control:** 65%, $p < 0.05$; 23%, $p < 0.10$; 17%, $p = 0.015$

Risperidone RCTs *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Rabinowitz 2001[234]	**Intervention:** risperidone ***N*:** 227 **Dose:** 4 mg **Control:** haloperidol ***N*:** 226 **Dose:** 10 mg **Duration:** 8 weeks **Washout:** not reported **Concomitant medications:** not reported	**Age:** mean 38.1 years for both control and intervention **Sex:** male/female: risperidone 152/75, haloperidol 150/76 **Illness:** schizophrenia **Diagnosis:** DSM-III ***N*:** 453 **Duration of illness:** not reported **Special characteristics:** *post-hoc* subgroup analysis of data from RCT comparing five regimens of risperidone (1, 4, 8, 12, 16 mg) with haloperidol (10 mg) for effectiveness in treating chronic schizophrenia **Inclusion/exclusion criteria:** included: patients randomised to 4 mg risperidone or 10 mg haloperidol	**Intervention group *n*:** 45/227 (20%) **Control group *n*:** 63/226 (28%)	Not reported	**Authors' conclusions** Results suggest patients respond more rapidly to risperidone than haloperidol. Future propective studies should re-examine comparative speed of action of risperidone versus haloperidol

Results		
General comments: full results presented graphically; limited results given as absolute improvements and rates of improvement in PANSS and CGI; no final PANSS or CGI scores given	**Outcome 1**	**Outcome 2**
	Outcome: PANSS **Intervention:** mean (SE): 89.6 (1.16); 9.02 (SE 0.98) point improvement from baseline to first week of treatment (p = 0.04 compared with improvement on haloperidol from baseline **Control:** mean (SE): 88.8 (1.10); 5.89 (SE 1.31) improvement from baseline to first week of treatment	**Outcome:** CGI **Intervention:** mean (SE): 4.8 (1.06) Difference in improvement from baseline to first week of trials 0.32 (SE 0.05) (p = 0.02 compared with haloperidol **Control:** mean (SE): 4.7 (1.03)

Risperidone RCTs *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
AstraZeneca 2000 **Trial ID:** QUEST	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed

Results

General comments: CGI severity of illness rating from baseline also reported but only in graphical form

Subset of QUEST trial

Outcome 1

Outcome: PANSS total (positive; negative; general subscales) (mean, SE)

Intervention: (n = 166) 66.9, 1.81 (16.0*, 0.54; 17.9, 0.56; 33.0, 0.90); on all subscales of PANSS, change from baseline significant in each group ($p < 0.001$) but not between treatments

Control: (n = 50) 61.3, 3.48 (13.9*, 1.00; 17.4, 1.10; 30.4, 1.67)

* Quetiapine/risperidone: n = 167/51

Outcome 2

Outcome: percentage participants experiencing substantial EPS

Intervention: n = 187

Control: significantly more participants treated with risperidone experienced EPS ($p < 0.01$); n = 60

Outcome 3

Outcome: percentage participants with EPS requiring adjunctive medication; at week 16

Intervention: n = 191; statistically significant for risperidone group (p-value not given); significant for risperidone, $p < 0.01$

Control: n = 60

Risperidone RCTs *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Liu 2000[235]	**Intervention:** risperidone ***N*:** 19 **Dose:** not stated **Control:** haloperidol ***N*:** 19 **Dose:** not stated **Duration:** 12 weeks **Washout:** 1 week	**Age:** mean (SD): 33.9 (10.8) years **Sex:** 40% male (*n* = 15) **Illness:** schizophrenia **Diagnosis:** DSM-III-R ***N*:** 38 **Duration of illness:** mean (SD): 7.8 (6.8) years **Inclusion/exclusion criteria:** total PANSS score > 65; patients with previous history of physical illness or substance abuse that cast diagnoses in doubt excluded	**Intervention group** ***n*:** seven dropped out; two did not complete CPT at end of study **Control group:** nine dropped out	Not reported	**Authors' conclusions** Results suggest that CPT performance deficits independent of changes in clinical symptoms and might be stable vulnerability indicators of schizophrenia. Alternatively, findings might imply that biochemical mechanisms other than combined dopamine–serotonin antagonism contributing to sustained attention deficits in schizophrenia

Results

General comments	Outcome 1	Outcome 2	Outcome 3	Outcome 4
General comments: although sample size comparable to those of most previous studies, it was nonetheless small. In addition, washout period might not have been long enough to eliminate effects of previous antipsychotic medications. Also, one-third of patients enrolled at beginning of study were not included in analysis	**Outcome:** PANSS total (positive; negative; general subscales) **Intervention:** 51.3, 18.5 (12.3, 6.7; 12.9, 4.8; 26.1, 10.0) **Control:** 54.5, 16.3 (13.7, 6.5; 14.3, 4.6; 26.4, 7.5)	**Outcome:** ESRS-P and -GP **Intervention:** 2.4, 2.5; 1.1, 1.2 **Control:** 4.1, 5.0; 1.7, 1.5	**Outcome:** CPT index – undegraded (hit rate; N alarm rate; d'; ln beta; adjusted z score of d') **Intervention:** 0.73, 0.29; 0.01, 0.02; 3.26, 1.35; 2.12, 0.96; –1.53, 1.86 **Control:** 0.57, 0.35; 0.04, 0.05; 2.15, 1.90; 1.38, 2.09; –2.98, 2.55	**Outcome:** CPT index 25% degraded (hit rate; N alarm rate; d'; ln beta; adjusted z score of d') **Intervention:** 0.47, 0.32; 0.03, 0.02; 1.82, 1.54; 1.51, 1.90; –3.50, 2.13 **Control:** 0.39, 0.33; 0.04, 0.03; 1.55, 1.68; 1.32, 1.67; –3.83, 2.37

CPT, Continuous Performance Test

Risperidone RCTs *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Wirshing 1999[236]	**Intervention:** risperidone ***N*:** 34 **Dose:** 6 mg daily for 4-week fixed dose period, then 3–15 mg daily (mean 7.5 mg) for 4-week flexible dose period; oral **Control:** haloperidol ***N*:** 33 **Dose:** 15 mg daily for 4-week fixed dose period, then 5–30 mg daily (mean 19.4 mg) for 4-week flexible dose period; oral **Duration:** 8 weeks (4-week fixed dose, 4-week flexible dose) **Washout:** 3–7 days **Concomitant medications:** anticholinergic medication and propranolol given for parkinsonism, dystonia and akathisia; lorazepam, up to 8 mg daily, given as necessary for severe acute anxiety or agitation; temazepam given for insomnia **Comments:** none responded to placebo (> 20% improvement) during washout phase. Baseline assessments at two sites conducted at placebo washout phase or at end of 3 weeks of treatment	**Age:** risperidone, mean 41.0 (SD 9.4) years; haloperidol, mean 40.0 (SD 8.2) **Sex:** male 55; female 12 **Illness:** schizophrenia **Diagnosis:** DSM-III-R **N:** 67 **Duration of illness:** risperidone mean 19.4 (SD 9.3) years, haloperidol mean 18.7 (SD 7.7) **Special characteristics:** treatment refractory by Kane criteria (total BPRS ≥ 45, minimum CGI rating of 4, item scores of ≥ 4 on two psychotic items on BPRS). All had 'failure to respond' or 'inability to tolerate' in at least three 6-week trials of antipsychotic drugs within last 5 years **Inclusion/exclusion criteria:** see above. Excluded: significant medical disease, history of seizure disorder, taken any investigational drug within 4 weeks; no severe physical or cognitive impairment; substantial substance abuse within 2 months or dependence within 6 months; those with high risk of violence towards themselves or others, or history of risperidone treatment failure **Further details:** no statistically significant differences between groups – demographic factors	**Intervention group *n*:** total 6 – lack of efficacy 3, side-effects, 3 **Control group *n*:** total 5, all lack of efficacy	BAS: 7/34 risperidone patients had observable akathisia compared with 16/33 haloperidol; p = 0.04; AIMS total and overall severity scores also lower in risperidone group, p = 0.0007 versus p = 0.03); no statistically significant differences in specific aspects of drug-induced parkinsonism (tremor, rigidity, bradykinesia) or on SAS	**Authors' conclusions** Risperidone better tolerated and more effective in subset of patients with treatment-refractory schizophrenia; positive psychotic symptoms and extrapyramidal side-effects at baseline appear to be powerful predictors of subsequent response to risperidone

Results

General comments	Outcome 1	Outcome 2	Outcome 3	Outcome 4
General comments: risperidone group dichotomised into robust responders (> 40% improved BPRS), n = 10, versus all others, n = 23. Clinical predictors of robust response: more severe positive symptoms, greater conceptual disorganisation, less rated depression at baseline. Subgroup also had significantly higher scores at baseline on measures of acute EPS (BAS, p = 0.02) and tardive dyskinesia (AIMS, p = 0.04)	**Outcome:** BPRS total (positive, negative, conceptual, anxiety, depression) **Intervention:** 57.3 (13.1; 9.4; 2.9; 2.2; 1.5) **Control:** 59.3 (14.4; 8.7; 3.2; 2.0; 1.5); no significant differences between groups at 8 weeks	**Outcome:** CGI ratings **Intervention:** 4.6 S, 3.1 I **Control:** 4.8 S, 3.5 I; no significant differences between groups	**Outcome:** improved (physician, patient, Kane criteria) **Intervention:** 7/34 (17/34; 9/34) **Control:** 7/33 (11/33; 4/33) Kane criteria = 20% improvement in BPRS, CGI score of 3 or less, or total score of 35 or less on 18-item BPRS	**Outcome:** use of concomitant medication **Intervention:** received fewer anticholinergic drugs than control group (p = 0.003) and fewer alpha blockers for akathisia (p = 0.04); no significant difference between groups for benzodiazepines

Risperidone RCTs *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Kern 1999[237]	**Intervention:** risperidone ***N*:** 32 **Dose:** 6 mg daily for 4 weeks then flexible dose for 4weeks; oral **Control:** haloperidol ***N*:** 32 **Dose:** 15 mg daily for 4 weeks then flexible dose for 4 weeks; oral **Duration:** 8 weeks preceded by 3-week baseline then washout **Washout:** 'brief' placebo washout **Concomitant medications:** lorazepam or chloral hydrate as needed; benztropine mesylate or propranolol for EPS at discretion of treating psychiatrist **Comments:** 3-week baseline period: most participants maintained on 20 mg (range 15–30 mg) haloperidol at one site, at other baseline was off-medication lead-in phase	**Age:** haloperidol mean 39.8 (SD 8.4) years; risperidone mean 41.5 (SD 9.5) **Sex:** male 53, female 11 **Illness:** schizophrenia **Diagnosis:** DSM-III-R ***N*:** 64 **Duration of illness:** haloperidol mean 18.3 (SD 7.8) years; risperidone mean 19.8 (SD 9.5) **Special characteristics:** all met Kane criteria for treatment-resistant schizophrenia **Inclusion/exclusion criteria:** not stated (refers to Green *et al. Am J Psychiatry* 1997;**154**:799–804) **Further details:** no further details	**Intervention group *n*:** none stated **Control group *n*:** none stated	Patients in haloperidol group received anticholinergic medication at rates two to three times that of risperidone-treated patients (reported in discussion)	**Authors' conclusions** Findings suggest that risperidone may exert facilitating effect on acquisition of new verbal information, an effect that does not appear to be due to activation of semantic encoding strategies

Results

General comments	Outcome 1	Outcome 2	Outcome 3	Outcome 4
General comments: when time-varying covariate of benztropine status entered into analyses, effect of group remained significant for learning acquisition ($p = 0.013$) and recall consistency ($p = 0.023$); significant group effect for recognition memory weakened slightly ($p = 0.073$). Trend for retention became nonsignificant. When additional time-varying covariates of change in positive and negative symptoms entered into analyses, effect of group remained significant for learning acquisition ($p = 0.045$) and p-value for recall consistency became trend ($p = 0.073$)	**Outcome:** California verbal learning test (CVLT) **Intervention:** significant group effects found for factor 1 variables: learning acquisition ($p = 0.016$); recognition memory ($p = 0.024$), recall consistency ($p = 0.004$). Factor 2 variable of retention, $p = 0.076$. No differences between groups for factor 3 variables	**Outcome:** CVLT learning acquisition, recall consistency (actual values) **Intervention:** 42.4, 15.0; 82.1, 11.1 **Control:** 36.7, 18.4; 71.6, 14.6	**Outcome:** CVLT total intrusions, recognition (actual values) **Intervention:** 12.1, 14.8; 87.0, 14.4 **Control:** 15.8, 13.2; 76.8, 17.2	**Outcome:** CVLT retention, semantic clustering ration (actual values) **Intervention:** 0.8, 1.4; 1.3, 1.0 **Control:** 1.6, 2.1; 1.5, 0.89

Risperidone RCTs *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Kern 1998[238]	**Intervention:** risperidone ***N*:** 27 **Dose:** 6 mg daily for 4 weeks; flexible dose for following 4 weeks (mean, 7 mg daily) **Control:** haloperidol ***N*:** 29 **Dose:** 15 mg daily for 4 weeks; flexible dose for following 4 weeks (mean, 19 mg daily) **Duration:** 8 weeks **Washout:** placebo washout: 3–7 days **Concomitant medications:** lorazepam or chloral hydrate as required; benztropine mesylate or propanolol administered at discretion of treating psychiatrist. On three occasions biperiden hydrochloride substituted for benztropine mesylate **Comments:** at site 1, patients received haloperidol, 15–30 mg daily, for 3 weeks before washout. At site 2, baseline phase consisted of 'off-medication lead-in phase' – duration not stated	Haloperidol versus risperidone **Age:** mean (SD): 39.6 (7.8) years; 40.8 (10.2) **Sex:** male:female, 25:4, 20:7 **Illness:** schizophrenia **Diagnosis:** DSM-III-R ***N*:** 56 **Duration of illness:** mean (SD): 18.5 (7.9) versus 19.2 (10.0) years **Special characteristics:** all included patients had treatment-resistant illness according to Kane criteria[9] **Inclusion/exclusion criteria:** met symptom severity and exclusionary criteria at time of the initial screening[a] **Further details:** BPRS total scores at baseline: 67.8 (12.0), 63.8 (10.6); thinking disturbance: 13.4 (3.2), 12.6 (3.4); withdrawal/retardation: 8.4 (3.0), 8.5 (3.2); EPS scores (SAS): 3.1 (4.2), 3.1 (5.2)	Not reported	None reported	**Authors' conclusions** Differences in performance in reaction time and manual dexterity may be due to specific beneficial effect of risperidone, as opposed to general reduction in extrapyramidal symptom liability compared with haloperidol

Results

General comments:	Outcome 1	Outcome 2	Outcome 3
	Outcome: serial reaction time **Intervention:** 492 ms; 19.7% improvement; F = 12.94, df = 1, 41, p = 0.0009; ANCOVA **Control:** 6.0% improvement; additional time-varying covariates (symptom changes amd EPS changes): F = 11.18, df = 1, 41, p = 0.0018; ANCOVA	**Outcome:** manual dexterity (pin test) **Intervention:** 14.6% improvement; F = 5.93, df =1, 53, p = 0.18; ANCOVA **Control:** 5.4% improvement; examination of data from each site separately revealed similar changes in performance. Additional time-varying covariates (symptom changes and EPS ratings): F = 4.55, df = 1, 53, p = 0.038; ANCOVA	**Outcome:** motor learning sequence and gross motor learning (pursuit rotor) **Intervention:** failed to reveal any significant differences between treatment groups

[a] See *Green* et al. Am J Psychiatry *1997;**154**:799–804*

Risperidone RCTs *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Kee 1998[239]	**Intervention:** risperidone ***N*:** 10 **Dose:** 6 mg daily for 4 weeks, followed by flexible dose for 4 weeks **Control:** haloperidol ***N*:** 10 **Dose:** 15 mg daily for 4 weeks, followed by flexible dose for 4 weeks **Duration:** 8 weeks **Washout:** 3–7 days **Concomitant medications:** as required: benztropine mesylate, lorazepam, propanolol, or chloral hydrate **Comments:** during baseline, patients received haloperidol, 15–30 mg daily, for 3 weeks before washout	**Age:** mean (SD): risperidone 35.00 (9.72) years; haloperidol 37.67 (8.37) **Sex:** male:female, risperidone 5:4; haloperidol 7:2 **Illness:** schizophrenia **Diagnosis:** DSM-III-R ***N*:** 20 **Duration of illness:** mean (SD): risperidone 17.89 (8.89) years; haloperidol 20.33 (8.53) **Special characteristics:** patients considered treatment-resistant using Kane criteria[9] **Inclusion/exclusion criteria:** at time of initial screening, patients met symptom severity and selection criteria[a] **Further details:** two patients from original sample had missing data at baseline assessment, hence in sample analysis, *n* = 18	**Intervention group *n*:** one patient's disorganised behaviour precluded testing **Control group *n*:** one patient's disorganised behaviour precluded testing	None reported	**Authors' conclusions** Findings suggest that risperidone may facilitate patients' ability to accurately perceive emotion; effect may be mediated either by risperidone's pharmacological action or perhaps indirectly by its influence on basic neurocognition

Results

General comments	Outcome 1	Outcome 2	Outcome 3
General comments: current study has some limitations: sample size too small and measures used to assess perception of emotion did not allow for separate analyses of positive versus negative valence	**Outcome:** perception of emotion (facial emotion identification test, voice emotion identification test, videotape affect perception test) **Intervention:** Pearson product-moment correlations: 0.55–0.81 (p = 0.0001–0.018), thus data from three measures summated into single measure of perception of emotion (maximum score = 70); risperidone versus haloperidol: F = 6.68, df = 1, 15, p = 0.02, ANCOVA	**Outcome:** perception of emotion and psychiatric symptoms **Intervention:** Pearson product-moment correlation (positive symptoms): –0.41, $p < 0.10$; Pearson product-moment correlation (positive symptoms): –0.52, $p < 0.03$; negative symptoms did not correlate with emotion perception at either time point. Subsequent ANCOVA including change in positive symptoms as additional covariate found same treatment effect (F = 5.59, df = 1, 14, p = 0.03)	**Outcome:** direction of change **Intervention:** Fisher's Exact test: all nine patients improved their ability to identify emotion **Control:** Fisher's Exact test: four patients improved their ability to identify emotions (p = 0.03)

[a] See *Green* et al. Am J Psychiatry *1997;**154**:799–804*

Risperidone RCTs *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Muller-Siecheneder 1998[240]	**Intervention:** risperidone ***N*:** 62 **Dose:** 3 x 1 mg capsules daily, dose escalation to 1 week = 8 mg daily; thereafter altered to take account of side-effects/clinical response (range 2–12 mg daily); oral **Control:** haloperidol/amitriptyline ***N*:** 61 **Dose:** haloperidol, 3 x 2.5 mg capsules daily, amitriptyline, 3 x 50 mg capsules daily, dose escalation at 1 week, haloperidol, 10 mg, amitriptyline, 200 mg; then altered according to clinical response/ side-effects (range haloperidol. 2.5–12 mg daily, amitriptyline, 50–300 mg daily); oral **Duration:** 6 weeks **Washout:** 3 days **Concomitant medications:** as required: anticholinergic (biperiden) for acute dystonia and other EPS; diazepam, up to 30 mg daily **Comments:** capsules double-blind dummy design	**Age:** 19-63 years **Sex:** 60–64% female **Illness:** schizoaffective/phreniform and schizophrenia **Diagnosis:** DSM-III-R ***N*:** 123 **Duration of illness:** not stated **Special characteristics:** depressive and psychotic symptoms combined. 64 (32 per group) with schizoaffective, depressive type; 2 (1 per group) with schizoaffective, bipolar type, 19 (10 risperidone, 9 control group) with schizophrenia or schizophreniform disorder with major depressive symptoms; 38 (19 per group) with major depression with psychotic features; comorbid axis II disorder, 9 risperidone, 8 control group; pretreated with antipsychotic drugs, 38 risperidone, 25 control group - antidepressants, risperidone 26, 27 control group; benzodiazepines, risperidone 14, control group 15 **Inclusion/exclusion criteria:** aged 18–65 years; coexisting major depression and paranoid and/or hallucinatory symptoms; PANSS ≥ 60, ≥ 4 on at least two PANSS positive subscale items, BRMES ≥ 15 with ≥ 3 points on depression item. Excluded: history of suicidal tendencies or serious suicide attempt, severe internal or neurologic disease; history of allergic or toxic reaction to psychotropics, participation in clinical trial within 4 weeks, pregnancy **Further details:** not possible to separate results of those with major depression with psychotic features from those with schizophrenia/affective/phreniform disorders	**Intervention group *n*:** 15 dropouts before 3 weeks, 20 before end of study: 13 side-effects, 7 insufficient response (9 protocol deviations) **Control group *n*:** 10 dropouts before 3 weeks, 13 by end of study: 7 side-effects, 4 insufficient response, (10 protocol deviations)	Risperidone, haloperidole/ amitriptyline ESRS changes scores: +6.2 (8.4), +3.2 (7.2), $p = 0.034$ – mainly due to significantly higher shift in parkinsonism subscale (+5.8 (7.8), +2.9 (6.4), $p = 0.028$) – no significant changes for dyskinesia or dystonia subscales; use of concurrent anticholinergic medication, 37.1%, 19.7%, $p = 0.05$; any adverse event, 41/62, 46/61, $p = 0.35$; extrapyramidal-like symptoms, 37.1%, 31.1%; fatigue, 4, 2; abnormal hepatic function, 3, 10; constipation, 5, 7; dry mouth, 4, 6; nausea/ vomiting, 4, 2; hypotension, 0, 4; dizziness, 2, 1; hyperprolactinaemia, 1, 2; tachycardia, 1, 2; abdominal pain, 0, 2; dysphagia, 2, 0. Severe adverse events reported by > 1 patient: agitation, 2, 1; suicidal ideations, 1, 2; akathisia tremor, 2, 0; speech disorder, 1, 1; dystonia abdominal pain and constipation, 0, 2. Significant increases in body weight in both groups but less pronounced in risperidone group (+0.8 kg, $p = 0.02$) than control group (+2.3 kg, $p = 0.001$); no clinically significant ECG changes in either group; no consistent changes in blood chemistry of haematology observed	**Authors' conclusions** Results suggest therapeutic effect of haloperidol/ amitriptyline superior to risperidone in total group of patients with combined depressive and psychotic symptoms; however, subgroup differences have to be considered

continued

Risperidone RCTs *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Muller-Siecheneder 1998[240] *contd* **Results**					
General comments: corresponding ITT analysis of BRMES data revealed mean score reduction of 15.2 (SD 9.4) in haloperidol/amitriptyline group and 10.5 (SD 9.0) in risperidone group, $p = 0.002$	**Outcome 1** **Outcome:** BPRS total (anxiety/depression) **Intervention:** $n = 47$; –21.5, 15.4 (–7.1, 4.8) **Control:** $n = 51$; -29.5, 10.5 (–10.4, 4.2), $p = 0.004$ (0.0006)	**Outcome 2** **Outcome:** PANSS total (positive; negative; general subscales) **Intervention:** –36.1, 27.8 (–10.1, 6.2; –8.3, 8.5; –17.7, 14.9) **Control:** –51.8, 18.9 (–10.8, 4.6; –14.2, 6.3; –26.8, 10.9) $p = 0.002$ (0.89; 0.0003; 0.001)	**Outcome 3** **Outcome:** at least 20% (50%) reduction in BPRS **Intervention:** 35/47 (17/47) **Control:** 48/51 (35/51) $p = 0.012$ (0.0018)	**Outcome 4** **Outcome:** BRMES scores **Intervention:** 12.7 (–13.1, SD 8.5) **Control:** 8.0 (–18.4, SD 6.8) $p = 0.0013$	
BRMES, Bech–Rafaelson Melancholia Scale					

Risperidone RCTs *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Bouchard 2000[249] **Trial ID:** Bouchard 1998,[253] new ESRS data (see appendix 3)	**Intervention:** risperidone ***N*:** 93 **Dose:** mean = 5.5 mg daily (range, 1.2–13.4 mg daily); oral **Control:** conventional neuroleptic drugs ***N*:** 91 **Dose:** mean = 1006 mg daily (range, 10–8174 mg daily) chlorpromazine equivalent units; oral **Duration:** 12 months **Washout:** unclear **Concomitant medications:** no restrictions other than lithium. At baseline, 104/175 patients receiving benzodiazepines; 32/175 receiving anticonvulsants; 51/175 receiving antidepressants; 124/175 receiving anticholinergic drugs **Comments:** protocol did not give specific guidance regarding target doses and titration	**Age:** mean (SD): 43 (11) years **Sex:** 68% male **Illness:** schizophrenia **Diagnosis:** DSM-IV ***N*:** 184 **Duration of illness:** mean (SD): 18 (11) years **Special characteristics:** mean (SD), PANSS score at baseline: total 81.2 (13.4); subscale, positive, 18.2 (5.5); negative, 24.3 (5.7); general 38.7 (6.9). Percentage (*n*) of schizophrenia subtype: catatonia 2 (3); disorganised 7 (12); paranoid 54 (95); undifferentiated 20 (35); residual 17 (30) **Inclusion/exclusion criteria:** suboptimal response to previous neuroleptic drugs, as indicated by baseline total PANSS score of 60–120 Excluded: pregnancy and lactation, serious medical illness, substance abuse or dependence, cocomitant use of lithium, previous use of clozapine	**Intervention group *n*:** four patients dropped out before 3-month assessment; two before end of study; one following switching of their medication **Control group *n*:** five patients dropped out before 3-month assessment; eight before end of trial	At 12 months, percentage of participants still taking antiparkinsonian medication: risperidone 46%, conventional 76% ($p = 0.0001$)	**Authors' conclusions** Compared with conventional neuroleptic drugs, risperidone beneficial in treatment of patients with chronic schizophrenia; some of these benefits may appear only after longer-term treatment

Results

General comments	Outcome 1	Outcome 2	Outcome 3	Outcome 4
General comments: investigators not blind to treatment, which may have introduced bias in favour of risperidone; also only stabilised and severely ill patients with chronic schizophrenia included, limiting external validity of present results	**Outcome:** PANSS total (positive; negative; general subscales) change scores **Intervention:** –10.2 (–3.0; –2.6; –4.6) **Control:** –3.4 (–1.2; –0.6; –1.5)	**Outcome:** 20% improvement in total PANSS score (30%) **Intervention:** 30% (17%) **Control:** 15%, $p = 0.03$ (6%, $p = 0.03$)	**Outcome:** change from baseline in total PANSS score ANCOVA **Intervention:** F = 0.56, df = 2, 137, $p = 0.57$; meaning that superiority of effectiveness relatively constant over three dose categories	**Outcome:** ESRS symptoms (*n*, %) (dyskinesia, parkinsonism, akathisia) **Intervention:** no symptoms: 52, 58.4; 14, 15.7; 59, 66.3; worse: 16, 18.4; 13, 14.9; 7, 8.1; unchanged: 50, 57.5; 31, 35.6; 62, 71.3; improved: 21, 24.1; 43, 49.4; 18, 20.7 **Control:** no symptoms: 40, 46.5; 12, 14.0; 57, 66.3; worse: 16, 20.8; 20, 26.0; 17, 22.1; unchanged: 43, 55.8; 30, 39.0; 44, 57.1; unchanged: 18, 23.4; 27, 35.1; 16, 20.8

Risperidone RCTs *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Cetin 1999[241]	**Intervention:** risperidone ***N*:** 50 **Dose (n):** 2 mg daily (10); 4 mg daily (10); 6 mg daily (10); 8 mg daily (10); 10 mg daily (10); oral **Control:** haloperidol ***N*:** 20 **Dose:** 20 mg daily; oral **Duration:** 6 weeks **Washout:** 1 week (placebo) **Concomitant medications:** for control of EPS; lorazepam (for sedation) **Comments:** purpose was to determine optimal dose of risperidone	**Age:** not stated **Sex:** not stated **Illness:** schizophrenia **Diagnosis:** not stated ***N*:** 70 **Duration of illness:** not stated **Inclusion/exclusion criteria:** not stated	**Intervention group *n*:** not stated **Control group *n*:** not stated	Incidence of extrapyramidal side-effects significantly higher in patients treated with risperidone, 8 and 10 mg, than in patients receiving risperidone, 2, 4 and 6 mg Optimal daily dose of risperidone for most schizophrenia patients in this study population was 6 mg. This replicates findings of previous studies (specifically Chouinard 1993[255] and Marder 1994[116])	**Authors' conclusions**
Results					
General comments: positive symptom scores significantly lower after risperidone, ≥ 6 mg, and haloperidol, 20 mg, than risperidone, 2 or 4 mg. Negative symptom scores lower after risperidone, ≥ 6 mg, than haloperidol or risperidone, 2 or 4 mg					

Risperidone RCTs *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Csernansky 2000[246] Harvey 1999[247] Csernansky 1999[248] Csernansky 2001 (commercial-in-confidence)	**Intervention:** risperidone ***N*:** 177 **Dose:** commercial-in-confidence: data removed **Control:** haloperidol ***N*:** 188 **Dose:** commercial-in-confidence: data removed **Duration:** 1 year minimum **Concomitant medications:** commercial-in-confidence: data removed	**Age:** commercial-in-confidence: data removed **Sex:** commercial-in-confidence: data removed **Illness:** combined diagnoses **Diagnosis:** commercial-in-confidence: data removed ***N*:** commercial-in-confidence: data removed (365 in final analysis) **Duration of illness:** commercial-in-confidence: data removed **Special characteristics:** patients with schizophrenia or schizoaffective disorders; commercial-in-confidence: data removed **Inclusion/exclusion criteria:** Stable outpatients; commercial-in-confidence: data removed	Commercial-in-confidence: data removed	Patients in risperidone group experienced weight gain (5.0 lbs at end-point); commercial-in-confidence: data removed. Those in haloperidol group had low rate of tardive dyskenesia (0.6%) and of EPS (no data) Commercial-in-confidence: data removed	**Authors' conclusions** Provides evidence for long-term effectiveness of rsiperidone and corroborates earlier pivotal trials in which it was found to be significantly superior to haloperidol for both positive and negative symptoms of schizophrenia; previous short-term trials have shown risperidone to be statistically superior in control of positive and negative symptoms and this confirms superior efficacy of risperidone over haloperidol in long-term treatment. Patients treated with risperidone also experienced desirable safety profile in long-term treatment

Results

General comments: length of study unclear

Commercial-in-confidence: data removed

Outcome 1	Outcome 2
Outcome: relapse rate	Commercial-in-confidence: data removed
Intervention: 1 year: 41/177; endpoint: 45/177; commercial-in-confidence: data removed	
Control: 1year: 65/188 (p = 0.009); endpoint: 75/188 (p = 0.002) commercial-in-confidence: data removed	

Risperidone RCTs *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Janicak 1999[245]	**Intervention:** risperidone **N:** not stated **Dose:** up to 10 mg daily; oral **Control:** haloperidol **N:** not stated **Dose:** up to 20 mg daily; oral **Duration:** 6 weeks **Washout:** not stated **Concomitant medications:** not stated	**Age:** not stated **Sex:** not stated **Illness:** schizoaffective disorder **Diagnosis:** not stated **N:** 60 **Duration of illness:** not stated **Inclusion/exclusion criteria:** not stated **Further details:** no differences between groups on such variables as age, sex, duration or severity of psychotic symptoms	Five in haloperidol group withdrew due to adverse events compared with none in risperidone group	Based on SAS, haloperidol produced significantly more extrapyramidal symptoms than risperidone ($p < 0.04$); more patients on haloperidol dropped out because of side-effects	**Authors' conclusions** None stated
Results					
General comments: abstract only, many details missing. Further schizoaffective subtypes depresssed or manic did not alter response to risperidone or haloperidol	**Outcome 1** **Outcome:** PANSS f04; PANSS cars-m; PANSS **Intervention:** no significant differences between risperidone and haloperidol for any outcome				

Risperidone RCTs *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Edgell 2000[170] **Trial ID:** subset of Tran 1997[171] (see appendix 3)	**Intervention:** risperidone ***N*:** 75 **Dose:** 4–12 mg daily; oral **Control:** olanzapine ***N*:** 75 **Dose:** 10–20 mg daily **Duration:** 28 weeks (maximum) **Washout:** 2–9 days **Concomitant medications:** see Tran 1997	See Tran 1997	Not stated	Not reported	**Authors' conclusions** Olanzapine-treated patients experienced clinical improvements that translated into savings in costs of care for both in- and outpatient services. These savings offset difference in medication acquisition cost between olanzapine and risperidone

Results

General comments:	Outcome 1	Outcome 2	Outcome 3	Outcome 4
	Outcome: response (≥ 20% on PANSS total scores; 30%; 40%; 50%): olanzapine: 44/75; 38/75; 21/75; 7/75; risperidone: 47/75; 31/75; 15/75; 5/75 Olanzapine-treated participants more likely to maintain response than risperidone treated (p = 0.048)	**Outcome:** required anticholinergic therapy: risperidone, 34/75 (45.3%); olanzapine, 19/75 (25.3%); p = 0.016 versus risperidone	**Outcome:** costs Total per patient medical costs over study interval were $US2843 (1997 values, 36%) lower in olanzapine group than in risperidone group (p = 0.342) Medication costs significantly higher for olanzapine-treated patients ($US2513 versus $US1581, p < 0.001) but difference offset by reduction of $US3774 (52%) in in-/outpatient service costs for olanzapine-treated patients	**Outcome:** treatment-emergent EPS (SAS; BAS; AIMS) – risperidone, 8/75; 18/76; 9/75; olanzapine, 5/75; 17/75; 2/75

Risperidone RCTs *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Littrell 1999[154]	**Intervention:** risperidone ***N*:** 12 **Dose:** mean 5.2 mg daily; oral **Control:** olanzapine ***N*:** 12 **Dose:** mean 19.2 mg daily; oral **Duration:** 1 year **Washout:** not stated **Concomitant medications:** not stated **Comments:** medication compliance quantitatively verified by monthly plasma drug levels	**Age:** not stated **Sex:** not stated **Illness:** schizophrenia **Diagnosis:** not stated ***N*:** 24 **Duration of illness:** not stated **Special characteristics:** switched from depot antipsychotic medication to atypical agents **Inclusion/exclusion criteria:** not stated	**Intervention group *n*:** 1/12 dropped out Reasons: not stated **Control group *n*:** 2/12 dropped out Reasons: not stated	Risperidone: changes in severity of extrapyramidal symptoms (SAS) not significant; olanzapine: severity of extrapyramidal symptoms not changed	**Authors' conclusions** Both risperidone and olanzapine well tolerated in patients switched from depot to oral antipsychotic drugs but superior efficacy seen with risperidone

Results

General comments: within-group comparisons only, no between-group *p*-values, no data suitable for inclusion in meta-analysis other than attrition; superior efficacy of risperidone not demonstrated

Outcome 1

Outcome: PANSS total; subscales

Intervention: significant reductions at 6 months in positive symptoms ($p < 0.01$), negative symptoms ($p < 0.05$) and general psychopathology ($p < 0.01$); significant reduction in positive symptoms at 1 year ($p < 0.001$)

Control: mean positive symptom scores reduced at 1 year (not significant) but no reductions seen in total scores, negative symptoms or general psychopathology

Risperidone RCTs *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Barak 2000[244]	**Intervention:** risperidone ***N*:** 26 **Dose:** not stated; oral **Control:** typical neuroleptic treatment ***N*:** 25 **Dose:** not stated; oral **Duration:** 18 months **Washout:** not stated **Concomitant medications:** not stated	**Age:** range 65–88 years **Sex:** 21 male, 30 female **Illness:** schizophrenia **Diagnosis:** DSM-IV ***N*:** 51 **Duration of illness:** > 30 years (mean) **Special characteristics:** elderly inpatients in psychogeriatric ward **Inclusion/exclusion criteria:** > 65 years	Not stated	Side-effects recorded in 3/26 risperidone-treated patients (sedation, tremor and agitation) and in 17/25 patients treated with typical neuroleptic drugs (EPS, sedation and hypotension)	**Authors' conclusions** Retrospective study demonstrates in cohort of elderly chronic schizophrenia patients that long-term (18 months) risperidone treatment had better effect on positive psychotic symptoms as well as on total PANSS scores. Patients treated with risperidone had fewer side-effects and better outcome as evaluated by CGI. Stable body mass index in both groups may be attributed to length of previous neuroleptic treatment. Suggest that risperidone efficient and better tolerated in chronic elderly schizophrenic patients

Results

General comments: not enough detail given to pool results in meta-analysis

Outcome 1	Outcome 2	Outcome 3
Outcome: PANSS	**Outcome:** CGI-I	**Outcome:** body mass index
Baseline: baseline PANSS scores did not differ between groups	**Endpoint:** ratings significantly different between groups, favouring risperidone	**Endpoint:** unchanged in both groups
Endpoint: more significant effect on positive symptoms in risperidone group ($p < 0.01$); no intergroup differences observed for negative symptoms; PANSS total scores, also significant difference (in favour of risperidone?), $p < 0.05$		

Sertindole RCTs

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Hale 2000[275]	**Intervention:** sertindole ***N*:** 492 **Dose (*n*):** 8 mg daily (120); 16 mg daily (127);20 mg daily (128); 24 mg daily (117); oral **Control:** haloperidol ***N*:** 125 **Dose:** 10 mg daily; oral **Duration:** 8 weeks **Washout:** 3–7 days **Concomitant medications:** not stated **Comments:** during active treatment phase, patients in sertindole groups initially received sertindole, 4 mg daily, for 3 days, then dose increased every 3 days by 4 mg until appropriate daily dose (8, 16, 20 or 24 mg) reached; patients in haloperidol group received haloperidol, 5 mg, for 3 days, then on day 4 dose increased to 10 mg. Patients administered matching placebo in addition to randomised treatment, all took 3 tablets and 2 capsules daily	**Age:** mean: 35.04 (range 17–66) years **Sex:** 400/595 male **Illness:** schizophrenia **Diagnosis:** DSM-III-R ***N*:** 617 **Duration of illness:** not stated **Special characteristics:** disorganised 82/595; catatonic 9/595; paranoid 305/595; residual 52/595; unspecified 173/595 **Inclusion/exclusion criteria:** aged 18–65 years; required hospitalisation; score > 2 for at least two of following PANSS items (sum of scores ≥ 8): conceptual disorganisation, hallucinatory behaviour, suspiciousness, unusual thought content; < 3 for all items on SAS and AIMS Excluded: non-responders to any antipsychotic agent within past 5 years; unrateable using battery of psychiatric and movement rating scales; current primary psychiatric diagnosis other than schizophrenia; confounding medical or neurological disorders; history of substance abuse; clinically relevant ECG abnormalities; decrease in PANSS score ≥ 20 over 7-day placebo run	**Intervention group *n*:** 8 mg versus 16 mg, 53/120, 48/127; unacceptable treatment response, 22/120, 23/127; patient's decision, 16/120, 11/127; adverse event, 8/120, 9/127; other, 7/120, 5/127 20 mg versus 24 mg, 47/128, 45/117; unacceptable treatment response, 19/128, 18/117; patient's decision, 13/128, 10/117; adverse event, 6/128, 13/117; other 9/128, 4/117 **Control group *n*:** 49/125; unacceptable treatment response, 18/125; patient's decision, 16/125; adverse event, 0/125; other, 6/125	Significantly fewer patients in sertindole groups experienced EPS than in haloperidol group (12–26% versus 53%); incidence overall also significantly lower in sertindole groups than in haloperidol group. Significant increase in mean Q-Tc interval in sertindole 16, 20 and 24 mg (see Hale, *et al.*, 1998[594] for more information	**Authors' conclusions** Sertindole, 16 mg, as efficacious as sertindole, 20 mg, suggesting that initial titration should be 16 mg daily; also confirms sertindole, 8 mg, sub-optimal with respect to efficacy

Results

General comments: Jonckheere–Terpstra analysis of change in total PANSS score showed no statistically significant differences between sertindole, 16, 20 and 24 mg, but a direct relationship between clinical response and sertindole dose between 8 and 16 mg ($p = 0.045$)

22 participants missing from ITT analysis

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome: PANSS total (positive; negative) **Intervention:** 8 mg, 51.5 (12.3; 14.7); 16 mg, 48.3* (11.0*; 14.2); 20 mg, 50.0 (11.1; 14.7); 24 mg, 47.9* (10.4*; 14.5) * $p = 0.05$ versus sertindole, 8 mg **Control:** 46.6* (10.0*; 14.3) * $p = 0.05$ versus sertindole, 8 mg	**Outcome:** CGI-S **Intervention:** 8 mg, 3.1; 16 mg, 3.0; 20 mg, 3.1; 24 mg, 3.0 **Control:** 3.0	**Outcome:** improvement in mean PANSS (30%; 40%; 50%) **Intervention:** 8 mg, 51/116, 37/116, 25/116; 16 mg, 73/120*, 57/120*, 46/120*; 20 mg, 66/121, 57/121*, 36/121; 24 mg, 63/115, 51/115*, 36/115* * $p = 0.05$ versus sertindole, 8 mg **Control:** 74/123*, 58/123*, 43/123* * $p = 0.05$ versus sertindole, 8 mg	**Outcome:** PANSS component subscales (negative; excitement; cognitive; positive; depression) **Intervention:** 8 mg, 12.0, 5.6, 7.7, 8.0, 7.4; 16 mg, 11.6, 4.8, 7.6, 7.3*, 7.3; 20 mg, 11.7, 4.8, 8.3, 7.5, 7.2; 24 mg, 11.7, 4.5*, 7.8*, 7.3*, 7.2 * $p = 0.05$ versus sertindole, 8 mg **Control:** 11.8, 4.3*, 7.2 *, 6.7*, 6.9 * $p = 0.05$ versus sertindole, 8 mg

Ziprasidone RCTs

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Gunnar 1999[279]	**Intervention:** ziprasidone ***N*:** not stated **Dose:** not stated; intramuscularly, 4 times daily **Control:** haloperidol ***N*:** not stated **Dose:** not stated (at discretion of investigators); intramuscularly, 4 times daily **Duration:** 1 week – intramuscularly (3 days) then oral (4 days)	**Age:** not stated **Sex:** not stated **Illness:** psychosis **Diagnosis:** not stated ***N*:** 8 **Duration of illness:** not stated **Inclusion/exclusion criteria:** not stated **Further details:** hospitalisation required for duration of study	One patient from haloperidol arm withdrew consent on day 1 after first intramuscular dose	Sedation was primary side-effect seen in ziprasidone, intramuscular phase, patients randomised to higher dose arms; also burning at site of injection, 5–10 minutes duration. One patient randomised to ziprasidone arm at moderate dose experienced extrapyramidal symptoms on day 7	**Authors' conclusions** Ziprasidone proven to be safe and well-tolerated at this site, with low extra-pyramidal system side-effect liability compared with currently available intra-muscular antipsychotic drugs
Results					
Comments Very small sample, *n* = 7! Similar to Brook 2000[287]					

Ziprasidone RCTs *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Pfizer 128-108 (2001)[280] **Trial ID:** 128-108	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed
Results Commercial-in-confidence: data removed					

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Pfizer 128-115 (2001)[281] **Trial ID:** 128-115	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed
Results Commercial-in-confidence: data removed					

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Pfizer 128-117 (2001)[242] **Trial ID:** 128-117	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed
Results Commercial-in-confidence: data removed					

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Pfizer 128-301 (2001)[282] **Trial ID:** 128-301	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed
Results Commercial-in-confidence: data removed					

Ziprasidone RCTs *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Pfizer 128-302 (2001)[243] **Trial ID:** 128-302	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed
Results Commercial-in-confidence: data removed					

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Pfizer 128-305 (2001)[46] **Trial ID:** 128-305	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed
Results Commercial-in-confidence: data removed					

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Pfizer 128-104 (2001)[284] **Trial ID:** 128-104	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed
Results Commercial-in-confidence: data removed					

Ziprasidone RCTs *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Brook 2000[287] **Trial ID:** originally abstract,[288] full report here	**Intervention:** ziprasidone ***N*:** 90 **Dose:** 10 mg i.m, followed by 5–20 mg intramuscularly every 4–6 hours (maximum daily 80 mg) followed by oral ziprasidone, 80–200 mg daily **Control:** haloperidol ***N*:** 42 **Dose:** 2.5–10 mg intramuscularly, followed by 2.5–10 mg every 4–6 hours (maximum daily dose 40 mg) followed by oral dose, 10–80 mg daily **Duration:** 7 days (up to 3 days intramuscularly) **Washout:** none stated **Concomitant medications:** as required, oral or intramuscularly lorazepam (up to 12 mg daily) for agitation; oral temazepam (up to 20 mg daily) for insomnia, oral anticholinergic drugs for extrapyramidal side-effects and/or beta-blockers for akathisia **Comments:** mean (SD) daily intramuscular dose for first 3 days of study: ziprasidone, 23.3 (14.9)–27.6 (21.3) mg; haloperidol, 7.6 (6.9)–11.0 (10.2) mg. Last mean (SD) oral dose: ziprasidone, 90.5 (44.9) mg; haloperidol, 14.0 (10.1) mg	**Age:** ziprasidone mean 34.5, haloperidol mean 32.8. **Sex:** 123/132 male **Illness:** acute psychosis Diagnosis: DSM-III-R ***N*:** 132 **Duration of illness:** not stated **Special characteristics:** acute psychosis related to schizophrenia, schizoaffective disorder, bipolar disorder, shcizophreniform disorder, delusional disorder, brief psychotic disorder or psychotic disorders not otherwise specified, as defined by DSM III-R. Diagnosis of schizophrenia: *n* = 92/132 **Inclusion/exclusion criteria:** excluded: if acute psychosis associated with substance abuse or of organic origin; if any clinically relevant medical history or abnormal ECG, at imminent risk of homicide or suicide, history of substance abuse or dependence in last 2 months. Women at risk of conception or breastfeeding	**Intervention group *n*:** 8/90 – two intramuscular (for reasons unrelated to drug), six oral (3 treatment-related adverse events, 1 lack of efficacy, 2 reasons unrelated to treatment) **Control group *n*:** 8/42 – one intramuscular (for reasons unrelated to treatment), seven oral (1 treatment-related adverse events, 3 lack of efficacy, 3 reasons unrelated to treatment)	Occurred in ≥ 10% patients Ziprasidone (intramuscular followed by oral): overall incidence 28/90, 41/90; tremor 1/90, 2/90; akathisia 2/90, 3/90; dystonia 1/90, 4/90; EPS 0/90, 1/90; hypertonia 0/90, 3/90; vomiting 3/90, 6/90 (3%) Haloperidol (intramuscular followed by oral): overall incidence 21/42, 25/42; tremor 1/42, 4/42; akathisia 0/42, 6/42; dystonia 3/42, 5/42; EPS 9/42, 16/42; hypertonia 3/42, 5/42; vomiting 0/42, 0/42 Two ziprasidone patients reported tachycardia compared with none on haloperidol. No other ECG, conduction changes were associated with either treatment	**Authors' conclusions** Intramuscular ziprasidone significantly more effective in reducing symptoms of acute psychosis and better tolerated than intramuscular haloperidol, particularly in movement disorders. Transition from intramuscular ziprasidone to oral effective and well tolerated

Results

General comments	Outcome 1	Outcome 2	Outcome 3	Outcome 4
General comments: data do not strongly support statement that ziprasidone better tolerated: dropouts due to adverse events not higher in haloperidol group; EPS much more commonly reported on haloperidol; vomiting reported only for ziprasidone Note very short-term study	**Outcome:** BPRS total (change from baseline) intramuscularly; intramuscular followed by oral (mean, SD) (*p*-value for treatment difference) **Intervention:** BPRS total, –6.24, 8.30 (p = 0.02); –8.76, 11.62(p = 0.09); BPRS agitation items, –1.93, 3.41 p = 0.015); –2.09, 4.41 (p = 0.19); BPRS total, –3.18, 6.55; –5.83, 9.50 **Control:** BPRS agitation items, –0.80, 2.81; 1.59, 3.61	**Outcome:** CGI-S (change from baseline) intramuscularly; intramuscular followed by oral (*p*-values for treatment difference **Intervention:** –0.49,0.68 (p = 0.002); –0.89, 1.23 (p = 0.025) **Control:** –0.15, 0.53; -0.38, 1.17	**Outcome:** CGI-I scores (mean) **Intervention:** during intramuscular phase 3.38 (p = 0.47); at endpoint 3.07 (p = 0.54) **Control:** during intramuscular period 3.49); at endpoint 3.14)	**Outcome:** change at endpoint from baseline in SAS; BAS (mean, SD) **Intervention:** –1.09, 4.33; –0.10, 0.79 **Control:** 6.00, 7.12; 0.80, 1.14

Ziprasidone RCTs *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Pfizer 2001[363] **Trial ID:** 128-301e	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed
Results Commercial-in-confidence: data removed					

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Pfizer 2001[285] **Trial ID:** 128-302e	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed
Results Commercial-in-confidence: data removed					

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Pfizer 2001[286] **Trial ID:** 128-304e	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed
Results Commercial-in-confidence: data removed					

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Pfizer 2001[283] **Trial ID:** NY-97-001	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed
Results Commercial-in-confidence: data removed					

Ziprasidone RCTs *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Pfizer 2001[281] **Trial ID:** R-0548	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed
Results Commercial-in-confidence: data removed					

Zotepine RCTs

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Knoll CTR ZT 4002 (2000)[295] **Trial ID:** ZT4002	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed
Results Commercial-in-confidence: data removed					

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Welch 1996[295] **Trial ID:** Study BPI1201	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed
Results Commercial-in-confidence: data removed					

Zotepine RCTs *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Fischer 1999[296]	**Intervention:** zotepine ***N*:** not stated **Dose:** up to 225 mg daily **Control:** placebo ***N*:** not stated **Duration:** 8 weeks **Washout:** not stated **Concomitant medications:** not stated	**Age:** not stated **Sex:** not stated **Illness:** schizophrenia, mainly negative symptoms **Diagnosis:** ICD10 ***N*:** 77 **Duration of illness:** not stated **Special characteristics:** none stated **Inclusion/exclusion criteria:** chronic residual schizophrenia on PANSS: negative scale, minimum 3 items with score > 3; positive scale, maximum 2 items with score > 3 **Further details:** numbers in each group not stated	Intervention group n: 68/83 participants (both groups) completed study; ITT population, *n* = 77	None presented	**Authors' conclusions** Provides further evidence of the efficacy of zotepine in schizophrenic patients with primary negative symptoms
Results					
Changes in total score of negative scale (not presented) showed trend in favour of zotepine					

Appendix 3

Data extraction tables for studies included in earlier review

Amisulpride

Study	Methods	Participants	Interventions	Outcomes	Notes
Boyer 1995[51]	**Allocation:** random; no further details **Blinding:** double; no further details **Duration:** 6 weeks, preceded by 6-week washout period (12 weeks if patients had previously received neuroleptic drugs) **Setting:** multicentre (20 centres/ psychiatrists); inpatients	**Diagnosis (*n*):** schizophrenia (DSM-III), disorganised (36), catatonic (10), undifferentiated (32) or residual (26) **Age:** range 19–49 years **Sex:** 65 male, 39 female ***N*:** 104 **History:** Mean duration of illness, 10 years; mean duration of negative symptoms, 8 years; fulfilled Andreasen's criteria for 'negative schizophrenia'; patients fulfilling criteria for positive schizophrenia excluded; SANS ≥ 75; SAPS < 60	1. amisulpride, 100 mg/day; *n* = 34 2. amisulpride, 300 mg/day; *n* = 36 3. placebo; *n* = 34	Leaving study early Side-effects: use of antiparkinsonism drugs; use of anxiolytic or sleep medication; reported side-effects **Unable to use** Mental state: SAPS, SANS (total + subscales) – no SD Side-effects: documented EPS scale total and akinesia subscore (no SD)	Authors only present results for completing patients since "ITT analyses for SANS and SAPS total scores and for the EPS scale gave the same results"
Martinot 1995[52]	**Allocation:** random; no further details **Blinding:** double; no further details **Duration:** 6 weeks, preceded by washout period of 8 days **Setting:** multicentre (two adolescent and two adult inpatient psychiatric wards (*n* = 23), plus two adolescent outpatient care units (*n* = 4))	**Diagnosis (*n*):** schizophrenia (21); schizotypal personality disorder (6) (DSM-III-R); disorganised type (18); undifferentiated type, (3) **Age:** mean, 20 years **Sex:** 20 male, 7 female ***N*:** 27 **History:** important negative schizophrenic symptoms, defined as mean items rating of 3 on at least two SANS subscales; short disease course, < 1 month neuroleptic treatment in all participants Organic brain disorder, somatic disease, alcohol/ drug abuse and prominent positive symptoms or depression all excluded Mean duration of illness, 34 months (SD 14); mean age of onset, 17 years; mean number of hospitalisations; 1.1 (range 0–2)	1. amisulpride, 50 mg/day for first 3 weeks, increased to 100 mg/day for next 3 weeks if patient not improved; *n* = 14 2. placebo; *n* = 13	Leaving study early Global state: developed positive symptoms and/or hypomania; worsened negative symptoms Mental state: MADRS; depressive retardation rating scale; SAPS; SANS Side-effects: documented EPS; insomnia; excitement; somnolence	ITT analysis used last observation carried forward for patients who remained in the study after 3 weeks

continued

Amisulpride *contd*

Study	Methods	Participants	Interventions	Outcomes	Notes
Delcker 1990[53]	**Allocation:** random; no further details **Blinding:** double; no further details **Setting:** single centre (Zwiefalten Psychiatric Hospital); inpatients **Duration:** 6 weeks, preceded by washout period of 4–28 days (mean, 8.7)	**Diagnosis (*n*):** schizophrenia (ICD9), paranoid (24); residual (16); hebephrenic (1) **Age:** amisulpride group: mean, 43.3 years; haloperidol group: mean, 40.1 years **Sex:** 33 male, 8 female ***N*:** 41 **History:** mean duration of illness, 14.3–17.3 years (range, 0.3–36)	1. amisulpride: 490–1000 mg/day (mostly 500–700 mg/day); *n* = 21 2. haloperidol: 5–40 mg/day (mostly 20–25 mg/day); *n* = 20	Leaving study early EPS side-effects: use of biperiden; documented EPS/scores Other adverse effects: use of sedatives (diazepam); use of flunitrazepam **Unable to use** Global state: CGI (graph) Mental state: BPRS (graph); AMDP (graph) Side-effects: Simpson (graph); Webster (graph)	Most results presented graphically, no exact values or SDs, so data unusable; stated that one patient who left haloperidol group early left clinic significantly improved but not clear whether discharge was because significantly improved (positive outcome) or whether improvement incidental to time of leaving study (not a positive outcome); hence, this outcome not reported, except as 'leaving study early'
Hillert 1994[54]	**Allocation:** random; no further details **Blinding:** double; no further details **Duration:** 6 weeks, preceded by washout period of 1–9 days **Setting:** multicentre (11 German centres); inpatients	**Diagnosis:** schizophrenia (DSM-III-R); paranoid or undifferentiated type **Age:** range 18–65 years **Sex:** 74 male, 58 female ***N*:** 132 **History:** currently acute with predominant positive symptomatology; duration of illness not described; BPRS score of 36 or higher; SANS score less than 55	1. amisulpride, 1000 mg/day fixed dose, could be adjusted to minimum 600 mg/day (mean, 956 mg/day); *n* = 70 2. flupentixol, 25 mg/day fixed dose, could be adjusted to minimum 15 mg/day (mean, 22.6 mg/day); *n* = 62	Leaving study early Global state: reduction in dose due to improvement; response (CGI); CGI-S; GAS Mental state: response (BPRS); BPRS total and subscores; SAPS; SANS EPS side-effects: documented EPS/scores; SAS; BAS; AIMS Weight gain; prolactin levels	Conference abstract only: some details missing, particularly demographic
Turjanski 1998 (1)[55]	**Allocation:** unclear whether randomised **Blinding:** double; no further details **Duration:** 2 weeks; washout period not specified **Setting:** not described	**Diagnosis:** schizophrenia (DSM-III-R); paranoid, undifferentiated or disorganised types **Age:** not specified **Sex:** not specified ***N*:** 186 **History:** acute exacerbation, minimal score (not stated) on BPRS psychotic cluster to be included; duration of illness not specified	1. amisulpride, 400 mg/day 2. amisulpride, 800 mg/day *n* = 125 (total for groups 1 and 2) 3. haloperidol, 15–20 mg/day; *n* = 61	Mental state: BPRS – response classed as decrease of at least 50% in total score from baseline at end of first week of treatment or after 2 weeks	Conference abstract only: at day 7, 18% responders to amisulpride versus 5% to haloperidol ($p = 0.016$)

continued

Amisulpride *contd*

Study	Methods	Participants	Interventions	Outcomes	Notes
Turjanski 1998 (2)[55]	**Allocation:** unclear whether randomised **Blinding:** double; no further details **Duration:** 2 weeks; washout period not specified **Setting:** not described	**Diagnosis:** schizophrenia (DSM-III-R); paranoid, undifferentiated or disorganised types **Age:** not specified **Sex:** not specified ***N*:** 188 **History:** currently acute exacerbation, minimal score (not stated) on BPRS psychotic cluster to be included; duration of illness not specified	1. amisulpride, 400–800 mg/day; *n* = 94 2. haloperidol, 15–20 mg/day; *n* = 94	Clinical response – mental state: BPRS, response classed as decrease of at least 50% in total score from baseline at end of first week of treatment or after 2 weeks	Conference abstract only: at 2 weeks, 28% of amisulpride patients were responders versus 14% of haloperidol patients ($p = 0.022$)
Puech 1998[56]	**Allocation:** random; no further details **Blinding:** double; no further details **Duration:** 4 weeks, preceded by washout period of 3–7 days **Setting:** inpatient	**Diagnosis:** schizophrenia (DSM-III-R); disorganised (50%), paranoid (24%) or undifferentiated (26%) **Age:** mean, 36 years **Sex:** 197 male, 122 female ***N*:** 319 **History:** currently acute exacerbation of chronic or subchronic illness; minimum score of 4 on at least two of four core positive symptoms; illness not treatment-resistant; duration of illness, 0–41 years (mean 10)	1. amisulpride, 100 mg/day* b.d.; *n* = 61 2. amisulpride, 400 mg/day b.d.; *n* = 64 3. amisulpride, 800 mg/day b.d.; *n* = 65 4. amisulpride, 1200 mg/day b.d.; *n* = 65 5. haloperidol, 16 mg/day b.d.; *n* = 64	Leaving study early Global state: response (defined as rating of 1 or 2 on CGI-I scale) Mental state: BPRS total; PANSS positive and negative subscales EPS side-effects: prescribed anti-parkinsonian medication; documented EPS/scores; SAS; BAS; AIMS Other adverse effects: UKU side-effects rating scale	Full paper: ITT analysis used last observation carried forward * Authors state amisulpride, 100 mg/day, is "ineffective" and that all other groups compared against this group; for purpose of this review, outcomes at this dose are not reported with those at higher doses **Authors' conclusions:** amisulpride, 400 and 800 mg per day, most effective for positive symptoms; parkinsonism did not increase significantly between baseline and endpoint with amisulpride, 400, 800 and 1200 mg/day, compared with 100 mg/day, whereas difference significant for haloperidol ($p < 0.05$)

continued

Amisulpride *contd*

Study	Methods	Participants	Interventions	Outcomes	Notes
Moeller 1997[57]	**Allocation:** random; no further details **Blinding:** double; no further details **Duration:** 6 weeks, preceded by washout period of 1 week (or 1 day if patient required immediate treatment) **Setting:** multicentre (31 European centres in six countries between March 1993 and March 1995); inpatient	**Diagnosis:** schizophrenia (DSM-III-R); paranoid (37%), disorganised (38%) or undifferentiated (25%) **Age:** mean, 36 years **Sex:** 119 male, 72 female ***N*:** 191 **History:** currently acute exacerbation of chronic or subchronic illness; score of 12 of more on four core BPRS productive symptoms; not treatment-resistant; first episode patients with at least 6 months duration of illness could also be recruited; mean duration of illness, 10 years	1. amisulpride, 800 mg/day b.d., reduced to 600 mg/day if needed; *n* = 95 2. haloperidol, 20 mg/day b.d., reduced to 15 mg/day if needed; *n* = 96	Death (suicide) Leaving study early Global state: CGI (response = item 2 or 1); reduced dose Mental state: improvement (BPRS, positive and negative PANSS); positive PANSS; negative PANSS; BPRS total and subscores; psychiatric adverse events EPS side-effects: use of anti-parkinsonian medication; documented EPS/scores; SAS; BAS; AIMS Other adverse events	ITT analysis used last observation carried forward Improvement in mean BPRS total score, amisulpride 48%, haloperidol, 38% (not significant), whereas improvement in negative PANSS sub-scale greater for amisulpride (37%) than haloperidol (24%), $p = 0.038$; CGI scores showed more responders for amisulpride (62%) than haloperidol (44%), $p = 0.014$; more EPS symptoms (on SAS) provoked with haloperidol ($p = 0.0009$) Authors' conclusions: amisulpride at least as effective as haloperidol in treatment of acute exacerbations of schizophrenia, and more effective in treatment of negative symptoms while causing less parkinsonism
Klein 1985[58]	**Allocation:** random; no further details **Blinding:** double; treatment blinding described adequately but outcome blinding not reported. **Duration:** 4 weeks, with no washout period **Setting:** single centre (implied); inpatient	**Diagnosis:** schizophrenia (ICD9) **Age:** 22–64 years (mean 41.4) **Sex:** 10 male, 9 female ***N*:** 19 **History:** currently acute; up to 6 previous hospital admissions (median, 2.5)	1. amisulpride, 10 mg per kg bodyweight per day, liquid form, for 8 days, then 5 mg per kg bodyweight per day thereafter; *n* = 9 2. haloperidol, 0.5 mg per kg bodyweight per day, liquid form, for 8 days, then 0.25 mg per kg bodyweight per day thereafter. *n* = 10	Leaving study early EPS side-effects: use of antiparkinsonism drugs; documented EPS Other adverse effects Laboratory tests: prolactin levels	Groups inhomogeneous at baseline for somatic depressive syndrome (AMPD) and BPRS total score, both $p < 0.05$; haloperidol group scored higher on both scales

continued

Amisulpride *contd*

Study	Methods	Participants	Interventions	Outcomes	Notes
Colonna 1998[49]	**Allocation:** random, open; no further details **Blinding:** open study; no further details **Duration:** 12 months; washout period not specified **Setting:** not described	**Diagnosis:** schizophrenia (DSM-III-R) **Age:** mean, 36.8 years (amisulpride), 39.6 years (haloperidol) **Sex:** 327 male, 161 female ***N*:** 488 **History:** currently acute exacerbation; mean duration, 12 years	1. amisulpride; *n* = 370 2. haloperidol; *n* = 118 Doses not specified	Leaving study early Global state: maintained efficacy (survival analysis). Mental state: BPRS (response defined as 20% decrease from baseline), survival analysis; BPRS total score; PANSS negative subscale EPS symptoms: use of antiparkinsonism medication Quality of life: QLS Other adverse events: endocrine events; weight gain	Conference abstract only 322 patients (amisulpride 253, haloperidol 69) reached at least 20% improvement in BPRS baseline total score after 1 month, and 59% and 55%, respectively, maintained efficacy to 12 months. On ITT basis, amisulpride superior in total BPRS score, PANSS negative subscore, quality of life; amisulpride provoked significantly less EPS and needed fewer antiparkinsonian drugs
Speller 1997[59]	**Allocation:** random; no further details **Blinding:** double; no further details **Duration:** 1 year, preceded by 3-month washout period for those previously on depot medication (during which equivalent dose of oral haloperidol given); otherwise no washout period **Setting:** multicentre; 18 continuing care and rehabilitation wards in two psychiatric hospitals; inpatient	**Diagnosis:** schizophrenia (DSM-III-R) **Age:** 35–76 years **Sex:** 46 male, 14 female ***N*:** 60 **History:** chronic, with moderate to severe negative symptoms; combined score ≥ 4 on flatness of affect and poverty of speech items on Manchester scale; excluded if taking antipsychotic drug dose equivalent to chlorpromazine, 1200 mg/day or more; duration, 109–660 months (mean 432–452)	1. amisulpride, initially either 800, 600, 450, 300, 150 or 100 mg*; dose reduced every 3 months, if possible, according to severity of symptoms; *n* = 29 2. haloperidol, 20, 16, 11.5, 8, 5, or 3 mg*; dose reduced every 3 months, if possible, according to severity of symptoms; *n* = 31 (* initial dose levels calculated as closest equivalent to previous antipsychotic medication; systematic dose reduction over course of trial, as symptoms allowed)	Leaving study early Global state: psychotic exacerbations; achieved or maintained low dose level at endpoint Mental state: negative subscale (response and change); SANS items; BPRS negative subscale; mental state positive subscale Side-effects: BARS **Unable to use** Social behaviour scale, no data	Efficacy analysis carried out on 54 patients remaining in study after 3 months

continued

Amisulpride *contd*

Study	Methods	Participants	Interventions	Outcomes	Notes
Danion 1998[60]	**Allocation:** random; no further details **Blinding:** double; no further details **Duration:** 3 months, preceded by 1-month washout period **Setting:** multicentre; inpatient	**Diagnosis:** schizophrenia (DSM-III-R); disorganised or residual type **Age:** not specified **Sex:** not specified ***N*:** 242 **History:** predominantly negative symptoms; SANS total ≥ 60; SAPS total < 50; duration not specified	1. amisulpride, 50 mg/day; *n* = 84 2. amisulpride, 100 mg/day; *n* = 75 3. placebo, *n* = 83	Leaving study early **Unable to use** Mental state: BPRS, MADRS, SAPS, SANS (no SD) EPS side-effects: SAS (no SD) Other adverse events	Conference abstract only 60% placebo-treated patients ended study, compared with 83% and 80% in amisulpride, 50 and 100 mg, groups, respectively; both groups showed statistically significant differences compared with placebo in SANS total score change, SANS factors, BPRS, SAPS and MADRS; safety comparable in all groups; psychiatric disorders, central and peripheral nervous system adverse events most frequently reported; SAS low at baseline and endpoint and change not different between groups
Boyer 1990[61]	**Allocation:** random; no further details **Blinding:** not described **Duration:** 6 weeks, preceded by 3-week washout period **Setting:** probably single centre; not clear whether in- or outpatient	**Diagnosis:** schizophrenia (DSM-III); disorganised, catatonic or residual **Age:** 21–53 years **Sex:** 43 male, 19 female ***N*:** 62 **History:** not specified (chronic?); all met Andreasen criteria for negative symptoms; absence of marked positive symptoms; score > 7 on Departement de la santé et de l'action sociale (DSAS) scale; duration, 1–20 years (means: amisulpride 9.2, fluphenazine 12.3); mean number of previous hospitalisations, amisulpride 2.9, fluphenazine 4.4	1. amisulpride, 50–300 mg/day (flexible); mean, 225 mg/day; *n* = 34 2. fluphenazine, 2–12 mg/day (flexible); mean, 10 mg/day; *n* = 28	Leaving study early Mental state: BPRS global, anxiety/depression and anergia subscores; NOSIE **Unable to use** Mental state: DSAS score (not validated)	No details of drop-outs or ITT analysis

continued

Amisulpride *contd*

Study	Methods	Participants	Interventions	Outcomes	Notes
Fleurot 1997[62]	**Allocation:** random; no further details **Blinding:** double; no further details **Duration:** 8 weeks, preceded by 3–6-day washout period **Setting:** multicentre; inpatient	**Diagnosis:** schizophrenia (DSM IV) **Age:** mean 36.5 years **Sex:** not specified ***N*:** 228 **History:** currently acutely ill; mean duration, 9.0 years	1. amisulpride, 800 mg/day 2. risperidone, 8 mg/day	Leaving study early Global state: response (CGI) Mental state: BPRS total; PANSS positive change scores Weight gain	Conference abstract only
Loo 1997[63]	**Allocation:** random; no further details **Blinding:** double; no further details **Duration:** 6 months initially, extended to 12 months in patients who responded to treatment; no washout period. **Setting:** not described	**Diagnosis:** schizophrenia (DSM-III-R), disorganised or residual **Age:** mean, 34 years **Sex:** 100 male, 41 female ***N*:** 141 **History:** SANS ≥ 60; fulfilled Andreasen's criteria for negative schizophrenia; SAPS total ≤ 50; 116 patients ill for more than 2 years; mean duration, 9.7–10.7 years	1. amisulpride, 100 mg/day; $n = 69$ 2. placebo; $n = 72$	Leaving study early Attrition, 57% at 6 months so no other outcomes can be used **Unable to use** Global state: CGI; GAF Mental state: SAPS; SANS total and subscores EPS side-effects: use of anti-parkinsonian drugs; use of benzodiazepines; documented EPS scores; Webster scale; AIMS; BAS Other adverse effects: endocrine	80 patients left study early over first 6-month treatment period: significantly more ($p = 0.007$) withdrew from placebo (49) than from amisulpride group (31); main reason, lack of efficacy (34 placebo, 19 amisulpride) Amisulpride produced significantly ($p < 0.0002$) greater improvement in SANS total score compared with placebo; significant differences in favour of amisulpride found in all five SANS component subscores; significantly more responders (defined as increase of at least 50% in SANS total) in amisulpride than in placebo group ($p < 0.001$); similar results when response defined by CGI (items 2 or 1, $p < 0.004$)

Clozapine versus typical antipsychotic drugs

Study	Methods	Participants	Interventions	Outcomes	Notes
Chiu 1976[78]	**Allocation:** random **Blinding:** double (medication in identical capsules) **Duration:** 6 weeks (preceded by 5-day washout period) **Setting:** hospital	**Diagnosis:** schizophrenia, acutely ill (no diagnostic criteria) ***N*:** 64 **Age:** < 60 years	1. clozapine capsules, initially 150 mg/day, increased by 50 mg/day to 300 mg/day; fixed dosing; *n* = 33 2. chlorpromazine capsules, initially 150 mg/day, increased by 50 mg/day to 300 mg/day; fixed dosing; *n* = 31	Relapse Acceptability: drop-outs Global effect: CGI (mean total scores not reported) Mental state: 18-item BPRS (mean total scores not reported) Behaviour: NOSIE Adverse effects Laboratory tests	Jadad score 4 Matching procedure may have resulted in selection bias in outcomes presented in original paper; high drop-out rate; equal doses (in mg) may have benefited clozapine outcomes
Guirguis 1977[79]	**Allocation:** random **Blinding:** double **Duration:** 7 weeks **Setting:** hospital	**Diagnosis:** schizophrenia, acute (no diagnostic criteria) ***N*:** 50 **Sex:** 15 female, 35 male **Age:** average, female 44 years; male 33 years **Average age of onset:** clozapine group, 33 years; chlorpromazine group, 26 years	1. clozapine capsules, 75–450 mg/day; *n* = 22 2. chlorpromazine capsules, 150–900 mg/day; *n* = 28	Death Relapse Acceptability: drop-outs Global effect: CGI (no data) Mental state: BPRS (mean total scores not reported) Behaviour: NOSIE (mean total scores not reported) Adverse effects: checklist	Jadad score 3 Clozapine patients had significantly higher ages of onset; were significantly older; had almost significantly worse NOSIE ratings
Xu 1985[80]	**Allocation:** random **Blinding:** assessed **Duration:** 8 weeks **Setting:** hospital	**Diagnosis:** schizophrenia (DSM-III); BPRS total score > 38 ***N*:** 60 **Age:** 18–55 years **Sex:** both	1. clozapine, 400 ± 72 mg/day (mean) 2. chlorpromazine, 693 ± 117 mg/day (mean)	Acceptability: drop-outs Mental state: BPRS; no data reported Global functioning: GAS, no data reported	Jadad score: assessment ongoing Reports higher rates of leucopenia (16/30 versus 10/30) in chlorpromazine group; as data may have been mistakenly reversed in paper, they were not included
Xu 1989[81]	**Allocation:** random **Blinding:** double **Duration:** 8 weeks **Setting:** hospital	**Diagnosis:** schizophrenia (DSM-III and Chinese criteria) ***N*:** 57 **Sex:** 22 female, 35 male **Age:** mean, 32 years **History:** mean duration of illness, 6 years	1. clozapine, 50–600 mg/day; flexible; *n* = 20 2. chlorpromazine, 100–600 mg/day; flexible; *n* = 17 3. clozapine, 50–400 mg/day, flexible, + chlorpromazine, 100–400 mg/day, flexible; *n* = 20	Mental state: BPRS	Jadad score 2. Average doses not reported and may have not have been equivalent to each other

continued

Clozapine versus typical antipsychotic drugs *contd*

Study	Methods	Participants	Interventions	Outcomes	Notes
Xu 1994[82]	**Allocation:** random **Blinding:** double **Duration:** 6 weeks **Setting:** Hospital	**Diagnosis:** schizophrenia **History:** clozapine group, 17 ± 11 months; thioridazine group, 25 ± 24 months ***N*:** 40 **Age:** mean, 25.5 years **Sex:** 16 female, 24 male	1. clozapine; *n* = 20 2. thioridazine; *n* = 20	Acceptability: drop-outs Mental state: BPRS Global effect: CGI	
Leon 1974[83]	**Allocation:** random **Blinding:** double **Duration:** 6 weeks, 3- and 4-year naturalistic follow-up **Setting:** hospital, some patients discharged to family care during study	**Diagnosis:** schizophrenia; heterogeneous subtypes (DSM II) ***N*:** sequential cohort; 50 **Sex:** 21 female, 29 male **Age:** average, clozapine, 30 years; chlorpromazine, 27 years	1. clozapine capsules, 600 mg/day (average), 1600 mg/day (maximum); *n* = 25 2. chlorpromazine capsules, 600 mg/day (average); *n* = 25 Clozapine not given during follow-up	Death Global effect: clinical evaluation Acceptability: drop-outs Mental state: symptom checklist Adverse effects Hospital admission Length of hospital stay Outpatient visits	Jadad score 2 Two schizo-affective patients, both in clozapine group By mistake, clozapine group received twice intended dose throughout trial – may have benefited clozapine group outcomes and resulted in more side-effects in clozapine group
Gerlach 1974[84]	**Allocation:** random **Blinding:** varied with outcome; crossover **Duration:** 28 weeks; first arm 82 days (preceded by 5–51-day washout period) **Setting:** hospital	**Diagnosis (*n*):** schizophrenia – paranoid (11), hebephrenic (7), catatonic (2); no diagnostic criteria ***N*:** 20 **Sex:** male **Age:** range, 18–60 years **History:** illness duration 2–33 years	1. clozapine tablets, initially 50 mg/day (median); median dose, day 82, 200 mg/day; then haloperidol after second washout period; *n* = 10 2. haloperidol tablets, initially 1 mg/day (median); median dose, day 82, 10 mg/day; then clozapine after second washout period; *n* = 10 Dose adjusted according to response; procyclidin, biperiden and nitrazepam as needed	Death Relapse Acceptability: drop-outs Global effect: non-blind clinical evaluation Mental state: blind 18-item BPRS (no SDs) Adverse effects: non-blind checklist ECG and laboratory tests	Jadad score 1

continued

Clozapine versus typical antipsychotic drugs *contd*

Study	Methods	Participants	Interventions	Outcomes	Notes
Gerlach 1975[84]	**Allocation:** random **Blinding:** double (medication in identical capsules); crossover **Duration:** 9 weeks, first arm 3 weeks (preceded by 3-week washout period) **Setting:** hospital	**Diagnosis:** schizophrenia (no diagnostic criteria) ***N*:** 8 **Sex:** male **Age:** range, 24–66 years	1. clozapine capsules, 225 mg/day; then haloperidol after second 21-day washout period 2. haloperidol capsules, 9 mg/day, then clozapine after second 21-day washout period Biperiden injections for acute dystonias	Death Relapse Acceptability: drop-outs Adverse effects Neurological condition (authors' rating scale)	Jadad score 2
Fischer-Cornelssen 1974[86]	**Allocation:** random **Blinding:** double (medication in identical capsules) **Setting:** hospital; five-country, multicentre (Czechoslovakia, Finland, The Netherlands, Sweden, Switzerland) **Duration:** 40 days (preceded by washout period of ≥ 4 days)	**Diagnosis:** schizophrenia, paranoid (62%), moderate to severe (~ 50%) symptoms (no diagnostic criteria) ***N*:** 223 **Sex:** 67 female; 155 male (1 unknown) **Age:** average, 34 years; range, 15–68 years	1. clozapine, 75–200 mg/day initially; average dose at end, 310 mg/day; range 50–1000 mg/day; *n* = 110 2. chlorpromazine, 75–200 mg/day initially; average dose at end, 360 mg/day; range 25–900 mg/day, *n* = 113 Fixed–flexible–fixed dose schedule	Global effect Acceptability: drop-outs Mental state: BPRS (no SDs) Adverse effects: Sandoz side-effect checklist	Jadad score 4 Data on patient dissatisfaction reported only in Czech and Swiss studies Side-effect frequency reports available only from Finnish (and partly Czech as well as Swedish) study
Fischer-Cornelssen 1976a[87]	**Blinding:** double (medication in identical capsules) **Duration:** 42 days (preceded by at least 7-day washout period) **Setting:** hospital	**Diagnosis:** schizophrenia, moderate to severe (no diagnostic criteria)	1. clozapine capsules, 200 mg/day initially, 300 mg/day median; *n* = 38 2. clopenthixol capsules, 100 mg/day initially, 100 mg/day median; *n* = 36 Fixed–flexible–fixed dose schedule	Global effect Mental state: BPRS (no data reported) Adverse effects: Sandoz side-effect checklist Laboratory tests and ECG	Jadad score 2

continued

Clozapine versus typical antipsychotic drugs *contd*

Study	Methods	Participants	Interventions	Outcomes	Notes
Fischer-Cornelssen 1976b[87]	**Blinding:** double (medication in identical capsules) **Duration:** 42 days (preceded by at least 7-day washout period) **Setting:** hospital	**Diagnosis:** schizophrenia, moderate to severe (no diagnostic criteria)	1. clozapine capsules, 200 mg/day initially, 300 mg/day median; *n* = 36 2. trifluoperazine capsules, 20 mg/day initially, 30 mg/day median; *n* = 36 Fixed–flexible–fixed dose schedule	Global effect Mental state: BPRS (no data reported) Adverse effects: Sandoz Side Effect Check List Laboratory tests and ECG	Jadad score 2 Clozapine dose progression may have been too slow compared with that for trifluoperazine
Honigfeld 1984[88]	**Blinding:** double **Duration:** 40 days **Setting:** hospital, two centres	**Diagnosis:** schizophrenia (no diagnostic criteria) ***N*:** 79	1. clozapine, 397 mg/day, average; *n* = 39 2. haloperidol, 7.6 mg/day average; *n* = 40	Death Relapse Global effect, ability to work Acceptability: drop-outs Mental state: BPRS Dischargeability	Jadad score 2 Low haloperidol doses may not have been comparable to clozapine doses
Klieser 1989[89]	**Blinding:** double **Duration:** 6 weeks (preceded by 14-day washout period) **Setting:** hospital	**Diagnosis:** schizophrenia, chronic, treatment-resistant (no diagnostic criteria) ***N*:** 32; those on depot medication excluded **Sex:** 19 female, 11 male **History:** duration of illness, average 17 years (SD, 8) **Age:** average, 48 years (SD, 11)	1. clozapine, 400 mg/day; *n* = 16 2. haloperidol, 20 mg/day; *n* = 16 Biperiden and chloral hydrate as needed	Relapse Acceptability: drop-outs Global effect: CGI Mental state: BPRS, AMDP, SANS	Jadad score 2
Klieser 1994[90]	**Allocation:** random **Blinding:** double (single for side-effects) **Duration:** 28 days **Setting:** hospital	**Diagnosis:** schizophrenia, acute paranoid (ICD9) ***N*:** 180 **Sex:** 96 female; 84 male **Age:** (average) clozapine, 35 ± 12 years; remoxipride, 35 ± 11 years; haloperidol, 33 ± 10 years; risperidone, 4 mg, 36 ± 12 years; risperidone, 8 mg, 33 ± 11 years; zotepine, 32 ± 9 years	1. clozapine, 400 mg/day; average, 350 mg/day; *n* = 37 2. remoxipride, 400 mg/day; average, 375 mg/day; *n* = 38 3. haloperidol, 15 mg/day; average, 16 mg/day; *n* = 45 4. risperidone, 4–8 mg/day; *n* = 40 5. zotepine, 225 mg/day; *n* = 0 Dose adjusted according to response; biperiden and chloral hydrate as needed	Relapse Mental state: BPRS, AMDP Adverse effects: SAS Acceptability: drop-outs Global effect: CGI, Global tolerance General intelligence: Kurz Adult Intelligence scale Cognitive functioning: Syndrome Kurz Test Patient satisfaction	Jadad score 2 No ITT analysis performed; drop-outs not reported

continued

Clozapine versus typical antipsychotic drugs *contd*

Study	Methods	Participants	Interventions	Outcomes	Notes
Singer 1974[91]	**Allocation:** random 'systematised random order' **Blinding:** double **Duration:** 40 days (preceded by 2-week washout period)	**Diagnosis:** schizophrenia, acute (no diagnostic criteria) ***N*:** 40 **Sex:** 22 female, 18 male **Age:** range 16–61 years; mean 32. **Ethnic group:** Chinese	1. clozapine capsules, 50–100 mg/day initially; average, 155 mg/day, range, 50–300; *n* = 20 2. chlorpromazine capsules, 50–100 mg/day initially; average, 196 mg/day, range 75–600 mg/day; *n* = 20 Dose adjusted according to need	Relapse Adverse effects Acceptability: drop-outs Global effect: global clinical scale (authors' own); no data Mental state: 18-item BPRS (no SDs)	Jadad score 3 Drop-outs excluded from analyses of results
Itoh 1977[92]	**Allocation:** random **Blinding:** double **Duration:** 12 weeks **Setting:** multicentre, hospital	**Diagnosis (*n*):** schizophrenia – hebephrenic (46); paranoid (22); undifferentiated (19); catatonic (4) (no diagnostic criteria) ***N*:** 91	1. clozapine tablets, 75 mg/day initially; 500 mg/day maximum; *n* = 47 2. haloperidol tablets, 2.25 mg/day initially; 15 mg/day maximum; *n* = 44 Fixed–flexible dose schedule	Global effect Mental state: BPRS; Keio University Psychiatric Rating Scale for Schizophrenia Adverse effects: Keio Univeristy´s EPS Rating Scale Acceptability: drop-outs Behavioural rating: two scales	Jadad score 3
Erlandsen 1981[93]	**Allocation:** double **Duration:** 40 days **Setting:** hospital	**Diagnosis:** schizophrenia (no diagnostic criteria) ***N*:** 40 **Sex:** male **Age:** average, 43 years, range, 22–75 **History:** mean duration of illness, 15 years	1. clozapine capsules, 50–400 mg/day; *n* = 19 2. haloperidol capsules, 1–8 mg/day; *n* = 21	Acceptability: drop-outs Mental state: BPRS (no SDs) Global assessment Laboratory tests	Jadad score 1 No washout period before trial reported; low haloperidol doses may not have been comparable to clozapine doses
Ciurezu 1976[94]	**Allocation:** random **Blinding:** double (medication in identical preparations) **Duration:** 40 days **Setting:** hospital	**Diagnosis (*n*):** schizophrenia – paranoid (16); simple (11); hebephrenic (11); 'other' (2); no diagnostic criteria ***N*:** 40 **Sex:** 25 female, 15 male **Age:** average, 25 years, range, 16–45	1. clozapine, 402 mg/day average; range, 100–900 mg/day; *n* = 20 2. haloperidol, 9 mg/day average; range, 4–20 mg/day; *n* = 20	Global effect, ability to work Adverse effects Acceptability: drop-outs Dischargeability Mental state: BPRS (no data reported)	Jadad score 4 Low haloperidol doses may not have been comparable to clozapine doses

continued

Clozapine versus typical antipsychotic drugs *contd*

Study	Methods	Participants	Interventions	Outcomes	Notes
Meyer-Lindberg 1996[108]	**Allocation:** random; no further details **Blinding:** double; no further details **Duration:** 6 weeks	**Diagnosis:** schizophrenia (DSM-III-R) ***N:*** 50 **Sex:** 18 male (only those reported on described) **Age:** mean ~ 33 years (SD, ~ 10) **History:** unresponsive to > 3 weeks of two typical antipsychotic drugs in effective doses; BPRS > 39	1. zotepine, 150–450 mg/day; *n* = 25 2. clozapine, 150–450 mg/day; *n* = 25	Leaving study early **Unable to use** Global function (CGI – no mean or SD); mental state (BPRS, SANS – no mean or SD); behaviour (CIPS[†], NOSIE – no mean or SD); side-effects (UKU); cognitive function (maze tests – no mean or SD); ECG (no data); weight gain (no data)	Data only provided for a subset (13 age-matched controls) [†] Centre d'information des professions de la santé
Hong 1997[95]	**Allocation:** random **Blinding:** double **Duration:** 12 weeks (preceded by haloperidol, 60 mg/day, baseline period lasting up to 6 weeks) **Setting:** hospital	**Diagnosis:** schizophrenia (DSM-IV) **History:** treatment-refractory[*] disease ***N:*** 40 **Sex:** 26 female, 14 male **Age:** clozapine, 40 ± 8 years; chlorpromazine, 37 ± 9 years	1. clozapine capsules: 25 mg/day initially for 1 week; mean, 543 ± 157 mg/day; maximum, 900 mg/day; *n* = 21 2. chlorpromazine capsules: 50 mg/day initially for 1 week; mean, 1163 ± 228 mg/day; maximum, 1800 mg/day; *n* = 19 Fixed–flexible dose schedule	Acceptability: drop-outs Mental state: PANSS; BPRS Global effect: CGI Improvement: decrease at least 20% in BPRS total score Adverse effects	Jadad score 5 [*] Treatment-refractory, severe psychotic symptoms according to BPRS item scores for > 6 months despite treatment with neuroleptic drugs from ≥ 2 different classes at doses equivalent to ≥ 1000 mg chlorpromazine
Shopsin 1979a[96]	**Allocation:** random **Blinding:** double **Duration:** 5 weeks (preceded by 3–7-day washout period) **Setting:** hospital	**Diagnosis:** schizophrenia, floridly psychotic; authors' checklist, no widely used diagnostic criteria mentioned ***N:*** 39 **Age:** range, 21–55 years	1. clozapine capsules, 25 mg/day initially; 1-week build-up to 300 mg/day; mean at week 4, 800 mg/day; maximum, 900 mg/day; *n* = 16 2. chlorpromazine capsules, 150 mg/day initially; 1-week build-up to 600 mg/day; mean at week 4, 1333 mg/day; maximum 1800 mg/day; *n* = 15 3. placebo, *n* = 8 After 7-day fixed-dose build-up, dose adjusted according to response; chloral hydrate and/or paraldehyde as needed	Relapse Acceptability: drop-outs Global effect: CGI Mental state: BPRS Behaviour: NOSIE Adverse effects: modified SAS Dischargeability ECG, blood pressure, ophthalmological examination	Jadad score 4 Number of drop-outs not specifically reported

continued

Clozapine versus typical antipsychotic drugs *contd*

Study	Methods	Participants	Interventions	Outcomes	Notes
Gelenberg 1979b[97]	**Allocation:** random **Blinding:** double **Duration:** 4–8 weeks (preceded by > 2-day washout period) **Setting:** hospital	**Diagnosis:** schizophrenia (DSM-II) **History:** 'neurologic reactions' to antipsychotic drugs ***N*:** 15 **Sex:** 7 female, 8 male **Age:** mean, 30 years; range, 18–43	1. clozapine, 25 mg/day initially; average 279 mg/day; range, 125–525 mg/day; *n* = 7 2. chlorpromazine, 50 mg/day initially; average, 606 mg/day; maximum, 1050 mg/day; *n* = 8 Dose based on clinical response; amobarbital, chloral hydrate and paraldehyde as needed	Death Relapse Behaviour: NOSIE Acceptability: drop-outs Mental state: BPRS (no SDs reported) Adverse effects: AIMS, SAS (not blind)	Jadad score 3 Trial terminated prematurely due to reports of clozapine-related agranulocytosis
Claghorn 1987[98]	**Allocation:** random **Blinding:** double (identical tablets) **Duration:** 4–8 weeks (preceded by 2-week washout period) **Setting:** multicentre, hospital	**Diagnosis:** schizophrenia (DSM-II) **History:** intolerant to at least two prior neuroleptic drugs ***N*:** 151 **Sex:** 59 female, 92 male **Age:** median, 30 years; range, 18–65	1. clozapine tablets, 25 mg/day initially; 1-week build-up to 300 mg/day; days 8–28, 150–900 mg/day; average, 417 mg/day; *n* = 75 2. chlorpromazine tablets, 50 mg/day initially; 1-week build-up to 600 mg/day; days 8–28, 300–1800 mg/day; average, 795 mg/day; *n* = 76 Fixed–flexible dose schedule	Relapse Global effect: CGI Acceptability: drop-outs Mental state: 18-item BPRS Behaviour: 30-item NOSIE Adverse effects: AIMS, SAS (not blind)	Jadad score 4
Kane 1988[99]	**Allocation:** random **Blinding:** double **Duration:** 6 weeks **Setting:** hospital; multicentre	**Diagnosis:** schizophrenia (DSM-III) – undifferentiated ~ 50%; paranoid ~ 33% History: treatment-resistant* illness, unresponsive/intolerant to 6 weeks haloperidol and benztropine period ***N*:** 268 **Sex:** 20% female, 80% male **Age:** (average) clozapine, 36 years (SD, 9); chlorpromazine, 36 years (SD, 8) years	1. clozapine capsules, up to 500 mg/day in week 1/2, flexible thereafter; maximum, 900 mg/day; *n* = 126 2. chlorpromazine capsules, up to 1000 mg/day in week 1/2, flexible thereafter; maximum 1800 mg/day; also benztropine, 6 mg/day; *n* = 142	Death Relapse Acceptability: drop-outs Improvement: decrease of > 20% in BPRS total score, and CGI score of < 3, or BPRS total score < 35 Global effect: CGI Mental state: BPRS Behaviour: NOSIE Adverse effects: AIMS; SAS	Jadad score 5 * Treatment-resistant = 3+ periods of neuroleptic treatment, 1000 mg/day of chlorpromazine equivalent without significant symptomatic relief and BPRS total score of at least 45

continued

Clozapine versus typical antipsychotic drugs *contd*

Study	Methods	Participants	Interventions	Outcomes	Notes
Kane 1994b[100]	**Blinding:** double **Duration:** 29 weeks **Setting:** community; multicentre	**Diagnosis:** schizophrenia (DSM-III-R), 'symptomatic but not profoundly treatment-refractory' ***N*:** 71 **Sex:** 21 female, 50 male **Age:** mean, 40 ± 9 years	1. clozapine, dose not specified; *n* = 37 2. haloperidol, 10 mg/day; *n* = 34	Relapse Mental state: BPRS, SANS Neuropsychological tests Improvement: > 20% reduction in BPRS psychosis factor score	Jadad score 3 Data extracted from abstracts
Lee 1994c[101]	**Allocation:** random **Blinding:** non-blind **Duration:** 24 months (preceded by ≥ 5-day washout period)	**Diagnosis:** schizophrenia, non-treatment-resistant; diagnostic criteria not mentioned ***N*:** 47 **History:** illness duration < 5 years; minimal positive symptoms during prior neuroleptic treatment	1. clozapine, dose not specified; *n* = 24 2. various typical neuroleptic drugs (mainly haloperidol) + benztropine as needed; *n* = 23	Mental state: BPRS Neuropsychological function: Digit Symbol, Category Instance Generation, Controlled Word Association, Wisconsin Card Sorting Test, Verbal List Learning	Jadad score 1 Only 12-month outcomes published; benztropine medication in group 2 may have affected results; possible assessment bias due to non-blind conditions
Tamminga 1994d[102]	**Allocation:** random **Blinding:** double **Duration:** 12 months (preceded by 1–6 month stabilisation with haloperidol and 1-month drug-free/fixed low-dose)	**Diagnosis:** schizophrenia with tardive dyskinesia; diagnostic criteria not mentioned ***N*:** 43 **Age:** data only available for completers	1. clozapine, 50 mg/day initially; final average dose, 294 mg/day + placebo; *n* = 25 2. haloperidol, 5 mg/day initially; final dose (average), 28.5 mg/day + benztropine; *n* = 14	Relapse Acceptability: drop-outs Mental state: BPRS Adverse effects: Maryland Psychiatric Research Centre Involuntary Motor Scale, videotape evaluation	Jadad score 3 Four patients had not completed protocol when report written; haloperidol doses seem high compared with clozapine doses; benztropine medication in group 2 may have affected results
Essock 1996a[103]	**Allocation:** random **Blinding:** non-blind **Duration:** 24 months **Setting:** hospital	**Diagnosis:** schizophrenia/schizo-affective disorder, severely ill **History:** unresponsive to 2 treatment trials/ unacceptable side-effects with conventional neuroleptic drugs; structural clinical interview (DSM-IV) with 173 participants ***N*:** 227 **Age:** average; clozapine, 42 years (SD 12); usual care, 40 years (SD 11) **Sex:** 90 female, 137 male	1. clozapine, 496 mg/day, average; average peak dose 671 mg/day; *n* = 136 2. usual care, chlorpromazine equivalent, 1386 mg/day, average; average peak dose, 2009 mg/day; *n* = 89 Most frequent control treatments – haloperidol, chlorpromazine and fluphenazine; almost no use of atypical neuroleptic drugs	Acceptability: drop-outs Mental state: BPRS Quality of life: Quality of Life Index Adverse effects: AIMS Clinical improvement: at least 20% on BPRS total score or at least 20% on BPRS psychotic item subscale Discharge Readmission	Jadad score 2. Two randomised to clozapine did not begin trial; during trial some patients in usual care group began clozapine treatment (ten at 6 months, 59 at 24 months)

continued

Clozapine versus typical antipsychotic drugs *contd*

Study	Methods	Participants	Interventions	Outcomes	Notes
Kumra 1996b[104]	**Allocation:** randomised **Blinding:** double **Duration:** 6 weeks (preceded by 4-week washout period). **Setting:** hospital	**Diagnosis (*n*):** schizophrenia (DSM III-R), neuroleptic-resistant – disorganised (10); undifferentiated (10); paranoid (1) **Age:** average, 14 years, range, (6–18) **Sex:** 10 girls, 11 boys **History:** onset by age 12 years	1. clozapine pills + placebo, 6.25–25 mg/day initially, depending on weight; average, 176 mg/day; range, 25–525 mg/day; *n* = 10 2. haloperidol pills, 0.25–1 mg/day initially, depending on weight; dose average, 16 mg/day, range 7–27 mg/day and benztropine as needed, 6 mg/day. *n* = 11 Flexible dose schedule	Mental state: BPRS, BPRS for children, SANS, SAPS, Bunney–Hamburg Rating Scale Global effect: CGI, children's global assessment scale Acceptability: drop-outs Adverse effects: SAS; AIMS; Subjective Treatment Emergent Symptoms Scale EEG; ECG; laboratory tests, including cerebro-spinal fluid sampling	Jadad score 5 Dispersion of Bunney–Hamburg ratings greater in haloperidol group – means groups not comparable in this respect; haloperidol doses seem high compared with clozapine; benztropine medication in group 2 may have affected results
Rosenheck 1997[105]	**Allocation:** random **Blinding:** double; placebo benztropine given to clozapine group, blood counts taken from haloperidol group **Duration:** 1 year **Setting:** hospital and outpatient services; multicentre	**Diagnosis:** schizophrenia (DSM III-R and SCID) **History:** mean age of onset, 22 years; treatment-resistant* illness; high-level use of inpatient services (30–364 days hospitalisation in preceding year ***N*:** 423 **Sex:** 10 female, 413 male **Age:** clozapine group, mean, 43 years (SD, 8); haloperidol group, mean, 44 years (SD, 8)	1. clozapine, 100–900 mg/day (flexible); average at week 26, 552 ± 229 mg/day; *n* = 205 2. haloperidol, 5–30 mg/day (flexible); average at week 26, 28 ± 5.3 mg/day Also, benztropine, 2–10 mg/day; *n* = 218	Acceptability: drop-outs Mental state: PANSS Improvement: decrease of > 20% in PANSS total Quality of life: Heinrichs–Carpenter quality-of-life scale Adverse effects: AIMS; BAS; SAS; adverse effects checklist Use of services: days of hospitalisation (skewed data), outpatient visits (no SDs) Costs: medication, healthcare, estimated non-healthcare costs	Jadad score 4 * Treatment-resistant, persisting psychotic symptoms despite treatment with > 1 antipsychotic drug at equivalent of chlorpromazine, 1000 mg; during trial 83 patients assigned to clozapine switched to conventional antipsychotic drugs and 49 assigned to haloperidol switched to clozapine for at least 4 weeks Crossover cases excluded from data on clinical improvement; benztropine medication in group 2 may have affected results

continued

Clozapine versus typical antipsychotic drugs *contd*

Study	Methods	Participants	Interventions	Outcomes	Notes
Howanitz 1999[106]	**Allocation:** random **Blinding:** double (medication in identical capsules) **Duration:** 12 weeks (preceded by 1–7 days' washout) **Setting:** hospital	**Diagnosis:** schizophrenia (DSM-IV) ***N*:** 42 **Sex:** 3 female, 39 male **Age:** > 55 years; average, clozapine, 65 years; chlorpromazine, 68.5 years **Symptoms:** PANSS > 60 **History:** average duration of illness – clozapine, 38 years; chlorpromazine, 40 years; average length of hospitalisation – clozapine, 19.4 years, chlorpromazine, 17.5 years	1. clozapine, 12.5 mg/day initially, maximum 300 mg/day; *n* = 24 2. chlorpromazine, 25 mg/day initially, maximum 600 mg/day; *n* = 18 Benztropine and chloral hydrate given as needed Fixed–flexible–fixed dose schedule	Global effect: CGI Mental state: PANSS Adverse effects: AIMS	Jadad score 3 Trialists did not perform ITT analysis with regard to efficacy. Eight patients excluded from efficacy analysis in original paper
Buchanan 1998[107]	**Allocation:** random **Blinding:** double **Duration:** 10 weeks (no washout) **Setting:** community	**Diagnosis:** schizophrenia (DSM-III-R; SCID), chronic **History:** non-complete response to at least two trials of therapeutic doses of neuroleptic drugs for at least 6 weeks; less than 30% improvement in prospective 6-week trial of fluphenazine 10–30 mg/day ***N*:** 75 **Sex:** 23 female, 52 male **Age:** mean, 35 years; range, 18–55	1. clozapine pills, increased to 400 mg/day, weeks 1–4; 200–600 mg/day, weeks 5–6; fixed, weeks 7–10; average at study end, 413 ± 60 mg/day + placebo; *n* = 38 2. haloperidol pills, increased to 20 mg/day, weeks 1–4; 10–30 mg/day, weeks 5–6; fixed, weeks 7–10; average at study end, 26 ± 7 mg/day + benztropine 4 mg/day; *n* = 37	Relapse Clinical improvement: 20% reduction in BPRS (data not reported) Acceptability: drop-outs Mental state: 18-item BPRS; SANS Quality of life: QLS Global functioning: Level of Functioning Scale Adverse effects: SAS; Maryland Psychiatric Research Centre Involuntary Movement Scale Compliance	Jadad score 4 Drop-outs (*n* = 2) excluded from original results included in present meta-analysis; benztropine medication in group 2 may have affected results

Clozapine versus atypical antipsychotic drugs

Study	Methods	Participants	Interventions	Outcomes	Notes
Beasley 1998[77]	**Allocation:** 'randomly allocated' **Blinding:** double, no further details **Statistical technique:** last observation carried forward **Duration:** 18 weeks (preceded by 2–9 day washout period) **Setting:** multicentre; no other details	**Diagnosis:** schizophrenia (DSM-IV) ***N*:** 180 **Sex:** 65 female, 115 male **Age:** mean, 38.6 years (SD, 10.6), range, 18–70 **History:** onset age about 23 years; duration of illness, about 16 years; treatment-resistant* illness	1. olanzapine, individual dose titration 15–25 mg/day, mean 22.2 mg/day; *n* = 90 2. clozapine, 25–200 mg/day initially for days 1–8; thereafter 200–600 mg/day, mean, 354.2 mg/day; *n* = 90 Benzodiazepine and chloral hydrate (agitation and insomnia), biperiden and benztropine mesylate (EPS) as required	Leaving study early Physiological monitoring (vital signs, laboratory tests) Mental state: PANSS; BPRS; CGI Adverse effects (dichotomous scale) **Unable to use** EPS: Barnes; modified SAS; AIMS; mean endpoint values and SDs not reported	Abstract only Insufficient description of drop-outs; 107 patients completed study – 60% in olanzapine group, 58.9% in clozapine group * Treatment-resistant: lack of response to two antipsychotic drugs of different class given for ≥ 6 weeks at dose of ≥ 500 mg/day, chlorpromazine equivalent, or highest tolerated dose; BPRS (1–7) ≥ 45, with score of ≥ 4 on at least two items on PANSS positive subscale (items 1–7)
Oliemeulen 2000[109]	**Allocation:** 'randomly assigned' **Blinding:** not specified **Duration:** 8 weeks	**Diagnosis:** schizophrenia or other psychotic disorders (DSM-IV) ***N*:** 36 **Sex:** not reported **Age:** mean, 34.1 years (olanzapine group, mean 30; clozapine group, mean 37) **History:** treatment-resistant* illness	1. olanzapine: dose not reported; *n* = 21 2. clozapine: dose not reported; *n* = 15	Mental state (PANSS) **Unable to use** Mental state: Calgary Depression Scale Cognitive and motor effects: figure copying test, simple motor aiming task, key-pressing task, Digit Symbol Test, Trail Making Test – maze test	Abstract only Missing description of drop-outs; additional information requested from authors * Treatment-resistant: no detailed description

continued

Clozapine versus atypical antipsychotic drugs *contd*

Study	Methods	Participants	Interventions	Outcomes	Notes
Kleiser 1994[264]	**Allocation:** 'randomly assigned' **Blinding:** double; no further details **Duration:** 4 weeks (preceded by period free from neuroleptic drugs) **Setting:** not described	**Diagnosis:** schizophrenia (ICD9) paranoid type ***N*:** 180 **Sex:** 71 female, 64 male* **Age:** mean 34.7 years (SD, 11) **History:** acutely ill; duration illness, about 4.5 years (SD, 4.3)	1. risperidone, individual dose titration for week 1, fixed dose, 4 mg/day, thereafter; *n* = 20 2. risperidone, individual dose titration for week 1, fixed dose, 8 mg/day, thereafter. *n* = 20 3. zotepine, fixed dose 225 mg/day; *n* = 20 4. remoxipride, individual dose titration for week 1, fixed dose, 400 mg/day, thereafter; *n* = 38 5. clozapine, 100 mg/day initially, individual dose titration for week 1, fixed dose, 400 mg/day, thereafter; *n* = 37 6. haloperidol, 15 mg/day (mean); *n* = 45 Biperiden (EPS) as required	Physiological monitoring (physical investigation, laboratory tests, ECG, EEG) Mental state (BPRS) Cognitive changes (Syndrome Kurz Test) EPS side-effects (SAS) Satisfaction with treatment (dichotomous scale) **Unable to use** Mental state (CGI), not reported	No description of whether there were drop-outs or not * Demographic data related to *n* = 135 (with haloperidol group excluded)

continued

Clozapine versus atypical antipsychotic drugs *contd*

Study	Methods	Participants	Interventions	Outcomes	Notes
Bondolfi 1998[110]	**Allocation:** 'randomly assigned', blocks of four **Blinding:** double, 'double-dummy' protocol **Duration:** 8 weeks, preceded by neuroleptic-free period **Setting:** multicentre; hospital (for first 3 weeks)	**Diagnosis:** schizophrenia (DSM-III-R) ***N*:** 86 **Sex:** 25 female, 61 male **Age:** mean 37.3 years (SD 12.6) **History:** moderate to severe illness; duration about 14 years; onset age ~ 26 years (SD 8.8); treatment-resistant* illness	1. risperidone, individual dose titration: first week, fixed dose; second week and thereafter, 6 mg/day adjusted according to response; mean, 6.4 mg/day; range, 3–12 mg/day; *n* = 43 2. clozapine, individual dose titration: first week, fixed dose; second week and thereafter, 300 mg/day, adjusted according to response; mean, 291 mg/day; range, 150–400 mg/day; *n* = 43 Lorazepam and oxazepam (sleep induction), biperiden and procyclidine (EPS), clothiapine (emergency treatment) as required	Leaving study early Mental state (PANSS; CGI) **Unable to use** EPS symptoms (ESRS): endpoint mean values and SDs not reported Other adverse events: UKU, mean endpoint data and SDs not reported	Description of drop-outs available, 34 patients completed study in both groups * Treatment-resistant: failed to respond or intolerant of ≥ 2 different classes of antipsychotic drugs in appropriate doses for ≥ 4 weeks each; total PANSS 60–120
Anand 1998[111]	**Allocation:** 'randomised' **Blinding:** double; no further details **Duration:** 12 weeks **Setting:** multicentre; no other details	**Diagnosis:** schizophrenia (DSM-IV) ***N*:** 273 **Sex:** 78 female, 195 male **Age:** mean 38.8 years **History:** treatment-resistant* illness	1. risperidone, individual dose titration; week 1–4, up to 6 mg, then kept within range, 2–15 mg/day, mean 8.3 mg/day; *n* = 135 2. clozapine, individual dose titration; week 1–4, up to 600 mg, then kept within range, 200–900 mg/day, mean 597.5 mg/day; *n* = 138	Leaving study early, relapse Physiological monitoring (laboratory tests) **Unable to use** Mental state: PANSS; BPRS; CGI; PAS, data not reported Adverse effects: data not reported	Raw scores of rating scales not available Insufficient description of drop-outs: 101 patients in risperidone group, 100 in clozapine group completed study * Treatment-resistant: severe, chronic disease and poor response to previous neuroleptic drugs (no period of good functioning for ≥ 24 months despite use of two antipsychotic drugs; current episode without significant improvement for ≥ 6 months despite use of antipsychotic equivalent to haloperidol, 20 mg, for ≥ 6 weeks; total BPRS ≥ 45; CGI ≥ 4)

continued

Clozapine versus atypical antipsychotic drugs *contd*

Study	Methods	Participants	Interventions	Outcomes	Notes
Breier 1999[112]	**Allocation:** 'randomly assigned' **Blinding:** double; no further details **Duration:** 6 weeks (preceded by fluphenazine treatment for ≥ 2 weeks; then, 66% patients underwent drug-free period, mean 18 days) **Setting:** not described	**Diagnosis:** schizophrenia (DSM-IV) ***N*:** 29 **Sex:** 10 female, 19 male **Age:** mean, 35.0 years, range 18–55 years **History:** duration of illness, about 12.5 years; chronic schizophrenia; partial response to neuroleptic drugs*	1. risperidone, gradual dose titration up to 6 mg/day for 2 weeks; adjustments over next 2 weeks within fixed limits, 2–9 mg/day; thereafter fixed dose, mean 5.9 mg/day; *n* = 15 2. clozapine, gradual dose titration up to 400 mg/day for 2 weeks; adjustments over next 2 weeks within fixed limits, 200–600 mg/day; thereafter fixed dose, mean 403.6 mg/day; *n* = 14 Benztropine mesylate (EPS) as required	Leaving study early Physiological monitoring (laboratory tests) Mental state (BPRS; SANS; Hamilton Rating Scale – depression) EPS side-effects (modified SAS)	No drop-outs after randomisation phase * Partial response to neuroleptic drugs: (i) history of residual positive and/or negative symptoms after ≥ 6 week trial of therapeutic dose of neuroleptic agent; (ii) at least minimum level of positive (4 positive BPRS items > 8) and/or negative (SANS score > 20) symptoms at time of evaluation for study; (iii) at least minimum level of positive and negative symptoms after prospective trial of ≥ 2 weeks of fluphenazine, 20 mg/day (range 10–30 mg/day)
Wahlbeck 2000[113]	**Allocation:** 'computer-generated randomisation' **Blinding:** single; a blind rater **Statistical technique:** last observation carried forward **Duration:** 10 weeks (preceded by 6-week treatment with haloperidol, ≤ 50 mg/day if no history of previous treatment with haloperidol, > 40 mg/day, or haloperidol intolerance); washout of previous neuroleptic medication, 1–3 days **Setting:** hospital (at beginning of trial)	**Diagnosis:** schizophrenia (DSM-IV) ***N*:** 20 **Sex:** 9 female, 11 male **Age:** mean, 35.9 years; range, 24–55 years **History:** duration of illness, ~ 12 years, range 0.5–33 years; treatment-resistant* illness	1. risperidone, fixed dose titration ≤ 6 mg/day for 3 days; flexible thereafter up to 10 mg/day, mean 7.8 mg/day; *n* = 9 2. clozapine, fixed dose titration up to 400 mg/day for 2 weeks; flexible thereafter ≤ 600 mg/day, mean 385 mg/day; *n* = 11 Biperiden (EPS) and lorazepam (anxiety) as required	Leaving study early, relapse, discharge rate; physiological monitoring (laboratory tests) Mental state (PANSS, CGI, PGI, Social Functioning Scale) EPS symptoms (non-structured assessment) Global assessment (GAF) Satisfaction with treatment (DAI-10)	Description of drop-outs available, eight patients in risperidone group and five in clozapine group completed study (one patient randomised to clozapine withdrew consent before trial began) * Treatment-resistant: persistent psychotic symptoms for < 6 months while on medication from ≥ 2 different classes of antipsychotic drugs in doses ≥ 1000 mg/day chlorpromazine for > 6 weeks each; in addition, non-tolerance to haloperidol or non-response to haloperidol, > 40 mg/day

continued

Olanzapine

Study	Methods	Participants	Interventions	Outcomes	Notes
Altamura 1999[181]	**Allocation:** randomised, computer-generated, blocks for each investigator 1:1, concealed from investigators **Blinding:** double, medication kits issues **Duration:** 14 weeks (preceded by screening phase, unspecified) **Setting:** Not described	**Diagnosis:** schizophrenia, paranoid (DSM-IV) ***N*:** 48 **Sex:** not specified **Age:** not specified **History:** partial or non-responders to treatment according to preset criteria	1. olanzapine, range 5–20 mg/day, mean, 12.4 mg/day, SD 3.2; *n* = 23 2. haloperidol, range 5–20 mg/day, mean 12.3 mg/day, SD 3.3; *n* = 25	Leaving study early Other adverse events: COSTART list, weight change **Unable to use** Global state: CGI, no data Mental state: BPRS; SANS; no data Side-effects: AIMS, no data	
Beasley 1996a[168]	**Allocation:** random; no further details **Blinding:** double; no further details **Duration:** 6 weeks (preceded by placebo lead-in of 4–7 days; 46-week extension for responders) **Investigators:** trained on BPRS and SANS **Setting:** hospital and community	**Diagnosis:** schizophrenia (DSM-III-R) **Inclusion criteria:** BPRS > 23; CGI > 3; off neuroleptic drugs before entering study; lead-in period responders (BPRS total decreased by > 24% or < 24) excluded ***N*:** 335. **Sex:** approximately 90% male **Age:** mode, in their 30s; range 18–65 years	1. olanzapine low dose, 2.5–7.5 mg/day; *n* = 65 2. olanzapine medium dose, 7.5–12.5 mg/day; *n* = 64 3. olanzapine high dose, 12.5–17.5 mg/day*; *n* = 69 4. haloperidol, 10–20 mg/day; *n* = 69 5. placebo, *n* = 68 Up to 10 mg/day lorazepam allowed day 1–21; benztropine, 6 mg/day, allowed throughout	Mental state: BPRS-anchored version**, SANS; needing additional benzodiazepines Leaving study early Side-effects: requiring benztropine; AIMS, BAS, SAS; weight gain, data only for olanzapine high dose Adverse events, COSTART list **Unable to use** Hospital status: no data Global state: CGI-S, CGI-I, PGI, no data Laboratory tests and physiological measures: no data	* Chosen as comparator with other trials as mean dose = 13.2 mg/day. ** *A priori* efficacy > 39 decrease from baseline or to < 19 BPRS total

continued

Olanzapine *contd*

Study	Methods	Participants	Interventions	Outcomes	Notes
Beasley 1996b[169]	**Allocation:** random; no further details **Blinding:** double, no further details **Duration:** 6 weeks (preceded by placebo lead-in of 4–7 days) **Investigators:** trained in PANSS **Setting:** multicentre (12), USA; initially all hospitalised*	**Diagnosis:** schizophrenia (DSM-III-R) **Inclusion criteria:** BPRS > 23; CGI > 3; not involved in previous olanzapine trial; off neuroleptic drugs before entering study; lead-in period responders (BPRS total decreased by > 24 or < 24) excluded ***N:*** 152 **Age:** mean 38 years **Sex:** ~ 70% male	1. olanzapine, 1 mg/day; *n* = 52 2. olanzapine, 10 mg/day; *n* = 50 3. placebo; *n* = 50 Up to 10 mg/day lorazepam allowed days 1–21; benztropine, 6 mg/day, allowed throughout	Global state, CGI-S Mental state: BPRS**, PANSS; needing additional benzodiazepines Leaving study early Side-effects: requiring benztropine; AIMS, BAS, SAS Adverse events (COSTART list) **Unable to use** Hospital status (no data) Global state (PGI, no data) Laboratory tests and physiological measures (no data)	* Eligible for discharge if BPRS total decreased by > 24% from baseline or was < 24 ** BPRS (scored 0–6) extracted from PANSS – no reference given for validity of procedure ** *A priori* efficacy > 39 decrease from baseline or to < 19 BPRS total
Beasley 1997[182]	**Allocation:** random; blocks of 5 **Blinding:** double; no further details **Duration:** 6 weeks (preceded by placebo lead-in of 4–7 days; 46-week extension for responders) **Setting:** *multicentre, 50 sites; initially all hospitalised	**Diagnosis:** schizophrenia (DSM-III-R) **Inclusion criteria:** BPRS > 23; CGI > 3; off neuroleptic drugs before entering study; lead-in period responders (BPRS total decreased by > 24 or < 24) excluded ***N:*** 431 **Age:** 18–65 years **Sex:** 275 male, 156 female	1. olanzapine, 1 mg/day; *n* = 88 2. olanzapine, 2.5–7.5 mg/day; *n* = 87 3. olanzapine, 7.5–12.5 mg/day; *n* = 86 4. olanzapine, 12.5–17.5 mg/day**; *n* = 89 5. haloperidol, 10–20 mg/day; *n* = 81 Benzodiazipine, up to 10 mg/day, allowed days 1–21; biperiden, up to 6 mg/day, allowed throughout	Global state (CGI-S) Mental state: BPRS***, PANSS; needing additional benzodiazepine Leaving study early Side-effects: requiring benztropine; AIMS, BAS, SAS Adverse events: COSTART list **Unable to use** Hospital status: no data Global state: PGI, no data Laboratory tests and physiological measures: no data	* Eligible for discharge if BPRS total decreased by > 24% from baseline or was < 24 ** Chosen as comparator with other trials as mean dose = 13.2 mg/day *** BPRS (score 0–6) extracted from PANSS; no reference given for validity of procedure; a priori efficacy > 39 decrease from baseline or to < 19 total

continued

Olanzapine *contd*

Study	Methods	Participants	Interventions	Outcomes	Notes
Beuzen 1998[176,177]	**Allocation:** random; no further details **Blinding:** double; no further details **Duration:** 18 weeks (preceded by washout period) **Setting:** not described	**Diagnosis:** schizophrenia (DSM-IV) **Inclusion criteria:** treatment-resistant, > 3 on at least two items on PANSS positive subscale ***N*:** 180 **Sex:** not specified **Age:** not specified	1. olanzapine, 15–25 mg/day; *n* = 90 2. clozapine, 200–600 mg/day; *n* = 90 Allowed benzodiazipines, biperiden, benztropine and chloral hydrate	Leaving study early Global improvement: CGI Mental state: PANSS, BPRS, Kane criteria **Unable to use** Mental state: BPRS, no SD Global change: CGI, no SD Behaviour: additional medication, no data Side-effects: only statistically significant differences reported Laboratory tests and physiological measures: no data	
Conley 1998a[183]	**Allocation:** random; no further details **Blinding:** double **Duration:** 8 weeks (preceded by 6/52 weeks' haloperidol and 1–2/52 weeks' washout) **Investigators:** trained on BPRS and SANS **Setting:** multicentre, three sites; hospitalised	**Diagnosis:** schizophrenia (DSM-III-R) **Inclusion criteria:** minimum BPRS score 45; CGI-S score > 3; non-responders with treatment-resistant illness during haloperidol phase ***N*:** 84 **Sex:** 62 male, 22 female	1. olanzapine, 25 mg/day; *n* = 42 2. chlorpromazine, 1200 mg/day, plus benztropine, 4 mg/day; *n* = 42 Allowed benzodiazipine during washout and first 3/52 weeks of trial	Global state: CGI Mental state: BPRS*; SANS Leaving study early Side-effects: BAS; SAS **Unable to use** Behaviour: use of benzodiazipines, no data Hospital status: no data Laboratory tests and physiological measures: no data	* *A priori* efficacy > 19 decrease from baseline or to < 34 total score Treatment-resistant defined as: (i) ≥ 2 periods of treatment in preceding 5 years with antipsychotic drug (from at least two different classes, excluding haloperidol) at doses ≥ 1000 mg, chlorpromazine, daily for 6 weeks without significant symptomatic relief; (ii) no period of good functioning within past 5 years; (iii) severity of psychopathology indicated by BPRS total score ≥ 45, CGI severity score ≥ 4, and score of ≥ 4 on ≥ 2 BPRS psychosis items

continued

Olanzapine *contd*

Study	Methods	Participants	Interventions	Outcomes	Notes
HGBJ, Finland (Eli Lilly: data on file); data supplied to Cochrane Schizophrenia Group, 1999	**Allocation:** random, computer-generated, blocks for each investigator 1:1, concealed from investigators **Blinding:** double; medication kits issued **Duration:** 26 weeks (preceded by screening phase, unspecified) **Setting:** multicentre, Finland	**Diagnosis:** schizophrenia (DSM-IV) ***N*:** 46 **Sex:** not specified **Age:** not specified	1. olanzapine, 5–20 mg/day; *n* = 23 2. perphenazine, 8–32 mg/day; *n* = 23	Leaving study early Other adverse events: COSTART list; weight change	
HGBL, 1997 (Eli Lilly: data on file); data supplied to Cochrane Schizophrenia Group, 1999	**Allocation:** random, computer-generated, blocks, 1:1 for each investigator, concealed from investigators **Blinding:** double; medication kits issued **Duration:** 4 weeks (preceded by placebo lead-in of 4–7 days **Setting:** inpatient	**Diagnosis:** schizophrenia (DSM-IV) ***N*:** 33 **Age:** not specified **Sex:** not specified	1. olanzapine, 5–20 mg/day; *n* = 15 2. flupentixol, 5–20 mg/day; *n* = 13	Leaving study early Other adverse events: COSTART list; weight change **Unable to use** Global state: no data Mental state: no data Side-effects: EPS, no data	
HGCJ, Hong Kong, 1999	**Allocation:** random, computer-generated, blocks, 1:1 for each investigator, concealed from investigators **Blinding:** double; medication kits issued **Duration:** 14 weeks **Setting:** in- and outpatient	**Diagnosis:** schizophrenia, schizophreniform disorder, schizoaffective disorder (DSM-IV) ***N*:** 31 **Age:** not specified **Sex:** not specified	1. olanzapine, 5–20 mg/day; *n* = 17 2. haloperidol, 5–20 mg/day; *n* = 14	Leaving study early Global state: CGI-S Mental state: BPRS; MADRS; PANSS Other adverse events: COSTART list; weight change **Unable to use** Side-effects: EPS, no data	
HGCQ, Turkey, 2000	**Allocation:** random, computer-generated blocks, 2:1 for each investigator, concealed from investigators **Blinding:** double; medication kits issued **Duration:** 6 weeks **Setting:** two centres, Turkey; otherwise not described	**Diagnosis:** not stated ***N*:** 30 **Age:** mean, ~ 32 years **Sex:** ~ 58% male	1. olanzapine, dose not reported; *n* = 20 2. chlorpromazine, dose not reported; *n* = 10	Leaving study early Other adverse events: COSTART list; weight change **Unable to use** Global state: CGI, no data Mental state: BPRS, PANSS; no data Side-effects: ESRS, UKU, weight change – no data	

continued

Olanzapine *contd*

Study	Methods	Participants	Interventions	Outcomes	Notes
HGCU, Taiwan, 1998	**Allocation:** random, computer-generated blocks, 1:1 for each investigator, concealed from investigators **Blinding:** double; medication kits issued **Duration:** 14 weeks **Setting:** not described	**Diagnosis:** schizophrenia, schizophreniform disorder, schizoaffective disorder (DSM-IV) ***N*:** 54 **Age:** not specified **Sex:** not specified	1. olanzapine, 5–20 mg/day; *n* = 26 2. haloperidol, 5–20 mg/day; *n* = 28	Leaving study early Global state: CGI-S Mental state: BPRS; MADRS; PANSS Other adverse events: COSTART list; weight change **Unable to use** Side-effects: EPS, no data	
HGDV, Morocco, 1999 (Eli Lilly: data on file) Data supplied to Cochrane Schizophrenia Group, 1999	**Allocation:** random, computer-generated blocks for each investigator, 2:1, olanzapine to chlorpromazine **Blinding:** open-label; medication kits issued **Duration:** 6 weeks (preceded by washout phase; extension for responders) **Setting:** single centre, Morocco; in- and outpatient	**Diagnosis:** schizophrenia (DSM-IV) ***N*:** 39 **Age:** not specified **Sex:** not specified	1. olanzapine, 5–20 mg/day; *n* = 27 2. chlorpromazine, 200–800 mg/day; *n* = 12	Leaving study early Other adverse events: COSTART list; weight gain	
HGFH, Korea, 1998 (Eli Lilly: data on file) Data supplied to Cochrane Schizophrenia Group, 1999	**Allocation:** random, computer-generated blocks for each investigator, 1:1 **Blinding:** open label **Duration:** 6 weeks (preceded by washout phase, unspecified; extension for responders) **Setting:** single centre, Korea; in- and outpatient	**Diagnosis:** schizophrenia, schizophreniform and schizoaffective disorders (DSM-IV) ***N*:** 104 **Age:** not specified **Sex:** not specified	1. olanzapine, 5–20 mg/day; *n* = 53 2. haloperidol, 1.5–20 mg/day; *n* = 51	Leaving study early Other adverse events: COSTART list, weight gain	

continued

Olanzapine *contd*

Study	Methods	Participants	Interventions	Outcomes	Notes
Jakovljevic 1999[184]	**Allocation:** random, computer-generated blocks, 1:1, concealed from investigators **Blinding:** double; medication kit issued **Duration:** 6 weeks followed by extension for 22 weeks (preceded by washout period of 2–9 days) **Setting:** Three sites, Croatia; no further details	**Diagnosis:** schizophrenia; no further details ***N*:** 60	1. olanzapine, 5–20 mg/day; *n* = 30 2. fluphenazine, 6–21 mg/day; *n* = 30	**22-week data** Leaving study early Global state: CGI-S Mental state: BPRS; PANSS Other adverse events: COSTART list; weight change Quality of life: Van Putten Scale, DAI, Leeds Sleep Evaluation Questionnaire **Unable to use** Side-effects: EPS, no data	
Jones 1998[180]	**Allocation:** random; no further details **Blinding:** double **Duration:** 54 weeks; 1-month stabilisation phase followed by 1-week washout, screening period **Setting:** outpatients; multicentre	**Diagnosis:** schizophrenia ***N*:** 65 **Exclusion criteria:** PANSS > 90 **History:** 'early phase'–first 5 years of illness	1. olanzapine, 5–20 mg/day; *n* = 21 2. risperidone, 4–10 mg/day; *n* = 21 3. haloperidol, 5–20 mg/day; *n* = 23	Leaving study early **Unable to use** Mental state: PANSS, no data Side-effects: ESRS, no data Cost: no data Cognitive function: GCIS, neuropsychological test battery, no usable data	
Lecrubier 1999[42]	**Allocation:** random, computer-generated blocks for each investigator, 2:2:2:1, concealed from investigator **Blinding:** double; medication kits issued **Duration:** 6 months **Setting:** not described	**Diagnosis:** 'schizophrenic patients with primarily negative symptoms'; no further details **Inclusion criteria:** minimum SANS summary score of 10 (excluding attention subscore) and no score > 4 on hallucination and delusion items of PANSS (normalised, score 0–6) ***N*:** 245 **Age:** not specified **Sex:** not specified	1. olanzapine, 5 mg/day; *n* = 70 2. olanzapine, 20 mg/day; *n* = 70 3. placebo, *n* = 35 4. amisulpride, 150 mg/day; *n* = 70	Leaving study early Mental state: SANS Other adverse events: COSTART list; weight change Quality of life: Carpenter QLS **Unable to use** Mental state: PANSS, no usable data Side-effects: EPS, no data	

continued

Olanzapine *contd*

Study	Methods	Participants	Interventions	Outcomes	Notes
Loza 1999[185]	**Allocation:** random, computer-generated, blocks for each investigator, 2:1 olanzapine: chlorpromazine, concealed from investigators **Blinding:** double; medication kits issued **Duration:** 6 weeks (preceded by washout phase of 2–9 days; extension for responders) **Setting:** multicentre, two sites, Egypt; in- and outpatient	**Diagnosis:** schizophrenia (DSM-IV) ***N*:** 41 **Age:** mean, ~ 32 years **Sex:** ~ 80% male	1. olanzapine, 5–20 mg/day; *n* = 27 2. chlorpromazine, 200–800 mg/day; *n* = 14	Leaving study early Other adverse events: COSTART list; weight change **Unable to use** Global state: CGI-S (no data) Mental state: BPRS, PANSS (no usable data) Side-effects: EPS – UKU (no data) Hospital status: no data Laboratory tests and physiological measures: no data	
Gureje 1998[186]	**Allocation:** random, computer-generated blocks for each investigator, 1:1, concealed from investigator **Blinding:** double; medication kits issued **Duration:** 30 weeks **Setting:** multicentre, Australia and New Zealand; otherwise not described	**Diagnosis:** schizophrenia, schizophreniform and schizoaffective disorders (DSM-IV) ***N*:** 65 **Age:** not specified **Sex:** not specified	1. olanzapine, 10–20 mg/day; *n* = 32 2. risperidone, 4–8 mg/day; *n* = 33	Leaving study early Global state: CGI-S Mental state: BPRS; PANSS Other adverse events: COSTART list, weight change Quality of life: QLS **Unable to use** QLS: SF-36, no total score	
Tollefson 1997[164]	**Allocation:** random; ratio 2:1; no further details **Blinding:** double; no further details **Duration:** 6 weeks (preceded by screening phase of 2–9 days, maintenance phase of 46/52 for responders) **Setting:** not described	**Diagnosis:** schizophrenia, schizophreniform or schizoaffective disorders (DSM-III-R) **Inclusion criteria:** > 18 BPRS score and/or intolerant of current antipsychotic medication ***N*:** 1996 **Age:** mean, 38.7 years **Sex:** male and female; no further details	1. olanzapine, 5–20 mg/day; *n* = 1336 2. haloperidol, 5–20 mg/day; *n* = 660 Benztropine and benzodiazepine as required	Global state: CGI Mental state: BPRS*, MADRS, PANSS; needing additional benzodiazepines Leaving study early Side-effects: requiring benztropine; AMDP, BAS, SAS) Adverse events: COSTART terms **Unable to use** Hospital status: no data Laboratory tests and physiological measures: no data	* BPRS (scored 0–6) extracted from PANSS; no reference given for validity of procedure * *A priori* efficacy response was 40% improvement in BPRS score and 3 weeks in study

continued

Olanzapine *contd*

Study	Methods	Participants	Interventions	Outcomes	Notes
Tran, 1997[171]	**Allocation:** random; no further details **Blinding:** double; no further details **Duration:** 28 weeks (preceded by 2–9-day washout period) **Investigators:** trained on PANSS **Setting:** in- or outpatient	**Diagnosis:** schizophrenia, schizophreniform or schizoaffective disorders (DSM-IV) ***N*:** 339 **Age:** 16–65 years **Sex:** 65% male **Exclusion:** individuals with treatment-resistant illness	1. olanzapine, 10–20 mg/day; *n* = 172 2. risperidone, 4–12 mg/day; *n* = 167 Benzodiazepines, chloral hydrate, benztropine mesylate, biperiden, as required	Mental state: BPRS*, PANSS, SANS Leaving study early Side-effects: requiring benztropine or biperiden; AIMS, BAS, SAS; prolactin, low neurophil counts Adverse events: AMDP, COSTART list Quality of life **Unable to use** Global state: CGI, change data Hospital status: no data Laboratory tests and physiological measures: no data Economic burden: no data	* BPRS (scored 0–6) extracted from PANSS; no reference given for validity of procedure PANSS response rates reported ≥ 20%, ≥ 30%, ≥ 40%, ≥ 50%

Quetiapine

Study	Methods	Participants	Interventions	Outcomes	Notes
Link 1997 (Europe–Africa 007)[215]	**Allocation:** random; no further details **Blinding:** double; no further details **Duration:** 6 weeks (preceded by 1-day washout period) **Setting:** not described	**Diagnosis:** schizophrenia (DSM-III-R) **Inclusion criteria:** BPRS* ≥ 27; CGI ≥ 4 ***N*:** 201 **Age:** mean, ~ 33 years **Sex:** 129 male, 72 female	1. quetiapine, 407 mg/day (mean); *n* = 101 2. chlorpromazine, 384 mg/day (mean); *n* = 100	Global state: CGI Mental state – general: BPRS; specific: PANSS negative Side-effects: EPS – AIMS, BAS, SAS; specific list Leaving study early	* 0–6 scoring system
Fleischhacker 1995 (multi-country 012)[216]	**Allocation:** random; no further details **Blinding:** double; no further details **Duration:** 6 weeks (preceded by at least 2-day washout period) **Setting:** not described	**Diagnosis:** schizophrenia (DSM-III-R) **Inclusion criteria:** BPRS* ≥ 27; CGI ≥ 4 ***N*:** 608 **Age:** mean, 26 years **Sex:** 409 male, 209 female **History:** mean age, first treatment, 25 years	1. quetiapine, 225 mg b.d.; *n* = 209 2. quetiapine, 150 mg t.d.s.; *n* = 209 3. quetiapine, 50 mg/day; *n* = 200	Death Global state: CGI Mental state – general: BPRS; specific – positive: BPRS positive; specific – negative: SANS Side-effects: EPS – AIMS, SAS; specific list Leaving study early	* 0–6 scoring system
Fleischhacker 1996 (multi-country 014)[217]	**Allocation:** random; no further details **Blinding:** double; no further details **Duration**: 6 weeks (preceded by 2-day washout period) **Setting:** not described	**Diagnosis:** schizophrenia (DSM-III-R) **Inclusion criteria:** PANSS ≥ 60; CGI ≥ 4 ***N*:** 448 **Age:** mean, 37 years **Sex:** 305 male, 143 female	1. quetiapine, 50–800 mg/day; *n* = 221 2. haloperidol, 1–16 mg/day; *n* = 227	Global state: CGI Mental state – general: PANSS Leaving study early Side-effects – EPS: AIMS, SAS	
Purdon 2000 (Canada 2000)[212]	**Allocation:** random; no further details **Blinding:** double; no further details **Duration:** 6 months (2-day washout period) **Setting**: not described	**Diagnosis:** schizophrenia (DSM-IV) **Inclusion criteria:** no details ***N*:** 25 **Age:** mean, 34 years **Sex:** 20 male, 5 female	1. quetiapine, 468 mg/day (modal); *n* = 13 2. haloperidol, 15.5 mg/day (modal); *n* = 12	Global state: CGI Mental state – general: PANSS; specific: PANSS-positive/ negative subscales Side-effects – EPS: AIMS, SAS	

continued

Quetiapine *contd*

Study	Methods	Participants	Interventions	Outcomes	Notes
Kudo 1999 (Japan 1999a)[214]	**Allocation:** random; no further details **Blinding:** double; no further details **Duration:** 8 weeks (no details of washout period) **Setting:** not described	**Diagnosis:** schizophrenia (DSM-IV or ICD10) **Inclusion criteria:** no details ***N*:** 180 **Age:** mean, 45 years **Sex:** 112 male, 68 female	1. quetiapine: 215 mg/day (mean); *n* = 90 2. mosapramine, 103 mg/day (mean); *n* = 90	Mental state – general: BPRS***, PANSS; specific: PANSS-positive/ negative subscales Leaving study early	*** No details of scoring system
Murasaki, 1999 (Japan 1999b)[214]	**Allocation:** random; no further details **Blinding:** double; no further details **Duration:** 8 weeks (no details of washout period) **Setting:** not described	**Diagnosis:** schizophrenia (DSM-IV or ICD10) **Inclusion criteria:** no details ***N*:** 197 **Age:** mean, 45 years **Sex:** 129 male, 68 female	1. quetiapine, 226 mg/day (mean); *n* = 100 2. haloperidol, 6.7 mg/day (mean); *n* = 97	Mental state – general: BPRS***, PANSS; specific: PANSS-positive/ negative subscales Side-effects – EPS: number reporting EPS-related events Leaving study early	*** No details of scoring system
Emsley 1999 (multi-country 1999)[219]	**Allocation:** random; no further details **Blinding:** double; no further details **Duration:** 8 weeks (no details of washout period) **Setting:** not described	**Diagnosis:** schizophrenia (DSM-IV) **Inclusion criteria:** persistent positive symptoms while previously taking antipsychotic drugs; PANSS-positive ≥ 15; CGI ≥ 3 ***N*:** 288 **Age:** mean, 39 years **Sex:** 204 male, 84 female	1. quetiapine, 600 mg/day; *n* = 143 2. haloperidol, 20 mg/day; *n* = 145		
Arvanitis 1996 (North America 013)[220]	**Allocation:** random; no further details **Blinding:** double; no further details **Duration:** 6 weeks (preceded by 7-day washout period) **Setting:** not described	**Diagnosis:** schizophrenia (DSM-III-R) **Inclusion criteria:** BPRS* ≥ 27; CGI ≥ 4 ***N*:** 361 **Age:** mean, 37 years **Sex:** 274 male, 87 female	1. quetiapine, 75 mg/day (fixed); *n* = 53 2. quetiapine, 150 mg/day (fixed); *n* = 48 3. quetiapine, 300 mg/day (fixed); *n* = 52 4. quetiapine, 600 mg/day (fixed); *n* = 51 5. quetiapine, 750 mg/day (fixed); *n* = 54 6. haloperidol, 12 mg/day (fixed); *n* = 52 7. placebo; *n* = 51	Global state: CGI Mental state – general: BPRS; specific: negative – modified SANS Side-effects – EPS: AIMS, modified SAS; specific list Leaving study early	* 0–6 scoring system

continued

Quetiapine *contd*

Study	Methods	Participants	Interventions	Outcomes	Notes
Fabre 1995 (USA 004)[189]	**Allocation:** random; 2:1; no further details **Blinding:** double; no further details **Duration:** 3 weeks (preceded by 2-day washout period) **Setting:** not described	**Diagnosis:** schizophrenia (DSM-III-R) **Inclusion criteria:** BPRS** ≥ 30; CGI ≥ 3 ***N*:** 12 **Age:** mean, ~ 34 years **Sex:** not specified **History:** mean age, first treatment, 22–23 years	1. quetiapine, 250 mg/day (mean); *n* = 8 2. placebo; *n* = 4	Global state: CGI Mental state – general: BPRS; specific: positive symptoms, BPRS positive; specific: negative symptoms, BPRS negative Leaving study early	** 1–7 scoring system
Borison 1996 (USA 006)[221]	**Allocation:** random; no further details **Blinding:** double; no further details **Duration:** 6 weeks (preceded by 2–10-day washout period) **Setting:** not described	**Diagnosis:** schizophrenia (DSM-III-R) **Inclusion criteria:** BPRS** ≥ 45; CGI ≥ 4 ***N*:** 109 **Age:** mean, 36 years **Sex:** 98 male, 11 female **History:** mean age, first treatment, 21 years	1. quetiapine, 307 mg/day (mean); *n* = 54 2. placebo; *n* = 55	Death Global state: CGI Mental state – general: BPRS; specific: negative symptoms, modified SANS Side-effects – EPS: AIMS, modified SAS; specific list Leaving study early	** 1–7 scoring system
Small 1997 (USA–Europe 008)[222]	**Allocation:** random; computer generated **Blinding:** double; no further details **Duration:** 6 weeks (preceded by at least 1-day washout period) **Setting:** not described	**Diagnosis:** schizophrenia (DSM-III-R) **Inclusion criteria:** BPRS* ≥ 27; CGI ≥ 4 ***N*:** 286 **Age:** mean, ~ 37 years **Sex:** 203 male, 83 female	1. quetiapine, 360 mg/day (mean); *n* = 96 2. quetiapine, 209 mg/day (mean); *n* = 94 3. placebo; *n* = 96	Global state: CGI Mental state – general: BPRS; specific: positive symptoms, BPRS positive; negative symptoms, SANS, PANSS-negative Side-effects – EPS: AIMS, BAS, SAS; specific list Leaving study early	* 0–6 scoring system

Risperidone versus typical antipsychotic drugs

Study	Methods	Participants	Interventions	Outcomes	Notes
Blin 1996[251]	**Allocation:** random; no further details **Blinding:** double; medication in identical capsules **Duration:** 4 weeks **Setting:** hospital	**Diagnosis:** schizophrenia (DSM-III-R) ***N*:** 62 **Sex:** 38 male, 24 female **Age:** mean, 34.3 years, range 16–63 years **History:** acute exacerbation and psychotic anxiety; nine ill < 1 year; five ill 1–3 years; 47 ill > 3 years	1. risperidone, 8.6 mg/day (mean), 12 mg/day (maximum); *n* = 21 2. haloperidol, 9.2 mg/day (mean), 12 mg/day (maximum); *n* = 20 3. methotrimeprazine, 125 mg/day (mean), 125 mg/day (maximum); *n* = 21 Individual dose titration in all groups Additional medication allowed: loprazolam (for sedation); biperiden (for EPS side-effects); heptaminal hydrochloride (for hypotension)	Clinical improvement (20% reduction in PANSS score) Global effect: GCI Mental state: BPRS; PANSS; PAS Side-effects: Asberg scale; ESRS Physiological monitoring: ECG; laboratory tests Leaving study early	Methotrimeprazine data not used in this review ITT analysis undertaken
Borison 1991[252]	**Allocation:** random; no further details **Blinding:** double; medication identical **Duration:** 6 weeks (preceded by 1-week washout period) **Setting:** hospital	**Diagnosis:** schizophrenia (DSM-III-R) ***N*:** 160 **Sex:** 6 female, 154 male **Age:** mean, 39.5 years; range, 21–63 years **History:** mean duration of illness, 15.1 years	1. risperidone, individual dose titration, 1 mg increments (2 weeks), fixed thereafter; 7.8 mg/day (mean), 10 mg/day (maximum); *n* = 53 2. haloperidol, individual dose titration, 2 mg increments (2 weeks), fixed thereafter; 15 mg/day (mean), 20 mg/day (maximum); *n* = 53 3. placebo, individual dose titration (2 weeks), fixed thereafter; 10 tablets maximum Additional medication allowed: lorazepam or sodium amytal (for agitation); chloral hydrate (for sedation); benztropine or trihexyphenidyl (for EPS)	Global effect: CGI Mental state: BPRS; SANS Side-effects: ESRS; AIMS; other adverse events; use of anti-parkinsonian medication Physiological monitoring: ECG; vital signs; laboratory tests Leaving study early	ITT analysis performed for side-effect outcomes but not mental state No SDs for continuous data; these data not used

continued

Risperidone versus typical antipsychotic drugs *contd*

Study	Methods	Participants	Interventions	Outcomes	Notes
Bouchard 1998[253]	**Allocation:** random; no further details **Blinding:** none; open label **Duration:** 2 years **Setting:** not described	**Diagnosis:** schizophrenia (PANSS score 60–120) ***N*:** 184 **History:** 81% outpatients	1. risperidone, 5.5 mg/day (mean); *n* = 93 2. classical neuroleptic drugs: 1 g/day (mean) chlorpromazine equivalent; *n* = 91	Clinical improvement: 20% reduction in PANSS Leaving study early **Unable to use** Global effect: CGI, too few data Subjective tolerance: ESRS part 1, two few data Movement disorders: ESRS part 2, too few data	Ongoing study; 12-month data only
Ceskova 1993[254]	**Allocation:** random; no further details **Blinding:** double; administered as monotherapy in oral solution **Duration:** 8 weeks **Setting:** hospital	**Diagnosis:** schizophrenia/schizoaffective disorder (ICD9) ***N*:** 62 **Sex:** 17 female, 45 male **Age:** mean 35.8 years **Duration of illness:** mean, 10.4 years	1. risperidone, individual dose titration, 9.5 mg/day (mean), 2–20 mg (range); *n* = 31 2. haloperidol, individual dose titration, 9.9 mg/day (mean), 2–20 mg (range); *n* = 31 Additional medication allowed: antiparkinsonian (EPS); minor tranquillisers or promethazine (insomnia, akathisia); dihydroergotamine (dry mouth or vertigo)	Global effect: Serejskij's modified scale Mental state: BPRS Side-effects: DVP scale; use of antiparkinsonian medication Leaving study early	ITT analysis for side-effects, unclear whether also done for efficacy analysis No SDs for continuous data; these data not used
Chouinard 1993a[255]	**Allocation:** random; no further details **Blinding:** double; identical tablets **Duration:** 8 weeks (preceded by 1-week washout period **Setting:** multicentre	**Diagnosis:** schizophrenia (DSM-III-R) ***N*:** 135 **Sex:** 96 male, 39 female **Age:** mean, 37 years; range, 19–67 years **History:** duration of current hospitalisation – mean 2 years, range 0–23 years; number of hospitalisations: mean, 7; range, 0–50	1. risperidone, 2 mg/day; *n* = 24 2. risperidone, 6 mg/day; *n* = 22 3. risperidone, 10 mg/day; *n* = 22 4. risperidone, 16 mg/day; *n* = 24 5. haloperidol, 20 mg/day; *n* = 21 6. placebo; n = 22 All fixed doses Additional medication allowed: chloral hydrate or benzodiazepine (sedation); procyclidine or biperidin (EPS)	Clinical improvement: 20% reduction of total PANSS score Global effect: CGI Mental state: BPRS – PANSS-derived; PANSS Side-effects: ESRS; UKU; use of antiparkinsonian medication; use of sedative medication Physiological monitoring: ECG; vital signs; laboratory tests Leaving study early	ITT analysis undertaken

continued

Risperidone versus typical antipsychotic drugs *contd*

Study	Methods	Participants	Interventions	Outcomes	Notes
Claus 1991[256]	**Allocation:** random; no further details **Blinding:** double; matched oral solutions; investigators asked to guess double-blind code **Duration:** 12 weeks (preceded by placebo washout week) **Setting:** multicentre; hospital	**Diagnosis:** schizophrenia with chronic course (DSM-III-R) ***N*:** 44 **Sex:** male 28, female 14 **Age:** mean, 38.2 years, range, 20–66 years **History:** duration of hospitalisation, < 10 years; age at onset, mean, 24.1 years, range 14–53 years	1. risperidone, 12 mg/day (mean); *n* = 21 2. haloperidol, 10.3 mg/day (mean); *n* = 21 Individual dose titration for first 6 weeks, fixed dose thereafter Additional medication allowed: diazepam (sedation); dexetimide (EPS); intramuscular etybezatropine (acute dystonia)	Clinical improvement: 20% reduction of total PANSS Global effect: CGI Mental state: PANSS; SADS-C† Behaviour: NOSIE-30 Individual target symptom (VAS) Sleep quality (VAS) Comparison with previous treatment (investigator and recipient) Side-effects: ESRS; symptom checklist Physiological monitoring: ECG; vital signs; weight; laboratory tests Leaving study early	ITT analysis for side-effects: two patients excluded from efficacy analysis No SDs given for continuous data; these data not used † Schedule for Affective Disorders and Schizophrenia-cognition
Emsley 1995[257]	**Allocation:** random; no further details **Blinding:** double; no further details **Duration:** 6 weeks **Setting:** multicentre, multinational	**Diagnosis:** first-episode schizophrenia/schizophreniform disorder (DSM-III-R) ***N*:** 183 **Age:** range, 15–50 years **Sex:** 122 male, 61 female **History:** median age at onset, 23 years (risperidone); 24 years (haloperidol)	1. risperidone, 6.1 mg/day (mean), range 2–16 mg/day; *n* = 99 2. haloperidol, 5.6 mg/day (mean), range 1–16 mg/day; *n* = 84 Flexible dose regime for both groups	Clinical improvement: > 50% in total PANSS Global effect: CGI Mental state: BPRS – PANSS derived; PANSS Side-effects: ESRS; specific reports Physiological monitoring: ECG; laboratory tests; body weight; vital signs Leaving study early	ITT analysis appears to have been undertaken No SDs for continuous data; these data not used
Hoyberg 1993[258]	**Allocation:** random; no further details **Blinding:** double; identical appearance **Duration:** 8 weeks **Setting:** multicentre, multinational	**Diagnosis:** schizophrenia (DSM-III-R) ***N*:** 107 **Sex:** 77 male, 30 female **Age:** mean, 36 years; range, 20–67 years **History:** chronic	1. risperidone, 5–15 mg/day, 8.5 mg/day (mean); *n* = 55 2. perphenazine, 16–48 mg/day, 28 mg/day (mean); *n* = 52 Individual dose titration for 4 weeks. fixed thereafter	Clinical improvement: > 20% reduction in total PANSS or BPRS score; CGI improvement Severity of illness: CGI severity Mental state: PANSS; BPRS – PANSS-derived Side-effects: ESRS; UKU; use of antiparkinsonian medication Physiological monitoring: laboratory tests Leaving study early	ITT analysis for side-effects No SDs for continuous data; these data not used

continued

Risperidone versus typical antipsychotic drugs *contd*

Study	Methods	Participants	Interventions	Outcomes	Notes
Huttunen 1995[259]	**Allocation:** random; no further details **Blinding:** double; no further details **Duration:** 6 weeks **Setting:** multicentre	**Diagnosis:** schizophrenia (DSM-III-R) ***N*:** 98 **Sex:** 47 male, 51 female **Age:** mean, 36 years; range, 11–43 **History:** chronic but acutely ill; mean age at onset, 23.5 years, range 11–43 years	1. risperidone, 8 mg/day (mean), 2–20 mg/day (range); *n* = 48 2. zuclopenthixol, 38 mg/day (mean), 10–100 mg/day (range); *n* = 50 Individual dose titration in both groups	Global effect: CGI Mental state: PANSS; BPRS – PANSS-derived Comparison with previous medication: categorical scale Side-effects: ESRS; UKU; use of anti-parkinsonism medication; investigator's and recipient's impression of interference to daily life by adverse events Physiological monitoring: vital signs; ECG; laboratory tests Leaving study early	ITT analysis No SDs for continuous data; these data not used
Mahmoud 1998[260]	**Allocation:** random; stratified by number of prior hospitalisations **Blinding:** none **Duration:** 1 year **Pragmatic:** minimal protocol interference **Setting:** not described	**Diagnosis:** schizophrenia **History:** diagnosed before age 35 years; ill > 2 years; > one hospitalisation in last 2 years, none > 60 days; no clozapine use ***N*:** 684 **Age:** mean, about 39 years (SD, 9) **Sex:** no details	1. risperidone, *n* = 349 2. conventional treatment strategy, *n* = 326	Clinical improvement: 20%, 40%, 60% reduction in PANSS Side-effects: SAS; BAS; AIMS Leaving study early **Unable to use** Quality of life: SF-36, Quality of Life Index – too few data	ITT analysis undertaken No SDs for continuous data
Marder 1994[116]	**Allocation:** random; blocks of 12 **Blinding:** double, no further details **Duration:** 8 weeks (preceded by 1-week washout period) **Setting:** hospital	**Diagnosis:** schizophrenia (DSM-III-R); PANSS score 60–120 ***N*:** 388 **Age:** mean, 37.4 years; range, 18–65 years **Sex:** 48 female, 340 male **History:** duration of illness, 15.7 years (mean); duration of current hospitalisation, 29 weeks (mean); number of previous hospitalisations, 9.1 (mean), 0–61 range	1. risperidone, 2 mg/day; *n* = 63 2. risperidone, 6 mg/day; *n* = 64 3. risperidone, 10 mg/day; *n* = 65 4. risperidone, 16 mg/day; *n* = 64 5. haloperidol, 20 mg/day; *n* = 66 6. placebo, *n* = 66 Dose titrated; week 1 to fixed maintenance dose Additional medication allowed: chloral hydrate/ lorazepam (for sedation); medication to control EPS	Clinical improvement: 20% reduction in total PANSS; 20% reduction in BPRS; 20% reduction in BPRS and either post-treatment CGI ≤ 3 or BPRS total score ≤ 35 Time to clinical improvement Global effect: CGI Mental state: BPRS; PANSS Side-effects: ESRS; modified UKU; spontaneous reports of adverse events Physiological monitoring: ECG; laboratory tests Leaving study early	ITT analysis

continued

Risperidone versus typical antipsychotic drugs *contd*

Study	Methods	Participants	Interventions	Outcomes	Notes
Mesotten 1991[261]	**Allocation:** random; no further details **Blinding:** double, identical medication **Duration:** 8 weeks (preceded by 1-week washout period) **Setting:** multicentre	**Diagnosis (*n*):** schizophrenia (46); schizophreniform disorder (2); schizo-affective disorder (6); paranoid disorder (4); other psychotic disorders (2); DSM-III criteria ***N*:** 60 **Age:** mean, 39.5 years; range, 20–65 years **Sex:** 37 male, 23 female **History:** time since first hospitalisation, 5.7 years (mean), 0–38 years (range)	1. risperidone, 9.1 mg/day (mean); *n* = 28 2. haloperidol, 9.4 mg/day (mean); *n* = 32 Individual dose titration weeks 1–4; fixed dose thereafter	Global effect: CGI, subjective comparison with previous neuro-leptic drug – investi-gator & recipient Mental state: BPRS Behaviour: NOSIE Side-effects: ESRS; use of medication for EPS; specific adverse experiences Physiological monitoring: ECG; vital signs; laboratory tests Leaving study early	ITT analysis appears to have been undertaken for side-effects No SDs for con-tinuous data; these data not used
Min 1993[262]	**Allocation:** random; sealed envelopes, no details of how code generated **Blinding:** double; identical medication **Duration:** 8 weeks (preceded by 1-week washout period) **Setting:** not described	**Diagnosis:** schizophrenia (DSM-III-R), PANSS score 60–120 ***N*:** 35 **Age:** mean, 34.1 years; range, 18–59 years **Sex:** 17 male, 18 female **History:** number of previous hospitalisations, 3.1 (mean), 15–41 (range); duration of current hospitalisation, 154 days (mean), 1–554 days (range); age at onset, 23.5 years (mean), 14–40 years (range)	1. risperidone, 5 mg/day, *n* = 8; 10 mg/day, *n* = 8 2. haloperidol, 5 mg/day, *n* = 4; 10 mg/day, *n* = 15 Dose for weeks 1–2, 5 mg/day; if insufficient response, increased to 10 mg/day Additional medi-cation allowed: lorazepam/ oxazepam (sedation); benztropine mesylate (EPS)	Clinical improvement: 20% reduction in PANSS score Global effect: GCI Mental state: BPRS – PANSS derived; PANSS Side-effects: ESRS; modified UKU Physiological monitor-ing: ECG; laboratory tests; vital signs Leaving study early Satisfaction with treatment: 7-point scale	ITT analysis No SDs for con-tinuous data; these data not used
Peuskens 1995[263]	**Allocation:** random; 'random permuted block procedure'; randomisation list transferred to sealed envelopes **Blinding:** double; no further details **Duration:** 8 weeks (preceded by 1-week washout period) **Setting:** multicentre; multinational	**Diagnosis:** schizophrenia (DSM-III-R); PANSS score 60–120 ***N*:** 1362 **Age:** mean, 38.1 years **Sex:** 467 female, 894 male **History:** mean duration of illness, 16.8 years; number of previous hospitalisations, median 3, range 1–7; duration of current hospitalisation, median 4 years	1. risperidone, 1 mg/day; *n* = 229 2. risperidone, 4 mg/day; *n* = 227 3. risperidone, 8 mg/day; *n* = 230 4. risperidone, 12 mg/day; *n* = 226 5. risperidone, 16 mg/day; *n* = 224 6. haloperidol, 10 mg/day; *n* = 226 Fixed doses after week 1	Clinical improvement: 20% reduction PANSS Global effect: CGI Mental state: BPRS – PANSS-derived; PANSS Side-effects: CGI; ESRS; modified UKU; use of antiparkin-sonian medication Physiological monitoring: ECG; laboratory tests Satisfaction with treat-ment: categorical scale Leaving study early	ITT analysis not undertaken

continued

Risperidone versus atypical antipsychotic drugs

Study	Methods	Participants	Interventions	Outcomes	Notes
Fleurot 1997[62]	**Allocation:** random; no further details **Blinding:** double; no further details **Duration:** 8 weeks, preceded by 3–6-day washout period **Setting:** not stated	**Diagnosis:** schizophrenia (DSM-IV) **History:** currently acutely ill, duration 9.0 years ***N*:** 228 **Sex:** not specified **Age:** mean, 36.5 years	1. amisulpride, dose not specified; *n* = 115 2. risperidone, dose not specified; *n* = 113	Leaving study early: all causes; lack of efficacy; adverse events Mental state: BPRS total change scores; PANSS positive change scores **Unable to use** Global state: response (CGI of 2, very much or much improved – no usable data) Weight change: no usable data	
Bondolfi 1998[110]	**Allocation:** 'randomly assigned'; blocks of 4 **Blinding:** double; 'double-dummy' protocol **Duration:** 8 weeks, preceded by neuroleptic drug-free period **Setting:** hospital, weeks 1–3; multicentre	**Diagnosis:** schizophrenia (DSM-III-R) ***N*:** 86 **Sex:** 25 female, 61 male **Age:** mean, 37.3 years (SD, 12.6) **History:** moderate–severe illness; duration, about 14 years; age of onset, about 26 years (SD, 8.8); treatment-resistant* illness	1. risperidone, individual dose titration: week 1, fixed dose, 6 mg/day; week 2 and thereafter, adjusted according to response; mean 6.4 mg/day, range 3–12 mg/day 2. clozapine, individual dose titration: week 1, fixed dose, 300 mg/day; week 2 and thereafter, adjusted according to response; mean 291 mg/day, range 150–400 mg/day Lorazepam and oxazepam (sleep induction), biperiden and procyclidine (EPS), clothiapine (emergency treatment) as required	Leaving study early Global state: CGI Mental state: PANSS EPS symptoms: ESRS Other adverse events: UKU	* Treatment-resistant: failed to respond to or intolerant of > 2 different classes of antipsychotic drugs in appropriate doses for > 4 weeks

continued

Risperidone versus atypical antipsychotic drugs *contd*

Study	Methods	Participants	Interventions	Outcomes	Notes
Anand 1998[111]	**Allocation:** 'random' **Blinding:** double; no further details **Duration:** 12 weeks **Setting:** multicentre; no other details	**Diagnosis:** schizophrenia (DSM-IV) ***N*:** 273 **Sex:** 78 female, 195 male **Age:** mean, 38.8 years **History:** treatment-resistant* illness	1. risperidone, individual dose titration: week 1–4, < 6 mg, then kept within range 2–15 mg; mean, 8.3 mg/day; *n* = 135 2. clozapine, individual dose titration: week 1–4, < 600 mg, then kept within range 200–900 mg; mean 597.5 mg/day; *n* = 138	Leaving study early; relapse Physiological monitoring: laboratory tests Mental state: PANSS; PAS; BPRS; CGI Adverse effects Raw scores of rating scales not available Insufficient description of drop-outs; 101 patients in risperidone group and 100 in clozapine group completed study	* Treatment-resistant: severe, chronic disease and poor response to previous neuroleptic drugs: no period of good functioning for ≥ 24 months despite use of two antipsychotic drugs, current episode without significant improvement for ≥ 6 months despite use of antipsychotic equivalent to haloperidol, 20 mg, for ≥ 6 weeks, total BPRS ≥ 45, CGI ≥ 4
Breier 1999[112]	**Allocation:** 'randomly assigned' **Blinding:** double; no further details **Duration:** 6 weeks, preceded by fluphenazine treatment for ≥ 2 weeks; then 66% of patients underwent drug-free period, mean 18 days **Setting:** not described	**Diagnosis:** schizophrenia (DSM-IV) ***N*:** 29 **Sex:** 10 female, 19 male **Age:** mean, 35.0 years, range, 18–55 years **History:** duration of illness, ~ 12.5 years; chronic schizophrenia; partial response to neuroleptic drugs*	1. risperidone, gradual dose titration < 6 mg for 2 weeks; adjustments over next 2 weeks within fixed limits, 2–9 mg/day; thereafter fixed dose, mean 5.9 mg/day; *n* = 15 2. clozapine, gradual dose titration < 400 mg/day for 2 weeks; adjustments over next 2 weeks within fixed limits, 200–600 mg/day; thereafter fixed dose, mean 403.6 mg/day; *n* = 14 Benztropine mesylate (EPS) as required	Leaving study early Physiological monitoring: laboratory tests Mental state: BPRS; SANS; Hamilton Rating Scale (depression) EPS side-effects: modified SAS No drop-outs after randomisation phase	* Partial response to neuroleptic drugs: (i) history of residual positive and/or negative symptoms after < 6-week trial of therapeutic dose of neuroleptic agent; (ii) < minimum level of positive (< 4/8 positive BPRS items) and/or negative (SANS score < 20) symptoms at time of evaluation for study; (iii) < minimum level positive and negative symptoms after prospective trial of < 2 weeks of fluphenazine, 20 mg/day (range 10–30 mg/day)

continued

Risperidone versus atypical antipsychotic drugs *contd*

Study	Methods	Participants	Interventions	Outcomes	Notes
Wahlbeck 2000[113]	**Allocation:** random; computer-generated **Blinding:** single; outcomes assessed blind **Duration:** 10 weeks, preceded by 1–3-day washout period **Setting:** hospitalised at start of study but could be discharged during trial	**Diagnosis:** schizophrenia (DSM-IV) ***N*:** 21 **Age:** range, 35.7–36.8 years **Sex:** 9 female, 10 male **History:** treatment-resistant* illness (persistent psychotic symptoms for 6 months or more, with drugs tried from < two chemical classes; dose equivalent to chlorpromazine, 1000 mg, plus 6-week trial of haloperidol for haloperidol-naive participants	1. clozapine, dose increased from 25 to 400 mg/day by day 14; from day 21, flexible dose < 600 mg/day 2. risperidone, dose increased from 2 to 6 mg/day by day 3; after day 21, flexible dose < 10 mg/day Lorazepam and biperiden as required	Leaving study early Mental state: response, 20% decrease in PANSS Discharge from hospital Global state: CGI-S endpoint score; GAF endpoint score Mental state: PANSS total endpoint score; PANSS positive endpoint score; PANSS negative endpoint score Description of drop-outs available – eight patients in risperidone and five in clozapine group completed study	* Treatment resistant: persistent psychotic symptoms for ≥ 6 months while on medication of at least two different classes of antipsychotic drugs, ≥ 1000 mg/day, chlorpromazine, for ≥ 6 weeks each; in addition, non-tolerance to haloperidol or non-response to halo-peridol, > 40 mg/day
Tran 1997[171]	**Allocation:** random; no further details **Blinding:** double; no further details **Duration:** 28 weeks, preceded by 2–9-day washout period **Investigators:** trained on PANSS **Setting:** in- or outpatient	**Diagnosis:** schizophrenia, schizophreniform disorder or schizo-affective disorder (DSM-IV) ***N*:** 339 **Age:** 16–65 years **Sex:** 65% male **Exclusion:** those with treatment-resistant illness	1. olanzapine, 10–20 mg/day; *n* = 172 2. risperidone, 4–12 mg/day; *n* = 167 Benzodiazepines, chloral hydrate, benztropine mesylate, and biperiden, as required	Mental state: BPRS*; PANSS; SANS Leaving study early Side-effects: requiring benztropine or biperiden; AIMS, BAS, SAS; prolactin, low neurophil counts Adverse events: AMDP; COSTART list; quality of life **Unable to use** Global state: CGI, change data Hospital status: no data Laboratory tests and physiological measures: no data Economic burden: no data	

continued

Risperidone versus atypical antipsychotic drugs *contd*

Study	Methods	Participants	Interventions	Outcomes	Notes
Jones 1998[193]	**Allocation:** random; computer-generated, blocks by investigator, concealed from investigator **Blinding:** double **Duration:** 54 weeks, preceded by 1-month stabilisation phase followed by 1-week washout and screening period **Setting:** outpatients, multicentre, Canada	**Diagnosis:** schizophrenia ***N*:** 42 **History:** 'early phase' (first 5 years of illness) excluded if PANSS > 90	1. olanzapine, 5–20 mg/day; *n* = 21 2. risperidone, 4–10 mg/day; *n* = 21 3. haloperidol, 5–20 mg/day; *n* = 23	Leaving study early Mental state: PANSS Side-effects: EPS – ESRS Other adverse events: COSTART list; weight change **Unable to use** Cost: no data Cognitive function: GCIS, neuro-psychological test battery (no usable data)	
Gureje 1998[186]	**Allocation:** random; computer-generated; blocks for each investigator, 1:1; concealed from investigator **Blinding:** double; medication kits issued **Duration:** 30 weeks **Setting:** not described; multicentre; Australia and New Zealand	**Diagnosis:** schizophrenia, schizophreniform and schizoaffective disorders (DSM-IV) ***N*:** 65 **Age:** not specified **Sex:** not specified	1. olanzapine, 10–20 mg/day; *n* = 32 2. risperidone, 4–8 mg/day; *n* = 33 Leaving study early Global state: CGI-S Mental state: BPRS; PANSS Other adverse events: COSTART list, weight change Quality of life: QLS **Unable to use** Quality of life – SF-36, no total score		

Sertindole

Study	Methods	Participants	Interventions	Outcomes	Notes
Daniel 1998[276] Study M93-132	**Allocation:** random; no further details **Blinding:** double; no further details **Duration:** 1 year, including 5-week, double-blind, transition period, preceded by 1–14 day screening period **Setting:** multicentre; 34 sites; outpatient **Power calculation:** undertaken and reported (designed to detect difference between 5% and 15% failure rate; power of 83%; sample size, 150 per group)	**Diagnosis:** schizophrenia (DSM-III-R, DSM-IV)* **Included:** moderate illness (CGI part 1 score of ≤ 4); stable on anti-psychotic drugs (except clozapine) for > 3 months with no other psycho-tropic drugs in preceding month; history of 2+ hospitalisations (≥ 72 hours) in last 5 years or one hospital-isation in last 2 years or two psychotic episodes in last 5 years associated with increase in dose of antipsychotic or new drug **Excluded:** violent or suicidal behaviour; prior psychosurgery; clinically significant medical problem; abnormal neurological examination; score of 4 on any AIMS, substance abuse ***N*:** 282 **Sex:** 153 male, 50 female** **Age:** range, 18–66 years**	1. sertindole, 24 mg/day; *n* = 141 2. haloperidol, 10 mg/day; *n* = 141	Leaving study early: non-complaince, adverse events, prolonged Q-T intervals, leucopenia Adverse effects: movement disorders – documented EPS, others Hospital utilisation: admission due to exacerbation **Unable to use** Global state: CGI – no results reported Mental state: BPRS, no data; PANSS total, no SD; SANS, no SD Laboratory tests and physiological measures: ECG, heart rate, weight – no SD Leaving study early: overall treatment failure, not reported Adverse effects: use of antiparkinsonism drugs, decreased ejaculatory volume, vaginitis – no usable data (sex of partici-pants by group unspecified) Hospital utilisation: number of psychiatric hospitalisations, no SD; number of days spent in hospital, no SD	ITT analysis used last observation carried forward Authors contacted for further information * All but one patient ** Subset in ITT dataset (those with measurement at end of week 5)

continued

Sertindole *contd*

Study	Methods	Participants	Interventions	Outcomes	Notes
Van Kammen 1996[277] Study M92-762	**Allocation:** random; no futher details **Blinding:** double; no further details **Duration:** 40 days (12-day titration period followed by 28-day active maintenance period) **Setting:** multicentre; 16 sites; inpatient	**Diagnosis:** schizophrenia (DSM-III-R) **Included:** 8 or more on 2/4 items on BPRS; < 2 on SAS items and < 3 for AIMS items; history of previous antipsychotic response **Excluded:** treatment with depot within standard treatment cycle for long-acting drugs; substance abuse; violent or suicidal behaviour ***N*:** 205 **Age:** range, 20–66 years **Sex:** ~ 95% male	1. sertindole, 8 mg/day; *n* = 52 2. sertindole, 12 mg/day; *n* = 51 3. sertindole, 20 mg/day; *n* = 54 4. placebo; *n* = 48	Global state: CGI (1–7 version) Part II, global improvement Mental state: PANSS total; BPRS Adverse effects: requiring benztropine mesylate; presence of EPS-related events; number of EPS symptoms; COSTART list Leaving study early: due to ineffectiveness of treatment; due to adverse events EPS side-effects: BAS; SAS; AIMS **Unable to use** Mental state: PANSS positive and negative subscales; PANSS general psychopathology – no SD Laboratory tests and physiological measures: ECG, no mean and SD; cholesterol values, prolactin levels, heart rate – no usable data; weight gain, no SD Adverse events: abnormal ejaculation, no usable data; sex of participants by group unspecified	ITT analysis used last observation carried forward All randomised patients included in safety analysis; two datasets defined for efficacy; ITT dataset (*n* = 198) included those with at least one BPRS rating scale evaluation after day 1; evaluable dataset (*n* = 153) included those who had received study drug for ≥ 13 days and had at least one BPRS evaluation at day 13 Authors contacted for further information

continued

Ziprasidone

Study	Methods	Participants	Interventions	Outcomes	Notes
Arato 1997[289] Study 303	**Allocation:** random; computer-generated pseudo-random code; blinded code envelopes; investigators, patients and study staff blind to treatment allocation **Blinding:** double; no further details **Duration:** 1 year **Setting:** inpatient; 27 centres	**Diagnosis:** schizophrenia (DSM-III-R) ***N*:** 294 **Age:** mean, ~ 50 years **Sex:** 214 male, 80 female **History:** illness duration, mean, about 70 months; seriously impaired social and occupational functioning **Excluded:** acute exacerbation; severely ill (CGI > 5); PANSS > 4 for hostility or uncooperativeness; treatment-resistant illness	1. ziprasidone, 40 mg/day; *n* = 76 2. ziprasidone, 80 mg/day; *n* = 72 3. ziprasidone, 160 mg/day; *n* = 71 4. placebo, *n* =75	Global impression: CGI-S; GAF Mental state: impending relapse; PANSS total, PANSS negative, BPRS total, BPRS core Side-effects: listed; SAS; BAS; AIMS Leaving study early Body weight **Unable to use** Side-effects: use of additional medication, no data Laboratory results: no data	
Brook 1998[288] Study 306	**Allocation:** random; no further details **Blinding:** single; outcomes rated blind but impossible to blind people giving treatment, as intramuscular ziprasidone has noticeably different viscosity from intramuscular haloperidol **Duration:** 1 week, 3-day intramuscularly phase, 4-day oral phase **Setting:** inpatient; international multicentre	**Diagnosis (*n*):** non-organic acute psychosis schizophrenia (92); schizoaffective (8); delusional, bipolar, psychotic disorders (DSM-III-R) ***N*:** 132 **Age:** range, 19–66 years **Sex:** 123 male, 9 female **History:** currently acute **Excluded:** epilepsy; febrile convulsions; mental retardation; organic mental syndromes; allergy to neuroleptic drugs; substance abuse; laboratory test abnormality	1. ziprasidone, 10 mg intramuscularly then 5–20 mg every 4–6 h (for 3 days), mean ~12 mg/day; then 80–200 mg/day orally (4 days maximum), mean ~ 91 mg/day; *n* = 90 2. haloperidol, 2.5–10 mg intramuscularly then 2.5–10 mg every 4–6 h (for 3 days), mean ~ 5 mg/day; then 10–80 mg/day orally (4 days maximum), mean ~ 14 mg/day; *n* = 42 Anticholinergic drugs and benzodiazepines as required	Mental state: BPRS total Leaving study early Side-effects **Unable to use** Global state: CGI-I; CGI-S; no SD Behaviour: NOSIE, no data Side-effects: AIMS, no data; SAS, BAS, no SD	Publication pending

continued

Ziprasidone *contd*

Study	Methods	Participants	Interventions	Outcomes	Notes
Daniel 1999[290] Study 114	**Allocation:** random; computer-generated pseudo-random code; blinded code envelopes used; investigators, patients and study staff blind to treatment allocation **Blinding:** double; no further details **Duration:** 6 weeks, following 3–7-day washout phase **Setting:** multicentre, hospitalised for first 2 weeks, unclear thereafter	**Diagnosis:** schizophrenia; schizoaffective disorder (DSM-III-R) ***N*:** 302 **Age:** range, 18–67 years **Sex:** 215 male, 87 female **History:** acute exacerbation; PANSS total > 59, > 4 on > 1 PANSS core item; CGI > 2 in previous 24 hours **Excluded:** treatment-resistant illness; substance abuse; long-term hospitalisation; suicidal/homicidal tendencies; depot medication in previous 4 weeks	1. ziprasidone, 80 mg/day; *n* = 106 2. ziprasidone, 80 mg/day (2 days), then 160 mg/day; *n* = 104 3. placebo; *n* = 92 Lorazepam, benztropine and B-adrenoceptor antagonists (akathisia) as required	Global impression: CGI-I; CGI-S Mental state: PANSS negative; PANSS total; BPRS total; BPRS core Leaving study early Laboratory test abnormalities Side-effects: COSTART; SAS; BAS; AIMS **Unable to use** Mental state: MADRS, skewed data	
Goff 1998[291] Study 101	**Allocation:** random; computer-generated, pseudo-random code; blinded code envelopes used; investigators, patients and study staff blind to treatment allocation **Blinding:** double; no further details **Duration:** 4 weeks, preceded by 4–7-day washout period **Setting:** Six centres in Boston, USA; two Veterans, three state psychiatric hospitals and one community mental health centre; Hospitalised for first 14 days, unclear thereafter **Power calculation:** undertaken, to demonstrate 25% difference between groups on BPRS, with 20 patients per group at 80%	**Diagnosis (*n*):** schizophrenia (63); schizoaffective disorder (27); DSM-III-R ***N*:** 90 **Age:** range, 21–61 years; mean ~ 40 years **Sex:** 84 male, 6 female **History:** acute exacerbation in last 2 weeks or 3 months' current hospitalisation; BPRS total > 24; BPRS core > 3 on 1+ items **Excluded:** treatment-resistant illness; co-morbid axis I psychiatric disorders; medical or neurologic disorders; depot medication in last 2 months; recent 'illicit' substance use	1. ziprasidone, 4 mg/day; *n* = 19 2. ziprasidone, 10 mg/day; *n* = 17 3. ziprasidone, 40 mg/day; *n* = 17 4. ziprasidone, 160 mg/day; *n* = 20 5. haloperidol, 15 mg/day; *n* = 17	Leaving study early **Unable to use** Global impression: CGI-S, no SD; CGI-I, no data; response, > 50% attrition Mental state: BPRS total, BPRS core, no SD; response, > 50% attrition; SANS, no data Side-effects: SAS, BAS, AIMS, no SD; any adverse event, use of additional medication, > 50% attrition Laboratory results: serum prolactin, > 50% attrition All outcomes except 'leaving study early' excluded – attrition 51% (46/90)	ITT analysis – last observation carried forward, or observed case analysis

continued

Ziprasidone *contd*

Study	Methods	Participants	Interventions	Outcomes	Notes
Hirsch 1999[292] Study 304	**Allocation:** random; using computer-generated pseudo-random code; blinded code envelopes used; investigators, patients and study staff blind to treatment allocation **Blinding:** double; no further details **Duration:** 28 weeks **Setting:** multicentre; stable outpatients	**Diagnosis:** schizophrenia (DSM-III-R) ***N*:** 301 **Age:** range, 18–64 years **Sex:** 197 male, 104 female **History:** without acute exacerbation; > 9 PANSS negative subscale; > 30 on GAF, stable outpatients **Excluded:** hospitalised in last 12 weeks; > 4 PANSS hostility or uncooperativeness; > 5 CGI-I; ECG or laboratory abnormality; substance abuse	1. ziprasidone, titrated, 80–160 mg/day; flexible, mode, 80 mg/day; *n* = 148 2. haloperidol, titrated, 5–15 mg/day; flexible, mode, 5 mg/day; *n* = 153	Global impression: CGI-S Mental state: response – PANSS negative subscale score; PANSS total; BPRS core; MADRS Leaving study early Side-effects: COSTART; SAS; BAS; AIMS	Poster only Attrition > 25% (data derived from efficacy tables)
Keck 1998[293] Study 106	**Allocation:** random; computer-generated, pseudo-random code; blinded code envelopes used; investigators, patients and study staff blind to treatment allocation **Blinding:** double; no further details **Duration:** 4 weeks, preceded by 4–7-day washout period **Setting:** multicentre, unclear whether hospitalised throughout	**Diagnosis:** schizophrenia, schizoaffective disorder (DSM-III-R) ***N*:** 139 **Age:** range, 19–76 years **Sex:** 110 male, 29 female **History:** acute exacerbation; duration > 1 year (mean ~ 16 years); BPRS total > 37; BPRS core > 3 on > two items **Excluded:** treatment-resistant illness; in residential care; substance abuse in last 6 months; residual schizophrenia; mental retardation; organic mental syndrome; brief reactive psychosis; depot medication in last 2 months; abnormal ECG, laboratory tests; abnormal weight	1. ziprasidone, 40 mg/day; *n* = 44 2. ziprasidone, 120 mg/day; *n* = 47 3. placebo; *n* = 48	Global impression: CGI-S, response Mental state: BPRS total, BPRS core item, SANS, response Leaving study early Side-effects: COSTART; SAS; BAS; AIMS Laboratory results **Unable to use** Mental state: BPRS depression cluster, BPRS anergia factor – skewed data Side-effects: cardiac data, no SD	ITT analysis, last observation carried forward, included all patients with baseline + 1 assessment; seven participants did not meet this criterion

continued

Ziprasidone *contd*

Study	Methods	Participants	Interventions	Outcomes	Notes
Swift 1998[294] Study 121	**Allocation:** random; no further details **Blinding:** single; outcomes rated blind but impossible to blind people giving treatment, as intramuscular ziprasidone has noticeably different viscosity from intramuscular haloperidol **Duration:** 1 week; 3 days intramuscular, 4 days oral medication **Setting:** inpatient; multicentre	**Diagnosis (*n*):** acutely psychotic – schizophrenia (207), schizophreniform (1), schizoaffective disorder (63), delusional disorder (2), bipolar with psychotic features (24), psychotic other (9); DSM-III-R ***N*:** 306 **Age:** range, 19–72 years **Sex:** 271 male, 35 female **History:** inpatients **Excluded:** substance abuse; received ziprasidone or clozapine in last 12 weeks; over- or underweight	1. ziprasidone, 80 mg/day intramuscularly (3 days), then 40–200 mg/day oral flexible (4 days maximum); *n* = 69 2. ziprasidone, 160 mg/day intramuscularly (3 days), then 40–200 mg/day oral flexible (4 days maximum); *n* = 71 3. ziprasidone, 320 mg/day intramuscularly (3 days), then 40–200 mg/day oral flexible (4 days maximum); *n* = 66 4. haloperidol, 10–40 mg intramuscularly x 2–4 times daily (3 days), then flexible oral dose (4 days maximum); *n* = 100	Leaving study early Side-effects **Unable to use** Global assessment: CGI-I, no SD; CGI-S, no SD Mental state: BPRS total, no SD; BPRS agitation, no SD; BPRS core, no data Side-effects: AIMS; SAS; BAS; use of antiparkinsonism medication – all no data	

Zotepine

Study	Methods	Participants	Interventions	Outcomes	Notes
Barnas 1987[297]	**Allocation:** random; no further details **Blinding:** double; used identical tablets **Duration:** 7 weeks; preceded by washout period of 7 days (oral) or 3 months (depot) **Setting:** not described	**Diagnosis:** schizophrenia (DSM-III-R) ***N*:** 30 **Age:** mean, about 34 years **Sex:** 20 male, 10 female **History:** duration, 6 months to > 5 years	1. zotepine, ~ 94 mg/day (mean) (SD ~ 29); *n* = 15 2. haloperidol, ~ 4 mg/day (mean) (SD ~ 1); *n* = 15	Leaving study early Global impression: CGI Mental state: BPRS; SANS (Munich version) Side-effects: DOTES (German version); laboratory tests **Unable to use** ECG/EEG: no data	ITT analysis used last observation carried forward
Cooper 1999a[298]	**Allocation:** blocks of 6; randomisation undertaken by drug company; code held by drug company **Blinding:** double; identical tablets; double dummy technique **Duration:** 8 weeks, preceded by one dosing interval for participants on depot **Inclusion criteria:** baseline CGI score = 4 **Power calculation:** to detect change of 8.8 from baseline in BPRS total score **Setting:** multicentre	**Diagnosis:** schizophrenia; acute exacerbation (DSM-III-R) ***N*:** 159 **Age:** 18–65 years; means, 39.6 years (zotepine), 41.0 years (chlorpromazine), 36.3 years (placebo) **Sex:** 115 male, 44 female **History:** mostly inpatients; duration (range) 6–440 months **Exclusion criteria:** physical ill-health; substance abuse	1. zotepine, titrated from 150 to 300 mg/day over first 7 days; *n* = 53 2. chlorpromazine, titrated from 200 to 600 mg/day over first 7 days; *n* = 53 3. placebo; *n* = 53 Benzodiazepines or chloral hydrate allowed; all other treatments permitted, including anticholinergic medication Allowed to drop to lower doses if intolerant of higher dose; withdrawn if intolerant of lower dose	Leaving study early Global impression: CGI, no data Mental state: BPRS; SANS Side-effects: AIMS; SAS; adverse events using COSTART terms; only reported side-effects if reported five or more times Weight Pulse **Unable to use** Benzodiazepine use: no data Blood pressure: no SD Discharge from inpatient status	ITT analysis used last observation carried forward One person did not provide post-baseline assessment so excluded from analysis but, as clear from which group, added back in as appropriate

continued

Zotepine *contd*

Study	Methods	Participants	Interventions	Outcomes	Notes
Cooper 1999b[299]	**Allocation:** block randomisation; code held by drug company **Blinding:** double; identical tablets; double dummy technique **Duration:** 26 weeks, preceded by one dosing interval for those on depot **Inclusion criteria:** baseline CGI-illness score of 3 or more; if currently maintained on antipsychotic medication, history of recurrence* in last 18 months **Power calculation:** to detect change between groups of 20% versus 50% recurrence with 90% power and 5% significance **Setting:** multicentre	**Diagnosis:** schizophrenia, chronic (DSM-III-R) ***N*:** 121 **Age:** range, 20–65 years; means, 43 years (zotepine), 41.6 years (placebo) **Sex:** 82 male, 37 female **History:** mostly outpatients; mean duration, 166.9 months (zotepine), 157.9 months (placebo) **Exclusion criteria:** physical ill-health; substance abuse	1. zotepine, titrated from 150 to 300 mg/day over first 4 days; allowed to drop to 150 mg/day if intolerant of higher dose; withdrawn if unable to tolerate dose; *n* = 63 2. placebo; *n* = 58	Leaving study early **Unable to use** Global impression: CGI Mental state: BPRS; SANS Side-effects: AIMS; SAS Benzodiazepine and night sedation use Blood pressure and pulse ECG Laboratory tests Weight gain Loss to follow-up greater than 50% in total (76%); only outcome used was 'loss to follow-up'	ITT analysis used last observation carried forward * Recurrence defined as: (i) increase of ≥ 2 points on CGI-S score, plus 2-point increase on two BPRS positive symptoms persisting over two assessments in 3 days not requiring hospitalisation; (ii) requiring hospitalisation and one assessment; (iii) increase in CGI-S score to 'severely ill' for 24 hours or, if hospitalised, requiring special observation for suicidal/aggressive behaviour
Dieterle 1991[300]	**Allocation:** random; no further details **Blinding:** double; capsules of identical appearance **Duration:** 28 days, preceded by washout period of 3–5 days (oral), 14 days (depot) **Setting:** single centre	**Diagnosis:** schizophrenia (ICD9) ***N*:** 40 **Age:** mean, 31.1 years (zotepine), 35.8 years (perazine) **Sex:** 13 male, 27 female **History:** inpatients; chronic diagnosis	1. zotepine, 241 mg/day (mean) (SD ~ 70); *n* = 20 2. perazine, 348 mg/day (mean) (SD ~ 98); *n* = 20	Leaving study early **Unable to use** Global impression: CGI, no mean/SD Mental state: BPRS; SANS Side-effects: Webster and SAS; AMDP; laboratory tests EEG/ECG	
Fleischhacker 1989[301]	**Allocation:** random; no further details **Blinding:** double; identical tablets **Duration:** 6 weeks **Setting:** not described	**Diagnosis:** schizophrenia (DSM-III) ***N*:** 40 **Age:** mean, ~ 33 years **Sex:** 29 male, 11 female **History:** duration, 3 months to > 5 years	1. zotepine, 309 mg/day (mean); *n* = 20 2. haloperidol, 14.5 mg/day (mean); *n* = 20	Side-effects: laboratory tests **Unable to use** Global effect: CGI, no usable data Mental state: BPRS, no SD Side-effects: DOTES, no mean/SD ECG: not reported	ITT analysis used last observation carried forward Authors contacted for further data

continued

Zotepine *contd*

Study	Methods	Participants	Interventions	Outcomes	Notes
Klieser 1996[302]	**Allocation:** random; no further details **Blinding:** double; no further details **Duration:** 4 weeks **Setting:** not described	**Diagnosis:** schizophrenia (ICD 9); acute, paranoid hallucinatory psychoses ***N*:** 180 **Age:** mean, 32.5 years (zotepine), 33.1 years (risperidone, 8 mg), 33.1 years (haloperidol) **Sex:** 84 male, 96 female **History:** duration, mean (SD), 2.3 (1.3) years (zotepine); 4.6 (4.1) years (haloperidol); 4.3 (5.8) years (risperidone, 8 mg)	1. zotepine, 3 x 75 mg/day 2. risperidone, increased to 4 mg/day over first 7 days (not included) 3. risperidone, increased to 8 mg/day over first 7 days (not included) 4. clozapine, increased to 400 mg/day over first 7 days (not included) 5. remoxipride, increased to 400 mg/day over first 7 days (not included) 6. haloperidol, 15 mg/day Biperiden (for side-effects), diazepam and chloral hydrate allowed	Global impression: CGI Mental state: BPRS Side-effects: SAS Cognition: Syndrome Kurz Test **Unable to use** ECG/EEG: no data Side-effects: laboratory tests, no data	Only data from zotepine, risperidone, 8 mg/day, and haloperidol groups used for continous outcomes
Meyer-Lindberg 1996[108]	**Allocation:** random; no further details **Blinding:** double; no further details **Duration:** 6 weeks **Setting:** not described	**Diagnosis:** schizophrenia (DSM-III-R) ***N*:** 50 **Age:** mean, ~ 33 years (SD ~ 10) **Sex:** 18 male (only describes those reported on)* **History:** unresponsive to > 3 weeks' treatment with two typical anti-psychotic drugs in effective doses; BPRS > 39	1. zotepine, 150–450 mg/day; *n* = 25 2. clozapine, 150–450 mg/day; *n* = 25	Leaving study early **Unable to use** Global function: CGI, no mean/SD Mental state: BPRS/SANS, no mean/SD Behaviour: Centre d'information des professions de la santé scale/NOSIE, no mean/SD Side-effects: UKU* Cognitive function: maze tests, no mean/SD ECG: no data Weight gain: no data	* Data provided only for subset (13 age-matched controls)

continued

Zotepine *contd*

Study	Methods	Participants	Interventions	Outcomes	Notes
Petit 1996[303]	**Allocation:** random; no further details* **Blinding:** double; identical and dummy capsules **Duration:** 8 weeks, preceded by omission of last depot injection **Setting:** 13 French hospitals **Power calculation:** undertaken to demonstrate difference of 8.2 between treatment groups on BPRS	**Diagnosis:** schizophrenia (DSM-III-R) ***N*:** 126 **Age:** range, 18–68 years, mean ~ 39 years **Sex:** 73 male, 63 female* **History:** currently acutely ill; in hospital; overall duration, 6 months to 41 years; 4+ score on CGI; not physically ill or abusing substances	1. zotepine, 150–300 mg/day; *n* = 63 2. haloperidol, 10–20 mg/day; *n* = 63	Mental state: 50% reduction in BPRS Leaving study early Side-effects **Unable to use** Global improvement: CGI, no mean/SD Mental state: SANS, no mean/SD Side-effects: AIMS/SAS, no SD ECG: no data Pulse: no SD	* Haloperidol group had twice as many women as zotapine group. ITT analysis used last observation carried forward
Sarai 1987[304]	**Allocation:** random; tablets in identical boxes; given random number (kept by pharmacist) stratified by hospital **Blinding:** double; identical tablets **Rating:** trained in use of BPRS **Duration:** 8 weeks **Setting:** multicentre; Japan	**Diagnosis:** schizophrenia* ***N*:** 94 **Age:** range, 29–> 50 years **Sex:** 47 male, 47 female **History:** 82/94 in hospital; duration 3–10 years; excluded if 'in an advanced stage of schizophrenia, severe psychomotor excitement, in sedative state, sleep disturbance, hallucinating or deluded, fixed delusions, pregnant or physically ill'	1. zotepine, 75–300 mg/day; *n* = 48 2. thiothixene, 15–60 mg/day; *n* = 46	Mental state: BPRS Excluded and leaving study early Side-effects Use of additional medication Laboratory results **Unable to use** Mental state: BPRS continuous data, no mean/SD	* Mainly people 'overshadowed by lack of spontaneity'
Wetzel 1991[305]	**Allocation:** random; no further details **Blinding:** double; capsules of identical appearance **Duration:** 28 days; no washout period **Setting:** single centre; inpatient	**Diagnosis:** schizophrenia (ICD9); acute phase	1. zotepine, 100–600 mg/day (average 250 mg/day); *n* = 20 2. perazine, 150–900 mg/day (average 500 mg/day); *n* = 21	Leaving study early Mental state: BPRS Use of additional medication **Unable to use** Global impression: CGI Mental state: SANS Side-effects: Webster and Simpson scale; AMDP; laboratory tests Blood pressure EEG/ECG	

Appendix 4

Non-randomised studies of rare or long-term events

Clozapine

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Margolese 2000[117] **Brief description** Review of literature (MEDLINE 1966–99) to examine evidence for association of extrapyramidal symptoms, in particular akathisia and tardive dyskinesia, with suicidality in schizophrenia and explore if atypical antipsychotic drugs with fewer expyramidal symptoms reduce risk	**Intervention:** various atypical and typical antipsychotic drugs	**Age:** not stated **Sex:** not stated **Illness:** schizophrenia **Diagnosis:** not stated ***N*:** not stated **Special characteristics:** no details reported **Inclusion/ exclusion criteria:** no details reported	No details of attrition rates reported for studies examined	**Intervention:** no suicide data from individual studies; no combined numerical data; summary statements only **Control:** no suicide data from individual studies; no combined numerical data; summary statements only	**Authors' conclusions** "Current evidence includes akathisia and TD as risk factors for suicide in schizophrenia. Akinesia and parkinsonism have not been adequately studied to ascertain their role. In the most suicidal patients clozapine appears to be the preferred antipsychotic, perhaps due to its low EPS potential. Classical antipsychotics should be avoided in suicidal schizophrenic patients" **Comments** No data provided to support authors' conclusions
Killian 1999[118] **Brief description** Surveillance using Australian Adverse Drug monitoring system	**Intervention:** clozapine ***N*:** 8000 **Dose:** as licenced in Australia; not controlled **Duration:** January 1993–March 1999 **Comments:** data from Adverse Drug Reactions Advisory Committee (ADRAC); further information from manufacturer	**Age:** not stated **Sex:** not stated **Illness:** not specified **Diagnosis:** not stated ***N*:** 8000 **Duration of illness:** not stated **Special characteristics:** all participants had taken clozapine; details not available **Inclusion/ exclusion criteria:** all patients starting clozapine between January 1993 and March 1999	Not stated	**Intervention:** 23 participants had objective evidence of myocarditis or cardiomyopathy (absolute risk 0.29%); 6 died – myocarditis, 5 (14–18 days after start of treatment); cardiomyopathy, 1. There were 15 cases of myocarditis (median time to occurrence after start of treatment, 15 days, range 3–21); in 6 patients, peripheral eosinophilia documented, and 5 complained of influenza-like symptoms Cardiomyopathy occurred in 8 individuals, median time to onset, 12 months, range 2–36 No confounding comorbidities were found. Of those who developed myocarditis or cardiomyopathy, concomitant medications taken as follows (*n*/*N*): benzatropine (5/23); chlorpropamide (3/23); lithium carbonate (3/23); haloperidol (2/23); aspirin (2/23); olanzapine, diazepam, cefaclor, amoxicillin, cefalexin, lactulose, clonazepam, paracetamol with codeine, amitripyline, sodium valproate, tetrabenazine, fluoxetine and sertraline (1/23 each)	**Authors' conclusions** Clozapine therapy may be associated with potentially fatal myocarditis and cardiomyopathy in physically healthy young adults with schizophrenia

continued

Clozapine *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Laker 1998[119] **Brief description** Naturalistic study comparing patients who continued clozapine with those who discontinued it	**Intervention:** clozapine ***N*:** 113 **Duration:** January 1990–June 1995	**Age:** mean (SD): 35 (10) years **Sex:** 81/113 male **Illness:** not stated **Diagnosis:** not stated ***N*:** 113 **Duration of illness:** mean (SD): 11.85 (7.9) years	In intervention group, 39/113 participants discontinued treatment (mean 11 months): 21/39 adverse events; 18/39 lack of response or poor compliance	**Intervention:** no real adverse event or safety data presented. Three patients died during study period, one by suicide and two from natural causes unrelated to clozapine	**Authors' conclusions** Recent reports on cost-effectiveness of clozapine should be interpreted with caution. No conclusions related to tolerability or safety of clozapine reported
Walker 1997[120] **Brief description** Database analysis of mortality rates and causes of death among clozapine patients	**Intervention:** clozapine ***N*:** 67072 **Control:** US population mortality rates, 1985–88 **Duration:** 3 years (April 1991–December 1993) **Concomitant medications:** not reported	**Age:** 10–95 years **Sex:** 37,571 female person-years; 57,973 male person-years **Illness:** not stated **Diagnosis:** not stated ***N*:** 67,072 **Duration of illness:** not stated **Special characteristics:** all past, current or pre-treatment clozapine patients to end of 1993 **Inclusion/ exclusion criteria:** Excluded: records with no valid social security number; born pre-1890 or post-1983; those with New York postcodes (local statistics office could not provide death certificates); not having at least two white blood cell (WBC) records, of which at least one was for active clozapine use and dated during period of study; WBC for active clozapine use dated > 7 days after matched date of death	Not stated	**Intervention:** mortality in patients aged 10–54 years All cause, 396; external (including suicide), 122 (suicide, 75); circulatory, 110 (acute myocardial infarction, 11; pulmonary embolism, 19; conduction disorders or sudden death, 12); respiratory, 31 (pneumonia/influenza, 11); neoplasms, 21; digestive, 16; mental, 13; nervous, 11 (seizures, 4); infections, 6 (septicemia or agranulocytosis, 3); other or unknown, 66 All-cause mortality, 396 versus general population, 229; SMR versus general population, 1.73 (95% CI, 1.56 to 1.91) All-cause mortality in current clozapine users (deaths/ 100,000 person years), 322 versus 693 in past (> 106 days since most recent WBC for active clozapine use) users; SMR, 0.46 (95% CI, 0.37 to 0.59) Suicide in current clozapine users, 39 versus 222 in past (> 106 days since most recent WBC for active clozapine use) users; SMR, 0.17 (95% CI, 0.10 to 0.30)	**Authors' conclusions** Clozapine appears to reduce mortality in severe schizophrenics by reducing suicide rates **Comments** Many subdivisions of data, no other significant results

continued

Clozapine *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Hasan 1998[135] **Brief description** Retrospective analysis of case reports of NMS	**Intervention:** clozapine ***N*:** 19 **Dose:** not stated **Control:** risperidone ***N*:** 13 **Dose:** not stated **Duration:** not stated **Concomitant medications:** not stated	**Age:** mean, 42 years (15–82) **Sex:** male 23; female 9 **Illness:** schizophrenia, psychosis, bipolar disorder, other **Diagnosis:** not stated ***N*:** 32 **Duration of illness:** not stated **Inclusion/ exclusion criteria:** NMS related to clozapine or risperidone and reported in English; identified from MEDLINE search Further details: no dates or details of search reported	Not stated	**Intervention:** reported cases were assessed using three sets of criteria (Caroff and Mann, DSM-IV, Levenson) for NMS Clozapine: high probability that true case of NMS, 9; low probability, 10 Risperidone: high probability that true case of NMS, 8; low probability, 5	**Authors' conclusions** NMS can occur in patients given atypical antipsychotic drugs and resembles 'classical' NMS. However, side-effect profiles overlap considerably with NMS criteria and atypical antipsychotic drugs may cause neurotoxicities unrelated to (but misattributed as) NMS. Insufficient evidence exists for 'atypical' NMS with novel antipsychotic drugs
Reid 1998[121] **Brief description** Reviewed records of all deaths of participants treated with clozapine in Texas mental health system between 1991 and 1996	**Intervention:** clozapine ***N*:** 1310 **Control:** all patients ***N*:** 30,130 **Duration:** 5 years **Comments:** numbers given are average annual numbers	**Age:** not stated **Sex:** clozapine group, 63% female; control group 45% **Illness:** schizophrenia and schizoaffective disorder **Diagnosis:** not stated ***N*:** 30,130 **Duration of illness:** not stated **Inclusion/ exclusion criteria:** receiving clozapine for ≥ 30 days; had not discontinued drug for > 14 days **Further details:** participants for whom clozapine prescribed but for whom no information about duration of treatment or drug discontinuation available also considered to have been clozapine recipients	Not stated	**Intervention:** number of suicides, 1; data unavailable, 0; total, 1 Suicide rate, 12.74 per 100,000 persons per year **Control:** number of suicides, 33 (May 1993–May 1995); data unavailable, 5; total, 38 Suicide rate, 63.1 per 100,000 persons per year	**Authors' conclusions** Results suggest that clozapine therapy associated with reduced risk of suicide among patients with schizophrenia and schizoaffective disorder

continued

Clozapine *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Erlandsen 2000[122] **Brief description** Prospective, long-term (22 years), uncontrolled study	**Intervention:** clozapine ***N*:** 103 **Dose:** initial, 50 mg/day, increasing by 50 mg per week; range 100–700 mg/day; average dose 300 mg/day **Duration:** 22 years **Comments:** dose adjusted in accordance with clinical effect	**Age:** not stated **Sex:** not stated **Illness:** schizophrenia **Diagnosis:** ICD10 ***N*:** 103 **Duration of illness:** mean: 13 years (range 1–58) **Special characteristics:** GAF scores Baseline: average 15/103; minimum 0/103; maximum 25/103 Endpoint (1995): average 55/79; 10/79; 90/79 EPS, especially akathisia, severe in all participants before clozapine therapy	**Intervention group *n*:** 24 participants missing from 1995 analysis (three discontinued due to adverse events, 12 died, nine unknown)	**Intervention:** mortality: 12 deaths (4 cardiovascular disease; 2 intestinal obstruction; 1 lung carcinoma; 1 mentally weak; 1 unknown; 1 advanced hepatic failure and diabetes); no excess mortality with clozapine when compared with Norwegian Central Bureau of Statistics' figures Drowsiness, especially in morning, was commonest side-effect; hypersalivation (reduced swallowing reflex) 20/103; tachycardia 2/103; episodes of epileptiform seizures 2/103; gastrointestinal symptoms and hypersalivation 1/103; agranulocytosis 1/103; leucopenia 2/103 – first after 1 year, second after 2.5 years (concurrent treatment with doxycyline) Deaths: 12 (cardiovascular disease 4; intestinal obstruction 2; lung carcinoma 1; mentally weak 1; unknown 1; advanced hepatic failure and diabetes 1)	**Authors' conclusions** Clozapine has proved breakthrough medicine **Comments** Changes in practice since 1973 must be taken into account
Modai 2000[123] **Brief description** Data from Sha'ah Menashe Mental Health Centre Database, Israel	**Intervention:** clozapine ***N*:** 561 **Dose:** not stated **Control:** non-clozapine ***N*:** 4918 **Duration:** 8 years, 6 months (January 1991–August 1997)	**Age:** not stated **Sex:** not stated **Illness:** schizophrenia **Diagnosis:** ICD10 and ICD9 ***N*:** 5479 **Duration of illness:** not stated **Further details:** all clozapine-treated patients had diagnoses of schizophrenia; unclear for non-clozapine-treated patients	Not reported	**Intervention:** total deaths, 10/561; sudden deaths, 6/561, $p < 0.01$; suicides, 2/561; disease-related deaths, 2/561 No significant difference in suicide rates between two groups **Control:** total deaths, 105/4918; sudden deaths, 14/4918; suicides, 5/4918; disease-related deaths, 86/4198, $p < 0.05$	**Authors' conclusions** Results suggest that treatment with clozapine may present greater risk of sudden death than treatment with other psychiatric medications; limited number of sudden death cases and deaths from other causes should be noted, so that these findings are considered with caution **Comments** Age at sudden death for clozapine-treated patients significantly lower than for non-clozapine-treated patients (10.37 years) and patients were in better physical health; suicide figures seem remarkably low for schizophrenia – could be cultural influence on reporting?

continued

Clozapine *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Buckman 1999[125] **Brief description** Retrospective, based on data from Illinois Department of Mental Health and Developmental Disabilities computerised information system	**Intervention:** clozapine ***N*:** 518 **Duration:** 1990–95	**Age:** not stated **Sex:** not stated **Illness:** schizophrenia **Diagnosis:** not stated ***N*:** 518 **Duration of illness:** not stated **Special characteristics:** treatment-refractory **Further details:** at year 5, 403/518 participants 'doing well' on clozapine; 243/403 patients discharged from hospital into community; 62/403 transferred because of medical problems; 99/403 remained hospitalised	**Intervention group *n*:** 115/518 participants dicontinued clozapine therapy	**Intervention:** clozapine similar to other low-potency agents in frequency of sedation, anticholinergic effects, and cardiovascular symptoms, and had lower incidence of extrapyramidal side-effects Incidence of agranulocytosis: 0.9%	**Authors' conclusions** In the future, with aid of clozapine therapy, institutional care may be only a stop along road to recovery for many previously uncontrollable schizophrenic patients. Long-term institutionalisation will still be option but one that will be needed for far fewer patients **Comments** Adverse events data not presented fully: only minimal information given
Wolstein 2000[143] **Brief description** Cohort study of frequency of thromboembolism in people treated with clozapine, other neuroleptic drugs or no neuroleptic drugs. Unclear whether retrospective or prospective.	**Intervention:** clozapine ***N*:** 13,081 **Dose:** not stated; oral **Control:** other neuroleptic drugs ***N*:** 59,637 **Dose:** not stated; oral **Control 2:** not treated with neuroleptic drugs ***N*:** 30,282 **Duration:** 1993–99 **Concomitant medications:** not stated	**Age:** not stated **Sex:** not stated **Illness:** other (see comments) **Diagnosis:** not stated ***N*:** 103,000 **Duration of illness:** not stated **Inclusion/exclusion criteria:** not stated **Further details:** inpatients of 35 psychiatric hospitals in Germany and Switzerland	Not stated	**Intervention:** thromboembolism, 5 episodes in 4 patients (0.038%); frequency, 1/2600 patients **Control:** thromboembolism, 17 cases (0.029%) **Control 2:** thromboembolism, 8 cases (0.026%)	**Authors' conclusions** Thromboembolism may not be clozapine-associated; other risk factors must be taken into account, such as reduced motor activity during psychiatric illness. In databases relying on spontaneous reporting, there may be bias towards reporting adverse events in clozapine-treated patients because of restricted use of drug. Further research needed to identify psychiatric patients at risk of developing this potentially fatal complication **Comments** No significant difference between groups

continued

Clozapine *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Hagg 2000[136] **Brief description** Retrospective study of adverse reactions database	**Intervention:** clozapine ***N*:** 12 **Dose:** mean, 277 mg/day (range, 75–500) **Duration:** April 1989–March 2000 (duration of study) **Concomitant medications:** phenoxymethyl penicillin; cyproterone acetate; haloperidol; clomipramine; lactulose and propantheline; erythromycin; perphenazine, levomepromazine and amitriptyline; zolpidem, clonazepam and carbamazepine; carbamazepine, orphenadrine and thioridazine; levonorgestrel/ethinyloestradiol, diazepam, terbutaline and budesonide; biperiden, flupentixol, lorazepam and clomipramine **Comments:** concominant medications for each patient listed above. Duration of therapy also varied widely (14 days–2 years) and for 2 patients was unknown	**Age:** mean, 38 (25–59) years **Sex:** male 9, female 3 **Illness:** schizophrenia, personality disorder, psychosis **Diagnosis:** not stated ***N*:** 12 **Duration of illness:** not stated **Special characteristics:** not stated **Inclusion/exclusion criteria:** all cases of venous thromboembolic complications that occurred during clozapine treatment and submitted to Swedish Adverse Reactions Committee between 1 April 1989 and 1 March 2000 **Further details:** except for one patient (using combined oral contraceptive) no predisposing risk factors identified; however, no information on factor V Leiden (blood clotting) or smoking habits available	Not stated	**Intervention:** deaths 5; pulmonary embolism 5; cardiac infarction 1; myocarditis 1; thrombosis in paraprostatic vein plexus 1; non-fatal pulmonary embolism, 1 + 1 suspected; deep vein thrombosis 6; agranulocytosis 1 In eight patients, symptoms occurred during the first 3 months of treatment	**Authors' conclusions** Venous thromboembolism might be associated with use of clozapine; effect seems to occur mainly in first 3 months of treatment. Clozapine should be stopped in any patient in whom reaction suspected **Comments** Very small sample size

continued

Clozapine *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Alvir 1993[126] **Brief description** Evaluated Clozaril® Patient Management System data by survival analysis	**Intervention:** clozapine ***N*:** 11,555 **Duration:** February 1990–April 1991	**Age:** not reported **Sex:** 7032/11,382* male **Illness:** other (see comments) **Diagnosis:** not stated ***N*:** 11,555 **Duration of illness:** not stated **Special characteristics:** schizophrenia 95%; affective psychosis 2.2%; organic psychosis 1.0% **Inclusion/exclusion criteria:** followed for ≥ 3 weeks; blood samples available for ≥ 3 time points	Not stated	**Intervention:** Cumulative incidence of agranulocytosis: At 1 year: 0.80% (95% CI, 0.61 to 0.99) At 1.5 years: 0.91% (95% CI, 0.62 to 1.20) Agranulocytosis developed in 23 participants within 2 months of therapy, in 61 within 3 months and in 70 within 6 months; in one patient it developed after 1 year. Hazard rate for agranulocytosis peaked during third month of treatment. In two patients with fatal agranulocytosis, disorder developed 1.5 months after starting treatment Univariate survival analyses showed that risk of agranulocytosis increased with age (RR, 1.06; 95% CI, 1.05 to 1.08) and was higher in women (RR, 2.23; 95% CI, 1.40 to 3.54). Adjustment for age reduced the effect of gender but not vice versa. Small association between baseline white cell count and risk of agranulocytosis not significant after adjustment for age and gender. RR for those aged < 21 years greater than for those aged 21–30 years and 31–40 years (RR, 1.75; 95% CI, 0.53 to 5.86) Dose of clozapine had no effect on risk of agranulocytosis in a conditional logistic-regression analysis	**Authors' conclusions** Occurrence of agranulocytosis is substantial hazard of administration of clozapine but can be reduced by monitoring white cell count. Increasing risk of agranulocytosis with age and reduced incidence after first 6 months of treatment provide additional guidelines for prescription and monitoring of clozapine treatment in future * Gender of remaining 173 patients not reported

continued

Clozapine *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Atkin 1996[127] **Brief description** Analysis of data from UK and Ireland Clozaril® Patient Monitoring Service	**Intervention:** clozapine ***N*:** 6316 **Dose:** 150–450 mg/day; mean (SE) 313 (2.9) mg/day **Duration:** 4.5 years **Comments:** 5.2% participants received > maximum dose of 900 mg/day	**Age:** mean 37 years (range 9–91) **Sex:** 4178/6316 male **Illness:** schizophrenia **Diagnosis:** not stated ***N*:** 6316 **Special characteristics:** 2858/6316 participants received clozapine for ≥ 1 year; 1625/6316 for ≥ 2 years; 338/6316 withdrew before starting or within 1 week of commencing treatment; 54% were on clozapine at time of study	**Intervention group *n*:** 2603/6316 withdrew for non-haematological reasons	**Intervention:** First 6–18 weeks therapy, neutropenia 1.2%; agranulocytosis 0.7% (43/48 cases of agranulocytosis occurred within first 18 weeks of treatment) Risk (*n*, % (95% CI): First year (*n* = 6316): agranulocytosis 46/6316, 0.7 (0.53 to 1.97); fatal agranulocytosis 2/6316, 0.03 (0.006 to 0.12); neutropenia 147/6316, 2.3 (1.97 to 2.73); fatal neutropenia 0/6316, 0 (0 to 0.06) Second year (*n* = 2858): agranulocytosis 2/2858, 0.07 (0 to 0.25); fatal agranulocytosis 0/2858, 0 (0 to 0.13); neutropenia 20/2858, 0.7 (0.41 to 1.04); fatal neutropenia 0/2858, 0 (0 to 0.13) Third year (*n* = 1625): agranulocytosis 0/1625, 0 (0 to 0.22; fatal agranulocytosis 0/1625, 0 (0 to 0.22); neutropenia 12/1625, 0.7 (0.39 to 1.3); fatal neutropenia 0/1625, 0 (0 to 0.23) Fourth year (*n* = 661): agranulocytosis 0/661, 0 (0 to 0.56); fatal agranulocytosis 0/661, 0 (0 to 0.056); neutropenia 3/661, 3 (0.09 to 1.3); fatal neutropenia 0/661, 0 (0 to 0.56) Earliest time to onset of agranulocytosis, 5 weeks; last case occurred at 16 months Incidence of agranulocytosis increased marginally with increasing age; mean age (at development) 42 years; no increased risk of neutropenia Africans and Afro-Caribbeans appeared to be at increased risk of developing neutropenia (5.3%) compared with whole population (2.6%) (*p* = 0.02) No association with dose or gender	**Authors' conclusions** Use of patient monitoring service kept haematological risks associated with using clozapine within acceptable limits, particulary in view of benefits of medication in those with treatment-resistant schizophrenia

continued

Clozapine *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Devinsky 1991[137] **Brief description** Reviewed information on patients treated with clozapine in USA between 1972 and 1988	**Intervention:** clozapine ***N*:** 1418 **Comments:** participants grouped as follows 1. low dose, < 299 mg/day 2. medium dose, 300–599 mg/day 3. high dose, 600–900 mg/day	**Age:** not stated **Sex:** not stated **Illness:** schizophrenia **Diagnosis:** not stated ***N*:** 1418	Not stated	**Intervention:** 41/1418 participants (26/41 male, average age 30.8 years, range 19–49) suffered at least one generalised tonic-clonic seizure. Crude incidence, 2.9%; eight participants had two convulsions and four had three Cumulative rate continued to increase with duration of therapy, ~ 9% at 156 weeks (3 years). Life-table analysis for ≤ 196 weeks (3.8 years) predicts 10% cumulative risk of seizure occurrence Median interval between onset of treatment and first seizure, 75 days (mean, 218 days; range 7–1336) Seizure frequency: ≥ 600 mg, 4.4%; 300–599 mg/day, 2.7%; < 300 mg/day, 1.0% Clozapine dose rapidly titrated upwards prior to seizure in eight cases (increase of 200 mg+ in 2 weeks or less); in six cases, 50 mg/week increase preceded seizure. Median cumulative dose prior to first seizure, 44.4 g (mean, 145.7 g; range, 0.63–892) 19 patients taking other medication with CNS activity; six took drugs known to lower seizure threshold (lithium 3; neuroleptic drugs 2; tricylic antidepressant 1); seven took benzodiazepines, three barbiturates; two with history of seizures took anti-epileptic drugs. In addition, one patient was undergoing electro-convulsive therapy at time of seizure	**Authors' conclusions** None stated

continued

Clozapine *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Grohmann 1989[128] **Brief description** Data from Departments of Psychiatry in Munich and Berlin	**Intervention:** clozapine ***N*:** 1100 **Control:** haloperidol ***N*:** 6800 **Control 2:** perazine ***N*:** 6000 **Duration:** 9 years **Concomitant medications:** about 450 patients exposed to both clozapine and perazine	**Age:** 3150 < 60 years; 750 ≥ 60 years **Sex:** 5600 male; 8300 female **Illness:** not stated **Diagnosis:** not stated ***N*:** 13,900 **Duration of illness:** not stated	Not reported	**Intervention:** agranulocytosis, 1/1100; leucopenia, 1/1100 **Control:** agranulocytosis 0/6800; leucopenia, 2/6800 **Control 2:** agranulocytosis, 6/6000; leucopenia, 2/6000	**Authors' conclusions** Continuous collection and careful documentation of all cases of agranulocytosis with neuroleptic drugs is necessary to reach better understanding of this serious risk of this treatment **Comments** Adverse drug reactions grade III collected by means of intensive drug monitoring and organised spontaneous reporting. Three cases of leucopenia with other agents (melperone; pipamperone and bofepramin; trifluoperazine)
Honigfield 1996[129] **Brief description** Based on data from US National Registry Database	**Intervention:** clozapine ***N*:** 99,502 **Duration:** February 1990–December 1994	**Age:** not stated **Sex:** not stated **Illness:** schizophrenia **Diagnosis:** not stated ***N*:** 99,502 **Duration of illness:** not stated **Inclusion/exclusion criteria:** not stated	Not stated	**Intervention:** 2931/99,502 cases of leucopenia (crude incidence rate: 2.95%); 382/99,502 cases of agranulocytosis (0.38%); 12/99,502 deaths associated with agranulocytosis (0.012%)	**Authors' conclusions** Clozapine National Registry system fostered early detection of white blood cell suppression, prevented retreatment with clozapine of patients who had previously developed white blood cell suppression and brought about lower than expected rates of agranulocytosis

continued

Clozapine *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
King 1998[130] **Brief description** MCA post-marketing database study of haematological safety of new antipsychotic drugs	**Intervention:** clozapine ***N*:** not stated **Intervention 2:** risperidone ***N*:** not stated **Control:** chlorpromazine, droperidol, haloperidol, loxapine, pimozide, remoxipride, risperidone; sulpiride, thioridazine, trifluoperazine, flupenthixol, fluphenazine, fluspirilene, pipothiazine, zuclopenthixol ***N*:** not stated **Duration:** 33 years (1963–96) **Concomitant medications:** not stated **Comments:** examines adverse reaction data on 16 antipsychotic drugs in 'common use'	**Age:** not reported **Sex:** not stated **Illness:** not stated **Diagnosis:** not applicable ***N*:** 999 **Duration of illness:** not stated **Special characteristics:** all adverse reaction reports involving haemopoetic disorders for any patient on any of 16 antipsychotic drugs listed **Inclusion/exclusion criteria:** not applicable	Not stated	**Intervention:** haematopoietic adverse reaction reports, 1963–96 total haematopoietic agranulocytosis aplastic anaemia disorders (fatalities): clozapine 552 (4); 91(2); –(–) adverse reaction reports for each drug in 5 years from first reported reaction total haematopoietic agranulo-cytosis aplastic reactions disorders anaemia: clozapine 1663; 392; 57, – Intervention 2: haematopoietic adverse reaction reports, 1963–96 total haematopoietic agranulocytosis aplastic anaemia disorders (fatalities): risperidone 29(1); – (–); 1(1) Adverse reaction reports for each drug in 5 years from first reported reaction total haematopoietic agranulocytosis aplastic reactions disorders anaemia: risperidone 679; 29; –; 1 Control: haematopoietic adverse reaction reports, 1963–96 total haematopoietic agranulocytosis aplastic anaemia disorders (fatalities): chlorpromazine 131(34), 56(27), 4(2); droperidol 2(–), – (–), – (–); haloperidol 21(1), 1(1), 1(–); loxapine 3(–), 1(1), – (–); pimozide 9(–), – (–), – (–); remoxipride 4(1), – (–), 5(1); sulpiride 16(–), 2(–), – (–); thioridazine 84(12), 24(9), 1(–); trifluoperazine 46(7), 3(2), 4(2); flupenthixol 46(1), 1, 1; fluphenazine 16(4), 3(2), 2(1); fluspirilene 3(–), – (–), – (–); pipothiazine – (–), – (–), – (–); zuclopenthixol 7(–), – (–), – (–) Adverse reaction reports for each drug in the 5 years from first reported reaction total haematopoietic agranulo-cytosis aplastic reactions disorders anaemia: chlorpromazine 238, 22, 12, 1; clozapine 1663, 392, 57, –; droperidol 17, –, –,–; haloperidol 50, –, –,– loxapine 74, 2, 1, –; pimozide 37, 1, –, –; remoxipride 236, 34, –, 5; sulpiride 233, 3, –, –; thioridazine 99, 16, 4, –; trifluoperazine 230, 4, –, –; flupenthixol 35, –, –, –; fluphenazine 74, 1, 1, –; fluspirilene 169, –, –, –; pipothiazine 27, –, –, –; zuclopenthixol 27, –, –, –	**Authors' conclusions** No evidence of increased risk of haemopoietic reactions with newer anti-psychotic drugs. Increased vigilance advocated given lower fatality rate with clozapine associated agranulocytosis compared with other antipsychotic drugs **Comments** Numbers of haematopoietic reactions during 5 years from first reported adverse reaction derrived from percentage figures quoted in study

continued

Clozapine *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Lambertenghi 2000[131] **Brief description** Data analysed from Italian Clozapine Monitoring System	**Intervention:** clozapine ***N*:** 2404 **Dose:** mean, 200–350 mg/day **Duration:** 1995–99 **Comments:** clozapine dose reached over period of 3–6 weeks and subsequently maintained	**Age:** not stated **Sex:** 1515 male **Illness:** schizophrenia **Diagnosis:** DSM-IV ***N*:** 2404 **Duration of illness:** male: 13.5 years (SD 9.3); female 15.4 years (SD 10) **Special characteristics:** paranoid schizophrenia, 47.3% male, 42.1% female; disorganised schizophrenia, 25.1% male, 26.1% female: catatonic schizophrenia, 2.9% male, 2.1% female; undifferenciated schizophrenia, 11.7% male, 15.5% female; residual schizophrenia, 8.5% male, 8.2% female; unknown, 4.5% male, 6% female	**Intervention group *n*:** 689 participants discontinued treatment after median 10 weeks (range 1–836 days); 6% poor clinical efficacy, 6.3% non-compliance, 12.5% reasons unrelated to drug, 3.3% various side-effects	**Intervention:** 40 patients discontinued treatment owing to neutropenia or agranulocytosis within 18 weeks (89%) of starting therapy or between 18 and 78 weeks (11%); 2/40 cases withdrawn from analysis Neutropenia, 22, incidence 0.9%; agranulocytosis, 16, incidence 0.7%; leukocytosis, 185, incidence 7.7%; eosinophilia, 52, incidence 2.2%; thrombocytopenia, 2 In four patients (2 neutropenia, 2 agranulocytosis), clozapine administered with other potentially myelotoxic drugs (carbamazepine, lamotrigine, methimazole) No significant correlations found for role of predisposing risk factors	**Authors' conclusions** Study confirms that regular haematologic monitoring highly effective in minimising incidence of clozapine-associated blood dyscrasia
Leppig 1989[142] **Brief description** Retrospective study of outpatients (medical charts)	**Intervention:** clozapine ***N*:** 121 **Duration:** not stated	**Age:** not stated **Sex:** not stated **Illness:** not stated **Diagnosis:** not stated ***N*:** 121 **Special characteristics:** outpatients	Not stated	Not stated	
Lieberman 1992[132] **Brief description** See Comments	**Intervention:** clozapine ***N*:** 11,555 **Dose:** mean maximum, 451.9 mg/day **Duration:** at least 3 weeks	**Age:** not stated **Sex:** 62% male **Illness:** not stated **Diagnosis:** not stated ***N*:** 11,555	Not stated	**Intervention:** 73 patients with agranulocytosis; incidence of clozapine-induced agranulocytosis was 0.8% at 1 year and 0.91% at 1.5 years (95% CI, 0.6 to 1.2). Maximum period of risk, first 24 weeks of treatment Older participants ($p < 0.0001$) and women ($p < 0.005$) appeared to have significantly greater risk of clozapine-induced agranulocytosis (Cox proportional hazards model of regression analysis); risk of agranulocytosis increased by about 6% (95% CI, 5 to 8; $p < 0.001$) with each year of age; RR (female), 2.2 (95% CI, 1.4 to 3.5; $p < 0.005$) individually and 1.6 (95% CI, 1.0 to 2.6) age-controlled	**Authors' conclusions** Pathophysiological significance of these associations requires further investigation **Comments** Footnote: 'This is a brief report of Dr. Lieberman's presentation at the meeting. Full details will be published shortly in an original article'

continued

Clozapine *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Macpherson 1998[138] **Brief description** Data from Gloucester clozapine clinic	**Intervention:** clozapine ***N*:** 19	**Age:** not stated **Sex:** not stated **Illness:** not stated **Diagnosis:** not stated ***N*:** 19	**Intervention group *n*:** four patients had treatment discontinued (1 no response, 1 non-fatal NMS; 1 recurrent chest infection plus no response; 1 fainting, hypotension, episodes of unconsiousness, seizures plus no response	**Intervention:** 15 patients took medication for mean of 2.3 years; 11/15 male, mean age 42.8 years (range 30–65); chronic, treatment-resistant schizophrenia; mean duration of illness, 21 years (range 10–45) Drowsiness/sedation, 11/15; sialorrhoea, 8/15; nausea/vomiting, 3/15; sweating, 3/15; hypotension/postural dizziness, 3/15; weight gain, 2/15; seizures, 1/15	**Authors' conclusions** None stated
Meltzer 1995[124] **Brief description** Open-labelled, non-controlled study of suicidality of patients with treatment-resistant illness taking clozapine	**Intervention:** clozapine ***N*:** 183 **Dose:** mean, 500 mg/day **Duration:** mean follow-up 3.5 years (SD 1.6) (range 6 months to 7 years) **Concomitant medications:** virtually all patients received only clozapine; benzodiazepines used intermittently during titration period	**Age:** 34 years (SD 10) **Sex:** 128 male **Illness:** schizophrenia or schizoaffective disorder **Diagnosis:** DSM-III-R ***N*:** 183 **Duration of illness:** mean 14 years (SD 8) **Special characteristics:** patients divided into neuroleptic-responsive (n = 237) and neuroleptic-resistant (n = 183) illnesses; only latter group treated with clozapine and followed-up in study Further details: of 88 participants included in final analysis, 15 had schizoaffective disorder and all had taken clozapine for ≥ 6 months	**Intervention group *n*:** 70 participants stopped taking clozapine before end of study. Reasons (n): non-compliance (35); adverse effects (12); lack of efficacy (10); agranulocytosis or granulocytopaenia (6); other (7) Six further patients excluded from final analysis because they had received < 6 months clozapine therapy and further 19 were lost to follow-up Total in final analysis, 88	**Intervention:** 70 participants who withdrew early took clozapine for mean period of 202 days (SD 205); none of these made any suicide attempts For 88 patients in final analysis, before-clozapine/after-clozapine results (in numbers of patients) are as follows: no suicidal thoughts, 47/77; suicidal thoughts, plans, or threats, 9/7; unintentional self-harm, 10/1; suicide attempts with low probability of success, 17/3; suicide attempts with high probability of success, 5/0 By examining frequencies as function of time (within-subjects or dependent-samples analysis) and using cumulative logits to represent suicidality ordinally, a significant time effect found (chi-squared, 35.82; df 2; $p < 0.0001$) indicating that pattern of suicidality changed over time and change was towards lowering of suicidality	**Authors' conclusions** Results suggest basis for re-evaluation of risk–benefit assessment of clozapine, that is, that overall morbidity and mortality of patients with neuroleptic-resistant schizophrenia are less with clozapine treatment than with typical neuroleptic drugs because of less suicidality. This conclusion also has implications for increasing use of clozapine with neuroleptic-responsive patients **Comments** No direct comparison of clozapine with other drugs or in neuroleptic-responsive patients

continued

Clozapine *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Miller 1997[133] **Brief description** Data from Sandoz Pharma (NZ) Ltd from blood monitoring programme in New Zealand	**Intervention:** clozapine ***N*:** 693 **Duration:** April 1988 and June 1995	**Age:** not stated **Sex:** not stated **Illness:** schizophrenia **Diagnosis:** not stated ***N*:** 693 **Duration of illness:** not stated **Special characteristics:** mostly treatment-resistant illness **Inclusion/exclusion criteria:** not stated	Not applicable	**Intervention:** agranulocytosis, 8/693 (no deaths); cumulative rate 1.15%; neutropenia, 14/693; cumulative rate, 2.02%	**Authors' conclusions** Agranulocytosis and neutropenia rates reported from New Zealand compare favourably with those from larger overseas studies, although exposed patient base is modest
Pacia 1994[139] **Brief description** Data from Clozaril® (Novartis Pharmaceuticals) Patient Management System	**Intervention:** clozapine ***N*:** 5629 **Dose (*n*):** 0–299 mg/day (1302); 300–599 mg/day (3192); ≥ 600 mg/day (1135) **Duration:** 6 months	**Age:** not stated **Sex:** not stated **Illness:** schizophrenia **Diagnosis:** not stated ***N*:** 5629	Not stated	**Intervention:** 71/5629 patients (low dose, 21; medium, 29; high, 21), (37/71 male; average age, 34.1 years (range 18–71)) had generalised tonic-clonic seizures, frequency 1.3%; 24/71 had recurrent seizures; one patient reported as having myoclonic seizure preceding generalised tonic-clonic seizure Cumulative seizure rate (approximately): 3 months, 1.1%; 6 months, 1.9% Median interval between onset of clozapine treatment and first seizure, 42 days (entire group). By dose at time of seizure: low, 12 days; medium, 47 days; high, 84 days 16 patients had history of 1+ seizures: 8 had seizure on clozapine dose < 300 mg; 3 on medium and 5 on high dose. 10 patients were on anti-epileptic drugs at time of seizure; 7/10 patients had past history of seizures 44 patients were taking other medications with CNS activity; 35 were taking concomitiant medications reported to lower seizure threshold, antipsychotic drugs 14, lithium 11, anti-depressant drugs 9, beta-blockers 6, diphenhydramine 2, aminophylline preparation 2; 11 were taking 2+ drugs reported to lower seizure threshold; 22 were taking benzodiazepines	**Authors' conclusions** None stated

continued

Clozapine *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Spiess-Kiefer 1988[364] **Brief description** Data from adverse events monitoring system in two psychiatric hospitals in West Germany	**Intervention:** clozapine ***N*:** 548 **Control:** other neuroleptic drugs ***N*:** 11,147 **Duration:** 6 years	**Age:** not stated **Sex:** not stated **Illness:** not stated **Diagnosis:** not stated ***N*:** 11,695	Not stated	**Intervention:** ADR [adverse drug reaction] grade III* (probable and definite cases); in combination with other drugs, 9.5%; alone, 6.6% **Control (*n*):** ADR grade III* (probable and definite); haloperidol (4133), in combination 10.1%, alone 8.2%; perazine (3583), in combination 5.9%; alone 3.1%; levomepromazine (2502), in combination 3.6%, alone 1.4%; thioridazine (929), in combination 4.7%, alone 2.6% Most frequent type of ADR III* (probable and definite cases) Haloperidol: parkinsonism, in combination 4.9%, alone 4.3%; akathisia, in combination 3.2%, alone 2.8%; sedation, in combination 1.1%, alone 0.7%; increased transaminases, in combination 0.2%, alone 0.02% Perazine: parkinsonism, in combination 0.5%, alone 0.3%; akathisia, in combination 0.5%, alone 0.2%; sedation, in combination 0.8%, alone 0.6%; increased transaminases, in combination 1.2%, alone 0.8%	**Authors' conclusions** Not stated **Comments** * ADR grade III is adverse event that leads to discontinuation of medication suspected of causing the events
Umbricht 1994[144] **Brief description** Retrospective chart review	**Intervention:** clozapine ***N*:** 82 **Dose:** 500–600 mg/day (titrated over 3–5 weeks) **Duration:** 3–90 months long term	**Age:** mean (SD): 28.7 (6.4) years **Sex:** 56/82 male **Illness:** schizophrenia **Diagnosis:** not stated ***N*:** 82 **Duration of illness:** 8.7 (5.5) years **Special characteristics:** positive treatment response defined as 20% reduction in BPRS total score plus either CGI of ≤ 3 or BPRS total score of ≤ 35 Further details: at baseline, participants classified as underweight or overweight if weight was below or above limits of ideal weight range (Metropolitan Height and Weight Table) for person of medium frame	**Intervention group *n*:** 14/82 participants did not provide data for long-term analysis	**Intervention:** data for long-term evaluation of participants available for 68/82 participants; follow-up ranged from 3–90 months Survival analysis (cumulative incidence of weight gain) showed cumulative incidence of 10% weight gain or more reached 60% within first 12 months of clozapine therapy Cumulative proportions of those who gained 10, 20, 30 and 40% over their baseline weight: at end of year 2 – 70, 34, 11, 6%; entire period – 86, 54, 23, 13% Weight status at baseline significantly correlated with maximal weight gain (multiple regression: beta = –6.31, df = 5, 50; p = 0.000) and reaching 20% overweight within 90 months (logistic regression: $p < 0.05$). Those who were underweight at baseline (n = 12; 31%, 20%) gained significantly more weight than those of ideal weight (n = 15; 18%, 9%) and those who were overweight at baseline (n = 34; 10%, 9%) (one-way ANOVA, F = 5.62, df = 2, 58; p = 0.006)	**Authors' conclusions** Treatment with clozapine associated with high incidence of sustantial weight gain, posing potential long-term health risk. Studies are needed of underlying mechanisms of weight gain as well as treatment for this side-effect

continued

Clozapine *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Coulter 2001[145] **Brief description** Data mining using Bayesian statistics implemented in neural network architecture, in WHO database	**Intervention:** clozapine ***N*:** not stated **Control:** other antipsychotic drugs ***N*:** not stated	**Age:** not stated **Sex:** not stated **Illness:** not stated **Diagnosis:** not stated ***N*:** not stated	Not stated	**Intervention:** reports of myocarditis and cardiomyopathy Clozapine has much higher information component than other antipsychotic drugs together and than general background database Number of case reports: 231/24,730; information component (–2 SD): 3.34 (3.14) **Control:** reports of myocarditis and cardiomyopathy Group of other antipsychotic drugs was significantly associated with myocarditis and cardiomyopathy together and compared individually with general database; these associations much weaker than for clozapine Number of case reports: 89/60,775; information component (–2 SD): 0.71 (0.40) Chlopromazine, lithium and fluphenazine significantly associated with mycarditis and cardiomyopathy; chlorpromazine also significantly associated with myocarditis and cardiomyopathy separately. Lithium, fluphenazine and risperidone significantly associated with cardiomyopathy but not myocarditis; haloperidol associated with myocarditis but not cardiomyopathy	**Authors' conclusions** Some antipsychotic drugs seem to be linked to cardiomyopathy and myocarditis. The study shows potential of Bayesian neural networks in analysing data on drug safety
Peacock 1996[141] **Brief description** Participants in long-term therapy evaluated for EPS. Study was both prospective (video-controlled evaluation of EPS) and retrospective (chart information)	**Intervention:** clozapine ***N*:** 100 **Control:** typical antipsychotic drugs (perphenazine, flupenthixol, zuclopentixol) ***N*:** 100 **Duration:** retrospective, 0.3–24 years; prospective, 1 year	**Age:** not stated **Sex:** not stated **Illness:** schizophrenia **Diagnosis:** not stated ***N*:** 200 **Duration of illness:** not stated **Special characteristics:** patients in long-term neuroleptic monotherapy **Further details:** clozapine-treated patients without tardive dyskinesia had started clozapine and ceased traditinal neuroleptic drugs at earlier age than those with tardive dyskinesia	Not stated	**Intervention:** significantly lower prevalence of tardive dykinesia ($p < 0.05$), lower induction of new cases ($p < 0.001$), and tendency towards greater disappearance ($p = 0.07$) Parkinsonian signs, 33%; mainly hypokinesia, tremor 3% and rigidity 0%; psychic akathsia, 14%; motor akathsia, 7% Also less neuroleptic-induced emotional indifference and depression but more autonomic side-effects **Control:** Parkinsonian signs, 61%; mainly hypokinesia, tremor 11% and rigidity 19%; psychic akathsia, 40%; motor akathsia, 29%	**Authors' conclusions** None stated

continued

Clozapine *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Cho 1999[134] **Brief description** Post-marketing database	**Intervention:** clozapine ***N*:** 2152 **Dose:** not stated **Duration:** 3 years **Concomitant medications:** not stated	**Age:** not stated **Sex:** not stated **Illness:** other (see comments) **Diagnosis:** not stated ***N*:** 2152 **Duration of illness:** not stated **Inclusion/exclusion criteria:** Included patients taking clozapine for period of study who had been followed for ≥ 3 weeks and had blood samples available for ≥ 3 time points	Not stated	**Intervention:** neutropenia, 127 (5.9%), of which 88 (69.3%) occurred within first 18 weeks; agranulocytosis, 11 (0.5%), of which 9 (81.8%) occurred in first 4–11 weeks, the remaining two occurring at 23 and 31 weeks, respectively. Cumulative incidence of agranulocytosis, 0.5% at 1 year, with none occurring in second and third years	**Authors' conclusions** Frequent (weekly) monitoring recommended during first 18 weeks of treatment, with relaxation thereafter
Lan 1999[140] **Brief description** Retrospective case series looking at incidence of epilepsy in people receiving clozapine and relation to dose	**Intervention:** clozapine ***N*:** 1303 **Dose:** split into high, medium or low dose groups; oral **Control:** none **Duration:** not stated **Concomitant medications:** not stated	**Age:** not stated **Sex:** not stated **Illness:** other (see comments) **Diagnosis:** not stated ***N*:** 1303 **Duration of illness:** not stated **Special characteristics:** not stated whether participants had schizophrenia **Inclusion/exclusion criteria:** not stated	Not stated	Total incidence of epilepsy was 11.5%; incidences for high, medium and low dose groups were 25.97, 6.46 and 9.05%, respectively. In addition, differences in incidence between high-dose, single-drug and multi-drug groups significant	**Authors' conclusions** Not stated **Comments** Abstract only, many details missing

Olanzapine

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Gomez 2000[194] **Brief description** Observational prospective phase IV study of 2967 patients in Spain	**Intervention:** olanzapine ***N*:** 2128 **Dose:** mean initial 12.23 mg (SD 4.85) (range 5–30 mg); mean 13.01 mg (SD 4.97) (range 5–30 mg) **Control:** other antipsychotic drugs (mainly risperidone or haloperidol) ***N*:** 821 **Control 2:** risperidone (as subgroup of other antipsychotic drugs) ***N*:** 414 **Dose:** mean initial 13.92 (SD 9.26) (range 2–50 mg); mean 13.64 (SD 8.72) (range 2–40 mg) **Control 3:** haloperidol (as subgroup of other antipsychotic drugs) ***N*:** 108 **Dose:** mean initial 13.92 mg (SD 9.26) (range 2–50 mg); mean 13.64 mg (SD 8.72) (range 2–40 mg) **Duration:** 6 months **Concomitant medications:** other antipsychotic medication and other medication as clinically indicated permitted during study **Comments:** selection of treatment made by investigator and hence bias could not be controlled Control drugs (*n*): as well as risperidone (417) and haloperidol (112), these included: sertindole (84), zuclopenthixol (74), fluphenazine (33), trifluoperazine (31), thioridazine (19), perphenazine (18), pimozide (11), clozapine (6), pipotiazine (4), sulpiride (4), chlorpromazine (3), levomepromazine (3), clotiapine (1), lorazepam (1)	**Age:** olanzapine 35.55 years (SD 11.68); control 35.15 years (SD 11.25) **Sex:** 64% male **Illness:** schizophrenia **Diagnosis:** ICD10 ***N*:** 2967 **Duration of illness:** mean 11 years, median 9 years **Special characteristics:** olanzapine group 64.7% paranoid, control group 66% paranoid **Inclusion/exclusion criteria:** Excluded: only patients in whom antipsychotic drug therapy contraindicated, those in whom clozapine indicated and those participating in clinical trials	**Intervention group *n*:** protocol completed, 1564/2128 Reason for discontinuation: adverse event 40; patient decision 29; lack of efficacy 31; death 3; lost to follow-up 381; other 80 **Control group *n*:** protocol completed 627/821	**Reason for discontinuation:** adverse event 18; patient decision 8; lack of efficacy 9; death 1; lost to follow-up 125; other 33 **Intervention:** any adverse event 48% ($p < 0.001$ compared with control); any EPS 37% ($p < 0.001$ compared with control) Adverse events that were statistically significantly less common in olanzapine group than in control group: akathisia 59/2128; dystonia 24/2128; EPS 6/2128; hypertonia 73/2128; hypokinesia 104/2128 Abnormal ejaculation and impotence also statistically significantly more common in control group (not reported for olanzapine) Somnolence (96/2128) and weight gain (146/2128) statistcially significantly more common in olanzapine group than in control group Hypotension also reported (4/2128) Any adverse event 64% Any EPS 57% Data for other adverse events in whole control group not presented in paper **Control:** adverse events statistically significantly more common with risperidone than with olanzapine: akathisia 30/417 ($p < 0.001$); hypertonia 35/417 ($p < 0.001$); hypokinesia 36/417 ($p = 0.002$); tremor 47/417 ($p < 0.001$); abnormal ejaculation 2/417 ($p \geq 0.028$); impotence 2/274 ($p = 0.028$); amenorrhoea 5/142 ($p = 0.011$) Adverse events statistically significantly more common for olanzapine than risperidone: somnolence 7/417 ($p = 0.007$); weight gain 8/417 ($p = 0.001$) Equally common adverse events: dystonia 9/417; EPS 3/417; hypotension 1/417 Adverse events statistically significantly more common with haloperidol than olanzapine: akathisia 19/112 ($p = 0.001$); dystonia 4/112 ($p = 0.048$); EPS 4/112 ($p = 0.001$); hypertonia 29/112 ($p = 0.001$); hypokinesia 30/112 ($p = 0.001$); hypotension 2/112 ($p = 0.033$); tremor 29/112 ($p = 0.001$) Adverse events reported more commonly with olanzapine than haloperidol: weight gain 1/112 ($p = 0.13$) Somnolence (5/112) was equally common for haloperidol and olanzapine	**Authors' conclusions** Results show that olanzapine is safe and effective in nonselected schizophrenic outpatients and consistent with efficacy and safety profile that olanzapine has shown in previous controlled clinical trials **Comments** Incidence of adverse events recorded is low, although it is probably true that some patients lost to follow-up did in fact discontinue because of adverse events

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Olanzapine *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Tamura 1998[200] **Brief description** Incidence of tardive dykinesia evaluated from results of three randomised, double-blind multicentre studies	**Intervention:** olanzapine ***N*:** not stated **Control:** haloperidol ***N*:** not stated **Duration:** up to 2.6 years	**Age:** not stated **Sex:** not stated **Illness:** combined diagnosis ***N*:** 1714 **Special characteristics:** schizophrenia, schizophreniform disorder or schizo-affective disorder	Not stated	**Intervention:** estimated risk higher with haloperidol than olanzapine ($p < 0.001$); estimated rate ratio for haloperidol compared with olanzapine 3.69 (95% CI, 2.10 to 6.50) Estimated 1-year risk of tardive dyskinesia (based on 6-month data), 0.52% **Control:** estimated 1-year risk of tardive dyskinesia (based on 6-month data) 7.45%; estimated risk with haloperidol higher than with olanzapine throughout follow-up period ($p = 0.002$) Estimated RR, 11.86 (95% CI, 2.30 to 61.14)	**Authors' conclusions** Results of multiple assessments of incidence of tardive dyskinesia indicated substantially lower risk with olanzapine than haloperidol
Biswas 2000[202] **Brief description** Post-marketing surveillance study of adverse events with olanzapine	**Intervention:** olanzapine ***N*:** 8858 **Dose:** not stated; oral **Duration:** December 1996–May 1998 **Concomitant medications:** not stated **Comments:** exposure data obtained from dispensed prescriptions; outcome data obtained by sending questionnaires to prescribing GPs	**Age:** not stated **Sex:** not stated **Illness:** schizophrenia **Diagnosis:** not stated ***N*:** 8858 **Duration of illness:** not stated **Special characteristics:** Inclusion/exclusion criteria: not stated **Further details:**	335/8858 stopped olanzapine in first month owing to: drowsiness/ sedation 153; weight gain 117; malaise/ lassitude 65 These were top three reasons; attrition may have been higher but other reasons not reported	One case of suspected NMS reported. Other adverse events reported not rare events and usually reported in RCTs	**Authors' conclusions** Safety profile of olanzapine defined in large cohort in general practice in England. No untoward features not already mentioned in prescribing guidance were identified **Comments** Abstract only; many details missing

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Olanzapine *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Kinon 2001[195] **Brief description** Retrospective analysis of data from RCT (Tollefson 1997[164]), with open-labal follow-up to 3 years for olanzapine-treated patients	**Intervention:** olanzapine ***N*:** 573 **Dose:** 5–20 mg/day **Control:** haloperidol ***N*:** 103 **Duration:** up to 3 years for olanzapine group and 100 weeks for haloperidol-treated group	**Age:** mean (SD): olanzapine 39.4 (11.5) years; haloperidol 38.4 (11.7) years **Sex:** olanzapine 367/573 male; haloperidol 64/103 male **Illness:** schizophrenia **Diagnosis:** DSM-III-R ***N*:** 1936 **Duration of illness:** **Special characteristics:** after 6 weeks of acute therapy, patients continued for ≥ 1 year with either double-blind or open-label olanzapine therapy or double-blind haloperidol therapy **Further details:** 293/573 olanzapine-treated participants observed for 2.5–3 years, 147/573 observed at final 3-year time point. In haloperidol group, maximum observation time was 100 weeks	Not stated	**Intervention:** within-group mean weight change at 39 weeks not significantly different from that seen at any subsequent time point; no significant difference in mean weight change seen between any time points between 1 and 3 years, inclusive. In 147 participants who completed entire 3-year observation period, no significant differences seen between adjacent time points after week 39 Mean weight change (last observation carried forward) (median 2.54 years' treatment): 6.26 kg (median, 5.90 kg); 26% lost weight or gained no weight, 44% gained > 0–10 kg, 22% gained > 10–20 kg, 9% gained > 20 kg; 52% gained > 7% of their body weight Influence of baseline body mass index (BBMI): effect on weight change significant at all time points after 13 weeks ($p < 0.002$); participants with high values (> 27.6) had mean weight change significantly lower than participants with medium (> 23.6–27.6) or low BBMI (< 23.6) ($p < 0.001$; both). Mean weight changes: high, 3.82 kg; medium, 6.88 kg; low, 8.07 kg; of those with low BBMI, 85.0% had either low or medium endpoint BBMI Dose not significant predictor of long-term changes in weight **Control:** weight change remained below that of olanzapine at all time points Mean weight change (median 1.15 years treatment): 0.69 kg ($p < 0.001$, compared with olanzapine) 26% gained > 7% of their body weight Influence of BBMI not assessed	**Authors' conclusions** Mean weight gain during olanzapine treatment trended towards plateau after initial 39 weeks of treatment with no further significant gain out to 3 years. Higher BBMI was predictive of lower long-term weight gain, while dose was not significant predictor of greater longer-term weight change

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Olanzapine *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Cadario 2000[196] **Brief description** Data from Canadian Adverse Drug Reaction Monitoring Programme	**Intervention:** olanzapine ***N*:** not stated **Duration:** July 1996–February 2000	**Age:** not stated **Sex:** not stated **Illness:** schizophrenia and related psychotic disorders **Diagnosis:** not stated ***N*:** not stated **Further details:** total number of patients not reported	Not stated	**Intervention:** reported as suspected drug in 22 deaths: suicide/overdose 8; NMS 2; arrhythmia 3; myocardial infarction 1; heart failure and pneumonia 1; pneumonia 1; sepsis 1; sudden death 1; mesenteric thrombosis 1; choking 1; unknown 1 Non-fatal adverse drug reactions: a number of reports of tachycardia or hypotension, and one of possible premature ventricular contractions Also, one instance of Q-T prolongation as result of overdose with both olanzapine and quetapine plus valproate Haematological reactions (including leucopenia, granulocytosis, neutropenia, pancytopenia, anaemia) 11; elevated alanine aminotransferase levels 2; NMS 11 (2 deaths); pancreatitis 3; diabetic ketoacidosis 1	**Authors' conclusions** None stated

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Olanzapine *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Czekalla 2001[199] **Brief description** ECG recordings obtained from four RCTs were analysed	**Intervention:** olanzapine ***N*:** 1342 **Control:** placebo, haloperidol and risperidone ***N*:** 1358 **Duration:** 6–8 weeks	**Age:** mean (SD) 38 (11) years **Sex:** 32% female **Illness:** schizophrenia and related **Diagnosis:** DSM-III-R and DSM-IV ***N*:** 2700 **Duration of illness:** not stated **Inclusion/exclusion criteria:** 430 milliseconds set prospectively as threshold value defining prolonged Q-Tc	Not stated	**Intervention:** distribution of change from baseline to minimum Q-Tc value: –120 to <–90: 0.4%; –90 to <–60: 2.4%; –60 to <–30: 15.0%; –30 to < 0: 41.5%; 0 to < 30: 35.5%; 30 to < 60: 4.8%; 60 to < 90: 0.4%; 90 to < 120: 0.1% Distribution of change from baseline to maximum Q-Tc value: –120 to <–90: 0.1%; –90 to <–60: 0.7%; –60 to <–30: 6.3%; –30 to < 0: 27.6%; 0 to < 30: 47.5%; 30 to < 60: 16.1%; 60 to < 90: 1.6%; 90 to < 120: 0.2% Changes to maximum ≥ 30 ms, 17.9% Changes to minimum ≤ 30 ms, 17.8% Potentially clinically significant measurements: 245/1555 participants Q-Tc increase ≥ 30 ms (within 5 days of last dose of olanzapine): 77/245 endpoint Q-Tc not increased ≥ 30 ms over baseline; 96 endpoint Q-Tc increased ≥ 30 ms over baseline but other postbaseline Q-Tc values not increased ≥ 30 ms over baseline; 45/245 only one postbaseline Q-Tc and that increased ≥ 30 ms over baseline; 27/245 multiple postbaseline Q-Tc values, all increased ≥ 30 ms over baseline 2/1555 participants endpoint Q-Tc increased by ≥ 70 ms 125/1424 participants (baseline ECG with Q-Tc < 430 ms and ≥ 1 postbaseline ECG) Q-Tc ≥ 430 ms: 41/125 endpoint Q-Tc < 430 ms; 55/125 endpoint Q-Tc ≥ 430 ms but other postbaseline Q-Tc values ≥ 430 ms; 21/125 only one postbaseline Q-Tc and that ≥ 430 ms; 8/125 multiple postbaseline Q-Tc values, all ≥ 430 ms	**Authors' conclusions** Results suggest that olanzapine, as therapeutically administered to patients with schizophrenia and related psychoses, does not contribute to prolonged Q-Tc, which can cause potentially fatal ventricular repolarisation

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Olanzapine *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Fung 1998[197] **Brief description** Post-marketing database	**Intervention:** olanzapine ***N*:** 688,000 **Duration:** first 12 months	**Age:** not stated **Sex:** not stated **Illness:** schizophrenia **Diagnosis:** not stated **N:** 688,000 **Duration of illness**: not stated	Not applicable	**Intervention:** 134 reports of attempted suicide (52/134 male, 10/134 unknown, mean age 32.6 years, range 18–64) Methods: drug overdose (86%); laceration (2%); impact-related injury (3%); gun-shot (1.5%); hanging (1.5%); unknown (6%) Outcomes: death (14%); hospitalised and recovered (69%); unknown (17%) Crude incidence of 0.02%; suicide attempt rate = 85/100,000 patient-years	**Authors' conclusions** Estimated rate of suicide attempts lower or at low end of range suggested by literature, consistent with observation in clinical trial data with regard to suicide behaviour
Anon 2001[201] **Brief description** Analysis of four double-blind studies and naturalistic data from Eli Lilly Company spontaneous safety database	**Intervention:** olanzapine ***N*:** 2284 **Control:** haloperidol ***N*:** 810 **Control 2:** placebo ***N*:** 118 **Duration:** database, 30 months	**Age:** not stated **Sex:** not stated **Illness:** not stated **Diagnosis:** not stated ***N*:** not stated	Not stated	**Intervention:** trials Suicide attempts per patient year: 0.046 In comparison of suicide attempts per 100 patient-years after treatment from single clinical trial, those treated with olanzapine attempted suicide less frequently than haloperidol-treated participants **Database:** 362 cases of suicide among 2,707,000 (estimated) participants exposed to olanzapine. Crude suicide attempt rate of 0.013% and rate of 40 per 100,000 patient-years of exposure **Control:** suicide attempts per patient-year: 0.062	
Anon 2001[201] **Brief description** HGBG study, 1997	**Intervention:** olanzapine ***N*:** 172 **Dose:** 10–20 mg/day (17.2 mg/day) **Control:** risperidone ***N*:** 167	**Age:** not stated **Sex:** not stated **Illness:** not stated **Diagnosis:** not stated ***N*:** 339	Not stated	**Intervention:** rate of suicide attempts, 0.6% **Control:** rate of suicide attempts, 0.6%, p = 0.029	

continued

Olanzapine *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Anon (DSRU) 2001[198] **Brief description** Postmarketing, prescription event monitoring study. Data based on prescriptions issued by GPs, death certificates, lifetime medical records and other follow-up information in particular cases	**Intervention:** sertindole ***N*:** 462 **Control:** risperidone ***N*:** 7684 **Control 2:** olanzapine ***N*:** 8858 **Duration:** sertindole, December 1996–December 1997; risperidone, July 1993–April 1996; olanzapine, December 1996–May 1998 **Comments:** patient year exposure: sertindole, 299 years; risperidone, 4449 years; olanzapine, 5805 years	**Age:** range of means – men 37–38 years, women 44–51 years **Sex:** not stated **Illness:** not stated **Diagnosis:** not stated ***N*:** 0	Not stated	**Intervention:** patient-years exposure, 299; deaths, 7; all-cause mortality rate/100 patient years exposure (95% CI), 2.34 (0.94 to 4.83) Mortality IRRs for sertindole compared with comparator cohort, drug A, drug B All deaths: 0.60 (0.24 to 1.26); 0.63 (0.25 to 1.32); 0.59 (0.23 to 1.24) Suicide: 0.95 (0.02 to 5.79); 0.96 (0.02 to 6.54); 0.95 (0.02 to 6.26) Open verdict and suicide: 0.60 (0.01 to 3.54); 0.55 (0.01 to 3.54); 0.64 (0.02 to 4.05) Cardiovascular: 0.50 (0.06 to 1.85); 0.56 (0.07 to 2.11); 0.45 (0.05 to 1.71) **Control:** patient-years exposure, 4449; deaths, 221; all-cause mortality rate/100 patient-years exposure (95%CI): 4.97 (4.27 to 5.60) **Control 2:** patient-years exposure, 5805; deaths, 194; all-cause mortality rate/100 patient-years exposure (95% CI): 3.34 (2.87 to 3.83)	**Authors' conclusions** Prescription event monitoring studies of risperidone, olanzapine and sertindole performed during immediate post-marketing period showed lower SMRs for sertindole, although not statistically different. If normal range for equivalence applied, 95% CI for all-cause mortality narrow enough to exclude sertindole being worse than comparator drugs **Comments** Questionnaire response rate: risperidone, 53.8%; olanzapine, 56.8%; and sertindole, 62.6%
Anon (UK Hospital Pharmacy Study) 2001 [#9992] **Brief description** Multicentre (n = 25), retrospective, record-based review of patients	**Intervention:** sertindole ***N*:** not stated **Control:** risperidone and olanzapine ***N*:** not stated **Duration:** sertindole and risperidone, July 1996–June 1997; olanzapine, October 1996–September 1997	**Age:** not stated **Sex:** not stated **Illness:** not stated **Diagnosis:** not stated ***N*:** not stated	**Intervention group *n*:** 4% of patients distributed evenly across groups excluded owing to data deficiencies that could not be resolved	**Intervention:** patient-year exposure, 143; deaths, 2; all-cause mortality rate/100 patient-year exposure (95% CI), 1.40 (0.17 to 5.06) IRR sertindole versus pooled cohort, 0.88 (95% CI, 0.09 to 4.12) **Control:** patient-year exposure, 626; deaths, 10; all-cause mortality rate/100 patient-years exposure (95% CI), 1.60 (0.77 to 2.94)	**Authors' conclusions** All-cause mortality rate during treatment with sertindole not significantly different from that with risperidone and olanzapine. Although CIs wide, results do not suggest higher risk of death with sertindole **Comments** Only deaths while patient receiving treatment or in 2 months after treatment had stopped included

continued

Quetiapine

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Jones 2000[226] **Brief description** Data from controlled (Phase II and III), uncontrolled and open-label extension trials	**Intervention:** quetiapine ***N*:** 2216 **Dose:** mean (completion): 475 mg/day	**Age:** mean (SD): 39.44 (14.11) years **Sex:** 1545/2216 male **Illness:** other (see comments) **Diagnosis:** not stated **N:** 2216 **Duration of illness:** not stated **Special characteristics:** weight (mean, SD), 75.86 (16.56) kg; weight distribution (*n*), data not collected, 10; < 50 kg, 56; 50–70 kg, 858; 71–90 kg, 921; > 90 kg, 371 **Further details:** schizophrenia 2023/2216; bipolar disorder 21/2023; other 172/2216	**Intervention group *n*:** 1 patient withdrew owing to adverse event (weight gain)	**Intervention:** mean weight change (kg) at 5–6 weeks ≤ 125 mg, 1.21; 125–225 mg, 2.95; > 225–450 mg, 2.13 kg; > 450–675 mg, 1.95; > 675 mg, 2.05 kg Mean weight change (kg) at 9–12 months ≤ 125 mg, 1.78; 125–225 mg, 1.38; > 225–450 mg, 3.83 kg; > 450–675 mg, 2.26; > 675 mg, 2.13 kg Mean weight change (kg) according to body mass index: 5–6 weeks ≤ 23, 2.63; 23–27, 3.12; > 27, 1.07; 9–10 weeks–23, 4.74; 23–27, 1.38; > 27, 1.81; 6–9 months ≤ 23, 2.40; 23–27, 2.50; > 27, 0.86; 9–12 months ≤ 23, 3.88; 23–27, 2.33; > 27, 2.49 No clinically relevant difference in mean weight gain between males and females Data from trials in which quetiapine was only antipsychotic medication permitted support these findings	**Authors' conclusions** Quetiapine's combination of efficacy, good tolerability and only moderate effects on weight suggest that drug has favourable benefit–risk profile as first-choice antipsychotic drug in treatment of schizophrenia
Rak 1998[227] **Brief description** Large cohort of patients from controlled, uncontrolled and open-label extension trials	**Intervention:** quetiapine ***N*:** 2216 **Dose:** average mean daily dose (9–12 months): 428 mg/day	**Age:** not stated **Sex:** not stated **Illness:** not stated **Diagnosis:** not stated ***N*:** 0	**Intervention group *n*:** one patient withdrew owing to adverse event of weight gain	**Intervention:** weight gain data grouped using last observation carried forward approach First 5–6 weeks, mean weight increase, 2.08 kg (SE 0.15; *n* = 778); 9–10 weeks, 2.16 kg (SE 0.46; *n* = 171); 6–9 months, 1.85 kg (SE 0.48; *n* = 556); 9–12 months, 2.77 kg (SE 0.56; *n* = 360)	**Authors' conclusions** Based on available weight gain data, weight gain during quetiapine treatment is approximately equal to weight gain associated with risperidone and approximately 50% of weight gain reported with olanzapine and clozapine
Meltzer 2000[229] **Brief description** AstraZeneca global safety database, Clintrace, was searched for all adverse event reports of suicide ideation, attempted suicide or completed suicide; analysis of formal clinical trial data	**Intervention:** quetiapine ***N*:** not stated **Dose:** 300–450 mg/day	**Age:** not stated **Sex:** not stated **Illness:** schizophrenia **Diagnosis:** not stated ***N*:** not stated **Duration of illness:** not stated **Special characteristics:** as of October 1999, there had been 77,000–116,000 patient-years of quetiapine use Numbers of patients not given	Not stated	**Intervention:** suicidal ideation, 37 (25 gave no nature of ideation; others contemplated or threatened suicide); attempted suicide 41 (overdose 22, severe laceration 4, jumping from building 2, hanging 1, poison 1, unknown 10); completed suicide 9 (overdose 2, jumping from building 2, hanging 1, drowning 1, unknown 3) Compared with other antipsychotic drugs (incidence of suicidality) from formal clinical trial reports: quetiapine, 0.3% (*n* = 2185); haloperidol, 1.3% (*n* = 320); risperidone, 0.5% (*n* = 208)	**Authors' conclusions** Reduced suicide rate in participants with schizophrenia treated with quetiapine has exciting implications that require further exploration

continued

Quetiapine *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Anon 2001[229] **Brief description** AstraZeneca	**Intervention:** quetiapine ***N*:** 826 **Control:** chlorpromazine ***N*:** 86 **Control 2:** placebo ***N*:** 155 **Control 3:** haloperidol ***N*:** 74	**Age:** not stated **Sex:** not stated **Illness:** not stated **Diagnosis:** not stated ***N*:** 826	Not stated	**Intervention:** number of participants with clinically significant Q-Tc intervals (> 0.500 s): 13/826 participants (1.6%) Report also presents individual patient data to show that "in almost all cases, the magnitude of Q-Tc interval change with quetiapine is not substantial" 1/13 participants had maximum Q-Tc interval of 0.606 s and was subsequently withdrawn from treatment 3/13 participants had baseline Q-Tc interval > 0.500 s. Only cardiovascular event reported was intermittent sinus tachycardia (1 patient) No apparent relationship between dose and mean change from baseline in Q-Tc interval or incidence of clinically significant Q-Tc intervals Number of participants with clinically significant Q-Tc intervals (> 0.500 s): 2/86 (2.3%) Control: number of participants with clinically significant Q-Tc intervals (> 0.500 s): 2/155 participants (1.3%) Number of participants with clinically significant Q-Tc intervals (> 0.500 s): 0/74	**Authors' conclusions** Quetapine may cause prolongation of Q-Tc interval, as do other antipsychotics in this drug class. However, magnitude of effect is modest and unrelated to dose. No important clinical sequelae have followed Q-Tc interval changes in patients treated with quetapine; in particular, no cases of Torsades de pointes. In addition, no patients had clinically significant prolongations in Q-Tc interval when quetapine co-administered with drugs known to prolong Q-Tc interval. In clinical trials, quetiapine was not associated with persistent increase in Q-Tc intervals; however, as with other antipsychotic drugs, caution should be exercised when quetiapine is prescribed with drugs known to prolong the Q-Tc interval, especially in the elderly

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Quetiapine *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Arvanitis 1997[226] **Brief description** Data from open-label extensions of 11 international Phase III clinical trials and clinical pharmacology trials	**Intervention:** quetiapine ***N*:** 1085 **Dose:** 50–800 mg/day **Duration:** 104 weeks	**Age:** mean: 37 years (range 18–85 years) **Sex:** 70% male **Illness:** other (see comments) **Diagnosis:** not stated **N:** 1085 **Duration of illness:** not stated **Special characteristics:** most common diagnosis was paranoid schizophrenia (57%)	Not stated	**Intervention:** adverse events occurring in at least 6% of participants – headache 132/1085; insomnia 122/1085; somnolence 113/1085; agitation 94/1085; dizziness 74/1085; constipation 57/1085; anxiety 58/1085 2/1085 participants died (one cardiopulmonary arrest, one car accident; neither attributed to quetiapine) 61/1085 withdrew owing to adverse event: leucopenia 8; overdose 6; postural hypotension 4; agitation 3; depression 3; SGPT increase 3 90/1085 anticholinergic adverse events: constipation 53; dry mouth 36; urinary retention 1 Extrapyramidal adverse events: total 77/1085; parkinsonism 60/1085; tremor 23/1085; hypertonia 20/1085; EPS 10/1085; cogwheel rigidity 5/1085; neck rigidity 3/1085; akinesia 1/1085; hypokinesia 1/1085; akathsia 21/1085; dystonia 2/1085	**Authors' conclusions** Results support long-term use of quetiapine in participants with schizophrenia or other psychotic disorders **Comments** Entry criteria included diagnosis of chronic or subchronic schizophrenia; participants entering from clinical pharmacology trials could also have diagnoses of schizoaffective disorder or bipolar disorder

continued

Risperidone

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
MacKay 1998[268] **Brief description** Post-marketing survey of GPs prescribing risperidone	**Intervention:** risperidone ***N*:** 14282 **Duration:** July 1993–April 1996 (duration of study)	**Age:** means, female 38.8 ± 16.8 years, male 50.5 ± 20.4 years **Sex:** not stated **Illness:** schizophrenia, psychosis, attention deficit-hyperactivity disorder, other **Diagnosis:** not stated ***N*:** 14,282 **Special characteristics:** patients identified from prescription data **Inclusion/exclusion criteria:** Excluded: questionnaire not returned (5108); patient no longer registered with doctor (913); questionnaire returned blank (329); no record of risperidone in notes (179); risperidone prescribed but not taken (65); doctor moved (4) **Further details:** difference in age distributions between men and women (presented graphically); distribution of males skewed towards younger	**Intervention group *n*:** attrition rate after 6 months 24% Most frequent reasons for stopping risperidone: not effective, 414; non-compliance, 119; drowsiness, 60; sedation, 48; hospital admission, 45; depression, 37; lassitude, 34; condition improved, 33; schizophrenia, 33; agitation, 32; effective, 29; dizziness, 28; malaise, 27; unspecified side-effects, 27; extra-pyramidal symptoms, 25; hallucinations, 22; headache, 21; anxiety, 20	**Intervention:** incidence per 1000 patient months – drowsiness/sedation, 4.6; non-surgical admissions, 7.3; dose increased, 3.0; malaise/ lassitude, 3.3; respiratory tract infection, 6.1; nausea/vomiting, 2.6; extrapyramidal symptoms, 3.2; agitation, 2.5; headache/ migraine, 1.7; depression, 3.7; dizziness, 1.6; hallucination, 2.8; menstrual disorder, 3.3; anxiety, 1.4; insomnia, 1.9; non-compliance, 2.2; tremor, 1.4; impotence/ejaculation failure, 1.7; constipation, 1.7; schizo-phrenia, 2.2; abdominal pain, 1.6; micturition disorder, 1.6; suicide attempt/drug overdose, 2.1; fall, 1.1; oedema, 1.5; weight gain, 1.4; galactorrhoea, 1.3; aggression, 1.2 Mortality: total 221 varified deaths, cause ascertained for 192. One death (mixed drug overdose) attributable to risperidone Incidence per 1000 patient months in patients aged 70 and over: drowsiness/sedation, 8.6; respiratory tract infection, 11.9; extrapyramidal symptoms, 7.8; non-surgical admissions, 8.1; oedema, 6.0; constipation, 4.4; agitation, 3.7; confusion, 4.7; fall, 4.7; tremor, 2.8; hallucination, 1.8	**Authors' conclusions** Incidence of extra-pyramidal symptoms on risperidone is low; drowsiness/sedation and extrapyramidal symptoms reported more frequently in elderly patients **Comments** As highlighted by authors, relatively short follow-up (6 months) may have led to underestimate of extrapyramidal symptoms

continued

Risperidone *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Amery 1998[266] **Brief description** Data from 27 studies, 15 RCTs and 12 open-label (risperidone integrated database)	**Intervention:** risperidone ***N*:** 3298 **Control:** haloperidol ***N*:** 588 **Control 2:** placebo ***N*:** 142 Other anti-psychotic drugs: thioridazine, zuclopenthixol, levomepromazine, perphenazine and remoxipride, 788	**Age:** not stated **Sex:** not stated **Illness:** schizophrenia **Diagnosis:** DSM-III-R ***N*:** 4816 **Inclusion/exclusion criteria:** not stated	Not stated	**Intervention:** insomnia 9.0% (4–6 mg/day); extrapyramidal symptome, no data; probability of developing tardive dykinesia: 0.0034 per treatment-year; weight change (n = 424, treated for ≥ 1 year) mean (SEM), 3.3 (0.34) kg; (n = 681, treated for ≥ 12 weeks) mean (SEM), 3.2 (0.29) kg (includes drop-outs and participants treated for up to 7.3 years) Hypotension 1.2% (1+ episodes, median dose 8 mg/day), 15 mild, 6 moderate and 1 severe; insomnia 10.7%; EPS 18.5%; probability of developing tardive dyskinesia, 0.019 per treatment-year **Control:** insomnia 7%; EPS 5.6%; headache and agitation 9.2% **Control 2:** insomnia 13.1%; EPS 15%	**Comments** Presented in poster format (Amery 1998[266])
Hasan 1998[135] **Brief description** retrospective analysis of case reports of NMS	**Intervention:** clozapine ***N*:** 19 **Intervention 2:** risperidone ***N*:** 13	**Age:** mean 42 (15–82) years **Sex:** female 9, male 23 **Illness:** schizophrenia, psychosis, bipolar disorder, other **Diagnosis:** not stated ***N*:** 32 **Duration of illness:** not stated **Inclusion/exclusion criteria:** cases of NMS related to clozapine or risperidone and reported in English; identified from MEDLINE search **Further details:** no dates or details of search reported	Not stated	**Intervention:** clozapine – reported cases were assessed using three sets of criteria (Caroff and Mann, DSM-IV, Levenson) for NMS; high probability true case of NMS, 9; low probability, 10 Risperidone – reported cases assessed using three sets of criteria (Caroff and Mann, DSM-IV, Levenson) for NMS; high probability true case of NMS, 8; low probability, 5	**Authors' conclusions** NMS can occur in patients given atypical antipsychotic drugs and resembles 'classical' NMS. However, side-effect profiles overlap considerably with NMS criteria and atypical antipsychotic drugs may cause neurotoxicities unrelated but misattributed to NMS. Insufficient evidence exists for 'atypical' NMS with novel antipsychotic drugs

continued

Risperidone *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Tooley 1997[267] **Brief description** Yearly reporting rates calculated from post-marketing adverse event data	**Intervention:** risperidone ***N*:** not stated **Control:** other agents (not specified) ***N*:** not stated **Duration:** 4 years	**Age:** not stated **Sex:** not stated **Illness:** not stated **Diagnosis:** not stated ***N*:** not stated **Duration of illness**: not stated **Inclusion/exclusion criteria:** not stated	Not stated	**Intervention:** (from February 1997) Tardive dykinesia, 0.0006%; prolactin elevation, 0.027%; NMS, 0.017%; EPS, 0.2% **Control:** tardive dykinesia, 3–5% (all patients); prolactin elevation, 0.2%; NMS, 0.2% (neuroleptic-treated); EPS, 2–90% (all patients)	**Authors' conclusions** Data show encouraging safety record for risperidone in therapeutic area in which side-effects have become the accepted norm – perhaps showing this need not be case. Nevertheless, vigilance in drug monitoring continues, not only for newer drugs but also for established agents
Anon (DSRU) 2001[198] **Brief description** Postmarketing, prescription event monitoring study. Data based on prescriptions issued by GPs, death certificates, lifetime medical records and other follow-up information in particular cases	**Intervention:** sertindole ***N*:** 462 **Control:** risperidone ***N*:** 7684 **Control 2:** olanzapine **N:** 8858 **Duration:** sertindole, December 1996–December 1997; risperidone, July 1993–April 1996; olanzapine, December 1996–May 1998 **Comments:** patient year exposure – sertindole 299 years; risperidone 4449 years; olanzapine 5805 years	**Age:** range of means – men 37–38 years, women 44–51 years **Sex:** not stated **Illness:** not stated **Diagnosis:** not stated ***N*:** 17,004	Not stated	**Intervention:** patient-years exposure: 299; deaths, 7; all-cause mortality rate/100 patient years exposure (95% CI): 2.34 (0.94 to 4.83) Mortality IRRs for sertindole compared with comparator cohort, drug A and drug B: all deaths – 0.60 (0.24 to 1.26); 0.63 (0.25 to 1.32); 0.59 (0.23 to 1.24); suicide – 0.95 (0.02 to 5.79); 0.96 (0.02 to 6.54); 0.95 (0.02 to 6.26); open verdict and suicide – 0.60 (0.01 to 3.54); 0.55 (0.01 to 3.54); 0.64 (0.02 to 4.05); cardiovascular: 0.50 (0.06 to 1.85); 0.56 (0.07 to 2.11); 0.45 (0.05 to 1.71) **Control:** patient-years exposure, 4449; deaths, 221; all-cause mortality rate/100 patient-years exposure (95% CI): 4.97 (4.27 to 5.60) **Control 2:** patient-years exposure, 5805; deaths, 194; all-cause mortality rate/100 patient-years exposure (95% CI): 3.34 (2.87 to 3.83)	**Authors' conclusions** Prescription event monitoring studies of risperidone, olanzapine, and sertindole performed during immediate post-marketing period showed lower SMRs for sertindole, although not statistically different. If normal range for equivalance applied, 95% CIs for all-cause mortality were narrow enoguh to exclude sertindole being worse than comparator drugs **Comments** Questionnaire response rate: risperidone, 53.8%; olanzapine, 56.8%; and sertindole, 62.6%

continued

Risperidone *contd*

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Anon (UK Hospital Pharmacy Study) 2001[198] **Brief description** Multicentre (*n* = 25), retrospective, record-based review of patients	**Intervention:** sertindole ***N*:** not stated **Control:** risperidone and olanzapine ***N*:** not stated **Duration:** sertindole and risperidone, July 1996–June 1997; olanzapine, October 1996–September 1997	**Age:** not stated **Sex:** not stated **Illness:** not stated **Diagnosis:** not stated ***N*:** not stated	**Intervention group *n*:** 4% of patients distributed evenly across groups excluded owing to data deficiencies that could not be resolved	**Intervention:** patient-years exposure: 143 Deaths, 2; all-cause mortality rate/100 person-years exposure (95% CI), 1.40 (0.17 to 5.06) IRR sertindole versus pooled cohort: 0.88 (95% CI, 0.09 to 4.12) **Control:** patient-years exposure: 626 Deaths, 10; all-cause mortality rate/100 patient-years exposure (95% CI), 1.60 (0.77 to 2.94)	**Authors' conclusions** All-cause mortality rate during treatment with sertindole not significantly different from that with risperidone and olanzapine. Although CIs wide, results do not suggest higher risk of death with sertindole **Comments** Only deaths while patient receiving treatment or within 2 months since treatment stopped included

Sertindole

Study	Intervention details	Participants	Withdrawals	Adverse events	Comments
Anon (DSRU) 2001[198]	Commercial-in-confidence; data removed	Commercial-in-confidence; data removed	Commercial-in-confidence; data removed	Commercial-in-confidence; data removed	Commercial-in-confidence; data removed
Anon (UK Hosp Pharm Study) 2001[364]	Commercial-in-confidence; data removed	Commercial-in-confidence; data removed	Commercial-in-confidence; data removed	Commercial-in-confidence; data removed	Commercial-in-confidence; data removed
Anon (ESES) 2001[198]	Commercial-in-confidence; data removed	Commercial-in-confidence; data removed	Commercial-in-confidence; data removed	Commercial-in-confidence; data removed	Commercial-in-confidence; data removed
Anon (Erasmus – Netherlands and Belgium) 2001 [198]	Commercial-in-confidence; data removed	Commercial-in-confidence; data removed	Commercial-in-confidence; data removed	Commercial-in-confidence; data removed	Commercial-in-confidence; data removed
Anon (EPOS) 2001[198]	Commercial-in-confidence; data removed	Commercial-in-confidence; data removed	Commercial-in-confidence; data removed	Commercial-in-confidence; data removed	Commercial-in-confidence; data removed
Anon (Named Patient Use) 2001 [#9996]	Commercial-in-confidence; data removed	Commercial-in-confidence; data removed	Commercial-in-confidence; data removed	Commercial-in-confidence; data removed	Commercial-in-confidence; data removed
Anon (p.36 main Lundbeck submission) 2001[198]	Commercial-in-confidence; data removed	Commercial-in-confidence; data removed	Commercial-in-confidence; data removed	Commercial-in-confidence; data removed	Commercial-in-confidence; data removed
Moore 1999 [278] **Brief description** Reanalysis of pooled data from clinical trials (trials not described) assessing risk of cardiac death with sertindole, risperidone and olanzapine	**Intervention:** sertindole ***N*:** not stated **Dose:** not stated **Control:** risperidone **N:** not stated **Dose:** not stated **Control 2:** olanzapine ***N*:** not stated **Dose:** not stated **Duration:** not stated **Concomitant medications:** not stated	**Age:** not stated **Sex:** not stated **Illness:** other (see comments) **Diagnosis:** not stated ***N*:** not stated **Duration of illness:** not stated **Special characteristics:** not stated that participants had schizophrenia **Inclusion/exclusion criteria:** not stated	Not stated	Sertindole increased Q-Tc by mean of 20 ms with significant relationship with plasma concentrations. Risk: of death overall, 1.9 per 100 patient-years; of cardiac death, 0.8 per 100 patient-years Compared with olanzapine and risperidone, overall death rate was identical. Risk of suicide lower with sertindole than risperidone and olanzapine, and risk of cardiac death higher; however, when risk of death corrected for duration of follow-up, no clear difference between sertindole and olanzapine	**Authors' conclusions** Higher risk of cardiac death with sertindole than with olanzapine or risperidone was not demonstrated; these deaths did not seem related to Q-T prolongation but to background risk of cardiovascular disease in patients at high risk who were often heavy smokers, had diabetes or were obese

Appendix 5

Validity assessment of systematic reviews

Study	Study design	Partici-pants	Inter ventions	Out-comes	Includes/ excludes > 1 reviewer	Validity	Validity > 1 reviewer	Validity used in synthesis	Data extraction > 1 reviewer	Study details	Synthesis	Meta-analysis	Heterogeneity
Appleby 1998[365]	Yes	Yes	Yes	Unclear	N/A	N/A	N/A	N/A	N/A	No	Unclear	Yes	N/A
Bech 1998[272]	Yes	Yes	Yes	Yes	N/A	No	N/A	N/A	N/A	Partially	Partially	Partially	No
Brown 1999[366]	Partially	No	Yes	Yes	N/A	No	N/A	No	N/A	No	Partially	No	N/A
Butler 2000[306]	Yes	Yes	Yes	Yes	Unclear	No	N/A	N/A	Unclear	Partially	Yes	Yes	Yes
Cheine 1999[367]	Yes	Yes	Partially	Yes	Unclear	No	N/A	N/A	Unclear	Yes	Partially	Yes	Yes
De Oliveira 1996[368]	Yes	Partially	Yes	Yes	Unclear	Yes	Yes	Unclear	Unclear	No	Yes	Yes	Partially
Disavayanish 2000[369]	No	Yes	Partially	Yes	N/A	Partially	Partially	N/A	Partially	N/A	No	No	No
Geddes, 2000[349]	Yes	Yes	Yes	Yes	Unclear	Yes	Unclear	Unclear	Unclear	No	Yes	Yes	Yes
Grilli Tissot 1999[370]	Yes	Partially	Yes	Partially	Unclear	No	N/A	N/A	Unclear	No	Unclear	Partially	Yes
Haddad 2000[371]	Yes	Yes	Yes	Yes	Unclear	No	N/A	N/A	Unclear	No	Partially	No	N/A
Keefe 1999[372]	Unclear	Yes	Yes	Yes	Unclear	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes
Lecrubier 1999[67]	No	Yes	Yes	Yes	N/A	N/A	N/A	No	N/a	No	Unclear	Partially	No
Lemmens 1998[270]	Yes	Yes	Yes	Unclear	N/A	No	N/A	No	Unclear	No	Unclear	Partially	No
Lemmens 1998[271]	Yes	Yes	Yes	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Partially	Partially	No
Leucht 2000[373]	Yes	Partially	Yes	Yes	N/A	N/A	N/A	N/A	N/A	N/A	Yes	Yes	N/A
Levinson 1999[374]	Yes	Yes	No	No	Unclear	No	N/A	N/A	Unclear	Partially	Partially	No	N/A
Lewis 1998[375]	Partially	Partially	Partially	Unclear	Unclear	No	N/A	N/A	Unclear	Yes	Partially	No	N/A
Liebzeit 2001[376]	Partially	Partially	Yes	Yes	Unclear	No	N/A	N/A	Unclear	Partially	Partially	No	N/A
Margolese 2000[117]	Unclear	Partially	Yes	Partially	Unclear	No	N/A	N/A	Unclear	No	Unclear	No	N/A
Markowitz 1999[377]	Partially	No	Yes	Yes	N/A	No	N/A	No	N/A	No	Partially	No	N/A
Mir 2001[378]	No	Unclear	Yes	Yes	Unclear	No	N/A	N/A	Unclear	Partially	Yes	No	N/A
Peuskens 2000[379]	Yes	No	Yes	No	N/A	N/A	N/A	No	N/A	No	Unclear	Yes	Yes
Peuskens 2001[203]	Yes	Unclear	Yes	Yes	Unclear	No	N/A	N/A	Unclear	Partially	Yes	Yes	Yes
Schulz 2000[230]	No	Yes	Yes	No	Unclear	N/A	N/A	No	N/A	No	Unclear	Yes	Yes
Srisunapont 1999[380]	Yes	Partially	Yes	Yes	N/A	No	N/A	No	N/A	Yes	No	Yes	Yes
Taylor 2000[354]	Yes	Unclear	Yes	Yes	Unclear	No	N/A	N/A	Unclear	Partially	Yes	No	N/A
Taylor 2000[381]	Partially	Yes	Yes	Unclear	Unclear	Partially	Unclear	Yes	Unclear	Yes	Partially	No	N/A
Wighton 1998[382]	No	No	Yes	Yes	N/A	N/A	N/A	No	N/A	No	Unclear	Yes	No
Woods 2001[383]	Yes	Partially	Yes	Yes	Unclear	No	N/A	N/A	Unclear	Partially	Yes	Yes	Yes

N/A, not applicable

Appendix 6

Data extraction sheets for economic evaluations

Study details	Source of data	Method for estimation of benefits/costs	Results/statistical analysis	Sensitivity analysis	Comments
Coley 1999[314] **Type of economic evaluation:** cost-effectiveness analysis **Country/currency:** USA/$ **Cost year:** 1995 **Perspective:** unclear **Study population:** 202 inpatients at WPIC psychiatric hospital; included if admitted between 1 January 1995 and 31 December 1995, and discharged on either risperidone, haloperidol or perphenazine. Mean age: risperidone, 40.6 years, perphenazine, 42.3, haloperidol, 42.7 **Interventions (including comparator):** risperidone, perphenazine, haloperidol	**Effectiveness data:** retrospective study of patients described; sub-group analyses on patients with primary diagnosis of psychotic disorder **Cost data:** antipsychotic drug costs based on 1995 Health Care Financing Administration federal upper price limit; hospital costs based on UPMC Medicare per diem cost in 1995 **Link:** retrospective/ disconnected	**Valuation for clinical outcomes or benefits:** primary efficacy measures were readmission rates and changes in antipsychotic treatment **Estimation of costs:** costs associated with index antipsychotic selection, readmissions and lengths of stay during 1 year after index hospitalisation considered. Outpatient services not considered in cost analysis **Modelling:** not undertaken	**Clinical outcome/benefits:** outcomes for 1-year follow up Readmission (unique patients): risperidone, 33 (41%); perphenazine, 20 (26%); haloperidol, 15 (35%) Total readmissions: risperidone, 73; perphenazine, 49; haloperidol, 26 Hospitalisation days: risperidone, 22 (SE 4.2): perphenazine, 12 (SE2.9); haloperidol, 14 (SE 3.4) Change of therapy on readmission: risperidone, 10/33 (33%); perphenazine, 5/20 (25%); haloperidol, 5/15 (33%) Overall treatment success Never readmitted: risperidone, 48; perphenazine, 58; haloperidol, 28 Readmitted treatment success: risperidone, 17; perphenazine, 10; haloperidol, 10 Overall treatment success: risperidone, 65 (80%); perphenazine, 68 (87%); haloperidol, 38 (88%) Subset analyses showed readmission rates similar among groups of patients not hospitalised in WPIC catchment area. For those with history of hospitalisation during previous year, risperidone-treated patients had higher readmission rate compared with perphenazine patients; readmission similar for risperidone and haloperidol patients. For patients with primary diagnosis of psychotic disorder, risperidone patients readmitted more than perphenazine patients **Costs:** estimated yearly mean cost per patient of drug: risperidone, $2321; perphenazine, $364; haloperidol, $21 Mean cost of treatment per patient per year following index hospitalisation: risperidone, $20,317; perphenazine, $19,298; haloperidol, $11,459 Total costs of treatment highest in risperidone group – figures not provided **Synthesis of costs and benefits:** costs and effects not combined **Statistical analysis:** associations between baseline factors and treatment groups tested using Fischer exact test and Wilcoxon rank sum test. Logistic regression and proportional hazards regression used to look at association between treatment and readmission and time to first readmission. Readmission free treated periods plotted using Kaplan–Meier. Median test used to look at associations between treatment and cost	**Sensitivity analysis:** not undertaken **Appropriateness:** –	**Authors' conclusions** Results of naturalistic study demonstrate that treatment with risperidone does not improve patient outcomes as measured by hospitalisation rates compared with conventional antipsychotic drugs. Costs also higher in risperidone population **Implications for practice** Study does not support hypothesis that cost of atypical drugs offset by improvement in patient outcomes

continued

Study details	Source of data	Method for estimation of benefits/costs	Results/statistical analysis	Sensitivity analysis	Comments
Drew 1999[311] **Type of economic evaluation:** cost-effectiveness analysis **Country/currency:** Australia/$ **Cost year:** 1996–97 **Perspective:** unclear **Study population:** cohort of 37 patients from community practice within Australian capital territory (ACT). Patients had not had clozapine elsewhere and commenced clozapine in study before 1 July 1994. Recorded and appropriately documented diagnosis of schizophrenia or schizoaffective disorder; psychiatric history known **Interventions (including comparator):** post-clozapine; pre-clozapine	**Source of effectiveness data:** data obtained from records maintained by ACT hospital and community health system, and health services in areas of New South Wales. Other hospital sources, health workers and Clozapine Patient Monitoring System estimates also used when appropriate **Source of cost data:** resource utilisation collected from patients in study; unit costs supplied by ACT health department **Link:** prospective/ concurrent	**Valuation for clinical outcomes or benefits:** clinical effectiveness determined by treating psychiatrist and recorded as perceived change in clinical status. Baseline BPRS scores recorded for some patients **Estimation of costs:** costs estimated for patients in study, and constituted costs of bed occupancy, clozapine, blood monitoring and clozapine co-ordinator. Employment and accommodation details also recorded **Modelling:** not undertaken	**Clinical outcome/benefits:** 3 years post-clozapine, significant improvement seen in clinical status, cohort (31 (86.1%), $p = 0.0001$) showed moderate or marked improvement, continuers (24, $p = 0.0001$) showed improvement; too few BPRS scores to permit analyses **Costs ($Australian):** estimated cost of psychiatric treatment for cohort Pre-clozapine: year 1, 33.40 (29.63); year 2, 30.83 (34.13) Post-clozapine: year 2, bed + clozapine use, 30.22 (41.21); bed, 26.70; 3rd year: bed + clozapine costs = 32.93(42.42), bed costs = 29.64 (42.53) **Synthesis of costs and benefits:** costs and effects not combined **Statistical analysis:** comparison of two treatment group characteristics based on Fischer's exact probability tests, Mann Whitney and *t*-tests. Separate variance test used when Levene's test revealed significant difference in variance for two groups. Effect of clozapine on hospital admission analysed using Cochran Q-test followed by binomial tests. Effect of clozapine on time spent in hospital, etc., examined using Friedman analyses followed by Wilcoxon tests, if appropriate. Additional statistical tests also carried out on differences between two groups	**Sensitivity analysis:** not undertaken **Appropriateness:** –	**Authors' conclusions** Findings of significant clinical improvement without evidence of increased cost lend support to selective use of clozapine in community practice **Implications for practice** Not stated

continued

Study details	Source of data	Method for estimation of benefits/costs	Results/statistical analysis	Sensitivity analysis	Comments
Tunis 1999[315] **Type of economic evaluation:** cost-effectiveness analysis **Country/currency:** USA/$ **Cost year:** 1995 **Perspective:** not stated **Study population:** subsample of 1155 English-speaking patients from 17-country trial; patients from either out- or inpatient setting; met DSM-II-R diagnostic criteria for schizophrenia, schizophreniform disorder or schizoaffective disorder; mean age, 39 years; 70% male **Interventions (including comparator):** olanzapine; haloperidol	**Effectiveness data:** double-blind RCT conducted in 17 countries **Cost data:** medical costs based on standardised list of prices for services **Link:** not stated	**Valuation for clinical outcomes or benefits:** SF-36 completed by 1155 patients at baseline, at end of 6-week acute phase and then, for those who entered extension phase, every 8 weeks during 46-week period **Estimation of costs:** analyses of cost data included only US patients (812), to avoid difficulties with pooling data from different countries **Modelling:** mixed linear model used to impute missing data	**Clinical outcome/benefits:** results over 52 weeks Effectiveness difference (olanzapine/haloperidol), 5.75 for physical factor, 1.66 for mental health factor **Costs:** results over 52 weeks: cost difference (olanzapine/haloperidol), –$9386.87 **Synthesis of costs and benefits:** results over 52 weeks Savings per one interval (point) of improvement (olanzapine/haloperidol), $1632.50 for physical health factor, $5654.74 for mental health factor **Statistical analysis:** Mann–Whitney test used to analyse differences in costs. Missing SF-36 data imputed using mixed linear model	**Sensitivity analysis:** cost-effectiveness planes presented for bootstrap replicates. For physical health factor, olanzapine more cost-effective than haloperidol 89% of time; for mental health factor, 62% of time **Appropriateness:** not stated	**Authors' conclusions** Findings suggest that patient-centred measures of functioning, such as SF-36, are important component of evaluation of cost-effectiveness of novel treatments for schizophrenia **Implications for practice** –

continued

Study details	Source of data	Method for estimation of benefits/costs	Results/statistical analysis	Sensitivity analysis	Comments
Galvin 1999[312] **Type of economic evaluation:** cost-effectiveness analysis **Country/currency:** USA/$ **Cost year:** 1997 **Perspective:** NHS/health service **Study population:** 37 patients receiving services through Tarrant County Mental Health Mental Retardation Services. Either schizophrenia, bipolar disorder, major depression and/or GAF score < 50. Excluded: those most intolerant or least responsive to older antipsychotic drugs and could not continue use of older medications for 1 year **Interventions (including comparator):** clozapine, risperidone; chlorpromazine, haloperidol	**Effectiveness data:** retrospective, uncontrolled, open, non-randomised, within-subjects pilot study. Data on effectiveness collected from medical charts **Cost data:** data on utilisation collected from medical charts. Source of unit costs not stated **Link:** retrospective/ disconnected	**Valuation for clinical outcomes or benefits:** effectiveness measured by severity rating of general symptoms, side-effects and focussed side-effects (tardive dyskinesia, suicidal ideation, agranulocytosis and seizures); these recorded as present or absent. Effectiveness measures recorded by psychiatrists, nurses or case managers **Estimation of costs:** costs collected included: medication, weekly clozapine blood tests, hospital services, mental health clinic services and transitional living placement costs **Modelling:** not undertaken	**Clinical outcome/benefits:** newer antipsychotic drugs associated with significant reduction in general symptoms, $p = 0.007$ (actual figures not given). For most patients, general symptoms less severe with newer antipsychotic drugs than with conventional agents. Tardive dyskinesia significantly reduced with newer antipsychotic drugs, $p = 0.015$. Fewer medication changes required with newer antipsychotic drugs, $p < 0.001$ **Costs:** total cost of care $3000 less per patient per year with newer antipsychotic drugs **Synthesis of costs and benefits:** graph of change in general symptoms versus change in total cost of care presented, actual figures not given. Large proportion of patients had fewer general symptoms and reduced costs while receiving newer antipsychotic drugs **Statistical analysis:** data analysed using matched sample *t*-tests for continuous variables and chi-squared analysis for dichotomous variables. Effect sizes calculated using power analysis	**Sensitivity analysis:** not undertaken **Appropriateness:** –	**Authors' conclusions** Results suggest that short-term investment in newer medications by community mental health centres offers superior clinical effectiveness and lower long-term costs of care **Implications for practice** Treatment with newer antipsychotic drugs represents active approach to rehabilitation that works to increase patients' quality of life by reducing symptoms

continued

Study details	Source of data	Method for estimation of benefits/costs	Results/statistical analysis	Sensitivity analysis	Comments
Blieden 1998[313] **Type of economic evaluation:** cost-effectiveness analysis **Country/currency:** USA/$ **Cost year:** 1993 **Perspective:** NHS/health service **Study population:** 33 patients with schizophrenia who met DSM-II-R diagnostic criteria. Mean age, 38.0 ± 8.9 years; mean age of onset, 19.6 ± 5 years **Interventions (including comparator):** starting clozapine; 6-months after starting clozapine	**Effectiveness data:** four clinical rating scales used: BPRS, negative symptom assessment scale, Hamilton Rating Scale (depression) and QLS. Ratings made by trained doctoral-level psychologist **Cost data:** data on patients' service utilisation and residential status collected. Costs estimated from Medicaid **Link:** prospective/ concurrent	**Valuation for clinical outcomes or benefits:** not stated **Estimation of costs:** not stated **Modelling:** not undertaken	**Clinical outcome/benefits:** baseline BPRS: all, 58.72 (13.92); continued, 60.82 (14.59); discontinued, 55.75 (12.93) Negative Symptom Assessment Scale: all, 91 (17.34); continued, 95.82 (14.92); discontinued, 84.17 (18.84) Hamilton Rating Scale (depression): all, 21.24 (9.84); continued, 21.47 (9.84); discontinued, 20.92 (10.18) QLS: all, 23.07 (15.68); continued, 20.71 (12.74); discontinued, 26.42 (19.20) 6 months later BPRS: all, 45.41 (14.74); continued, 40.76 (15.07); discontinued, 52.00 (11.91) Negative Symptom Assessment Scale: all, 77.10 (20.62); continued, 74.41 (23.53); discontinued, 80.92 (15.81) Hamilton Rating Scale (depression): all, 13.38 (9.43); continued, 12.59 (11.00); discontinued, 14.50 (6.92) QLS: all, 40.45 (24.48); continued, 44.94 (28.77); discontinued, 34.08 (16.35) **Costs:** mean total healthcare costs per person, 6 months before: all, $48,114 (19,901); continued, $42, 423 (18,576); discontinued, $54,160 (20,028) Mean total healthcare costs 6 months after: all, $44,847 (16,488); continued, $36,914 (14,286); discontinued, $53,276 (14,670) **Synthesis of costs and benefits:** costs and outcomes not formally combined **Statistical analysis:** SDs reported for costs and outcomes	**Sensitivity analysis:** not stated **Appropriateness:** –	**Authors' conclusions** Continued clozapine treatment associated with reduced days of psychiatric hospital care, reduced costs even after including increased costs for outpatient treatment and residential costs, and improved health status for patients who continued clozapine treatment **Implications for practice** Not stated

continued

Study details	Source of data	Method for estimation of benefits/costs	Results/statistical analysis	Sensitivity analysis	Comments
Palmer 1998[316] **Type of economic evaluation:** cost-effectiveness analysis **Country/currency:** USA/$ **Cost year:** 1995 **Perspective:** unclear **Study population:** Patients who had experienced multiple episodes of schizophrenia **Interventions (including comparator):** olanzapine, haloperidol, risperidone	**Effectiveness data:** majority of model parameters taken from two international double-blind clinical trials of olanzapine versus haloperidol and olanzapine versus risperidone. Remaining parameter estimates from published medical literature and multidisciplinary expert advisory panel **Cost data:** direct medical costs based on expected use of hospital, day hospital, outpatient physician and other mental health provider services. Majority of data regarding resourse utilisation from expert panel supplemented by data from published literature **Link:** retrospective/ disconnected	**Valuation for clinical outcomes or benefits:** not stated **Estimation of costs:** not stated **Modelling:** 5-year Markov model used, with 3-month iterations. Model assumed suicide attempts only occurred during relapses; treatment discontinuations only occurred in first 12 months and patients who continued on therapy for ≥ 12 months had sufficient response	**Clinical outcome/benefits:** base case results BPRS scores: olanzapine, 3.18; haloperidol, 2.61; risperidone, 3.15 Non-relapse %: olanzapine, 31.2%; haloperidol, 18.2%; risperidone, 29.3% Base case results, QALYs: olanzapine, 3.15; haloperidol, 2.96; risperidone, 3.12 **Costs:** base case results: olanzapine, $92,593; haloperidol, $94,132; risperidone, $94,468 **Synthesis of costs and benefits:** using all measures of effect, both olanzapine versus haloperidol and olanzapine versus risperidone are cost saving **Statistical analysis:** –	**Sensitivity analysis:** conducted on antipsychotic drug doses, discount rate, BPRS, hospital length of stay and suicide attempt rate. Model robust to most changes, barring drug dose and hospital length of stay. Type of sensitivity analysis performed not stated **Appropriateness:** –	**Authors' conclusions** Compared with both haloperidol and risperidone therapy, olanzapine less expensive and provided superior effectiveness outcomes even with conservative values for key parameters such as relapse and discontinuation rates **Implications for practice** –

continued

Study details	Source of data	Method for estimation of benefits/costs	Results/statistical analysis	Sensitivity analysis	Comments
Sacristan 1998[34] **Type of economic evaluation:** cost-effectiveness analysis **Country/currency:** Spain/peseta **Cost year:** 1995 **Perspective:** unclear **Study population:** Inpatients from five psychiatric research units entered 6-week pilot trial; those showing initial response entered extension phase for < 26 weeks. Participants required to have DSM-II schizophrenia, documented treatment-refractory statusand severity of psychotic symptoms as defined by BPRS, PANSS and CGI (n = 25) Patients' mean age, 32.32 years; predominately male **Interventions (including comparator):** olanzapine; before olanzapine initiation	**Effectiveness data:** uncontrolled pilot study conducted **Cost data:** resource utilisation survey conducted alongside above study. Unit costs used estimated by research group based on governmental and hospital data for recent study into costs of schizophrenia in Spain	**Valuation for clinical outcomes or benefits:** PANSS, BPRS, CGI and PGI scores recorded for patients. Response defined as baseline to endpoint decrease in normailsed BPRS ≥ 35%, plus either endpoint BPRS < 18 or endpoint CGI severity < 4. Data recorded weekly during 6-week phase and monthly thereafter **Estimation of costs:** mirror image design used to determine resource utilisation. Utilisation 6 months prior to olanzapine initiation collected at beginning of study for each patient (A). Utilisation at end of 6 months olanzapine treatment also collected (B) and resource use for these two periods compared. Costs considered: direct medical and informal care. Protocol costs not considered in olanzapine period **Modelling:** not undertaken	**Clinical outcome/benefits:** mean improvement from baseline to 6 months after olanzapine treatment (SD) (95% CI) BPRS total, –15.24 (21.81) (–6.24 to –24.24); PANSS total, –25.56 (36.70) (–10.41 to –40.70); PANSS positive, –5.52 (9.47) (–1.61 to –9.43); PANSS negative, –7.28 (10.25) (–3.05 to –11.51); PANSS general, –12.76 (19.45) (–4.73 to –20.79); CGI severity, –1.44 (1.53) (–0.81 to –2.07) **Costs (pesetas):** mean direct medical costs per patient (± SD) Visits: period A, 20,532 (16,803); period B, 59,856 (99,099), $p < 0.01$ Total medication: period A, 86,367 (66,960); period B, 185,059 (102,278), $p < 0.001$; olanzapine: period B, 151,517 (85,601), NS; other medication: period A, 86,367 (66,960); period B, 33,541 (94,051), NS Partial/complete hospitalisation: period A, 771,258 (839,534); period B, 600,300 (727,067), NS Diagnostic procedures: period A, 5941 (15,249); period B, 5759 (6247), NS Total: period A, 884,098 (889,482); period B, 850,974 (760,580), NS **Synthesis of costs and benefits:** costs and effects not combined **Statistical analysis:** means, SDs and 95% CIs used to compare differences in efficacy. Wilcoxon matched pairs rank test used to compare use of resources between two periods	**Sensitivity analysis:** not conducted **Appropriateness:** –	**Authors' conclusions** Results suggest that olanzapine may be effective in significant number of patients with neuroleptic-resistant schizophrenia, and efficacy obtained does not necessarily imply increase in cost of treatment **Implications for practice** Study can be used as preliminary evidence of cost-effectivenes of olanzapine

continued

Study details	Source of data	Method for estimation of benefits/costs	Results/statistical analysis	Sensitivity analysis	Comments
Percudani 1999[309] **Type of economic evaluation:** cost-effectiveness analysis **Country/currency:** Italy/lira **Cost year:** 1995 **Perspective:** hospital **Study population:** 12 patients receiving clozapine treatment for at least 1 year. Average age at initiation, 34.8 years (SD 7.4). Considered to be severely ill population (7 most extremely ill, 4 severely ill, 1 markedly ill). Started clozapine therapy between May 1993 and May 1996, and refractory to ≥ 2 conventional antipsychotic drugs in 12 months prior to clozapine initiation **Interventions (including comparator):** post-clozapine; pre-clozapine	**Effectiveness data:** mirror image study of 12 severely ill patients **Cost data:** utilisation derived from Psychiatric Information Computerised System. Use of laboratory tests derived from Clozapine Monitoring Programme. Apart from drugs and laboratory test service, costs evaluated according to full cost accounting proceedure. Unit costs for laboratory tests derived from Italian National Health Service fee schedule. Medication costs taken from national price list **Link:** retrospective /disconnected	**Valuation for clinical outcomes or benefits:** clinical outcomes recorded prior to clozapine treatment and 1 year after initiation. Measures recorded: CGI and GAF scales **Estimation of costs:** costs estimated using 2-step procedure (i) recording all healthcare costs provided to patients (ii) assigning monetary value to each of services Hospitalisation, outpatient care, domicilliary care, social services, rehabilitation care, drug costs and laboratory costs considered in cost analysis **Modelling:** not undertaken	**Clinical outcome/benefits:** mean pre-clozapine scores: CGI-I, 6.3 (SD ± 0.8); GAF, 20.9 (SD ± 7.4) Mean post-clozapine scores: CGI-I, 4.8 (SD ± 0.9); GAF, 43 (SD ± 13.4) After 1 year, five patients considered 'very much improved', two 'much improved', five 'minimally improved' **Costs:** total cost per patient for therapy: pre-clozapine, 534,085 lira (US$299.1); post-clozapine, 3,441,439 lira (US$1972.2) Total cost per patient (including all services): pre-clozapine, 63,406,584 lira (US$35,507.7); post-clozapine, 55,521,464 lira (US$31,092) **Synthesis of costs and benefits:** costs and effects not combined **Statistical analysis:** *T*-paired tests used to assess statistical significance of differences in outcomes and costs	**Sensitivity analysis:** not undertaken **Appropriateness:** –	**Authors' conclusions** In Italian setting, use of clozapine in patients refractory to therapy may also represent rational option from both clinical and economic perspectives **Implications for practice** Clozapine is viable option in settings in which outpatient, rehabilitative and residential care are well-established and provide potential alternative to hospital care **Comments** Participants were very ill patients; results may not be easily transferable to other populations

continued

Study details	Source of data	Method for estimation of benefits/costs	Results/statistical analysis	Sensitivity analysis	Comments
Obenchain 1999[320] **Type of economic evaluation:** cost-effectiveness analysis **Country/currency:** USA/$ **Cost year:** 1996 **Perspective:** unclear **Study population:** 817 patients aged 18+ years who met DSM-II revised criteria for schizophrenia, schizoaffective disorder or schizophreniform disorder **Interventions (including comparator):** olanzapine; haloperidol	**Effectiveness data:** trial of 1996 patients, US cohort of 817 used to populate model **Cost data:** medical service utilisation collected in trial. Costs collected from pricing algorithms for 1996 price lists of drugs and medical services **Link:** unclear	**Valuation for clinical outcomes or benefits:** not stated **Estimation of costs:** not stated **Modelling:** mixed model imputation used to impute missing data	**Clinical outcome/benefits:** difference in estimated average responder days, 18.3 (olanzapine – haloperidol) **Costs:** mean costs for five models: last value carried forward: olanzapine, $52,700; haloperidol, $60,239; heterogeneous components: olanzapine, $28,334; haloperidol, $51,523; homogeneous components: olanzapine, $27,765; haloperidol, $38,066; log-predict-exponential-smear: olanzapine, $25,217; haloperidol, $42,593; completers only: olanzapine, $15,143; haloperidol, $11,214 **Synthesis of costs and benefits:** ICER (complete dataset using homogeneous components mixed model), –$563 per year per responder day **Statistical analysis:** various models for imputing missing data presented	**Sensitivity analysis:** bootstrap estimates produced for ICER; 96.4% of replications fell into minus, plus quadrant of plane **Appropriateness:** –	**Authors' conclusions** More than 95% confident that olanzapine treatment for schizophrenia is, on long-range average, both less costly and more effective than haloperidol **Implications for practice** –

continued

Study details	Source of data	Method for estimation of benefits/costs	Results/statistical analysis	Sensitivity analysis	Comments
Schiller 1999[310] **Type of economic evaluation:** cost-effectiveness analysis **Country/currency:** USA/$ **Cost year:** 1994 **Perspective:** not stated **Study population:** patients treated as outpatients between 1 February 1993 and 30 June 1995 at San Francisco Department of Mental Health Services. Patients had diagnosis of DSM-II-R schizophrenia or schizoaffective disorder and 18–65 years old (mean age, risperidone 39.5, comparator 40) **Interventions (including comparator):** risperidone; never received risperidone	**Effectiveness data:** abstracted from patients' outpatient charts for 12 months before and 12 months after risperidone initiation **Cost data:** utilisation data for psychiatric services collected from county mental health system or private hospitals. Outpatient visits and laboratory tests collected from patients chart reviews. Outpatient charts examined for medication and hospitalisation data Mental health service costs from county year-end cost report for 1994; laboratory costs from SmithKline Beecham clinical laboratories' price list; medication costs from average wholesale price lists **Link:** retrospective/ disconnected	**Valuation for clinical outcomes or benefits:** monthly GAF scores used as primary measure of effectiveness. Scores determined by chart reviews assessed by trained research assistants **Estimation of costs:** – **Modelling:** not undertaken	**Clinical outcome/benefits:** average GAF score during pre-risperidone period: comparison, 33.9 ± 6; average GAF score in post-risperidone period: risperidone, 32.2 ± 4.3; comparison, 34.3 ± 5.4 Mixed model repeated measures analysis showed no differences in monthly GAF scores over study period **Costs:** mean total annual costs pre-risperidone period: risperidone, $20,790; comparison, $14,053; mean total annual costs post-risperidone period: risperidone, $18,695; comparison, $10,907; mixed model analysis of effect of risperidone treatment: total treatment costs, $370.18 more per month for risperidone group **Synthesis of costs and benefits:** costs and effects not formally combined **Statistical analysis:** power analysis undertaken; demographic data compared using student's *t*-test or chi-squared test; primary analyses done using repeated measures analyses with serial correlation and random patient effect. Cost data logarithmically transformed. Permutation tests used to estimate how large treatment effect would tend to be under null. Evaluated potenial bias of defining risperidone group by treatment initiation	**Sensitivity analysis:** not undertaken **Appropriateness:** –	**Authors' conclusions** No significant differences in treatment effectiveness or costs found between risperidone and comparison groups, despite trend to higher treatment costs for risperidone group **Implications for practice** Not stated

continued

Study details	Source of data	Method for estimation of benefits/costs	Results/statistical analysis	Sensitivity analysis	Comments
Launois 1998[321] **Type of economic evaluation:** cost-effectiveness analysis **Country/currency:** USA/$ **Cost year:** 1996 **Perspective:** hospital **Study population:** models estimated for four different healthcare systems; data presented in paper for French model **Interventions (including comparator):** sertindole; olanzapine; haloperidol	**Effectiveness data:** adverse events taken from registration dossiers for three drugs studied; rates of relapse from survey of published meta-analysis; transitions from one care group to another calculated from two French cohorts[a] for French model, cohort of 294 German patients for German model and cross-sectional study of 1051 UK patients for UK model **Cost data:** two fixed French databases used to derive resource use. Three sources used for cost data: daily tariff charges; actual costs of professional procedures; public prices of anti-psychotic drugs **Link:** not stated	**Valuation for clinical outcomes or benefits:** not reported **Estimation of costs:** not reported **Modelling:** 10-year Markov model used with 6-month cycles. Pathways depend on whether or not patient responds to treatment and clinical benefit of treatment measured by time without relapse Three cohorts evaluated: sertindole, 12–24 mg/day; haloperidol, 10–20 mg/day; olanzapine, 10–20 mg/day Three health states defined: relapse, non-relapse, chronic disease	**Clinical outcome/benefits:** during 10-year period, 72% sertindole patients remained on treatment, 18% lost to follow-up, 10% died, and, of patients maintained on treatment, 2% chronically hospitalised, 32% relapsed, 66% stabilised Haloperidol patients had higher risk of relapse, same % died. Of 68% maintained, 2% chonically hospitalised, 45% relapsed and 53% stabilised RR of relapse on olanzapine compared with sertindole, 1.2. Mean time without relapse: sertindole, 57 months; olanzapine, 51.3; haloperidol, 43.5 months **Costs:** predicted total 10-year mean costs per patient: sertindole, $198,800; haloperidol, $205,300; olanzapine, $205,484 **Synthesis of costs and benefits:** ICER for different countries: sertindole versus haloperidol: France (1) – sertindole dominates; France (2) – sertindole more effective, more costly; Germany – sertindole dominates; UK – sertindole more effective but more costly Sertindole versus olanzapine: France (1) – sertindole dominates; France (2) – sertindole dominates; Germany – sertindole dominates; UK – sertindole dominates **Statistical analysis:** not stated	**Sensitivity analysis:** carried out on adverse events, compliance, relapse and drop-out rates; conclusions did not alter over specified ranges **Appropriateness:** –	**Authors' conclusions** Results show that compared with haloperidol or olanzapine, long-term treatment of schizophrenic patients with sertindole improves compliance, reduces number of relapses and results in net savings to psychiatric healthcare services **Implications for practice** Results suggest sertindole is cost-effective option for long-term treatment of patients with schizophrenia **Comments** –

[a] *Launois* et al. *Association d'Econométrie Appliqué. Mâtrise de la Complexité en Santé. 1998 9–10 July; Lyon, France. Proceedings: p.341–5*

continued

Study details	Source of data	Method for estimation of benefits/costs	Results/statistical analysis	Sensitivity analysis	Comments
Hamilton 1998[322] **Type of economic evaluation:** cost-effectiveness analysis **Country/currency:** USA/$ **Cost year:** not stated **Perspective:** unclear **Study population:** patients with DSM-II-R schizophrenia entered 6-week trial, responders eligible to enter 46-week double-blind maintenance phase **Interventions (including comparator):** olanzapine; haloperidol	**Effectiveness data:** collected from trial as described **Cost data:** resource use collected from patients in trial. Source of cost data not stated **Link:** prospective/ concurrent	**Valuation for clinical outcomes or benefits:** responder days (BPRS improvement ≥ 40%, or final BPRS ≤ 18) and BPRS minimal symptom days (BPRS ≤ 18) **Estimation of costs:** medical resource use collected and assigned costs using standard prices **Modelling:** none undertaken	**Clinical outcome/benefits: acute phase:** olanzapine patients achieved significantly more responder days (3.3 additional days) and BPRS-based minimal symptom days (2.8 additional days); maintenance phase: olanzapine patients achieved significantly more responder days (20.1 additional days) and significantly more BPRS-based minimal symptom days (23.3 additional days) than haloperidol patients **Costs:** acute phase: mean medical costs for olanzapine patients averaged $431 per month less than for haloperidol patients; maintenance phase: mean medical costs for olanzapine patients $345 per month lower than for haloperidol patients **Synthesis of costs and benefits:** costs and outcomes not formally combined **Statistical analysis:** *p*-values for cost and outcome estimates reported	**Sensitivity analysis:** not stated **Appropriateness:** –	**Authors' conclusions** Demonstrated that both acute and maintenance treatment of schizophrenia with olanzapine resulted in greater efficacy and cost-benefit advantage over haloperidol **Implications for practice** Not stated

continued

Study details	Source of data	Method for estimation of benefits/costs	Results/statistical analysis	Sensitivity analysis	Comments
Johnstone 1998[318] **Type of economic evaluation:** cost-effectiveness analysis **Country/currency:** USA/$ **Cost year:** not stated **Perspective:** unclear **Study population:** 814 patients with schizophrenia in USA participating in RCT **Interventions (including comparator):** olanzapine; haloperidol	**Effectiveness data:** RCT of 814 schizophrenic patients **Cost data:** not stated **Link:** not stated	**Valuation for clinical outcomes or benefits:** not stated **Estimation of costs:** not stated **Modelling:** mixed linear-effects models used to estimate 95% CI for ICER Bootstrapping used to resample data	**Clinical outcome/benefits:** difference in average number of symptom-free days (olanzapine/haloperidol), 17.72 **Costs:** difference in average annual costs (olanzapine/haloperidol), –$10,179 **Synthesis of costs and benefits:** ICER, –$575 **Statistical analysis:** mixed-effects linear models used to impute missing outcome data	**Sensitivity analysis:** re-sampling bootstrap estimates, showed olanzapine to be more effective and less costly 96.5% of time **Appropriateness:** –	**Authors' conclusions** Olanzapine displayed significant cost and effectivenesss advantages for treatment of schizophrenia compared with haloperidol over 1-year therapeutic interval from ITT perspective **Implications for practice** –

continued

Study details	Source of data	Method for estimation of benefits/costs	Results/statistical analysis	Sensitivity analysis	Comments
Wang 1998[384] **Type of economic evaluation:** cost–utility analysis **Country/currency:** Canada/$ **Cost year:** not stated **Perspective:** NHS/health service **Study population:** not stated **Interventions (including comparator):** risperidone; oral haloperidol; depot haloperidol; fluphenazine	**Effectiveness data:** probabilities used in model from systematic review of literature **Cost data:** from provincial formulary and fee schedules, standard lists for community resources and hospital case costing **Link:** not stated	**Valuation for clinical outcomes or benefits:** utilities measured using standard gamble technique in 25 stable patients with schizophrenia **Estimation of costs**: – **Modelling:** decision-analytic model used to assess costs and outcomes of alternative antipsychotic drugs	**Clinical outcome/benefits:** risperidone dominated all comparators, with the highest clinical success rate of 67%. Risperidone dominated all comparators, with the greatest number of QALYs, 0.89. Fluphenazine had lowest number of QALYs, 0.85 **Costs:** risperidone dominated all comparators with lowest expected cost, $69,885, over 1-year period. Fluphenazine had highest expected cost, $82,264 **Synthesis of costs and benefits:** costs and outcomes not formally combined **Statistical analysis:** not stated	**Sensitivity analysis:** not stated **Appropriateness:** –	**Authors' conclusions** Use of risperidone in place of haloperidol in Canada would be associated with annual savings of $832 million in hospital expenditure, $113 million in incremental drug expenditure and $180 million in annual incremental community care expenses **Implications for practice** Generalisability of results to UK setting may not be wise, without validation

continued

Study details	Source of data	Method for estimation of benefits/costs	Results/statistical analysis	Sensitivity analysis	Comments
Byrom 1998[324] **Type of economic evaluation:** cost-effectiveness analysis **Country/currency:** USA/$ **Cost year:** 1992–93 **Perspective:** societal **Study population:** patients presenting with acute episode of chronic schizophrenia **Interventions (including comparator):** typical antipsychotic drugs; atypical antipsychotic drugs	**Source of effectiveness data:** model parameters estimated on basis of published data for typical antipsychotic drugs[a,b,9,116,164,168,255] Meta-analysis results used for average compliance and relapse rates for compliant and non-compliant patients **Source of cost data:** costs of care based on English unit cost data **Link:** not stated	**Valuation for clinical outcomes or benefits:** outcomes simulated in model **Estimation of costs:** costs simulated in model **Modelling:** decision-analytic model used to estimate costs and outcomes of various treatments Experiment 6 looked at effect of hypothetical new drug on possible economic outcomes	**Clinical outcome/benefits:** for atypical antipsychotic drugs, 49% effectiveness for 8 weeks' management of acute episode. After 1 year, effectiveness was 25.7% For typical antipsychotic drugs, 31.6% effectiveness for 8 weeks' management of acute episode. Effectiveness after 1 year was 12.8% Proportion of patients achieving 40% reduction in BPRS in first 8 weeks, and subsequently not suffering relapse over 1-year period, doubled from 12.8% to 25.7% with atypical antipsychotic treatment **Costs:** atypical antipsychotic drug costs: 8 weeks management of acute episode, $7963; 1 year of treatment following acute episode, $34,663 Typical antipsychotic treatment costs: 8 weeks management of acute episode, $8920; 1 year of treatment following acute episode, $36,900 **Synthesis of costs and benefits:** costs and outcomes not formally combined **Statistical analysis:** ECOS software application used to investigate how changes in model parameters would influence cost and effectiveness results	**Sensitivity analysis:** not stated; however, experiments did look at changes in certain model parameters **Appropriateness:** –	**Authors' conclusions** Results show that high price of atypical antipsychotic drugs can be justified if claims of improved efficacy in positive and negative symptoms and improved side-effect profiles translate into health economic benefit **Implications for practice** Not stated

[a] *Arvanitis* et al. *Biol Psychiatry 1997;**42**:233–46*
[b] *Kavanagh* et al. *Soc Psychiatr Epidemiol 1995;**30**:206–12*

continued

Study details	Source of data	Method for estimation of benefits/costs	Results/statistical analysis	Sensitivity analysis	Comments
Hammond 1999[327] **Type of economic evaluation:** cost-effectiveness analysis **Country/currency:** USA/$ **Cost year:** not stated **Perspective:** not stated **Study population:** patients with severe mental disabilities (68%/55% schizoprenia, 19%/25% schizo-affective disorder, 13%/15% bipolar disorder for study and control group, respectively. 31 patients recruited to study group and 20 to control group **Interventions (including comparator):** post-risperidone; pre-risperidone	**Effectiveness data:** data on concomitant medications from Central Pharmacy medication profile **Cost data:** Summit County ADM board developed computer program that provided service codes, hours of service use and cost of ADM services for each client Hospitalisation dates for each patient obtained from Ohio Department of Mental Health patient-care system database **Link:** not stated	**Valuation for clinical outcomes or benefits:** not reported **Estimation of costs:** not reported **Modelling:** not reported	**Clinical outcome/benefits:** **Costs:** **Synthesis of costs and benefits:** **Statistical analysis:**	**Sensitivity analysis:** not reported **Appropriateness:** –	**Authors' conclusions** From perspective of the community ADM board, risperidone treatment did not reduce cost of services provided to these clients but substantially and significantly increased total costs, including medication

ADM, Alcohol, Drug Abuse and Mental Health

continued

Study details	Source of data	Method for estimation of benefits/costs	Results/statistical analysis	Sensitivity analysis	Comments
Finley 1998[317] **Type of economic evaluation:** not stated **Country/currency:** USA/$ **Cost year:** not stated **Perspective:** unclear **Study population:** all adult patients initiated on risperidone therapy at inpatient psychiatric facility of Department of Veterans Affairs. Patients had to satisfy one of following criteria: (i) treatment-resistant illness or (ii) treatment intolerence 57 patients included; 100% male, average age 45.8 years at time of initiation **Interventions (including comparator):** after risperidone initiation; before risperidone initiation	**Effectiveness data:** collected from variety of sources, computerised records, in- and outpatient treatment records, telephone contact with mental health providers **Cost data:** inpatient expenditure – estimated hospitalisation rates and financial data obtained from administrative offices of department of psychiatry for services during 1994–95; drug costs taken from wholesale acquisition costs **Link:** retrospective/ disconnected	**Valuation for clinical outcomes or benefits:** data collected on number of days hospitalised in 12 months before and after risperidone initiation, change in CGI scores. CGI scores determined from documented evidence of patient progress in medical records **Estimation of costs:** direct care costs considered were inpatient expenditureand wholesale drug acquisition costs **Modelling:** not undertaken	**Clinical outcome/benefits:** days hospitalised (12 month period): responders, before 43.9, after 25.2, $p = 0.030$; non-responders, before 59.1, after 58.3, $p = 0.447$ CGI severity scores: responders, before 5.04, after 3.96, $p = 0.001$; non-responders, before 4.91, after 4.39, $p = 0.015$ Concurrent psychotropic medications: responders, before 3.3, after 2.6, $p = 0.017$; non-responders, before 3.3, after 2.7, $p = 0.029$ **Costs:** annual cost of medication: responders $49,472; non-responders $5,602; total $55,074 Annual cost savings with reduced hospitalisation: net change in cost of hospitalisation $203,036 Annual savings associated with risperidone trial $147,962 **Synthesis of costs and benefits:** costs and effects not combined **Statistical analysis:** data tested for normality using Wil-Shapiro statistic. To test for potential differences between paired data, Wilcoxon signed rank test used. Unpaired data tested for significant differences using Mann–Whitney rank sum test. Nominal data tested for significant using Yates corrected chi-squared analysis of Fischer exact test for small samples. Univariate logistic regression analysis used to identify variables significantly influencing dependent variable	**Sensitivity analysis:** not undertaken **Appropriateness:** –	**Authors' conclusions** Significant decline in days hospitalised observed among responsive patients seems to indicate that risperidone may be a cost-effective approach to management of psychotic symptoms **Implications for practice** Results of naturalistic indicate that risperidone may be an alternative for management of psychotic symptoms in patients for whom convential anti-psychotic treatment had failed

continued

Study details	Source of data	Method for estimation of benefits/costs	Results/statistical analysis	Sensitivity analysis	Comments
Davies 2000[308] **Type of economic evaluation:** cost–utility analysis **Country/ currency:** UK/£ sterling **Cost year:** 1997 **Perspective:** NHS/health service **Study population:** population targeted by current guidelines; first-episode patients **Interventions (including comparator):** risperidone; clozapine; olanzapine; chlorpromazine; haloperidol	**Effectiveness data:** principally from review of clinical data, identified from search of MEDLINE, Econlit, CINAHL and Cochrane Library; Cochrane systematic reviews used when available **Excluded:** trials with no active comparator, non RCTs, pharmacologic or pharmacokinetic studies, dosing/ titration studies or studies without final outcomes in terms of symptom control or patient acceptability Utilities taken from Glennie, 1997;[18] however, values generated by Chouinard *et al.*[20] used as plausible ranges in sensitivity analysis **Cost data:** review of economic literature conducted to derive estimates of resource use; where possible, this estimated from clinical guidelines or best practice. Costs estimated from measures of health and social care service use associated with events **Link:** retrospective/ disconnected	**Valuation for clinical outcomes or benefits:** – **Estimation of costs:** assumptions for costing consistent with objectives and patient group in analysis **Modelling:** probabilistic model used to estimate costs and effects associated with initial decision to prescribe antipsychotic drug for first-episode schizophrenia patients	**Clinical outcome/benefits:** simulated expected QALYs (per cohort of 1000 patients) *Truncated normal distribution*: chlorpromazine (all doses) 2374 (2367–2377); chlorpromazine (lower dose) 2397 (2391–2402); haloperidol (all doses) 2303 (2299–2307); haloperidol (lower dose) 2305 (2302–2309); risperidone 2426 (2422–2429); olanzapine 2327 (2324–2331) *Triangular distribution*: chlorpromazine (all doses) £2336 (2334–2339); chlorpromazine (lower dose) £2300 (2295–2304); haloperidol (all doses) 2298 (2295–2301); haloperidol (lower dose) 2199 (2193–2206); risperidone 2414 (2411–2416); olanzapine 2326 (2324–2329) Simulated expected QALYs per patient completing or switching therapy also presented **Costs:** simulated expected costs *Truncated normal distribution*: chlorpromazine (all doses) £17,227,550 (17,073,277–17,381,823); chlorpromazine (lower dose) £17,252,360 (17,085,623–17,419,097); haloperidol (all doses) £19,822,160 (19,637,972–20,006,348); haloperidol (lower dose) £19,963,110 (19,781,420–20,144,800); risperidone £20,440,480 (20,280,038–20,600,922); olanzapine £21,923,940 (21,738,406–22,109,474) *Triangular distribution*: chlorpromazine (all doses) £17,982,170 (17,844,285–18,120,055); chlorpromazine (lower dose) £19,921,520 (19,739,726–20,103,314); haloperidol (all doses) £20,160,470 (19,994,590–20,326,350); haloperidol (lower dose) £23,944,640 (23,727,756–24,161,524); risperidone £20,653,000 (20,507,377–20,798,623); olanzapine £22,312,200 (22,146,241–22,478,159) Simulated expected costs per patient completing or switching therapy also presented **Synthesis of costs and benefits:** cost/QALY by comparator *Truncated normal distribution*: chlorpromazine (all doses) versus chlorpromazine (lower dose) – chlorpromazine (all doses) dominates; haloperidol (all doses) versus chlorpromazine (all doses) – haloperidol (all doses) dominates; haloperidol (lower dose) versus chloropromazine (all doses) – haloperidol dominates; risperidone versus chloropromazine (lower dose) – £109,935; olanzapine versus chlorpromazine (all doses) – olanzapine dominates *Triangular distribution*: chlorpromazine (lower dose) versus chlorpromazine (all doses) – chlorpromazine (lower dose) dominates; haloperidol (all doses) versus chlorpromazine (all doses) – haloperidol dominates; haloperidol (lower dose) versus chlorpromazine (all doses) – haloperidol (all doses) dominates; haloperidol (lower dose) versus chlorpromazine (all doses) – haloperidol (lower dose) dominates; risperidone versus chlorpromazine (all doses) – £34,241; olanzapine versus chlorpromazine (all doses) – olanzapine dominates **Statistical analysis:** not undertaken outside the model	**Sensitivity analysis:** model constructed as stochastic model, hence results recalculated over number of iterations; this allowed uncertainty in all specified model parameters to be estimated. CIs for results presented **Appropriateness:** this type of analysis appropriate given type and quality of data available	**Authors' conclusions** Overall, data from simulation analysis of 3-year expected costs and outcomes suggest that chlorpromazine, risperidone and clozapine (third- and fourth-line therapy only) were more efficient in terms of expected costs and QALYs than haloperidol or olanzapine **Implications for practice** Results from model suggest that for this patient population clozapine and risperidone may be more effective than typical antipsychotic drugs but at higher cost. However, uncertain what would be acceptable cost per QALY; hence difficult to suggest suitable treatment choice for NHS patients of this type

continued

Study details	Source of data	Method for estimation of benefits/costs	Results/statistical analysis	Sensitivity analysis	Comments
Almond 2000[326] **Type of economic evaluation:** cost-effectiveness analysis **Country/currency:** UK/£ sterling **Cost year:** 1999 **Perspective:** unclear **Study population:** not applicable **Interventions (including comparator):** olanzapine; risperidone; haloperidol	**Effectiveness data:** model parameters from clinical trials conducted in UK. If trial data not available, published data and expert opinion used **Cost data:** service utilisation, as in previous model	**Valuation for clinical outcomes or benefits:** outcomes measured as BPRS scores and non-relapse rates **Estimation of costs:** – **Modelling:** 5-year Markov decision tree simulation model. As previous study (Almond & O'Donnell, 1998[a]) – Almond *et al.* 1999[37], with third initial treatment node added	**Clinical outcome/benefits:** average percentage of 5-year period in which individual BPRS scores less than 18: olanzapine 63.6%; risperidone 63.0%; haloperidol 52.2% Non-relapse rates: olanzapine 31.2%; risperidone 29.3%; haloperidol 18.2% **Costs:** cumulative (annual) costs over 5 years (discounted at 6%) year 1: olanzapine £15,020; risperidone £15,468; haloperidol £15,414 year 2: olanzapine £20,734 (5714); risperidone £21,319 (5851); haloperidol £21,423 (6009) year 3: olanzapine £25,970 (5236); risperidone £26,665 (5346); haloperidol £26,813 (5390) year 4: olanzapine £30,894 (4924); risperidone £31,688 (5023); haloperidol £31,814 (5001) year 5: olanzapine £35,701 (4807); risperidone £36,590 (4902); haloperidol £36,653 (4839) **Synthesis of costs and benefits:** costs and outcomes not formally combined **Statistical analysis:** not stated	**Sensitivity analysis:** one-way sensitivity analysis conducted on drug doses and sources of cost differences **Appropriateness:** –	**Authors' conclusions** Given evidence of efficacy gains to atypical drugs, these represent cost-effective treatment options. Prospective data from non-trial treatment settings would help to substantiate model findings **Implications for practice** Olanzapine and risperidone should be offered to this patient population in favor of haloperidol **Comments** BPRS scores for risperidone set equal to those for olanzapine for all but initial treatment period

[a] *Almond S, O'Donnell O. Pharmaeconomics 1998;**13**:575–88*

continued

Study details	Source of data	Method for estimation of benefits/costs	Results/statistical analysis	Sensitivity analysis	Comments
Chinchilla 1998[319] **Type of economic evaluation:** cost-effectiveness analysis **Country/currency:** USA/$ **Cost year:** not stated **Perspective:** unclear **Study population:** 30 patients diagnosed with schizophrenia according to DSM-IV criteria Mean age, 34.4 years; mean age at onset, 24.1 years with mean of 3.3 episodes of exacerbation during illness follow-up **Interventions (including comparator):** year with risperidone; year before risperidone	**Effectiveness data:** prospective study of population **Cost data:** costs collected alonside study **Link:** prospective/ concurrent	**Valuation for clinical outcomes or benefits:** effect measured by CGI **Estimation of costs:** overall cost calculated by adding number of days of hospitalisation to number of outpatient visits and pharmacy cost for previous year and year with risperidone for patient sample **Modelling:** not undertaken	**Clinical outcome/benefits:** year before, mean CGI score 5.06; year after, mean CGI score 2.46 **Costs:** year before, mean total cost of hospitalisation $3.422 per patient/per year, $102.666 for whole sample; year after, mean total cost of hospitalisation $833 per patient/per year, $25.000 for whole sample **Synthesis of costs and benefits:** costs and outcomes not formally combined **Statistical analysis:** not stated	**Sensitivity analysis:** not stated **Appropriateness:** –	**Authors' conclusions** Risperidone is first-line treatment for patients with schizophrenia based on clinical and economic evidence **Implications for practice** Not stated

continued

Study details	Source of data	Method for estimation of benefits/costs	Results/statistical analysis	Sensitivity analysis	Comments
Oh 1999[323] **Type of economic evaluation:** cost–utility analysis **Country/currency:** Canada/$ **Cost year:** 1998 **Perspective:** NHS/health service **Study population:** stable patients with chronic schizophrenia **Interventions (including comparator):** risperidone; haloperidol; haloperidol decanoate; fluphenazine decanoate	**Effectiveness data:** random effects single arm meta-analysis of clinical trials of agents of interest (no references in abstract) Utilities derived from interviews with patients **Cost data:** costs of care from case-specific costing at author's institution, community agencies and provincial sources **Link:** unclear	**Valuation for clinical outcomes or benefits:** not stated **Estimation of costs:** not stated **Modelling:** deterministic decision analysis used to model costs and outcomes	**Clinical outcome/benefits:** only QALYs reported Expected QALYs over 1 year: risperidone 0.87; haloperidol 0.83; haloperidol dec 0.84; fluphenazine dec 0.83 Lifetime incremental benefit of risperidone 0.70 **Costs:** expected cost over 1 year: risperidone $69,855; haloperidol $76,365; haloperidol dec $78,388; fluphenazine dec $82,264 Lifetime expected cost saving of risperidone $114,230 **Synthesis of costs and benefits:** not formally combined **Statistical analysis:** not stated	**Sensitivity analysis:** undertaken but not described in abstract **Appropriateness:** –	**Authors' conclusions** Risperidone appears very cost-effective therapy compared with haloperidol and depot neuroleptic drugs in patients with chronic schizophrenia **Implications for practice** Risperidone should be considered treatment of choice compared with haloperidol and depot neuroleptic drugs for patients with chronic schizophrenia

continued

Study details	Source of data	Method for estimation of benefits/costs	Results/statistical analysis	Sensitivity analysis	Comments
De Hert 2000[330] **Type of economic evaluation:** cost-effectiveness analysis **Country/currency:** Belgium/euro (€) **Cost year:** not stated **Perspective:** NHS/health service **Study population:** not stated **Interventions (including comparator):** risperidone; olanzapine; haloperidol	**Effectiveness data:** not stated **Cost data:** not stated **Link:** not stated	**Valuation for clinical outcomes or benefits:** effectiveness measured as time with minimal symptoms and toxicity (CWMST) **Estimation of costs:** direct medical costs collected over 1-year period in current healthcare setting in Belgium Direct medical costs for five different patient care settings, consultations, neuroleptic medication, laboratory tests and treatment of side-effects **Modelling:** 1-year semi-Markov model constructed; nine 6-week cycles defined. Events comprised: survival, response, adverse events and compliance. Compliance modelled as function of health stated, time and adverse events	**Clinical outcome/benefits:** first-line therapy – risperidone/olanzapine, 69.4% time with minimum symptoms and minimum toxicity **Costs:** first-line therapy – total expected direct medical costs Risperidone 28,202.85 €; haloperidol 28,309.44 €; olanzapine 28,554.86 € **Synthesis of costs and benefits:** risperidone versus olanzapine 4512.46 €/CWMST; risperidone versus haloperidol, risperidone dominant; olanzapine more effective than haloperidol but more expensive **Statistical analysis:** not stated	**Sensitivity analysis:** one-way performed; changing hospital cost per day (± 20%) did not affect order of strategies but changed total cost per strategy by ± 14.6%. Acquisition costs per mg reimbursed were alsovaried by ± 50%. With price 40% lower, olanzapine would become most cost-effective strategy (31% cheaper); olanzapine and risperidone equally cost-effective Increasing/decreasing doses of risperidone and olanzapine also investigated, none of which changed results **Appropriateness:** full stochastic sensitivity analysis would have been more appropriate, given nature of data	**Authors' conclusions** Over 1 year, risperidone and olanzapine more cost-effective than haloperidol and of two major atypical antipsychotic drugs, risperidone more cost-effective **Implications for practice** Model developed for European country, hence results should be reasonably transferable to UK setting **Comments** Minimal effectiveness results reported; ICER for olanzapine versus haloperidol not reported

CWMST, Time with minimal symptoms and toxicity

continued

Study details	Source of data	Method for estimation of benefits/costs	Results/statistical analysis	Sensitivity analysis	Comments
Gregor 2000[328] **Type of economic evaluation:** cost-effectiveness analysis **Country/currency:** France/franc (fr) **Cost year:** not stated **Perspective:** unclear **Study population:** subset of French patients (*n* = 275) who participated in large RCT **Interventions (including comparator):** olanzapine; haloperidol	**Effectiveness data:** RCT data **Cost data:** utilisation data collected alongside RCT. Source of unit cost data not stated **Link:** prospective/ concurrent	**Valuation for clinical outcomes or benefits:** primary clinical measure, 'marked clinical response', taken from BPRS scores Secondary measure 'marked clinical improvement', derived from CGI severity of illness scores **Estimation of costs:** costs defined as mean per diem per patient total direct medical costs. **Modelling:** not undertaken	**Clinical outcome/benefits:** 'marked clinical response' – olanzapine 54%, haloperidol 40%; 'marked clinical improvement' – olanzapine 69%, haloperidol 54% **Costs:** mean per diem, per patient total direct medical costs – olanzapine 619 fr ± 509; haloperidol 756 fr ± 478 **Synthesis of costs and benefits:** costs and effects not formally combined **Statistical analysis:** *p*-values for results reported	**Sensitivity analysis:** not undertaken **Appropriateness:** –	**Authors' conclusions** Olanzapine treatment associated with significantly better clinical outcomes and significantly lower per diem total direct medical costs than haloperidol. Findings indicate that olanzapine is cost-effective **Implications for practice** Not stated **Comments** Details of costs included in total direct costs not given. Few details regarding valuation of outcomes offered

continued

Study details	Source of data	Method for estimation of benefits/costs	Results/statistical analysis	Sensitivity analysis	Comments
Kasper 2000[329] **Type of economic evaluation:** cost-effectiveness analysis **Country/currency:** USA/$ **Cost year:** not stated **Perspective:** unclear **Study population:** included if (i) diagnosis of schizophrenia or schizoaffective disorder; (ii) discharged or at least 120 days of follow-up; (iii) aged < 65 years; (iv) treated with either risperidone or olanzapine Patients, *n* = 1901, from 61 hospitals in nine countries (Australia, Austria, Denmark, Great Britian, Germany, The Netherlands, Norway, Spain and Sweden) **Age at admission:** risperidone 38 ± 12 years; olanzapine 38 ± 12 years **Interventions (including comparator):** risperidone; olanzapine	**Effectiveness data:** obtained via retrospective chart review **Cost data:** utilisation determined through chart review; source of unit cost data not stated **Link:** retrospective/disconnected	**Valuation for clinical outcomes or benefits:** data collected on numbers of patients discharged before or at day 120, average length of hospital stay, numbers of patients with effective treatment, numbers of days before efficacy established, numbers of patients who discontinued treatment Measure of efficacy considered not stated **Estimation of costs:** average total cost and average daily cost of inpatient drugs calculated **Modelling:** not undertaken	**Clinical outcome/benefits:** number of patients discharged before or at day 120: risperidone 834 (90%); olanzapine 875 (90%); $p = 0.6$ Average length of stay: risperidone 43.5 ± 35 days; olanzapine 47.4 ± 35 days; $p = 0.004$ Number of patients with effective treatment: risperidone 765 (84%); olanzapine 766 (79%); $p = 0.01$ Number of days before efficacy established: risperidone 13.6 ± 13; olanzapine 18.6 ± 18; $p < 0.0001$ Number of patients discontinuing treatment: risperidone 138 (15%); olanzapine 162 (17%); $p = 0.3$ **Costs:** average total cost of all inpatient drugs: risperidone $159.9 ± 183; olanzapine $297.5 ± 305; $p < 0.0001$ Average daily cost of all inpatient drugs: risperidone $4.6 ± 2.9; olanzapine 7.7 ± 4.0; $p < 0.0001$ **Synthesis of costs and benefits:** costs and effects not combined **Statistical analysis:** *p*-values reported for outcomes	**Sensitivity analysis:** not undertaken **Appropriateness:** –	**Authors' conclusions** With shorter length of hospital stay and substantially lower medication costs, risperidone treatment significantly less costly than olanzapine. In addition, risperidone appears more likely to be effective and efficacy seems to be achieved sooner **Implications for practice** Finding should be of particular interest to public health system **Comments** Valuation of effectiveness and efficacy not described

continued

Study details	Source of data	Method for estimation of benefits/costs	Results/statistical analysis	Sensitivity analysis	Comments
Loos 2000[331] **Type of economic evaluation:** cost-effectiveness analysis **Country/currency:** The Netherlands/fl **Cost year:** not stated **Perspective:** hospital **Study population:** patients under 65 years old, within Delta Psychiatric Hospital; first-episode patients **Interventions (including comparator):** risperidone; olanzapine	**Effectiveness data:** retrospective review of 64 psychotic patients who received either risperidone or olanzapine shortly after admission, as first line therapy. Patients character-istics recorded but not reported in abstract **Cost data:** not stated **Link:** not stated	**Valuation for clinical outcomes or benefits:** effectiveness (measure not stated), duration of time to efficacy, length of admission, adverse events and dose of study medication recorded **Estimation of costs:** medication cost per day calculated **Modelling:** not undertaken	**Clinical outcome/benefits:** effectiveness: risperidone 72%; olanzapine 68%; $p = 0.79$; treatment duration bfore efficacy established similar, 7 days $p = 0.98$ Length of admission: risperidone 38.5; olanzapine 42.5; $p = 0.62$ Adverse events: risperidone 9 (28%); olanzapine 14 (44%) **Costs:** average daily cost of inpatient medication: risperidone 8.87 fl; olanzapine 12.34 fl; $p < 0.03$ **Synthesis of costs and benefits:** costs and effects not combined **Statistical analysis:** not stated	**Sensitivity analysis:** not stated **Appropriateness:** –	**Authors' conclusions** Both risperidone and olanzapine appeared to satisfy as first-line drugs for treatment of newly admitted psychotic patients. Treatment with risperidone less expensive than expected **Implications for practice** Not stated **Comments** Details of measure of effectiveness not given; costs only included medication costs

continued

Study details	Source of data	Method for estimation of benefits/costs	Results/statistical analysis	Sensitivity analysis	Comments
Martin 2000[332] **Type of economic evaluation:** cost-effectiveness analysis **Country/currency:** UK/£ sterling **Cost year:** not stated **Perspective:** unclear **Study population:** 65 newly diagnosed schizophrenia in patients discharged from hospital or who had been in hospital for 12 days; naturalistic clinical setting in English centres **Interventions (including comparator):** risperidone; olanzapine	**Effectiveness data:** outcomes data collected from retrospective chart review **Cost data:** utilisation presumable collected from chart reviews; source of unit cost data unknown **Link:** retrospective/disconnected	**Valuation for clinical outcomes or benefits:** proportion of patients discharged before 120 days, patients who discontinued or switched treatments, duration of treatment, efficacy, time to efficacy, side-effects **Estimation of costs:** use and costs of all inpatient medications **Modelling:** not undertaken	**Clinical outcome/benefits:** median time before efficacy established: risperidone 7.0 days; olanzapine 12.5 days; $p = 0.04$ Proportion of patients treated effectively: risperidone 84%; olanzapine 85% Patients experiencing adverse events: risperidone 8; olanzapine 6 **Costs:** mean daily cost of inpatient medications: risperidone £3.34; olanzapine £6.05; $p = 0.0057$ Mean daily cost of study medication: risperidone £2.45; olanzapine £4.71 **Synthesis of costs and benefits:** costs and effects not combined **Statistical analysis:** *p*-values given for costs and outcomes	**Sensitivity analysis:** not stated/undertaken **Appropriateness:** not stated/undertaken	**Authors' conclusions** Data suggest that risperidone more cost-effective treatment than olanzapine in naturalistic clinical setting. When working within a constrained budget, more patients may therefore be treated with risperidone than olanzapine without compromising efficacy **Implications for practice** Not stated **Comments** Total costs not reported; measure of effectiveness or efficacy not stated

continued

Study details	Source of data	Method for estimation of benefits/costs	Results/statistical analysis	Sensitivity analysis	Comments
Essock 2000[335] **Type of economic evaluation:** cost-effectiveness **Country/currency:** USA/$ **Cost year:** 1993 **Perspective:** not stated **Study population:** patients from three state hospitals with specified diagnosis of schizophrenia **Interventions (including comparator):** clozapine; conventional antipsychotic medications	**Effectiveness data:** open-label, RCT **Cost data:** chart reviews provided resource use **Link:** conducted for same population	**Valuation for clinical outcomes or benefits:** BPRS; Quality-of-Life Inventory; AIMS **Estimation of costs:** reviewing fiscal records, e.g. Medicare cost report **Modelling:** none undertaken	**Clinical outcome/benefits:** once discharged from hospital, clozapine group less likely to be readmitted. Clozapine patients experienced significantly fewer extrapyramidal effects. Groups did not differ with respect to changes in BPRS scores **Costs:** clozapine patients accrued, on average, $1112 greater costs in year 1 and $7149 lower cost in year 2; 95% CIs for these estimates given **Synthesis of costs and benefits:** ICERs calculated for four effectiveness measures **Statistical analysis:** bootstrap replicates calculated to construct 95% CIs for ICERs	**Sensitivity analysis:** bootstrap (10,000) replicates calculated for ICERs; cost-effectiveness planes drawn **Appropriateness:** –	**Authors' conclusions** Clozapine demonstrated cost-effectiveness on some but not all measures of effectiveness when alternative was range of conventional antipsychotic medications **Implications for practice** Not stated

continued

Study details	Source of data	Method for estimation of benefits/costs	Results/statistical analysis	Sensitivity analysis	Comments
Duchesne 1999[336] **Type of economic evaluation:** cost-effectiveness **Country/currency:** USA/$ **Cost year:** not stated **Perspective:** not stated **Study population:** 601 patients with schizophrenia or schizoaffective disorder **Interventions (including comparator):** risperidone; olanzapine	**Effectiveness data:** pooled from series of retrospective single-centre studies **Cost data:** pooled from series of retrospective single-centre studies **Link:** same source	**Valuation for clinical outcomes or benefits:** retrospective chart review **Estimation of costs:** retrospective chart review **Modelling:** none undertaken	**Clinical outcome/benefits:** efficacy rates: risperidone 78%; olanzapine 77% **Costs:** mean daily treatment costs: risperidone $3.3; olanzapine 6.5 Daily mean all-medical costs: risperidone $4.2; olanzapine $7.3 **Synthesis of costs and benefits:** not undertaken **Statistical analysis:** Cox regression model used to model length of stay. Contribution of key cost drivers examined through regression analysis	**Sensitivity analysis:** not undertaken **Appropriateness:** –	**Authors' conclusions** Choice and dose of atypical antipsychotic drug major driver of inpatient therapy cost **Implications for practice** Not stated

continued

Study details	Source of data	Method for estimation of benefits/costs	Results/statistical analysis	Sensitivity analysis	Comments
Bille 1999[337] **Type of economic evaluation:** cost-effectiveness **Country/currency:** Denmark/kroner (DDK) **Cost year:** not stated **Perspective:** not stated **Study population:** 68 patients in Vordingborg hospital **Interventions (including comparator):** risperidone; olanzapine	**Effectiveness data:** retrospective chart reviews **Cost data:** retrospective chart reviews **Link:** same source	**Valuation for clinical outcomes or benefits:** efficacy and median time to efficacy taken from chart reviews **Estimation of costs:** costs of inpatient medication **Modelling:** not undertaken	**Clinical outcome/benefits:** efficacy: risperidone 77%; olanzapine 78%; mean time to efficacy: risperidone 14 days; olanzapine 19.5 days **Costs:** mean daily cost of inpatient medication: risperidone 51.6 DDK; olanzapine 22.9 DDK **Synthesis of costs and benefits:** not undertaken **Statistical analysis:** not stated	**Sensitivity analysis:** not stated **Appropriateness:** –	**Authors' conclusions** Results indicated that treatment with risperidone more cost-effective than treatment with olanzapine and shows efficacy earlier **Implications for practice** Not stated

continued

Study details	Source of data	Method for estimation of benefits/costs	Results/statistical analysis	Sensitivity analysis	Comments
Edgell 2000[170] **Type of economic evaluation:** cost-effectiveness **Country/currency:** USA/$ **Cost year:** 1997 **Perspective:** payer or healthcare system perspective **Study population:** patients recruited from 13 clinical centres in USA **Interventions (including comparator):** risperidone; olanzapine	**Effectiveness data:** randomised , double-blind, prospective study **Cost data:** case record forms of patients in trial **Link:** same source	**Valuation for clinical outcomes or benefits:** PANSS; CGI; SAS; BAS; AIMS **Estimation of costs:** resource use collected from patients in trial; several sources used to estimate costs **Modelling:** not undertaken	**Clinical outcome/benefits:** no difference found in PANSS scores. No significant differences found in categorical analysis of other outcome scales **Costs:** total per patient costs $2843 lower in olanzapine group **Synthesis of costs and benefits:** not undertaken **Statistical analysis:** not undertaken	**Sensitivity analysis:** sensitivity analysis undertaken on doses **Appropriateness:** –	**Authors' conclusions** Olanzapine-treated patients experienced clinical improvements that translated into savings in costs of care for both in- and out-patient services. Savings offset difference in medication acquisition cost between olanzapine and risperidone **Implications for practice** Not stated

continued

Study details	Source of data	Method for estimation of benefits/costs	Results/statistical analysis	Sensitivity analysis	Comments
Rosenheck 1998[115] **Type of economic evaluation:** cost-effectiveness **Country/currency:** USA/$ **Cost year:** not stated. **Perspective:** not stated **Study population:** patients with refractory schizophrenia and 30–364 days of hospitalisation, during previous year **Interventions (including comparator):** clozapine; haloperidol	**Effectiveness data:** prospective double-blind clinical trial **Cost data:** direct and indirect costs estimated from various sources **Link:** some data from same source (prospective trial)	**Valuation for clinical outcomes or benefits:** PANSS; QLS; other measures; used to construct composite health index for schizophrenia (analogous to QALY measures) **Estimation of costs:** direct costs = healthcare and drug costs Indirect costs = administrative costs of transfer payments, criminal justice system, productivity and family burden costs **Modelling:** not undertaken	**Clinical outcome/benefits:** clozapine yielded 0.049 worst health–good health units, compared with haloperidol (0.027 units) **Costs:** average annual costs were $2733 lower in clozapine group **Synthesis of costs and benefits:** cost-effectiveness ratios ranged from –$431,585 to $177,352 **Statistical analysis:** primary outcomes analysed with random-effects regression models	**Sensitivity analysis:** CIs for cost-effectiveness ratios calculated **Appropriateness:** –	**Authors' conclusions** Among high hospital users with refractory schizophrenia, clozapine more cost-effective than standard treatment, although magnitude of effect small, with considerable uncertainty about cost estimates **Implications for practice** Not stated

Appendix 7

Validity of new RCTs

Study	Random-isation procedure adequate	Allocation concealed	Number random-ised stated	Baseline com-parison achieved	Eligibility criteria	Co-interventions stated	Blinding of outcome assessors	Blinding of admin-istrators	Participants blinded	Success of blinding checked	Follow-up adequate	Outcome of with-drawals	ITT
Barak 2000[244]	Not stated	Not stated	Yes	Unclear	Not stated	No	Not stated	Not stated	Not stated	Not stated	Unclear	No	Not stated
Bitter 1999[74]	Not stated	Not stated	Yes	Unclear	Yes	No	Not stated	Not stated	Not stated	Not stated	Unclear	Not stated	Not stated
Bouchard 1998[385]	Not stated	Not stated	No	Unclear	No	No	No	No	Unclear	Not stated	Unclear	No	Unclear
Bouchard 2000[249]	Not stated	Not stated	Yes	Yes	Yes	Yes	No	No	Not stated	Not stated	Yes	No	Yes
Breier 2000[159]	Not stated	Not stated	No	Unclear	No	No	Yes	Yes	Yes	Unclear	Unclear	No	Unclear
Brook 2000[287]	Not stated	Not stated	Yes	Yes	Yes	Yes	No	No	No	Not stated	Yes	Yes	Not stated
Carriere 2000[47]	Not stated	Not stated	Yes	Yes	Yes	Yes	Not stated	Not stated	Not stated	Not stated	Yes	Yes	Yes
Cetin 1999[241]	Not stated	Not stated	Yes	Not stated	No	Yes	Not stated	Yes	Yes	Not stated	Unclear	No	Unclear
Chow 2000[73]	Not stated	Not stated	Yes	Yes	No	No	No	No	No	No	Yes	No	Not stated
Chowdhury 1999[71]	Not stated	Not stated	Not stated	Yes	Yes	No	Not stated	Not stated	Not stated	Not stated	No	Yes	Not stated
Colonna 2000[361]	Not stated	Not stated	Yes	Yes	Yes	Yes	No	No	No	No	Yes	Yes	Yes
Conley 2001[161]	Not stated	Not stated	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	No	No	Yes	Unclear
Cosar 1999[75]	Not stated	Not stated	Unclear	Not stated	No	No	Not stated	Not stated	Not stated	No	Unclear	No	Unclear
Covington 2000[69]	Not stated	Not stated	Yes	Yes	No	No	Unclear	Unclear	Unclear	No	Unclear	Not stated	Not stated
Csernansky 2000[246]	Not stated	Not stated	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not stated	Unclear	No	Yes
Edgell 2000[170]	Not stated	Not stated	Yes	No	Yes	Yes	Unclear	Yes	Yes	Not stated	Not stated	No	Unclear
Fischer 1999[296]	Not stated	Not stated	Yes	Not stated	Not stated	Not stated	Yes	Yes	Yes	Not stated	Unclear	No	Yes
Fleming 1998[70]	Not stated	Not stated	Unclear	Yes	No	No	Yes	Yes	Yes	Not stated	Unclear	No	Not stated
Gomez 2001[150]	Not stated	Not stated	Yes	Yes	Yes	No	Yes	Yes	Yes	Not stated	Unclear	No	Yes
Gregor 1999[163]	Not stated	Not stated	Yes	Not stated	No	No	Unclear	Yes	Yes	No	Unclear	No	Unclear
Gunnar 1999[279]	Not stated	Not stated	No	Unclear	No	No	No	No	No	Not stated	Yes	Yes	Unclear
Gureje 1998[186]	Not stated	Not stated	No	Not stated	Unclear	No	Unclear	Yes	Yes	No	Unclear	Not stated	Not stated
Hale 2000[275]	Not stated	Not stated	Yes	Yes	Yes	No	Yes	Yes	Yes	Not stated	Unclear	Yes	Yes
Hamilton 2000[162]	Not stated	Not stated	Yes	Yes	Yes	No	Not stated	Not stated	Not stated	Not stated	Yes	Yes	Yes
Harvey 1999[247]	Not stated	Not stated	Yes	Unclear	Yes	No	Yes	Yes	Yes	Not stated	Unclear	No	Unclear
Heck 2000[233]	Not stated	Not stated	Yes	Yes	Yes	Yes	Not stated	Yes	Yes	No	No	No	Unclear
Janicak 1999[245]	Not stated	Not stated	Unclear	Yes	Unclear	No	Unclear	Yes	Yes	Not stated	Unclear	No	Unclear
Johnstone 1998[148]	Not stated	Not stated	Yes	Not stated	No	No	Unclear	Yes	Yes	Not stated	Unclear	Not stated	Yes
Kee 1998[239]	Not stated	Not stated	Yes	Yes	No	Yes	Not stated	Not stated	Not stated	Not stated	Yes	Yes	No
Kern 1999[237]	Not stated	Not stated	Yes	Yes	Yes	Yes	Not stated	Yes	Yes	No	Yes	Not stated	Not stated

continued

Study	Random-isation procedure adequate	Allocation concealed	Number random-ised stated	Baseline com-parison achieved	Eligibility criteria	Co-interventions stated	Blinding of outcome assessors	Blinding of admin-istrators	Participants blinded	Success of blinding checked	Follow-up adequate	Outcome of with-drawals	ITT
Knoll BPI1201	Commercial-in-confidence: data removed												
Knoll CTR ZT 4002 0[295]	Commercial-in-confidence: data removed												
Kolff 2000[152]	Not stated	Not stated	Yes	Not stated	No	No	Not stated	Not stated	Not stated	Not stated	Not stated	Unclear	Not stated
Lecrubier 1999[42]	Not stated	Not stated	Yes	Unclear	Yes	No	Yes	Yes	Yes	Not stated	Unclear	No	Unclear
Lecrubier 2000[43]	Not stated	Not stated	Yes	Unclear	No	No	Yes	Yes	Yes	Not stated	Unclear	No	Unclear
Littrell 1999[154]	Not stated	Not stated	Yes	Not stated	No	No	No	No	No	No	Yes	No	Unclear
Ljubin 2000[158]	Not stated	Not stated	No	Unclear	Yes	No	No	No	Yes	Not stated	Unclear	No	Unclear
Malyarov 1999[153]	Not stated	Not stated	Yes	Unclear	Yes	Not stated	Yes	Unclear	Unclear	Not stated	No	Yes	Unclear
Mullen 1999[208]	Not stated	Not stated	Unclear	Not stated	No	No	No	Unclear	Unclear	Not stated	Unclear	No	Unclear
Muller 1998[41]	Not stated	Not stated	Yes	Unclear	No	No	Unclear	Yes	Yes	No	Unclear	No	Unclear
Muller-Siecheneder 1998[240]	Not stated	Not stated	Yes	Yes	Yes	No	Not stated	Yes	Yes	No	No	Yes	Yes
Murasaki 2000[213]	Not stated	Not stated	Yes	Yes	Yes	No	Yes	Yes	Yes	Not stated	Yes	Yes	Unclear
Naukkarinen 1999[147]	Not stated	Not stated	Yes	Unclear	Yes	No	Yes	Yes	Yes	Not stated	Unclear	No	Unclear
Oliemeulen 2000[109]	Not stated	Not stated	Yes	Unclear	Yes	No	Unclear	Unclear	Unclear	Not stated	Unclear	No	Unclear
Pfizer 128-108 2001[280]	Commercial-in-confidence: data removed												
Pfizer 128-117 2001[242]	Commercial-in-confidence: data removed												
Pfizer 128-301 2001[282]	Commercial-in-confidence: data removed												
Pfizer 128-302 2001[243]	Commercial-in-confidence: data removed												
Pfizer 128-305 2001[46]	Commercial-in-confidence: data removed												
Pfizer 2001[279]	Commercial-in-confidence: data removed												
Pfizer 128-104 2001[284]	Commercial-in-confidence: data removed												
Pfizer NY-97-001[283]	Commercial-in-confidence: data removed												
Pfizer R-0548[283]	Commercial-in-confidence: data removed												
Purdon 2001[211]	Not stated	Not stated	Yes	Yes	Yes	No	Unclear	Yes	Yes	No	Yes	No	Yes
Rabinowitz 2001[234]	Commercial-in-confidence: data removed												

continued

Study	Random-isation procedure adequate	Allocation concealed	Number random-ised stated	Baseline com-parison achieved	Eligibility criteria	Co-interventions stated	Blinding of outcome assessors	Blinding of admin-istrators	Participants blinded	Success of blinding checked	Follow-up adequate	Outcome of with-drawals	ITT
Reams 1998[149]	Not stated	Not stated	Yes	Unclear	No	No	Unclear	Yes	Yes	Not stated	Not stated	No	Unclear
Rein 1999[50]	Not stated	Not stated	Yes	Not stated	Not stated	Not stated	No	No	Not stated	Not stated	Unclear	No	Not stated
Reinstein 1999[209]	Not stated	Not stated	Yes	Not stated	Unclear	No	No	No	No	Not stated	Not stated	No	Not stated
Salganik 1998[72]	Not stated	Not stated	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not stated	No	Yes	Unclear
Sanger 1998[173–175]	Not stated	Not stated	Unclear	Not stated	Yes	No	Unclear	Yes	Yes	Not stated	Unclear	Not stated	Not stated
Szafranski 1999[155]	Not stated	Not stated	Yes	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	No	Yes	Not stated
Tohen 1999[172]	Not stated	Not stated	Unclear	Not stated	No	No	Unclear	Yes	Yes	Not stated	Unclear	No	Not stated
Tollefson 1998[167]	Not stated	Not stated	Yes	Yes	Yes	Yes	Not stated	Not stated	Not stated	Not stated	Not stated	No	Yes
Tollefson 1999[165]	Not stated	Not stated	Yes	Unclear	Yes	Yes	Not stated	Not stated	Not stated	Not stated	Yes	No	Not stated
Tys 1999[232]	Not stated	Not stated	Yes	Not stated	No	No	Not stated	Not stated	Not stated	Not stated	Unclear	Not stated	Unclear
Velligan 1999[210]	Not stated	Not stated	No	Unclear	Yes	No	Yes	Yes	Yes	Not stated	Unclear	No	Unclear
Wetzel 1998[45]	Not stated	Not stated	Yes	No	Yes	Yes	Unclear	Yes	Yes	Not stated	Yes	Yes	Yes
Wirshing 1999[236]	Computer-generated random numbers	Not stated	Yes	Yes	Yes	Yes	Not stated	Yes	Yes	No	No	Yes	Yes
Wright 2000[151]	Not stated	Not stated	Yes	Not stated	Yes	No	Not stated	Not stated	Not stated	Not stated	Unclear	Not stated	Not stated
Ziegler 1989[44]	Not stated	Not stated	Yes	No	Unclear	No	Not stated	Yes	Yes	Not stated	Unclear	Unclear	No
Zhang 1999[156]	Not stated	Not stated	Yes	Not stated	No	No	Unclear	Yes	Yes	Not stated	Unclear	No	Not stated
Zhang 1999[157]	Not stated	Not stated	Yes	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Unclear	No	Not stated

Appendix 8

Validity assessment of non-randomised studies

Validity assessment of case series-type studies

Validity criteria[16]

- Is the study based on a representative sample selected from a relevant population?
- Are the criteria for inclusion explicit?
- Did all individuals enter the survey at a similar point in their disease progression?
- Was follow-up long enough for important events to occur?
- Were outcomes assessed using objective criteria or was blinding used?
- If comparisons of subseries are being made, was there sufficient description of the series and the distribution of prognostic factors?
- If another series is being used as a comparison group, were these concurrent and appropriate in terms of disease, measurement, etc?

Study	Sample relevant?	Inclusion explicit?	Similar at baseline?	Follow-up long enough?	Outcomes blind?	Subseries appropriate?	Comparators appropriate?	Comments
Alvir 1993[126]	Partially	Yes	Unclear	Partially	Unclear	Not stated	Not stated	No comparator group. Retrospective database study – survival analysis of clozapine patient monitoring database. People who had been taking clozapine for at least 3 weeks (not stated whether they had schizophrenia)
Atkin 1996[127]	Yes	Partially	Unclear	Yes	Unclear	Yes	Not stated	No comparator group. UK & Ireland clozapine patient monitoring database – retrospective study
Buckman 1999[125]	Yes	Yes	Unclear	Yes	No	Not stated	Not stated	No comparator group. Prospective case series of patients with treatment-refractory schizophrenia treated with clozapine
Cadario 2000[196]	Yes	No	Unclear	Yes	No	Not stated	Not stated	No comparator; data from CADRMP
Cho 1999[134]	Yes	Yes	Unclear	Partially	No	Not stated	Not stated	No comparator group. Clozapine patient monitoring database, Korea. Retrospective study over 3 years, in which each patient followed-up for at least 3 weeks
Coulter 2000[145]	Partially	Partially	Unclear	Yes	Unclear	Not stated	No	Data mining of drug monitoring database, looking at all antipsychotic drugs with respect to cardiomyopathy or cardiac complications
Devinsky 1991[137]	Partially	Yes	Unclear	Yes	No	Not stated	Not stated	No comparator group. Retrospective review of clozapine treated patients in USA, looking at seizure rates
DSRU 2001[198]	Commercial-in-confidence: data removed							

continued

Study	Sample relevant?	Inclusion explicit?	Similar at baseline?	Follow-up long enough?	Outcomes blind?	Subseries appropriate?	Comparators appropriate?	Comments
Erlandsen 1999[122]	Yes	Yes	Yes	Yes	No	Not stated	Not stated	No comparator group. Prospectve case series of schizophrenic patients treated with clozapine
ESES 2001[198]	Commercial-in-confidence: data removed							
Fung 1998[197]	Partially	No	Unclear	Partially	Unclear	Not stated	Not stated	No comparator group. Retrospective study of spontaneous safety database for olanzapine. Not stated whether all had schizophrenia
Hagg 2000[136]	Unclear	Partially	Unclear	Yes	No	Not stated	Not stated	No comparator group. Retrospective database analysis of venous thromboembolism incidence during clozapine treatment. Not stated whether all had schizophrenia
Honigfeld 1996[129]	Yes	Partially	Unclear	Yes	No	Not stated	Not stated	No comparator group. Retrospective study of clozapine patient monitoring database
Killian 1999[118]	Partially	Yes	Unclear	Yes	Unclear	Not stated	Not stated	No comparator group. Retrospective database analysis of Australian Adverse Drug Reaction Committee. Does not state that all patients had schizophrenia
Lambertenghi Deliliers 2000[131]	Yes	Yes	No	Yes	Unclear	Not stated	Not stated	No comparator group, no comparisons of subgroups. Clozapine patient monitoring system in Italy – seems to be all people on database
Lan 1999[140]	Unclear	Partially	Unclear	Not stated	Not stated	Yes	No	No comparator group. Abstract only, many details missing
Lieberman 1992[132]	Unclear	Partially	Unclear	Partially	No	Not stated	Not stated	No comparator group. Retrospective study of clozapine patient monitoring database. Not stated whether all patients had schizophrenia
Macpherson 1998[138]	Yes	Yes	Unclear	Yes	No	Not stated	Not stated	No comparator group. Retrospective audit of clozapine-treated patients at one clinic in the UK
Meltzer 1995[124]	Yes	Yes	Yes	Yes	No	Not stated	Not stated	No comparator group. Prospective case series of suicidality in neuroleptic-resistant patients treated with clozapine
Meltzer 2000[228]	Yes	No	Unclear	Yes	No	Not stated	Not stated	No comparator; data from Clintrace (AstraZeneca)
Miller 1997[133]	Partially	Yes	Unclear	Yes	Unclear	Not stated	Not stated	No comparator group. Retrospective study of clozapine patient monitoring database in New Zealand
Modai 2000[123]	Partially	Partially	Unclear	Yes	No	Not stated	Yes	Retrospective study of mortality, presented as number of fatalities in those taking clozapine versus in those not taking clozapine. All clozapine-treated patients had schizophrenia but not stated for those not taking clozapine

continued

Study	Sample relevant?	Inclusion explicit?	Similar at baseline?	Follow-up long enough?	Outcomes blind?	Subseries appropriate?	Comparators appropriate?	Comments
Pacia 1994[139]	Partially	Partially	Unclear	Partially	No	Not stated	Not stated	No comparator group. Retrospective study of clozapine patient monitoring system, looking at frequency of seizures
Spiess-Kiefer 1988[364]	No	No	Unclear	Yes	Unclear	Not stated	Unclear	Retrospective study of adverse drug reaction database in all psychiatric patients (not just schizophrenia); results for clozapine and for 'other neuroleptics'
Tooley 1997[267]	Partially	Partially	Unclear	Yes	No	Not stated	Not stated	Post-marketing database analysis of 'reporting rates' of adverse events for risperidone and 'other agents'. Denominator estimated from number of prescriptions. Not stated whether all had schizophrenia
Umbricht 1994[144]	Yes	Yes	Yes	Yes	No	Not stated	Not stated	No comparator group. Retrospective chart review of weight gain in patients receiving clozapine
Walker 1997[120]	Unclear	Partially	Unclear	Yes	No	Not stated	Not stated	No comparator group. Retrospective database analysis of mortality in clozapine users

Validity assessment of cohort-type studies

Validity criteria[16]

- Is there sufficient description of the groups and the distribution of prognostic factors?
- Are the groups assembled at a similar point in their disease progression?
- Is the intervention/treatment reliably ascertained?
- Were the groups comparable on all important confounding factors?
- Was there adequate adjustment for the effects of these confounding variables?
- Was a dose-response relationship between intervention and outcome demonstrated?
- Was outcome assessment blind to exposure status?
- Was follow-up long enough for the outcomes to occur?
- What proportion of the cohort was followed-up?
- Were drop-out rates and reasons for drop-out similar across intervention and unexposed groups?

Study	Groups described?	Groups similar at baseline?	Treatment details reliable?	Comparable on confounding factors?	Adjust for confounding factors?	Dose response?	Outcomes blind?	Follow-up long enough?	Percentage followed up?	Drop-out rates?	Control group?	Comments
Biswas 2000[202]	Commercial-in-confidence: data removed											
EPOS 2001[198]	Commercial-in-confidence: data removed											
Erasmus 2001[198]	Commercial-in-confidence: data removed											
Gomez, 2000[194]	Partially	Unclear	Partially	Yes	Yes	Not stated	Not stated	No	Olanzapine 82%; control 85%	Yes	Yes	Prospective pharmaco-epidemiological study. Follow-up only 6 months
Grohmann 1989[128]	No	Unclear	Unclear	Unclear	Unclear	Not stated	Not stated	Yes		Not stated	Yes	Retrospective and prospective adverse drug reaction monitoring in people treated with clozapine, haloperidol and perazine. Number with schizophrenia not specified
King 1998[130]	No	Unclear	No	Unclear	No	Not stated	No	Yes	Unclear	Not stated	Yes	Retrospective study of adverse reaction reports and prescription numbers or unit sales for clozapine and typical antipsychotic drugs. Not stated whether all had schizophrenia
Kinon, 2001[195]	Yes	Unclear	Yes	Yes	Yes	Not stated	Not stated	Yes		Not stated	Yes	Retrospective analysis of data from Tollefson 1997,[164] comparing olanzapine and haloperidol
Laker 1998[119]	Yes	Yes	Yes	Yes	Yes	Not stated	Not stated	Yes	100%	Not stated	Yes	Compared people who continued and discontinued clozapine; retrospective
Moore 1999[278]	Partially	No	Unclear	Unclear	Partially	Not stated	Not stated	Unclear	Unclear	Unclear	Unclear	Looks like indirect comparisons from treatment arms of several trials. Abstract only so many details missing
NPU 2001[198]	Commercial-in-confidence: data removed											
Peacock 1996[141]	Partially	Yes	Unclear	Partially	Yes	Not stated	Not stated	Yes	Not stated	Not stated	Yes	Retrospective study of clozapine versus typical antipsychotic drugs in people with schizophrenia
UK Hospital Pharmacy Study 2001[198]	Commercial-in-confidence: data removed											
Wolstein 2000[143]	Not stated	Not stated	Unclear	Unclear	Unclear	Not stated	Not stated	Unclear	Not stated	Not stated	Unclear	Letter only; many details missing

Validity assessment of case–control-type studies

Validity criteria[16]

- Is the case definition explicit?
- Has the disease state of the cases been reliably assessed and validated?
- Were the controls randomly selected from the source of population of the cases?
- How comparable are the cases and controls with respect to potential confounding factors?
- Were interventions and other exposures assessed in the same way for cases and controls?
- How was the response rate defined?
- Were non-response rates and reasons for non-response the same in both groups?
- Is it possible that over-matching has occurred, in that cases and controls were matched on factors related to exposure?
- Was an appropriate statistical analysis used (matched or unmatched)?

Study	Case definition explicit?	Disease state confirmed?	Control selection random?	Groups comparable?	Exposure assessment comparable?	Response definition	Non response comparable	Matching appropriate?	Statistics appropriate?	Comments
Reid 1998[121]	Yes	Yes	No	Partially	No	Yes	Not stated	Unclear	Unclear	

Appendix 9

Continuous data results

Amisulpride

Amisulpride versus typical antipsychotic drugs

Outcome	Included studies	Number of participants	WMD (95% CI)
Short term			
CGI-S change scores	Hillert 1994[54]	132	–0.50 (–1.03 to 0.03)
GAS change scores	Hillert 1994[54]	132	2.20 (–3.94 to 8.34)
PANSS positive subscale endpoint scores (< 500 mg/day amisulpride)	Puech 1998[56]	123	–0.10 (–2.96 to 2.76)
PANSS positive subscale endpoint scores (> 500 mg/day amisulpride)	Moeller 1997[57] Puech 1998[56]	188 124	–1.36 (–3.02 to 0.29)
BPRS productive factor endpoint subscores	Moeller 1997[57]	188	–0.40 (–2.02 to 1.22)
BPRS total endpoint scores (< 500 mg/day amisulpride)	Boyer 1990[61] Puech 1998[56]	57 123	–4.91 (–6.25 to –3.56)
BPRS total endpoint scores (> 500 mg/day amisulpride)	Hillert 1994[54] Moeller 1997[57] Puech 1998[56]	132 188 123	–3.26 (–6.21 to –0.32)
BPRS anxiety–depression cluster endpoint scores	Boyer 1990[61]	57	–2.60 (–2.84 to –2.36)
BPRS anergia cluster endpoint scores	Boyer 1990[61]	57	–3.40 (–4.21 to –2.59)
PANSS negative subscale endpoint scores (< 500 mg/day amisulpride)	Puech 1998[56]	123	–0.40 (–3.39 to 2.59)
PANSS negative subscale endpoint scores (> 500 mg/day amisulpride)	Moeller 1997[57] Puech 1998[56]	188 123	–2.51 (–4.34 to –0.68)
BPRS anergia subscale change scores	Hillert 1994[54]	132	–1.50 (–2.65 to –0.35)
BPRS thought disturbance subscale change scores	Hillert 1994[54]	132	–2.20 (–3.79 to –0.61)
BPRS activation subscale change scores	Hillert 1994[54]	132	–1.10 (–2.35 to 0.15)
BPRS hostile suspiciousness subscale change scores	Hillert 1994[54]	132	0.00 (–1.32 to 1.32)
SAPS endpoint scores	Hillert 1994[54]	132	–5.40 (–14.89 to 4.09)
SANS endpoint scores	Hillert 1994[54]	132	0.50 (–6.62 to 7.62)
BPRS anxiety/depression subscale change scores	Hillert 1994[54]	132	–2.00 (–3.44 to –0.56)
Movement disorders (SAS < 500 mg/day amisulpride)	Puech 1998[56]	123	–0.20 (–0.35 to –0.05)
Movement disorders (> 500 mg/day amisulpride) SAS endpoint scores	Moeller 1997[57] Puech 1998[56]	186 124	–0.19 (–0.30 to –0.07)
Movement disorders (> 500 mg/day amisulpride) SAS change scores	Hillert 1994[54]	132	–2.70 (–4.41 to –0.99)
Movement disorders (>500 mg/day amisulpride) AIMS change scores	Hillert 1994[54]	132	–1.80 (–3.08 to –0.52)
Movement disorders (> 500 mg/day amisulpride) BAS change scores	Hillert 1994[54]	132	–1.40 (–2.14 to –0.65)
Prolactin levels	Klein 1995[58] Hillert 1994 (men)[54] Hillert 1994 (women)[54]	14 35 23	44.70 (30.16 to 59.24)

continued

Amisulpride *contd*

Amisulpride versus typical antipsychotic drugs *contd*

Outcome	Included studies	Number of participants	WMD (95% CI)
Long term			
PANSS negative subscale change scores	Colonna 1998[49]	322	3.40 (1.41 to 5.39)
BPRS total score change	Colonna 1998[49]	322	4.20 (0.06 to 8.34)
MS negative subscale endpoint scores	Speller 1997[59]	54	–0.56 (–1.27 to 0.15)
SANS affective flattening change scores	Speller 1997[59]	54	–0.39 (–0.82 to 0.04)
SANS alogia change scores	Speller 1997[59]	54	–0.17 (–0.68 to 0.34)
SANS avolition and apathy change scores	Speller 1997[59]	54	–0.40 (–0.84 to 0.04)
SANS anhedonia/associality change scores	Speller 1997[59]	54	–0.22 (–0.55 to 0.11)
SANS attention change scores	Speller 1997[59]	54	–0.24 (–0.63 to 0.15)
BPRS negative subscale change scores	Speller 1997[59]	54	–0.54 (–1.87 to 0.79)
BPRS total endpoint scores	Colonna 1998[49]	488	–5.50 (–9.01 to –1.99)
PANSS positive endpoint scores	Colonna 1998[49]	488	–2.00 (–3.79 to –0.21)
PANSS negative endpoint scores	Colonna 1998[49]	488	–3.20 (–4.87 to –1.53)

Amisulpride versus olanzapine

Outcome	Included studies	Number of participants	WMD (95% CI)
Long term			
SANS summary change scores	Lecrubier 1999[42]	140	1.10 (–0.54 to 2.74)

Amisulpride versus risperidone

Outcome	Included studies	Number of participants	WMD (95% CI)
BPRS total change scores	Fleurot 1997[62] Lecrubier 2000[43]	159 310	0.67 (–1.87 to 3.21)
PANSS positive change scores	Fleurot 1997[62]	159	4.30 (1.93 to 6.67)
PANSS total change scores	Lecrubier 2000[43]	310	–0.80 (–5.82 to 4.22)
PANSS negative change scores	Lecrubier 2000[43]	310	–1.20 (–2.45 to 0.05)

Clozapine

Clozapine versus typical antipsychotic drugs (overall)

Outcome	Included studies	Number of participants	WMD (95% CI)
Short term			
BPRS total endpoint scores	Potter 1989[81]	37	–5.54 (–7.17 to –3.91)
	Liu 1994[82]	33	
	Honigfeld 1984[88]	79	
	Klieser 1989[89]	30	
	Klieser 1994[90]	92	
	Itoh 1977[92]	88	
	Hong 1997[95]	38	
	Claghorn 1987[98]	125	
	Kane 1988[99]	265	
	Kumra 1996[104]	21	
	Buchanan 1998[107]	75	
SANS (or corresponding) endpoint scores	Klieser 1989[89]	30	–3.44 (–5.45 to –1.43)
	Hong 1997[95]	38	
	Kumra 1996[104]	21	
	Buchanan 1998[107]	75	
Long term			
BPRS total endpoint scores	Lee 1994[101]	52	0.80 (–5.70 to 7.30)

Clozapine versus typical antipsychotic drugs (patients with treatment-resistant illness)

Outcome	Included studies	Number of participants	WMD (95% CI)
BPRS endpoint scores	Klieser 1989[89]	30	–7.83 (–10.01 to –5.64)
	Hong 1997[95]	38	
	Kane 1988[99]	265	
	Kumra 1996[104]	21	
	Buchanan 1998[107]	75	
Negative symptoms	Klieser 1989[89]	30	–3.44 (–5.45 to –1.43)
	Hong 1997[95]	38	
	Kumra 1996[104]	21	
	Buchanan 1998[107]	75	

Clozapine versus typical antipsychotic drugs (children and adolescents)

Outcome	Included studies	Number of participants	WMD (95% CI)
BPRS endpoint scores	Kumra 1996[104]	21	–12.20 (–25.44 to 1.04)
SANS endpoint scores	Kumra 1996[104]	21	–26.20 (–49.99 to –2.41)

Olanzapine versus clozapine

Outcome	Included studies	Number of participants	WMD (95% CI)
PANSS total change scores	Beasley 1998[77]	176	–3.50 (–10.69 to 3.69)
BPRS total change from baseline	Beasley 1998[77]	176	–1.20 (–5.43 to 3.03)
SAS total change scores	Beasley 1998[77]	172	–1.80 (–3.03 to –0.57)
AIMS total change scores	Beasley 1998[77]	172	–0.10 (–0.81 to 0.61)
BAS global change scores	Beasley 1998[77]	172	0.10 (–0.18 to 0.38)
Weight change at endpoint	Beasley 1998[77]	180	–0.50 (–1.95 to 0.95)
Change in orthostatic blood pressure (endpoint)	Beasley 1998[77]	180	3.20 (–1.59 to 7.99)
Short/medium term			
CGI endpoint score	Beasley 1998[77]	176	–0.09 (–0.46 to 0.28)
Negative symptoms (PANSS/SANS) endpoint scores SMD	Beasley 1998[77]	176	–0.10 (–0.40 to 0.19)
Psychosis symptoms (BPRS/PANSS) endpoint scores	Beasley 1998[77]	176	–0.00 (–0.29 to 0.30)

Risperidone versus clozapine

Outcome	Included studies	Number of participants	WMD (95% CI)
PANSS total endpoint score	Chowdhury 1999[71]	52	–42.52 (–52.68 to –32.36)
CGI endpoint score	Bondolfi 1998[110] Wahlbeck 2000[113]	86 19	0.00 (–0.47 to 0.46)
GAF endpoint score	Wahlbeck 2000[113]	19	–9.00 (–18.44 to 0.44)
Negative symptoms (PANSS/SANS) endpoint scores SMD	Bondolfi 1998[110] Breier 1999[112] Wahlbeck 2000[113] Chowdhury 1999[71]	86 29 19 52	–0.40 (–0.70 to –0.11)
Positive symptoms (BPRS/PANSS) endpoint scores (SMD)	Chowdhury 1999[71] Bondolfi 1998[110] Breier 1999[112] Wahlbeck 2000[113]	52 86 29 19	–0.28 (–0.58 to 0.03)
Psychosis symptoms (BPRS/PANSS) endpoint scores	Bondolfi 1998[110] Breier 1999[112] Wahlbeck 2000[113] Chowdhury 1999[71]	86 29 19 52	–0.38 (–0.69 to –0.07)
SFS endpoint score	Wahlbeck 2000[113]	19	–47.00 (–93.55 to –0.45)
DAI-10 endpoint score	Wahlbeck 2000[113]	19	0.10 (–2.57 to 2.77)

Remoxipride/risperidone/zotepine versus clozapine

Outcome	Included studies	Number of participants	WMD (95% CI)
Psychosis symptoms (BPRS/PANSS) endpoint scores	Klieser 1996[90]	135	0.00 (–0.38 to 0.38)

Olanzapine

Olanzapine versus placebo

Outcome	Included studies	Number of participants	WMD (95% CI)
CGI endpoint score (6 weeks)	Beasley 1996a[168] Beasley 1996b[169]	132 98	–0.53 (–0.89 to –0.17)
BPRS total endpoint scores (6 weeks)	Beasley 1996b[169]	98	–6.86 (–12.34 to –1.38)
PANSS total endpoint scores (6 weeks)	Beasley 1996b[169]	98	–12.43 (–22.54 to –2.32)
SANS endpoint scores	Lecrubier 1999[42]	94	–0.50 (–2.87 to 1.87)
PANSS negative endpoint scores	Beasley 1996b[169]	98	–1.39 (–4.42 to 1.64)
PANSS positive endpoint scores	Beasley 1996b[169]	98	–4.00 (–7.10 to –0.90)
Weight (6–8 weeks)	Beasley 1996a[168] Beasley 1996b[169]	129 98	3.58 (–1.18 to 8.34)
Weight (3–12 months)	Lecrubier 1999[42]	104	–0.52 (–6.14 to 5.10)
QLS total endpoint scores	Lecrubier 1999[42]	80	8.20 (–2.47 to 18.87)
BPRS anxiety/depression factor (2.5–7.5 mg)	Beasley 1996a[168]	133	–0.29 (–2.07 to 1.49)
BPRS anxiety/depression factor (7.5–12.5 mg)	Beasley 1996a[168]	132	–1.82 (–3.48 to –0.16)
BPRS anxiety/depression factor (12.5–17.5 mg)	Beasley 1996a[168]	137	–1.03 (–2.06 to –0.10)

Olanzapine versus typical antipsychotic drugs

Outcome	Included studies	Number of participants	WMD (95% CI)
Up to 3 months			
CGI total endpoint scores	Conley 1998[183] Tollefsen 1997[164]	81 1958	–0.32 (–0.43 to –0.22)
BPRS total endpoint scores	Conley 1998[183]	81	–2.80 (–8.43 to 2.83)
BPRS total change scores	Gomez 2001[150] Hamilton 2000[162]	1658 778	–2.61 (–3.70 to –1.51)
BPRS positive endpoint scores	Conley 1998[183]	81	–1.30 (–2.90 to 0.30)
BPRS positive change scores	Gomez 2001[150]	1658	–0.46 (–0.87 to –0.05)
BPRS negative change scores	Gomez 2001[150]	1658	–0.70 (–1.00 to –0.40)
PANSS total endpoint scores	Tollefson 1997[183]	1948	–6.32 (–8.51 to –4.13)
PANSS total change scores	Gomez 2001[150]	1658	–3.49 (–5.67 to –1.31)
PANSS negative endpoint scores	Tollefsen 1997[183]	1948	–1.72 (–2.37 to –1.07)
PANSS negative change scores	Gomez 2001[150] Hamilton 2000[162]	1658 778	1.89 (1.35 to 2.43)
PANSS positive endpoint scores	Tollefsen 1997[183]	1948	–1.21 (–1.87 to –0.55)
PANSS positive change scores	Gomez 2001[150] Hamilton 2000[162]	1658 778	–0.80 (–1.36 to –0.25)
QLS change scores (total)	Hamilton 2000[162]	778	4.90 (2.38 to 7.42)
Weight increase	HGBL 1997 HGCQ 2000 HGDV 1999 HGFH 1998 Loza 1999[185] Tollefson 1997[183]	26 30 39 90 41 1936	0.91 (–0.56 to 2.38)

continued

Olanzapine versus typical antipsychotic drugs *contd*

Outcome	Included studies	Number of participants	WMD (95% CI)
3–12 months			
CGI total endpoint scores	HGCJ 1999	30	–0.62 (–1.07 to –0.16)
	HGCU 1998	52	
	Jakovljevic 1999[184]	55	
PANSS total endpoint scores	HGCJ 1999	30	–15.01 (–22.93 to –7.10)
	HGCU 1998	52	
	Jakovljevic 1999[184]	55	
BPRS change scores	Hamilton 2000[162]	778	–1.80 (–4.14 to 0.54)
PANSS positive endpoint scores	HGCJ 1999	30	–4.03 (–7.21 to –0.85)
	HGCU 1998	52	
PANSS positive change scores	Hamilton 2000[162]	778	–1.00 (–2.15 to 0.15)
PANSS negative endpoint scores	HGCJ 1999	30	–2.98 (–5.52 to –0.45)
	HGCU 1998	52	
	Jakovljevic 1999[184]	54	
PANSS negative change scores	Hamilton 2000[162]	778	–0.40 (1.56 to 0.76)
QLS change scores (total)	Hamilton 2000[162]	778	11.50 (8.52 to 14.48)
Weight increase	Altamura 1999[181]	47	4.03 (0.30 to 7.76)
	HGBJ (Finland)	46	
	HGCJ 1999	30	
	HGCU 1998	51	
	Jakovljevic 1999[184]	59	
Cognitive measurements (WAIS overall performance)	Ljubin 2000[158]	18	–0.70 (–17.85 to 16.45)

Olanzapine versus typical antipsychotic drugs (patients with treatment-resistant illness)

Outcome	Included studies	Number of participants	WMD (95% CI)
CGI total endpoint scores	Conley 1998[183]	81	–0.10 (–0.49 to 0.29)
BPRS total endpoint scores	Conley 1998[183]	81	–2.80 (–8.43 to 2.38)
BPRS positive endpoint scores	Conley 1998[183]	81	–1.30 (–2.90 to 0.30)
Weight	Altamura 1999[181]	47	0.35 (–9.69 to 10.39)

Olanzapine versus atypical antipsychotic drugs

Outcome	Included studies	Number of participants	WMD (95% CI)
Any time			
QLS total endpoint scores	Tran 1997[171]	240	2.42 (–3.93 to 8.77)
Movement disorder – ESRS scale total	Conley 2001[161]	278	–0.60 (–1.63 to 0.43)
Up to 3 months			
PANSS endpoint scores (total)	Conley 2001[161]	278	1.10 (–2.83 to 5.03)
Weight	Conley 2001[161]	316	1.79 (0.83 to 2.75)
3–12 months			
SANS summary scores	Lecrubier 1999[42]	140	–1.10 (–2.74 to 0.54)
CGI total endpoint scores	Beuzen 1998[176,177] Tran 1997[171]	176 332	–0.06 (–0.28 to 0.15)
PANSS total endpoint scores	Beuzen 1998[176,177] Tran 1997[171]	176 331	–6.08 (–10.41 to –1.74)
PANSS negative endpoint scores	Beuzen 1998[176,177] Tran 1997[171]	176 331	–0.79 (–1.98 to 0.41)
Weight	Tran 1997[171]	331	2.16 (–1.62 to 5.94)

Olanzapine versus atypical antipsychotic drugs (patients with treatment-resistant illness)

Outcome	Included studies	Number of participants	WMD (95% CI)
PANSS total endpoint scores	Beuzen 1998[176,177]	176	0.03 (–8.07 to 8.13)
PANSS negative endpoint scores	Beuzen 1998[176,177]	176	–0.475 (–2.94 to 1.44)
PANSS positive scores (18 weeks)	Beuzen 1998[176,177]	176	0.50 (–1.69 to 2.69)
SAS rating scale (18 weeks)	Beuzen 1998[176,177]	172	–0.90 (–2.13 to 0.33)
AIMS rating scale (18 weeks)	Beuzen 1998[176,177]	172	–0.30 (–1.01 to 0.41)
BAS rating scale (18 weeks)	Beuzen 1998[176,177]	172	0.20 (–0.08 to 0.48)

Olanzapine versus ziprasidone

Outcome	Included studies	Number of participants	WMD (95% CI)
Commercial-in-confidence: data removed			

Quetiapine

Quetiapine versus placebo

Outcome	Included studies	Number of participants	WMD (95% CI)
CGI change scores	Arvanitis 1996[220] Fabre 1995[189] Borison 1996[221] Small 1997[222]	306 11 106 281	–0.52 (–0.72 to –0.31)
BPRS total change scores	Arvanitis 1996[220] Fabre 1995[189] Borison 1996[221] Small 1997[222]	306 11 106 184	–7.04 (–9.85 to –4.24)
BPRS positive change scores	Arvanitis 1996[220] Fabre 1995[189] Borison 1996[221] Small 1997[222]	306 11 106 278	–0.69 (–0.91 to –0.47)
BPRS negative change scores	Fabre 1995[189]	11	–4.30 (–9.30 to 0.43)
PANSS negative change scores	Small 1997[222]	113	–1.75 (–4.47 to 0.97)
SANS change scores	Arvanitis 1996[220] Borison 1996[221] Small 1997[222]	306 106 162	–1.23 (–1.94 to –0.52)

Quetiapine versus typical antipsychotic drugs

Outcome	Included studies	Number of participants	WMD (95% CI)
CGI change scores	Copolov 1996 Arvanitis 1996[220]	439 305	0.25 (0.05 to 0.44)
PANSS total change scores	Copolov 1996	437	3.40 (–1.12 to 7.92)
PANSS total endpoint scores	Murasaki 1999[214]	197	0.20 (–7.09 to 7.49)
PANSS negative endpoint scores	Murasaki 1999[214]	197	0.40 (–1.83 to 2.63)
PANSS positive endpoint scores	Murasaki 1999[214]	197	0.40 (–1.75 to 2.55)
PANSS general psychopathology endpoint scores	Murasaki 1999[214]	197	–0.70 (–4.74 to 3.34)
BPRS total endpoint score	Murasaki 1999[214]	197	0.00 (–4.47 to 4.47)
Cognitive summary endpoint score (300 mg/day quetiapine)	Velligan 1999[210]	31	1.04 (–2.18 to 4.26)
Cognitive summary endpoint score (600 mg/day quetiapine)	Velligan 1999[210]	40	1.68 (–1.25 to 4.61)

Quetiapine versus atypical antipsychotic drugs

Outcome	Included studies	Number of participants	WMD (95% CI)
Commercial-in-confidence: data removed			

Risperidone

Risperidone versus atypical antipsychotic drugs

Outcome	Included studies	Number of participants	WMD (95% CI)
Clozapine			
CGI endpoint score	Bondolfi 1998[110] Wahlbeck 2000[113]	86 19	0.00 (–0.47 to 0.46)
GAF endpoint score	Wahlbeck 2000[113]	19	–9.00 (–18.44 to 0.44)
PANSS total endpoint score	Bondolfi 1998[110] Breier 1999[112] Chowdhury 1999[71] Wahlbeck 2000[113]	86 29 46 19	1.71 (–2.86 to 6.28)
Positive symptom endpoint score (BPRS/PANSS)	Bondolfi 1998[110] Breier 1999[112] Chowdhury 1999[71] Wahlbeck 2000[113]	86 29 46 19	0.62 (–0.71 to 1.96)
Negative symptom endpoint score (BPRS/PANSS)	Bondolfi 1998[110] Breier 1999[112] Chowdhury 1999[71] Wahlbeck 2000[113]	86 29 46 19	–1.31 (–3.25 to 0.63)
SFS total endpoint score	Wahlbeck 2000[113]	19	47.00 (0.45 to 93.55)
DAI 10 total endpoint score	Wahlbeck 2000[113]	19	–0.10 (–2.77 to 2.57)
PANSS general psychopathology endpoint scores	Chowdhury 1999[71]	46	0.03 (–5.41 to 5.47)
Olanzapine			
CGI endpoint scores	Tran 1997[171]	332	0.05 (–0.21 to 0.31)
PANSS total endpoint scores	Tran 1997[171] Conley 2001[161]	321 278	2.45 (–0.67 to 5.57)
PANSS positive endpoint scores	Conley 2001[161]	278	–0.10 (–1.61 to 1.41)
PANSS negative endpoint scores	Tran 1997[171] Conley 2001[161]	321 278	0.18 (–0.81 to 1.17)
PANSS disorganised thoughts	Conley 2001[161]	278	0.30 (–0.79 to 1.39)
PANSS uncontrolled hostility	Conley 2001[161]	278	–0.10 (–0.75 to 0.55)
PANSS anxiety/depression	Conley 2001[161]	278	–0.60 (–1.42 to 0.22)
QLS endpoint scores	Tran 1997[171]	240	–2.42 (–8.77 to 3.93)
Weight gain	Tran 1997[171] Conley 2001[161]	321 316	–1.76 (–2.69 to –0.82)
ESRS total endpoint scores	Conley 2001[161]	278	0.60 (–0.43 to 1.63)
Amisulpride			
BPRS total endpoint scores	Fleurot 1997[62]	228	1.50 (–2.39 to 5.39)
PANSS positive endpoint scores	Fleurot 1997[62]	228	0.00 (–1.87 to 1.87)
PANSS negative endpoint scores	Fleurot 1997[62]	228	1.80 (–0.22 to 3.82)
BPRS total change scores	Lecrubier 2000[43]	310	0.20 (–2.89 to 3.29)
PANSS total change scores	Lecrubier 2000[43]	310	0.80 (–4.22 to 5.82)
PANSS negative change scores	Lecrubier 2000[43]	310	1.20 (–0.05 to 2.45)
Quetiapine			
Commercial-in-confidence: data removed			

Risperidone versus. typical antipsychotic drugs

Outcome	Included studies	Number of participants	WMD (95% CI)
CGI change scores	Blin 1996[251] Chouinard 1993[255] Marder 1994[116]	41 113 314	–0.20 (–0.44 to 0.04)
PANSS total change scores	Blin 1996[251] Chouinard 1993[255] Marder 1994[116] Peuskens 1995[263]	41 113 271 1352	–2.00 (–4.86 to 0.85)
PANSS negative change scores	Blin 1996[251] Chouinard 1993[255] Marder 1994[116] Peuskens 1995[263]	41 113 314 1352	–0.77 (–1.62 to 0.07)
PANSS positive change scores	Blin 1996[251] Chouinard 1993[255] Marder 1994[116] Peuskens 1995[263]	41 113 314 1352	–0.24 (–1.09 to 0.60)
BPRS change scores	Blin 1996[251] Chouinard 1993[255] Marder 1994[116] Peuskens 1995[263]	41 113 314 1352	–1.70 (–3.22 to –0.17)
Severity of dyskinesia – CGI change scores	Chouinard 1993[255] Marder 1994[116] Peuskens 1995[263]	113 314 1351	–0.20 (–0.34 to –0.06)
Severity of parkinsonism – CGI change scores	Blin 1996[251] Chouinard 1993[255] Marder 1994[116]	41 113 314	–0.78 (–1.18 to –0.39)
CGI parkinsonism change scores	Csernansky 2000[246,248]	365	–0.40 (–0.42 to –0.38)
CGI dyskinesia change scores	Csernansky 2000[246,248]	365	–0.20 (–0.22 to –0.18)
Severity of parkinsonism – ESRS change scores	Blin 1996[251] Chouinard 1993[255] Peuskens 1995[263]	41 113 1353	–2.07 (–2.91 to –1.23)
Total – ESRS change scores	Blin 1996[251] Csernansky 2000[246,248] Marder 1994[116] Peuskens 1995[263]	41 365 314 1353	–1.29 (–1.37 to –1.20)
ESRS parkinsonism change scores	Csernansky 2000[246,248]	365	–1.20 (–1.26 to –1.14)
Movement disorder questionnaire change scores	Csernansky 2000[246,248]	365	–0.60 (–0.64 to –0.56)
UKU change score	Peuskens 1995[263]	1350	–0.49 (–0.51 to –0.47)

Sertindole

Sertindole versus placebo

Outcome	Included studies	Number of participants	WMD (95% CI)
Sertindole, 8 mg			
CGI total endpoint scores	Van Kammen 1996[277]	73	0.20 (–0.48 to 0.88)
BPRS total endpoint scores	Van Kammen 1996[277]	73	0.80 (–4.55 to 6.15)
PANSS total endpoint scores	Van Kammen 1996[277]	73	2.80 (–6.76 to 12.36)
Sertindole, 12 mg			
CGI total scores	Van Kammen 1996[277]	78	–0.30 (–0.92 to 0.32)
BPRS total endpoint scores	Van Kammen 1996[277]	78	–2.20 (–7.76 to 3.36)
PANSS total endpoint scores	Van Kammen 1996[277]	78	–4.80 (–14.45 to 4.85)
Sertindole, 20 mg			
CGI total scores	Van Kammen 1996[277]	78	–0.90 (–1.57 to –0.23)
BPRS total endpoint scores	Van Kammen 1996[277]	78	–6.20 (–11.79 to –0.61)
PANSS total endpoint scores	Van Kammen 1996[277]	78	–9.50 (–19.16 to 0.16)

Ziprasidone

Ziprasidone versus placebo

Outcome	Included studies	Number of participants	WMD (95% CI)
Ziprasidone, 40 mg			
CGI-S change scores	Keck 1998[293]	90	–0.20 (–0.63 to 0.23)
BPRS total change scores	Keck 1998[293]	90	–1.10 (–6.50 to 4.30)
BPRS core item change scores	Keck 1998[293]	90	–0.30 (–2.13 to 1.53)
SANS total change score	Keck 1998[293]	90	–6.20 (–14.47 to 2.07)
Ziprasidone, 120 mg			
CGI-S change scores	Keck 1998[293]	88	–0.40 (–0.81 to 0.01)
BPRS total change scores	Keck 1998[293]	88	–6.00 (–11.31 to –0.69)
BPRS core item change scores	Keck 1998[293]	88	–1.80 (–3.66 to 0.06)
SANS total change score	Keck 1998[293]	88	–5.00 (–12.43 to 2.43)
Ziprasidone, any dose			
BPRS total endpoint scores long term	Arato 1997[289]	150	–8.64 (–14.35 to –2.93)
BPRS total endpoint scores short term	Daniel 1999[290]	195	–3.02 (–7.84 to 1.80)
BPRS core endpoint scores long term	Arato 1997[289]	147	–2.05 (–3.76 to –0.34)
BPRS core endpoint scores short term	Daniel 1999[290]	195	–0.86 (–2.43 to 0.71)
PANSS total endpoint scores long term	Arato 1997[289]	147	–14.85 (–24.06 to –5.64)
PANSS total endpoint scores short term	Daniel 1999[290]	195	–6.09 (–14.66 to 2.48)
PANSS negative endpoint scores long term	Arato 1997[289]	147	–3.29 (–5.60 to –0.98)
PANSS negative endpoint scores short term	Daniel 1999[290]	195	–1.81 (–4.22 to 0.60)
CGI-S endpoint scores long term	Arato 1997[289]	147	–0.83 (–1.25 to –0.41)
CGI-S endpoint scores short term	Daniel 1999[290]	196	–0.28 (–0.60 to 0.04)
GAF endpoint scores, 80 mg	Arato 1997[289]	149	–8.57 (–14.26 to –2.88)
Body weight – long term, 80 mg	Arato 1997[289]	139	–1.78 (–6.06 to 2.50)

Ziprasidone versus typical antipsychotic drugs

Outcome	Included studies	Number of participants	WMD (95% CI)
Immediate term			
CGI-S change scores	Brook 1998[288]	132	–0.50 (–0.94 to –0.06)
SAS change scores	Brook 1998[288]	132	–7.10 (–9.42 to –4.78)
BAS change scores	Brook 1998[288]	132	–0.90 (–1.27 to –0.53)
Short term			
Commercial-in-confidence: data removed			
Long term			
Commercial-in-confidence: data removed			

Ziprasidone versus risperidone

Outcome	Included studies	Number of participants	WMD (95% CI)
Commercial-in-confidence: data removed			

Ziprasidone versus olanzapine

Outcome	Included studies	Number of participants	WMD (95% CI)
Commercial-in-confidence: data removed			

Zotepine

Zotepine versus placebo

Outcome	Included studies	Number of participants	WMD (95% CI)
CGI endpoint scores	Cooper 1999a[298]	106	–1.00 (–1.50 to –0.50)
BPRS endpoint scores	Cooper 1999a[298]	105	–11.60 (–18.32 to –4.88)
SANS endpoint scores	Cooper 1999a[298]	105	–12.50 (–22.68 to –2.32)
Pulse rate	Cooper 1999a[298]	106	1.90 (–1.91 to 5.71)
Weight change	Cooper 1999a[298]	106	1.70 (–3.54 to 6.94)

Zotepine versus typical antipsychotic drugs

Outcome	Included studies	Number of participants	WMD (95% CI)
CGI endpoint scores	Barnas 1987[297] Cooper 1999a[298]	30 105	–0.61 (–1.01 to –0.21)
BPRS endpoint scores	Barnas 1987[297] Cooper 1999a[298] Klieser 1996[302] Wetzel 1991[305]	30 105 65 34	–6.92 (–11.02 to –2.83)
SANS endpoint scores	Barnas 1987[297] Cooper 1999a[298]	30 102	–8.66 (–16.93 to –0.39)
Pulse rate	Cooper 1999a[298]	105	–1.30 (–5.38 to 2.78)
Weight change	Cooper 1999a[298]	105	–1.30 (–6.26 to 3.66)

Zotepine versus atypical antipsychotic drugs

Outcome	Included studies	Number of participants	WMD (95% CI)
BPRS endpoint scores	Klieser 1996[302]	40	–13.0 (–12.95 to 10.35)

Appendix 10

Excluded studies

The studies listed below, found as a result of the searches, were ordered for but not used in this review.

Reference	Schizophrenia	Atypical	RCT	Side-effect	Economic	Reasons for exclusion
Anon 1991[386]	Yes	Yes	No	No	No	Russian. Not an RCT or relevant side-effects study. Study looking at clozapine treatment of 749 patients and side-effects in USSR
Anon 1998[387]	No	No	No	No	No	Overview (not systematic) of olanzapine
Anon 2000[388]	Yes	Yes	No	No	No	Review (not systematic)
Ackenheil 1980[389]	Yes	Yes	No	No	No	Information on biochemical and neuroendocrinological effects of neuroleptic drugs over time; no clinical effectiveness or safety information
Ackenheil 1989[390]	Yes	No	No	No	No	Pharmacokinetics and pharmacology
Addington 1995[391]	Yes	Yes	No	Yes	No	Case report
Addonizio 1987[392]	Yes	Yes	No	No	No	Review of case histories; not systematic review
Adityanjee 1991[393]	No	Yes	No	No	No	Comment (letter)
Aguirre 1998[394]	Yes	Yes	No	Yes	No	Spanish. Letter, case report
Alao 1999[395]	Yes	Yes	No	No	No	Letter, case report
Alfaro 2001[396]	Yes	No	No	No	No	Points drawn from RCTs and open trials – not really a trial
Allison 1999[397]	Yes	Yes	No	Yes	No	*n* = 304
Allison 2001[398]	Yes	Yes	No	No	No	Pooled data from RCTs looking at blood glucose levels. Outcome not within scope of this review
Alpert 1996[399]	Yes	Yes	No	No	No	Not a randomised comparison
Altamura 1999[400]	Yes	Yes	No	No	No	Not an RCT or economic evaluation, no long-term follow-up
Alvir 1994[401]	Yes	Yes	No	Yes	No	Diagnoses not specified.
Amminger 1992[402]	Yes	Yes	No	No	No	Not an RCT; retrospective study of 53 patients, < 2 years follow-up
Anon 1999[403]	Yes	Yes	No	No	No	Economic overview (not systematic)
Anstee 1996[404]	Yes	Yes	No	No	No	Not an RCT or a study of long-term or rare events
Antal 1999[405]	Yes	Yes	No	No	No	Not an RCT or economic evaluation; no long-term follow-up
Aquila 1999[406]	No	Yes	No	No	No	Comment (letter); weight gain
Aronson 1997[407]	Yes	Yes	No	No	No	Economic evaluation based on case reports
Aubry 2000[408]	Yes	Yes	No	No	No	MEDLINE search for case reports of mania and hypomania induced by olanzapine and risperidone; only 26 cases identified
Awad 1999[409]	Yes	Yes	No	No	No	Discussion paper; not results of study

continued

Reference	Schizophrenia	Atypical	RCT	Side-effect	Economic	Reasons for exclusion
Baker 1992[410]	Yes	Yes	No	No	No	*n* = 49; review of case reports
Baldwin 1997[411]	Yes	Yes	No	No	No	Review (not systematic)
Ballesteros 1998[412]	Yes	No	No	Yes	No	Neuroleptic drugs not specified
Bamrah 2001[413]	No	Yes	Yes	No	No	Elderly patients with dementia and psychosis; not schizophrenia
Bandelow 1998[414]	Yes	Yes	No	No	No	Review (not systematic)
Barbui 1999[415]	No	No	No	No	No	Methodology paper
Barcia 1996[416]	Yes	Yes	No	Yes	No	*n* = 980, follow-up < 2 years
Barnes 1999[417]	Yes	Yes	No	Yes	No	Non-systematic review
Barzega 1999[418]	Yes	Yes	Yes	No	No	Subgroup (*n* = 6): patients from one centre of multicentre trial already included in report
Barzega 2000[419]	Yes	Yes	No	No	No	No control group; small dose comparison for quetiapine
Basson 2000[420]	Yes	Yes	No	Yes	No	Study of factors influencing weight gain
Bauer 1983[421]	Yes	Yes	No	Yes	No	*n* = 478
Beasley 1999[422]	Yes	Yes	Yes	No	No	Switching therapy
Benkert 1999[423]	Yes	Yes	No	No	No	Non-systematic review
Bergstrom 1999[424]	No	No	No	No	No	Study in healthy volunteers
Berk 2000[425]	No	Yes	No	No	No	Cannabis-induced psychotic disorder
Bersani 1995[426]	No	Yes	No	No	No	Italian. Looks like non-systematic review of risperidone
Bilsker 1996[427]	Yes	Yes	No	No	No	Commentary on previous research, not full economic evaluation
Biour 2000[428]	No	Yes	No	No	No	French. Looks like very long list of various medications and their hepatic toxicity. No real references of any use
Bitter 2000[429]	Yes	Yes	No	No	Yes	Hungarian
Blasco 1995[430]	Yes	Yes	No	No	No	Spanish. Not an RCT; no mention of randomisation
Bocker 2000[431]	Yes	No	No	No	No	Not a drug comparison
Boitz 1999[432]	Yes	Yes	No	No	No	German with English summary. Not an RCT; looks like interview-based study of 80 patients treated with clozapine
Brecher 1997[433]	No	Yes	No	Yes	No	Non-systematic review on weight gain, no original data
Brecher 1999[434]	No	Yes	No	No	No	Elderly patients with dementia
Brecher 2000[435]	Yes	Yes	No	Yes	No	No control group, only 427 participants
Brecher 2001[436]	Yes	Yes	No	Yes	No	Mean follow-up = 18.6 months
Breier 1999[437]	Yes	Yes	Yes	No	No	Outcomes presented only for olanzapine, not comparator drug
Bristow 1993[438]	No	No	No	No	No	Conventional review, no original data
Brook 2000[439]	Yes	Yes	No	No	No	Not an RCT
Brown 1997[440]	Yes	No	No	Yes	No	Study of excess mortality in schizophrenia: not related to atypical antipsychotic drugs
Buckley 1994[441]	Yes	Yes	No	No	No	Not an RCT. Cohort study of 118 patients
Buckley 1994[442]	Yes	Yes	No	No	No	Not an RCT. Cohort of 118 patients monitored for side-effects
Buckley 1998[443]	Yes	Yes	No	No	No	Non-systematic review
Buckley 1998[444]	Yes	Yes	No	No	No	Non-systematic review

continued

Reference	Schizophrenia	Atypical	RCT	Side-effect	Economic	Reasons for exclusion
Buckley 2000[445]	No	No	No	No	No	Conventional review, no original data
Budman 2001[446]	No	Yes	No	Yes	No	Patients with Tourette's syndrome
Buitelaar 1998[447]	No	Yes	No	No	No	Not schizophrenic patients
Bunker 1995[448]	Yes	Yes	No	No	No	Few details; doesn't look like an RCT but more like general discursive review (not systematic)
Cabaret 2000[449]	Yes	Yes	No	Yes	No	Protocol for study on hepatotoxicity with atypical antipsychotic drugs
Caligiuri 2000[450]	No	No	No	No	No	Conventional review, no original data
Campbell 1999[451]	Yes	Yes	No	No	No	Non-systematic review
Campbell 1999[452]	Yes	No	No	No	No	Non-systematic review; not primarily atypical drugs
Capehart 1998[453]	Yes	No	No	No	No	Letter
Cardwell 1995[454]	Yes	Yes	No	No	No	Not an RCT or case–control; retrospective chart review of seven patients
Caroff 2000[455]	Yes	Yes	No	No	No	Report of cases of NMS collected via MEDLINE search
Carpenter 1999[456]	Yes	No	No	No	No	Comparison of two dose regimens, not an atypical drug
Carter 1995[457]	Yes	Yes	No	Yes	No	$n < 300$
Casey 1989[458]	Yes	No	No	No	No	Non-systematic review
Casey 1998[459]	Yes	Yes	No	No	No	Few details; doesn't look like an RCT but like general discursive review (not systematic)
Caspi 1997[460]	No	Yes	No	No	No	Non-systematic review, no original data
Castagna 1999[461]	Yes	Yes	No	No	No	Spanish. Systematic review
Cerulli 1999[462]	Yes	Yes	No	No	No	Not a relevant design; looks like general discursive review of side-effects of psychotrophic medications on pancreas (not systematic)
Chabannes 1997[463]	Yes	Yes	No	Yes	No	Not retrospective review but hypothesis generating analysis
Chan 2000[464]	Yes	Yes	No	No	No	Comment (letter)
Chatterton 1997[465]	No	Yes	No	Yes	No	$n = 160$
Chong 2000[466]	Yes	Yes	No	No	No	Systematic review of clozapine augmentation; outside remit of this review
Chow 1995[467]	Yes	Yes	No	No	No	Efficacy but not an RCT
Christensen 1999[468]	Yes	Yes	No	No	No	Cost study; not full economic evaluation
Chustecka 1998[469]	Yes	Yes	No	No	No	News report of RCTs already in included
Clardy 1995[470]	Yes	Yes	No	Yes	No	Not an RCT or case–control study; 2-year follow-up study of mortality in group of 70 patients
Clozapine Study Group 1993[471]	Yes	Yes	No	No	No	$n = 54$; follow-up = 26 weeks
Cohen 1990[472]	Yes	Yes	No	Yes	No	Not relevant design. Series of case-reports about weight gain associated with clozapine
Cohen 1990[473]	Yes	No	No	Yes	No	Not about antipsychotic drugs
Cohen 1991[474]	No	Yes	No	No	No	Includes diagnoses other than schizophrenia; data not separated
Collaborative Group 1998[475]	No	Yes	No	No	No	Non-systematic review
Conley 1998[476]	Yes	Yes	No	No	No	Not an RCT or full economic study

continued

Reference	Schizophrenia	Atypical	RCT	Side-effect	Economic	Reasons for exclusion
Conley 1999[477]	Yes	Yes	Yes	No	No	Gender differences in response but only includes 7/27 females; subset of study by Conley
Conley 1999[478]	Yes	Yes	No	No	No	Non-randomised study of rehospitalisation rates
Connelly 1998[479]	No	Yes	No	Yes	No	*n* = 46, not case–control design, follow-up unknown
Cookson 1998[480]	Yes	Yes	No	No	No	Non-systematic overview of economic evaluation of risperidone (preliminary decision based on abstract)
Covell 1999[481]	Yes	Yes	Yes	No	No	No useful data reported
Crawford 2000[482]	Yes	Yes	Yes	No	No	*Post-hoc* analysis of published trial
Currier 2000[483]	No	No	No	No	No	Looks at agitated patients; not an RCT
Currier 2000[484]	Yes	Yes	No	No	No	Does not state that it is randomised trial
Czekalla 1999[485]	Yes	Yes	No	No	No	Not an RCT or economic evaluation; no long-term follow-up
Czekalla 2001[199]	Yes	Yes	No	No	No	Non-systematic review
Daniel 1999[486]	Yes	Yes	No	No	No	Interim phase of one arm of an RCT (switching from olanzapine to ziprasidone); no control group
Daniel 1999[487]	Yes	Yes	No	No	No	Report of one arm of an RCT (switching from olanzapine to ziprasidone); no control group
Daniel 1999[488]	Yes	Yes	No	No	No	Switching therapy
Daniel 1999[489]	Yes	Yes	No	No	No	Switching therapy
Daniel 2000[490]	Yes	Yes	No	No	No	Selected data from two RCTs already included in original report
Daniel 2000[491]	Yes	Yes	No	No	No	Not an RCT or economic evaluation; no long-term follow-up
David 1999[179]	Yes	Yes	Yes	No	No	Same as Jones 1998; extra cognition data but > 50% attrition so data excluded
David 1999[492]	Yes	Yes	No	No	No	Non-systematic review
David 1999[493]	Yes	Yes	No	No	No	Not an RCT or economic evaluation, no long-term follow-up
David 2000[494]	Yes	Yes	No	No	No	Presents data from two RCTs, both already in original report
David 2000[495]	Yes	Yes	No	No	No	Non-systematic review of RCTs already included
Davies 2000[496]	Yes	Yes	No	No	Yes	Abstract reporting economic model used in original report, which was updated for this report
Davis 1999[497]	No	Yes	No	No	No	Meta-analysis but minimal data reported; diagnosis not specified
Dayem 1999[498]	Yes	Yes	No	No	No	Not an RCT, no comparator
De Hert 1998[499]	Yes	Yes	No	No	No	No drug comparison
Degner 2000[500]	No	Yes	No	No	No	Non-systematic review, no original data
Deirmenjian 1998[501]	Yes	Yes	No	Yes	No	Case report
Delgado Sanchez 1993[502]	No	Yes	No	No	No	Italian; appears to report methods of clozapine dispensing
Dellva 1998[503]	Yes	Yes	Yes	No	No	Olanzapine for clozapine discontinuation syndrome
Demb 1999[504]	Yes	No	No	No	No	Letter, chart review, not an RCT, short-term side-effects (movement disorders)
Dennis 1996[505]	Yes	Yes	No	No	No	No comparison drug; not an RCT; not full economic evaluation

continued

Reference	Schizophrenia	Atypical	RCT	Side-effect	Economic	Reasons for exclusion
Derichs 1982[506]	Yes	Yes	No	No	No	Not an RCT. Conference abstract about study with 54 participants treated with clozapine
Dernovsek 1997[507]	Yes	Yes	No	Yes	No	Letter: discussing case-report
Dev 1994[508]	Yes	Yes	No	No	No	Letter: about clozapine blood monitoring programme
Devarajan 2000[509]	Yes	Yes	No	No	No	Comment (letter)
Devinsky 1991[137]	Yes	Yes	No	No	No	Retrospective review of 1418 clozapine-treated patients in USA, looking at incidence of seizures
Devinsky 1994[510]	Yes	Yes	No	No	No	Non-systematic overview of seizure rates in clozapine therapy; not a study (preliminary decision based on abstract)
Dewey 2000[511]	No	Yes	No	No	No	Drug-induced psychosis in Parkinson's disease
Dickson 1997[512]	Yes	Yes	No	No	No	Considers small number of case reports of clozapine treatment and pregnancy
Dittert 1999[513]	Yes	Yes	No	No	No	Non-randomised effectiveness study
Dittman 1999[514]	Yes	Yes	No	No	No	Not an RCT or economic evaluation; no long-term follow-up
Earnst 1999[515]	Yes	Yes	No	No	No	Non-randomised efficacy study
Edwards 1998[516]	Yes	Yes	Yes	No	No	Preliminary report. No real data
Emmanuel 1999[517]	No	No	No	No	No	Not about atypical antipsychotic drugs
Emsley 1999[518]	Yes	Yes	Yes	No	No	Reanalysis of study already in earlier report
Erhart 2001[519]	Yes	Yes	Yes	No	No	EEG results only
Essock 1995[520]	Yes	Yes	No	No	No	Comment on economic evaluation already included in earlier report
Evans 2001[521]	No	Yes	Yes	No	No	Elderly patients with dementia and psychosis; not schizophrenia
Feeney 1996[522]	No	Yes	No	Yes	No	Case report, not schizophrenia
Feer 1992[523]	Yes	No	No	No	No	General discursive review of side-effects not based on eligible studies
Feldman 1996[524]	Yes	Yes	No	No	No	Review (not systematic)
Ferber 1995[525]	No	Yes	No	No	No	German. Review (not systematic)
Fichtner 1998[526]	Yes	Yes	No	No	No	Economic review, not systematic
Finkel 1995[527]	No	Yes	No	No	No	Not an RCT, outcome study or economic evaluation
Fleischhacker 1991[528]	Yes	Yes	No	No	No	$n = 40$
Fleischhacker 1994[529]	No	No	No	No	No	Conventional review, no original data
Fortier 2000[530]	Yes	Yes	No	No	No	Non-systematic review of sexual and sociosexual functioning
Foster 1998[531]	Yes	Yes	No	No	No	Pharmacoeconomic review (not efficacy)
Frankenburg 1996[532]	No	No	No	No	No	Letter: does not describe a study
Frankenburg 1996[533]	Yes	Yes	No	No	No	Letter: bladder dysfunction in clozapine therapy focussing on just ten patients
Frankenburg 1998[534]	Yes	Yes	No	Yes	No	12 months follow-up, only 42 participants, no control group
Frankle 2001[535]	Yes	Yes	No	Yes	No	Mixed diagnoses; no separate analysis
Fras 1995[536]	Yes	Yes	No	No	No	Letter: treatment of six patients
Fridrich 2000[537]	Yes	Yes	No	No	No	Czech. Systematic review
Friedman 1993[538]	Yes	Yes	No	No	No	Letter: re previous study
Friedman 1999[539]	No	Yes	No	No	No	Patients with Parkinson's disease

continued

Reference	Schizophrenia	Atypical	RCT	Side-effect	Economic	Reasons for exclusion
Fritze 1998[540]	No	Yes	No	No	No	German. Considers adverse cardiac events with sertindole but doesn't appear relevant study design. Could be review (but doesn't look systematic)
Fuchs 1994[541]	Yes	Yes	No	No	No	Letter: data on suicide rates in Clozaril®-treated patients
Fuchs 1994[542]	Yes	Yes	No	No	No	Letter: special report on schizophrenia that doesn't appear to be relevant trial
Fuller 1996[543]	Yes	Yes	No	Yes	No	*n* = 57; non-RCT design
Gabriel 1976[544]	No	No	No	No	No	German. Appears to be study of confused patients (not schizophrenia)
Gaile 1998[545]	Yes	Yes	No	No	No	Letter: mentions four case reports. Not an RCT or relevant study
Galletly 1997[546]	Yes	No	No	No	No	Outcomes not relevant
Galletly 1999[547]	Yes	Yes	No	No	No	*n* = 19; non-RCT design
Ganguli 1999[548]	Yes	Yes	No	No	No	General discursive review of weight gain associated with antipsychotic drugs (not systematic)
Garcia-Cabeza 2000[549]	Yes	Yes	No	No	No	Naturalistic effectiveness study, not randomised
Gardner 1997[550]	Yes	Yes	No	No	No	Not an RCT or case–control study; retrospective chart review of 28 patients
Gardner 1999[551]	Yes	Yes	No	No	No	Resource-use study: not randomised and not full economic evaluation
Gardos 1995[552]	No	No	No	No	No	Case reports. Not atypical antipsychotic drugs
Gaszner 2000[553]	No	Yes	No	No	No	Mixed diagnoses (mainly affective psychosis), not analysed separately; no comparator, only brief mention of side-effects
Gaszner 2000[554]	Yes	No	No	No	No	Case reports on treatment of agranulocytosis caused by clozapine
Gaussares 1992[555]	Yes	Yes	No	No	No	French. Not an RCT. Appears to be general discursive review on side-effects of clozapine (not systematic review)
Geller 1998[556]	Yes	Yes	No	No	No	Letter. Not an RCT
Gerlach 1989[557]	Yes	No	No	No	No	Non-systematic review; includes some adverse event data but follow-up (for these events) only 6 months; *n* = 216
Gerlach 1990[558]	Yes	Yes	No	No	No	Review (not systematic)
Gerlach 1996[559]	Yes	Yes	No	No	No	Review (not systematic)
Gerlach 1997[560]	Yes	No	No	No	No	Review (not systematic)
Gillman 1999[561]	No	Yes	No	No	No	Letter: about previous study
Ginestet 1998[562]	No	Yes	No	No	No	French. Review (not systematic)
Gitlin 1994[563]	Yes	Yes	No	No	No	Review of case-reports, case series and animal studies relating to effects of psychotropic medications on sexual function
Giudicelli 1999[564]	Yes	Yes	Yes	No	No	Selected data from three RCTs presented; not systematic review
Glazer 2000[565]	Yes	Yes	No	Yes	No	Review (not systematic)
Gleason 1997[566]	Yes	Yes	No	No	No	Case reports
Gmurkowski 1999[567]	No	No	No	No	No	Polish (no English summary). Appears to be general literature review

continued

Reference	Schizophrenia	Atypical	RCT	Side-effect	Economic	Reasons for exclusion
Goetz 2000[568]	No	Yes	No	No	No	Patients with Parkinson's disease
Goff 1995[569]	Yes	No	No	No	No	Brief discussion-type overview
Goff 1998[570]	Yes	No	Yes	No	No	RCT of adjunctive treatment for clozapine (clozapine in both arms)
Gomez 1999[571]	Yes	Yes	No	No	No	Non-randomised effectiveness study
Gomez 2000[572]	Yes	Yes	No	No	No	Non-randomised short-term naturalistic study; *n* = 904
Gonul 1999[573]	Yes	Yes	No	No	No	Not an RCT or economic evaluation; no long-term follow-up
Gonul 2000[574]	Yes	Yes	No	No	No	Not an RCT; short-term cohort study of prolactin secretion
Gouzoulis 1994[575]	No	Yes	No	No	No	German. Non-systematic review of cases of seizures with clozapine
Grainger 1998[576]	Yes	Yes	Yes	No	No	Another report of Tollefson 1997[164] (already included); no new data
Grainger 1998[577]	Yes	Yes	Yes	Yes	No	Another report of RCT already included; no new data
Gram 1976[578]	Yes	Yes	No	No	No	General discussion about withdrawal and safety of Leponex®; not based on large, case-controlled, long-term study
Gram 2000[579]	Yes	Yes	No	No	No	Appears to be review of adverse effects of antipsychotic drugs but all included studies small (17–66 participants)
Grcevich 1996[580]	Yes	Yes	No	No	No	*n* = 16; follow-up ranges from 1–12 months
Green 1990[581]	No	Yes	No	No	No	Non-systematic review; no original data
Green 1999[607]	Yes	Yes	No	No	No	German; appears to be general discursive review (not systematic)
Green 2000[582]	No	No	No	No	No	Conventional review; no original data. Not a full economic evaluation although some economic data included
Gregor 1999[163]	Yes	Yes	Yes	No	No	Duplicate report of Hamilton 2000;[162] no extra data
Gregor 2000[583]	Yes	Yes	Yes	No	No	Data already presented in conference abstract (Gregor 1999[163])
Grieger 2001[584]	Yes	No	No	No	No	Letter: about naturalistic study of which medications given to those hospitalised with schizoaffective disorder over 6-year period; not effectiveness study
Guith 1996[585]	Yes	Yes	No	No	No	Non-systematic overview of clozapine
Gunasekara 1998[586]	Yes	Yes	No	No	No	Non-systematic review
Gunther 1993[587]	Yes	Yes	No	No	No	Mixed diagnoses; not analysed separately
Gupta 1995[588]	No	No	No	No	No	One-page summary: dose schedules for risperidone
Gupta 1995[589]	No	No	No	No	No	Letter: comment
Gupta 1999[590]	Yes	Yes	No	Yes	No	*n* = 16; length of follow-up unclear; not case–control design
Gury 1995[591]	Yes	No	No	No	No	French; *n* = 14
Haase 1982[592]	Yes	Yes	No	No	No	German; non-systematic review
Haberfellner 1999[593]	Yes	Yes	No	No	No	German; not an RCT, appears to be single case study
Haddad 2000[371]	Yes	Yes	No	No	No	Synthesis of four studies already included in earlier study

continued

Reference	Schizophrenia	Atypical	RCT	Side-effect	Economic	Reasons for exclusion
Hale 1998[594]	Yes	Yes	No	No	No	Non-systematic review
Haller 1990[595]	Yes	Yes	No	No	No	Discussion; case reports
Hamilton 1998[192]	Yes	Yes	Yes	No	No	Another report Beasley 1996a;[168] only includes data up to 24 weeks; *n* = 95
Hamner 1999[596]	Yes	Yes	No	No	No	Not an RCT; appears to be prospective cohort study of < 800 people to monitor safety of sertindole; appears to have been cancelled when drug withdrawn
Hankoff 2000[597]	No	No	No	No	No	No data
Hansen 1997[598]	Yes	No	No	No	No	Non-systematic review
Harada 1986[599]	Yes	Yes	No	No	No	Not an RCT
Harpe 1987[600]	Yes	Yes	No	No	No	Not a systematic review
Harvey 2000[601]	Yes	Yes	No	No	No	Not an RCT or economic evaluation; no long-term follow-up
Hasan 1998[135]	Yes	Yes	No	Yes	No	Not a case–control design; *n* = 32; case reports
Hayes 1995[602]	Yes	Yes	No	No	No	Letter: clozapine-induced constipation in 53 patients
Heiden 1998[603]	Yes	Yes	No	No	No	General discursive review of cardiac side-effects of neuroleptic drugs
Heila 1999[604]	Yes	No	No	Yes	No	Not looking at atypical antipsychotic drugs
Heimann 1999[605]	Yes	Yes	No	No	No	Letter: case study on effectiveness
Heinrich 1991[606]	No	No	No	No	No	German; conference preface
Hellewell 1998[608]	Yes	Yes	No	No	No	Some results from four RCTs presented; not enough detail to judge whether meta-analysis is real
Hellewell 2001[609]	Yes	Yes	No	No	No	Letter: about another article; not an RCT
Helmchen 1989[610]	Yes	No	No	No	No	Non-systematic review
Hemphill 1975[611]	Yes	Yes	No	No	No	Uncontrolled study of only 52 patients
Herman 1999[612]	No	No	No	No	No	Drug interactions with statins
Ho 1999[613]	Yes	Yes	No	No	No	Non-randomised effectiveness study
Hoes 1980[614]	No	No	No	No	No	Dutch: review (not systematic)
Hoes 1995[615]	Yes	Yes	No	No	No	Non-systematic review
Hori 1992[616]	Yes	Yes	No	No	No	Cohort study of 129 patients treated with zotepine to look at the incidence of seizures; average follow-up 48 days
Hosak 2000[617]	Yes	Yes	No	No	No	Czech: non-systematic review of drug costs
Hummer 1992[618]	No	Yes	No	No	No	Small uncontrolled study of neutropaenia with clozapine
Hummer 1994[619]	Yes	Yes	No	No	No	*n* = 68; considers transient white blood cell count disorders in clozapine treatment
Hummer 1995[620]	Yes	Yes	No	Yes	No	Not long-term follow-up or case–control design; *n* = 42
Hummer 1999[621]	Yes	Yes	No	Yes	No	Sexual side-effects; not listed in protocol as non-RCT study design
Huq 2000[622]	Yes	Yes	No	No	No	Not randomised, effectiveness study
Hutton 2000[623]	Yes	Yes	No	No	No	Unclear whether randomised
Idanpaan-Heikkila 1997[624]	Yes	Yes	No	No	No	Non-systematic review
Inada 1991[625]	No	Yes	No	No	No	Includes diagnoses other than schizophrenia

continued

Reference	Schizophrenia	Atypical	RCT	Side-effect	Economic	Reasons for exclusion
Iskedjian 1998[626]	Yes	Yes	No	No	No	Not systematic review
Jackson 1995[627]	Yes	Yes	No	Yes	No	Case reports
Jalenques 1995[628]	Yes	Yes	No	No	No	Not an RCT or a study of long-term or rare events
Jalenques 1996[629]	Yes	Yes	No	Yes	No	*n* = 15; no comparator and not long term
Jann 1998[630]	Yes	Yes	No	No	No	Not a full economic evaluation
Jarema 1999[631]	Yes	Yes	No	No	No	Non-randomised efficacy study
Jeste 1997[632]	Yes	Yes	No	No	No	Cohort study of 945 patients treated with risperidone over 10-week period
Jeste 1999[633]	No	Yes	No	Yes	No	*n* = 122; < 2 years' follow-up; diagnoses other than schizophrenia with results presented together
Jimenez 1990[634]	No	No	No	No	No	Italian; letter
Joffe 1998[635]	Yes	Yes	No	No	No	Not one of atypical antipsychotic drugs listed in protocol
John 1995[636]	Yes	Yes	No	Yes	No	*n* = 99
Johnstone 1998[148]	Yes	Yes	Yes	No	No	Another report of Johnstone;[318] no additional data
Jones 1998[180]	Yes	Yes	Yes	No	No	Outcome not relevant
Jones 2001[637]	Yes	Yes	No	No	No	*n* = 100; 1-year follow-up; not case–control design
Jones 2001[638]	Yes	Yes	No	No	No	Not systematic
Ju 2000[639]	Yes	No	No	No	No	Not about atypical antipsychotic drug (sulpiride)
Jungi 1977[640]	Yes	Yes	No	No	No	Two case reports
Kalali 1998[641]	Yes	Yes	No	No	No	6-month study of patient satisfaction; not an RCT
Kane 1991[642]	Yes	Yes	No	No	No	French; not an RCT; appears to be general discursive review of use of clozapine in schizophrenia (not systematic review)
Kane 1991[643]	No	No	No	No	No	Conventional review; no original data
Kane 1997[644]	Yes	Yes	No	No	No	Non-systematic review
Kane 1999[645]	Yes	Yes	No	No	No	Not an RCT? Not clear if participants randomised (*n* = 520 in total) but they receive either risperidone or olanzapine and are followed-up for unspecified period to monitor development of tardive dyskinesia
Kaplan 1999[646]	Yes	Yes	No	No	No	Considers safety of 1000 patients who previously participated in Abbott sertindole study. Follow-up for side-effects over 2-year period after first trial ended. No comparison group
Karagianis 1999[647]	Yes	Yes	No	No	No	Design not relevant; reports two case reports and MEDLINE search to identify previous reports
Kasper 1998[648]	Yes	Yes	No	No	No	Non-systematic review
Kasper 1998[649]	Yes	Yes	No	No	No	Narrative review using case histories to illustrate
Katz 1999[650]	No	Yes	Yes	No	No	People with dementia, not schizophrenia
Keck 1996[651]	Yes	No	No	No	No	General literature review of olanzapine (not systematic)
Keck 2000[652]	No	Yes	Yes	No	No	Participants with bipolar disorder, not schizophrenia

continued

Reference	Schizophrenia	Atypical	RCT	Side-effect	Economic	Reasons for exclusion
Keck 2000[653]	Yes	Yes	No	No	No	Non-systematic review
Keks 1997[654]	Yes	Yes	No	No	No	Non-systematic review
Keks 1999[655]	Yes	Yes	No	No	No	Non-systematic overview of risperidone (preliminary decision based on abstract)
Kellam 1990[656]	No	Yes	No	No	No	Non-systematic review
Kelly 1998[657]	No	Yes	No	Yes	No	*n* = 60; retrospective chart review over 6-month period
Kerwin 1993[658]	No	No	No	No	No	Review article; no data
Kerwin 1999[659]	Yes	Yes	No	No	No	Non-systematic review
Kerwin 2000[660]	No	Yes	No	Yes	No	Reply to letter: commenting on dose–response with clozapine and blood problems. Not a study; unclear whether schizophrenia
King 1998[661]	Yes	Yes	No	No	No	Non-systematic review of RCTs already included
Kinon 1998[662]	Yes	Yes	Yes	No	No	Olanzapine in both arms
Kinon 1998[663]	Yes	Yes	Yes	No	No	Reports prolactin levels only – not an outcome of interest for this study
Kinon 1998[664]	Yes	No	No	No	No	Non-systematic review
Kinon 1999[665]	Yes	Yes	No	No	No	Switching medication
Kinon 1999[666]	Yes	Yes	No	No	No	Not an RCT or economic evaluation; no long-term follow-up
Kinon 2001[667]	Yes	Yes	No	No	No	Not an RCT (no control group)
Kirkegaard 1977[668]	No	Yes	No	No	No	Not an RCT; *n* = 58; < 2 years' follow-up
Kirkegaard 1979[669]	Yes	Yes	No	No	No	*n* = 47; considers side-effects of clozapine
Kirkegaard 1982[670]	Yes	Yes	No	No	No	*n* = 17; considers side-effects of clozapine
Knapp 1998[671]	Yes	Yes	No	No	No	Economic review (not systematic)
Knegtering 2000[672]	No	No	No	No	No	Doesn't specifically state schizophrenic patients included; not an RCT, considers side-effects (sexual dysfunction); small study
Kocmur 2000[673]	Yes	Yes	No	No	No	Not an RCT or economic evaluation; no long-term follow-up
Koester 2000[674]	Yes	Yes	No	Yes	No	Case report of NMS with clozapine
Kohen 1999[675]	No	Yes	No	No	No	Letter: comment; reports on case studies
Koivumaa-Honkanen 2001[676]	No	No	No	Yes	No	Suicide study in adults unselected for mental health status
Kontaxakis 2000[677]	Yes	Yes	No	No	No	Review of case studies
Kopala 1996[678]	No	No	No	No	No	Conventional review article
Kopala 1996[679]	Yes	Yes	No	No	No	Not an RCT; all 22 participants treated with risperidone
Kopala 2000[680]	Yes	Yes	No	No	No	Interim report of economic study; no synthesis of costs–benefits
Kraus 1999[681]	Yes	No	No	No	No	Case report
Krayenbuhl 1998[682]	Yes	Yes	No	No	No	Not an RCT; retrospective study of 162 patient records
Krebs 1995[683]	Yes	No	No	No	No	Non-systematic review
Krebs 1999[684]	Yes	Yes	No	No	No	Case report on two patients
Krentz 2001[685]	Yes	Yes	No	No	No	Not an RCT; case report
Krupp 1989[686]	Yes	Yes	No	No	No	Not an RCT but general discursive review (not systematic) about agranulocytopenia and Leponex®

continued

Reference	Schizophrenia	Atypical	RCT	Side-effect	Economic	Reasons for exclusion
Krupp 1992[687]	Yes	Yes	No	No	No	Conventional review; no original data reported
Kuchenhoff 1993[688]	Yes	Yes	No	No	No	Non-systematic review
Kuha 1986[689]	Yes	Yes	No	Yes	No	*n* = 108; average follow-up, 1.5 years
Kumar 1998[690]	No	Yes	No	Yes	No	Includes diagnoses outside inclusion criteria
Kumari 1999[691]	Yes	Yes	No	No	No	Outcome outside inclusion criteria; not an RCT
Kumari 2000[692]	Yes	Yes	No	No	No	Not randomised, effectiveness study
Kumra 1998[693]	Yes	Yes	No	Yes	No	Appears to be study of how existing tardive dyskinesia responds to antipsychotic drugs rather than study of treatment-emergent disease
Kuntz 1998[362]	Yes	Yes	Yes	No	No	Same as Reams 1998[149] (already included); no new data
Kursawe 1985[694]	Yes	Yes	No	No	No	German; *n* = 25
La Pia 2000[695]	Yes	Yes	No	No	No	Not an RCT or economic evaluation; no long-term follow-up
Lader 1999[696]	Yes	Yes	No	No	No	General discursive review of side-effects and their prevention using antipsychotic treatment
Lader 2000[697]	Yes	No	No	No	No	Effectiveness of rating scales
Lamarque 1996[698]	Yes	No	No	No	No	Effects of precautionary procedures on agranulocytosis incidence and outcome
Lambert 1999[699]	Yes	Yes	No	No	No	German; not an RCT; appears to be general discursive review of olanzapine (not systematic)
Lan 1999[138]	Yes	Yes	No	Yes	No	Chinese
Lanctot 1999[323]	Yes	Yes	No	No	No	Not full economic evaluation
Langbehn 2000[700]	Yes	No	No	No	No	Clozapine + carbamazepine; non-systematic review
LaPorta 1994[701]	Yes	Yes	No	No	No	Letter: not an RCT; about previous study and recounting authors own experiences
Launer 1992[702]	Yes	Yes	No	No	No	Letter: about previous article
Launer 1992[703]	Yes	Yes	No	No	No	Non-systematic review
Launer 1994[704]	Yes	Yes	No	No	No	Letter: about trial
Leadbetter 1990[705]	Yes	Yes	No	No	No	Letter: about previous study; not relevant design
Leadbetter 1992[706]	Yes	Yes	No	Yes	No	Not an RCT or case–control study; *n* = 21; < 2-year follow-up
Lecompte 1999[707]	Yes	Yes	No	No	No	Non-systematic review of economic studies applying current optimal dose information
Lecomte 2000[708]	Yes	Yes	No	No	No	Description of economic model
Lee 1998[709]	Yes	Yes	No	No	No	Long-term case series; no adverse events or rare outcomes of interest reported
Legal 1985[710]	No	No	No	No	No	French: non-systematic review
Lehman 1998[711]	Yes	No	No	No	No	Non-systematic review (treatment recommendations)
Lemmens 1999[712]	Yes	Yes	No	Yes	No	Not systematic review
Leo 1996[713]	Yes	Yes	No	No	No	Case report
Lesem 2001[714]	Yes	Yes	Yes	No	No	Ziprasidone in both arms
Levin 1996[715]	Yes	Yes	No	No	No	Case report

continued

Reference	Schizophrenia	Atypical	RCT	Side-effect	Economic	Reasons for exclusion
Lieberman 1989[716]	Yes	Yes	No	Yes	No	*n* = 37; average follow-up 18 months
Lieberman 1992[717]	Yes	Yes	No	No	No	Non-systematic review
Lim 1997[718]	Yes	Yes	No	No	No	Pilot review of risperidone usage
Lin 1999[719]	Yes	Yes	No	Yes	No	*n* = 61; only 3 months' follow-up
Linazasoro 1995[720]	No	No	No	No	No	Spanish, no English abstract; doesn't appear relevant. Appears to be general review of clozapine, mainly focussing on Parkinson's disease
Lindenmayer 1998[721]	Yes	Yes	No	No	No	Open-label trial, not an RCT
Lindenmayer 2000[722]	Yes	Yes	No	No	No	Non-systematic review
Lindstrom 1988[723]	Yes	Yes	No	No	No	Not an RCT; no meaningful adverse event data
Lindstrom 1994[724]	Yes	Yes	No	Yes	No	Outcome not relevant
Lindstrom 2000[725]	Yes	Yes	No	No	No	Economic review (non-systematic)
Llorca 1997[726]	Yes	Yes	No	Yes	No	Non-systematic review; data reported elsewhere
Loewenthal 1999[727]	Yes	Yes	No	No	No	Not an RCT or economic evaluation; no long-term follow-up
Louwerens 2000[728]	Yes	No	No	No	No	Not an RCT; not rare or long-term event study; not economic evaluation
Louwerens 2000[729]	No	No	No	No	No	Considers healthy volunteers; not an RCT
Lu 1991[730]	No	Yes	No	Yes	No	Chinese; may or may not relate to patients with schizophrenia
Lublin 1997[731]	Yes	Yes	No	No	No	Non-systematic review
Lucey 1999[732]	Yes	Yes	No	No	No	Non-systematic review
Mackay 1998[268]	Yes	Yes	No	Yes	No	No outcomes of interest
Mahmoud 1998[733]	Yes	Yes	No	No	No	Not full economic evaluation
Mahmoud 1998[734]	Yes	Yes	No	No	No	Comment on economic evaluation
Mahmoud 1999[735]	Yes	Yes	Yes	Yes	No	Reports trial design but no results
Maidment 1998[736]	Yes	Yes	No	No	No	Estimation of drug costs but not full economic evaluation
Malek-Ahmadi 1996[737]	No	No	No	No	No	Letter: *in-vitro* study of possible mechanisms of agranulocytosis
Malla 1999[738]	Yes	Yes	No	Yes	No	*n* = 38; follow-up 1 year; not case–control design
Malow 1994[739]	No	No	No	Yes	No	*n* = 10
Mangrella 1998[740]	No	Yes	No	Yes	No	Does not specify whether schizophrenia or other diagnoses
Manschreck 1994[741]	Yes	Yes	No	Yes	No	*n* = 50; follow-up < 2 years
Marcus 1995[742]	No	Yes	No	No	No	Letter: includes results from another study but doesn't include patients with schizophrenia
Marder 1998[743]	Yes	Yes	No	No	No	Only one outcome reported (ongoing)
Marecek 1975[744]	Yes	Yes	No	No	No	*n* = 47; uncontrolled study of Leponex®
Marlowe 2000[745]	No	Yes	No	No	No	Comment (letter)
Martenyi 1999[746]	Yes	Yes	No	No	No	Not an RCT or economic evaluation; no long-term follow-up
Martin 1995[747]	Yes	No	No	No	No	Non-systematic economic review, not focused on antipsychotic drugs
Martin 1998[748]	Yes	No	No	No	No	Not a full economic evaluation of atypical antipsychotic drug
Martin 2000[749]	Yes	Yes	No	Yes	No	Mixed diagnoses

continued

Reference	Schizophrenia	Atypical	RCT	Side-effect	Economic	Reasons for exclusion
Martinez 1998[750]	Yes	Yes	Yes	No	No	No outcomes reported (ongoing)
Masand 1999[751]	Yes	Yes	No	No	No	Letter: considers weight gain associated with antipsychotic drug treatments
Masand 2000[752]	Yes	Yes	No	No	No	Retrospective chart review of only 35 patients
Masand 2000[753]	Yes	Yes	No	No	No	Not real systematic review
Matheson 2000[754]	No	Yes	No	No	No	Patients with psychotic symptoms in Parkinson's disease
Matsuda 1996[755]	Yes	Yes	No	No	No	Not an RCT; compares Caucasian with Korean-American patients (*n* = 34)
Mattes 1998[756]	Yes	No	No	No	No	Letter: comment on RCT already included
Mauskopf 1999[757]	Yes	No	No	No	No	Economic evaluation but not specifically about antipsychotic drugs
Maynard 1998[758]	Yes	Yes	No	No	No	Economic overview
McGlashan 1988[759]	Yes	No	No	No	No	Non-systematic review, not about atypical antipsychotic drugs
McGurk 1999[760]	Yes	Yes	No	No	No	Non-systematic review
Meehan 1999[761]	Yes	Yes	No	No	No	Non-systematic review
Meehan 2000[762]	Yes	Yes	No	No	No	Pooled data from eight trials on EPS with olanzapine but trials not referenced
Melkersson 2000[763]	Yes	Yes	No	No	No	Short-term study of weight gain, insulin and leptin levels
Meltzer 1992[764]	Yes	Yes	No	No	No	Little information apart from title, which states that it is long-term follow-up study of treatment resistant illness treated with clozapine
Meltzer 1999[765]	Yes	No	No	No	No	Comment
Meltzer 1999[766]	Yes	Yes	No	No	No	Reanalysis of RCT already included
Meltzer 1999[767]	Yes	No	No	No	No	Economic methodology
Meltzer 2000[768]	Yes	Yes	No	No	No	Non-systematic review; InterSePT study protocol
Meltzer 2000[769]	Yes	Yes	No	No	No	Non-systematic review
Menkes 1993[770]	Yes	Yes	No	No	No	Letter: about previous study
Meterissian 1996[771]	Yes	Yes	No	Yes	No	Systematic review of case reports
Meynard 1995[772]	Yes	Yes	No	No	No	*n* = 5 (with schizophrenia); not an RCT; not looking at any adverse events listed in protocol
Miller 1995[773]	Yes	No	No	Yes	No	Study of tardive dyskinesia but not related to type of antipsychotic drug taken
Miller 1997[133]	Yes	Yes	No	Yes	No	Too small; *n* = 693
Miller 1997[774]	Yes	Yes	No	No	No	Not an RCT or economic study; no long-term follow-up
Miller 2000[775]	Yes	Yes	No	No	No	General discursive review (not systematic)
Mimica 1998[776]	Yes	Yes	Yes	No	No	New report of study already included; no new data
Min 2000[262]	Yes	Yes	No	No	No	Not an RCT; not study of long-term or rare adverse events
Mockler 1998[777]	Yes	Yes	No	No	No	Risperidone in both arms: patients with schizophrenia compared with healthy control group
Mohr 1998[778]	Yes	Yes	No	No	No	Comment on economic evaluation

continued

Reference	Schizophrenia	Atypical	RCT	Side-effect	Economic	Reasons for exclusion
Moller 1998[779]	Yes	Yes	No	No	No	Non-systematic review
Moller 1999[780]	No	No	No	No	No	Non-systematic review
Moller 2000[781]	Yes	Yes	No	No	No	Non-systematic review
Montalenti 1996[782]	Yes	Yes	No	No	No	Not an RCT or economic study
More 1992[783]	No	No	No	No	No	Reply to letter (case report)
Mullen 1999[784]	Yes	Yes	Yes	No	No	Abstract already reported and included
Mullen 2001[785]	Yes	Yes	No	Yes	No	*n* = 54
Murschel 1993[786]	Yes	Yes	No	Yes	No	Survey; *n* = 58 (preliminary decision based on abstract)
Naber 1989[787]	Yes	Yes	No	No	No	Not relevant study design retrospective chart review of 387 patients. Treated for 48 days as inpatients
Naber 1992[788]	No	Yes	No	No	No	*n* = 480; follow-up < 2 years
Naber 1998[789]	Yes	Yes	No	No	No	Non-systematic review
Nahunek 1975[790]	Yes	Yes	No	No	No	Czech; *n* = 151
Nair 1998[791]	Yes	Yes	Yes	No	No	No comparator: risperidone in both arms
Negron 1996[792]	Yes	Yes	No	Yes	No	Diagnoses other than schizophrenia
Newman 1991[793]	Yes	No	No	Yes	No	Suicide study but no information on antipsychotic drugs
Nightengale 1998[794]	Yes	Yes	No	No	No	Not full economic evaluation
Nittenson 1102[795]	No	Yes	No	No	No	Letter; retrospective chart review of 51 patients treated with clozapine; doesn't state if participants have schizophrenia
Nitzsche 1986[796]	Yes	Yes	No	No	No	German; prospective study of only 35 patients looking at side-effects of clozapine
Norrie 2000[797]	Yes	Yes	No	No	No	Protocol of augmentation (valproate/ olanzapine) trial
Nyberg 1998[798]	Yes	No	No	No	No	Experimental brain imaging study
Oefele 1989[799]	No	No	No	No	No	German; no separate analysis of drugs; mixed diagnoses
Offerhaus 1991[800]	No	No	No	No	No	Dutch with no English abstract; clozapine only one small paragraph – doesn't appear relevant
Oliemeulen 1999[801]	Yes	Yes	Yes	No	No	Brief methods only; no results
O'Neill 1999[802]	Yes	Yes	No	No	No	Efficacy but not RCT
Ortola 1997[803]	Yes	Yes	No	No	No	Retrospective short-term efficacy study (not an RCT); preliminary decision based on abstract
Owens 1994[804]	Yes	Yes	No	No	No	General discursive review (not systematic) about risperidone and its side-effects
Pacia 1994[139]	No	Yes	No	No	No	Not stated if patients have schizophrenia; retrospective review of 5629 US clozapine-treated patients and clozapine-related seizures. Not case–control study
Pallanti 1999[805]	Yes	Yes	No	No	No	Not an RCT or economic evaluation; no long-term follow-up
Palmgren 2000[806]	Yes	Yes	No	No	No	No control group
Palva 1976[807]	No	Yes	No	No	No	Swedish; appears to be non-systematic review
Panteleeva 1987[808]	Yes	Yes	No	Yes	No	*n* = 120; follow-up 2 months only

continued

Reference	Schizophrenia	Atypical	RCT	Side-effect	Economic	Reasons for exclusion
Penn 1996[809]	Yes	Yes	No	No	No	Case report
Pere 1995[810]	No	No	No	No	No	Non-systematic review of pharmacology
Perquin 1998[811]	Yes	Yes	No	No	No	No comparator drug (naturalistic study of switching to sertindole from conventional antipsychotic drugs)
Perry 2001[812]	Yes	Yes	Yes	No	No	Further report of Beasley 1996;[168] plasma concentrations reported – outside remit of this review (not clinical outcome)
Peruche 1996[813]	Yes	Yes	No	No	No	Non-systematic review
Peuskens 1998[814]	No	No	No	No	No	Conventional review, no original data
Peuskens 2000[815]	Yes	Yes	No	No	No	Non-systematic review of six studies
Pezawas 2000[816]	Yes	Yes	No	Yes	No	*n* = 34; < 2 years follow-up; not case–control design
Pillans 1997[817]	No	No	No	No	No	General report of adverse events reported in New Zealand
Pollack 1998[818]	Yes	Yes	No	No	No	Not randomised trial
Pope 1986[819]	Yes	Yes	No	Yes	No	Not relevant design. Survey of 500 patients admitted during 1-year period looking for cases of NMS
Pourcher 1998[820]	Yes	Yes	No	No	No	Unclear whether randomised
Pradhan 2000[821]	No	No	No	No	No	Letter: contains no data; not an RCT
Prakash 1998[822]	No	No	No	No	No	Conventional review; no original data
Preterre 1995[823]	Yes	No	No	No	No	French; review-type discussion
Puras 1998[824]	Yes	Yes	No	No	No	No control group
Purdon 1999[825]	Yes	Yes	Yes	No	No	New report of RCT already included; no new data
Purdon 2000[178]	Yes	Yes	Yes	No	No	Same as Jones 1998 (included);[180] extra cognition data but attrition > 50% so data excluded
Rabinowitz 2000[27]	Yes	Yes	No	No	Yes	Not an RCT or full economic evaluation; psychiatrists' preferences
Rabinowitz 2001[826]	Yes	Yes	No	No	No	Study of rehospitalisation rates, not randomised
Rak 1999[827]	Yes	Yes	No	No	No	No control group, quetiapine only
Ramaekers 2000[828]	No	Yes	No	No	No	Dutch. Appears to be letter about another study looking at clozapine
Raoul 1997[829]	Yes	Yes	No	Yes	No	*n* = 22; outcome not relevant
Rasmussen 1999[830]	Yes	Yes	Yes	No	No	No results; protocol
Rastogi 2000[831]	Yes	Yes	No	No	No	Uncontrolled cohort study of clozapine/ use of health resources (preliminary decision based on abstract)
Ratakonda 1998[832]	Yes	Yes	No	No	No	Probably not an RCT
Reeves 1998[833]	Yes	Yes	No	No	No	No control group, comparison of ziprasidone doses only
Reeves 1999[834]	Yes	Yes	Yes	No	No	Ziprasidone in both arms of study
Reid 1980[835]	No	No	No	No	No	Not about atypical drugs. References too old
Reid 1994[836]	Yes	Yes	No	No	No	Economic review (not systematic)
Reid 1994[837]	Yes	Yes	No	Yes	No	Outcome not relevant
Reid 1998[838]	Yes	Yes	No	No	No	Not randomised trial; not full economic evaluation
Reid 1998[839]	Yes	No	No	No	No	Non-systematic review

continued

Reference	Schizophrenia	Atypical	RCT	Side-effect	Economic	Reasons for exclusion
Reilly 2000[840]	No	Yes	No	No	No	*n* = 495; diagnoses other than schizophrenia; includes drugs other than atypical antipsychotics
Reine 1992[841]	Yes	Yes	No	Yes	No	*n* = 53; follow-up < 2 years
Remington 1996[842]	No	Yes	No	No	No	Non-systematic review, no original data
Remington 1998[843]	Yes	No	No	No	No	Non-systematic review
Repo 1989[844]	Yes	Yes	No	No	No	Considers safety of antipsychotic drugs but only features five case reports relating to NMS
Revicki 1998[845]	Yes	Yes	No	No	No	Authors' reply to comments re economic evaluation
Revicki 1999[846]	Yes	Yes	No	No	No	Non-systematic review
Reznik 2000[847]	Yes	Yes	No	No	No	Experimental outcomes (not listed in inclusion criteria for review), not randomised
Reznik 2000[848]	Yes	Yes	No	No	No	Case report
Rimon 1994[849]	Yes	No	No	No	No	Retrospective survey
Risby 1995[850]	Yes	Yes	No	Yes	No	*n* = 16; follow-up on average < 2 years; not case–control design
Rittmannsberger 1985[851]	No	No	No	No	No	German; appears to be non-systematic review
Robinson 2000[852]	Yes	Yes	No	No	No	Extension to an RCT; *n* = 5; < 2 years, no long-term/ rare outcomes of interest reported
Rosenheck 1999[853]	Yes	Yes	Yes	No	No	RCT included in earlier review; no new data
Rosenheck 1999[854]	Yes	Yes	No	No	No	Letter; comment
Rosenheck 2000[855]	Yes	Yes	Yes	No	Yes	Already included; no new data
Rosenheck 2000[856]	Yes	Yes	No	Yes	No	*n* = 221; follow-up 12 months; not case–control design
Rossi 1998[857]	No	No	No	No	No	Italian; non-systematic review
Russell 1999[858]	Yes	Yes	No	Yes	No	*n* = 31
Ruther 1999[859]	Yes	Yes	No	No	No	Open trial, no comparator
Ruther 1999[860]	Yes	Yes	No	No	No	Not an RCT or economic evaluation; no long-term follow-up
Rybakowski 1998[861]	Yes	Yes	No	No	No	Not an RCT or economic evaluation; no follow-up
Sachdev 1995[862]	Yes	Yes	No	No	No	Review of case reports
Safferman 1992[863]	No	No	No	No	No	Comment (letter)
Safferman 1993[864]	Yes	Yes	No	No	No	Not an RCT
Sagud 2000[865]	Yes	Yes	No	Yes	No	Case report of agranulocytosis with risperidone and clozapine
Sanada 1985[866]	Yes	Yes	No	Yes	No	Japanese; otherwise meets inclusion criteria
Sax 1998[867]	Yes	Yes	No	No	No	Non-randomised study
Schooler 1999[868]	Yes	Yes	Yes	No	No	No results
Schooler 2000[869]	Yes	Yes	No	No	No	Not an RCT or economic evaluation, no long-term follow-up
Scrip 1998[870]	Yes	Yes	No	No	No	News report of 1998 economic evaluation
Sekine 1999[871]	No	No	No	No	No	Not patient study
Selim 1999[872]	No	Yes	No	No	No	General discursive review of safety of psychotropic drugs
Selten 2000[873]	No	No	No	No	No	Non-systematic review

continued

Reference	Schizophrenia	Atypical	RCT	Side-effect	Economic	Reasons for exclusion
Sernyak 1999[874]	Yes	No	No	No	No	Not report of study
Serrano-Duenas 2000[875]	No	Yes	No	Yes	No	Cardiac complications in people with Parkinson's disease
Shader 1991[876]	Yes	No	No	No	No	Consensus statement by American College of Neuropsychopharmacology council
Shader 1998[877]	No	Yes	No	No	No	Editorial; *in-vitro* studies investigating potential potassium-channel mechanism for pro-arrhythmic effects
Sharma 1996[878]	Yes	Yes	No	No	No	Case report
Sharma 1999[879]	Yes	Yes	No	No	No	Not RCT and same study as O'Neill 1999[802]
Shelton 1999[880]	No	Yes	No	No	No	Participants with major depressive disorder, not schizophrenia
Shepski 1996[881]	Yes	No	No	No	No	Considers prescribing practices and criteria to measure prescribing practices for risperidone
Shermock 2001[882]	Yes	Yes	No	No	No	Cost analysis only (not full economic evaluation)
Shore 1995[883]	Yes	No	No	No	No	Report of workshop on clozapine discontinuation
Short 2000[884]	Yes	Yes	No	Yes	No	No usable results reported
Shuster 1998[885]	No	No	No	No	No	Single adverse reaction report from case report published elsewhere
Shuster 2000[886]	No	No	No	No	No	Single adverse reaction report from case report published elsewhere
Shuster 2000[887]	No	No	No	No	No	Single adverse reaction report from case report published elsewhere
Siefen 1986[888]	Yes	Yes	No	No	No	Not an RCT or case–control study; $n = 21$
Silva 1997[889]	No	Yes	No	No	No	Non-systematic review
Silva de Lima 1999[890]	Yes	Yes	No	No	No	Not an RCT
Silvestri 1998[891]	Yes	Yes	No	No	No	Not an RCT or economic study
Simpson 1996[892]	No	Yes	No	No	No	Letter: about another letter looking at dystonia
Simpson 1999[893]	Yes	Yes	Yes	No	No	Compares three doses of clozapine but no comparator
Simpson 1999[894]	Yes	Yes	No	No	No	Report of one arm of RCT (switching from risperidone to ziprasidone); no control group
Simpson 1999[895]	Yes	Yes	No	No	No	Switching therapy
Simpson 2000[896]	Yes	Yes	No	No	No	Not a RCT or economic evaluation, no long-term follow-up
Singer 1983[897]	No	Yes	No	No	No	Letter: about previous study
Sitarz 1996[898]	No	No	No	No	No	Letter: about case report
Snaterse 2000[899]	Yes	Yes	No	No	No	Non-RCT design efficacy study
Soni 2000[900]	Yes	Yes	No	No	No	Non-randomised, effectiveness study
Spatz 1978[901]	No	Yes	No	No	No	German; not clear if patients have schizophrenia, but only 127 patients included
Special Hospitals' TRS Research Group 1996[902]	Yes	Yes	No	No	No	Non-systematic review; non-systematic overview of clozapine and risperidone use in violent patients
Spigset 1996[903]	Yes	No	No	No	No	Control group healthy volunteers; small study based on biochemical tests to identify hyponatremia during treatment

Reference	Schizophrenia	Atypical	RCT	Side-effect	Economic	Reasons for exclusion
Spivak 1998[904]	Yes	Yes	No	Yes	No	*n* = 30; only 1-year follow-up; not case–control design
Spivak 1999[905]	Yes	Yes	No	Yes	No	*n* < 100; 6-months follow-up; not randomised, not case–control design
Stanniland 2000[906]	No	No	No	No	No	Conventional review; no literature search
Stevens 1992[907]	Yes	Yes	No	No	No	General literature review (not systematic) about clozapine; also features animal studies
Stevens 1995[908]	Yes	Yes	No	No	No	General discursive review of seizures associated with clozapine treatment (not systematic)
Stewart 2000[909]	No	Yes	No	No	No	Comment (letter)
Stip 1996[910]	Yes	Yes	No	No	No	Not an RCT; not study of long-term or rare events
Stip 1999[911]	No	No	No	No	No	Letter: about animal studies; no original data
Stoner 2001[912]	No	No	No	No	No	Diagnoses not specified; various drug treatments
Storosum 1998[913]	No	No	No	No	No	Trial methodology
Street 2000[914]	No	Yes	No	No	No	Participants with Alzheimer's disease, not schizophrenia
Stubner 2000[915]	Yes	Yes	No	No	No	Considers cases of Pisa syndrome (rare adverse event of neuroleptic medication) identified over 7-year period in population of 45,000 patients monitored in multicentre drug safety surveillance project
Stuppack 1999[916]	Yes	Yes	No	No	No	Not an RCT; no control group
Suppes 1999[917]	Yes	Yes	No	No	No	12 schizoaffective (26 bipolar) not reported separately
Suttmann 2000[918]	Yes	Yes	No	No	No	Comment (letter); case report
Sweeney 1997[919]	Yes	Yes	No	Yes	No	*n* = 9; follow-up < 2 years; eye movement effects not listed as adverse event
Swift 1999[224]	Yes	Yes	Yes	No	No	Already in earlier review; no new data
Szabadi 1995[920]	Yes	Yes	No	No	No	Discursive paper, not based on a large, case-controlled, long-term study
Szabadi 1997[921]	No	Yes	No	No	No	Comment (mechanisms of clozapine-induced hypersalivation); letter
Takahashi 1999[922]	Yes	Yes	Yes	No	No	Considers risperidone as adjunctive therapy; outside scope of this review
Takebayashi 1999[923]	Yes	Yes	No	No	No	Open trial, not randomised
Takebayshi 2000[924]	Yes	Yes	No	No	No	Not randomised
Tamminga 1997[925]	Yes	Yes	No	No	No	Non-systematic review of pharmacology, no original data
Tapson 2000[926]	Yes	Yes	No	No	No	Commentary on another study
Tarsy 1984[927]	No	No	No	No	No	Non-systematic review
Tavcar 2000[928]	Yes	Yes	No	Yes	No	Comment (letter)
Taylor 1996[929]	Yes	Yes	No	No	No	Conventional review; no data
Tegeler 1986[930]	No	No	No	No	No	Non-systematic review
Tegeler 1987[931]	No	No	No	No	No	Non-systematic review
ten Brink 1998[932]	No	No	No	No	No	Dutch with English abstract; not an RCT but review of patients' subjective experiences of using antipsychotic drugs

continued

Reference	Schizophrenia	Atypical	RCT	Side-effect	Economic	Reasons for exclusion
Theret 1995[933]	Yes	Yes	No	No	No	Three case reports of intestinal occlusion in 30 patients receiving clozapine treatment for schizophrenia
Thomassen 2000[934]	No	No	No	Yes	No	Not clear whether patients had schizophrenia ('psychiatric' patients); not stated which neuroleptic drugs given
Thompson 1990[935]	No	No	No	No	No	Conventional review; no original data reported
Thornberg 1993[936]	Yes	Yes	No	No	No	Six case reports
Toalsom 2001[937]	Yes	Yes	No	No	No	Study outcome not relevant
Tohen 1999[938]	No	Yes	No	No	No	Participants with bipolar disorder, not schizophrenia
Tohen 1999[939]	No	Yes	No	No	No	Participants with bipolar disorder, not schizophrenia
Tohen 1999[940]	No	Yes	Yes	No	No	Participants had bipolar disorder, not schizophrenia
Tohen 1999[941]	No	Yes	No	No	No	Not an RCT or economic evaluation; no long-term follow-up; participants with bipolar disorder not schizophrenia
Tohen 1999[942]	No	Yes	Yes	No	No	Participants with major depressive disorder not schizophrenia
Tollefson 1998[943]	Yes	Yes	Yes	No	No	Another report of Tollefson 1997 (already included);[164] no new data
Tollefson 1998[944]	Yes	No	No	No	No	Reply to comments
Tollefson 1998[945]	Yes	Yes	No	No	No	Comments on RCT already included
Tollefson 1999[946]	Yes	Yes	Yes	No	No	Comparison of switching drug regimens
Tollefson 1999[947]	Yes	Yes	No	No	No	Non-systematic review
Toren 1998[948]	No	Yes	No	No	No	Includes diagnoses other than schizophrenia
Tran 1998[949]	Yes	Yes	No	No	No	Non-systematic review, RCTs already included
Trandafir 1999[950]	No	Yes	No	No	No	Not an RCT; people with cannabis-induced psychosis not schizophrenia
Travis 1997[951]	No	Yes	No	No	No	Non-systematic review
Trenckmann 1999[952]	Yes	Yes	No	No	No	Not randomised or a full economic evaluation, or a study of rare events
Trezise 1996[953]	No	Yes	No	No	No	Comment (letter)
Truffinet 1999[954]	Yes	Yes	No	No	No	Not an 'atypical' drug
Tueth 1993[955]	Yes	Yes	No	No	No	Letter: about author's own experiences with clozapine
Tunis 1999[930]	Yes	Yes	No	No	No	Not full economic evaluation
Tunis 2000[956]	Yes	Yes	No	No	No	Not full economic evaluation
Ulferts 1999[957]	Yes	Yes	No	No	No	Non-randomised effectiveness study
Ulrich 1999[958]	Yes	Yes	No	No	No	Two preparations of haloperidol compared with each other; not randomised
Umbricht 1996[959]	Yes	Yes	No	No	No	Non-systematic review of side-effects of risperidone and clozapine
Van Zonneweld 2000[960]	Yes	Yes	No	No	No	Diagnoses other than schizophrenia; *n* = 64
Vencovsky 1976[961]	Yes	Yes	No	No	No	Czech; non-systematic review?
Versiani 1984[962]	Yes	Yes	No	No	No	Spanish; appears to be general discursive review (not systematic)

continued

Reference	Schizophrenia	Atypical	RCT	Side-effect	Economic	Reasons for exclusion
Vesterby 1980[963]	Yes	Yes	No	No	No	Case report
Veys 1992[964]	No	Yes	No	No	No	Not patient study, methods of investigating cell samples to test for neutropenia
Voris 1999[965]	No	Yes	No	No	No	Describes patterns of prescribing; mixed diagnoses
Voruganti 2000[966]	Yes	Yes	No	No	No	Non-randomised, 6-month effectiveness and safety study
Wahlbeck 2000[967]	Yes	Yes	No	No	No	Systematic review of RCT quality (not effectiveness)
Wang 1994[968]	No	Yes	No	Yes	No	Patients with schizophrenia?; English abstract but not enough information
Warner 1999[969]	Yes	Yes	No	No	No	Critique of systematic review already included
Warner 2000[970]	Yes	Yes	No	No	No	Comment (letter)
Wee 1998[971]	Yes	Yes	No	No	No	Not an RCT; retrospective study of small number of patients treated with olanzapine. Does mention costs but doesn't appear that full economic evaluation performed
Wehnert 1998[972]	Yes	Yes	No	Yes	No	Protocol
Wehnert 1999[973]	Yes	Yes	No	No	No	Brief summary of data from studies published in 1994 and 1996
Weiden 1995[974]	Yes	No	No	No	Yes	Not about atypical drugs
Weiden 1996[975]	Yes	Yes	No	No	No	Non-systematic review
Weiden 1999[976]	Yes	Yes	No	No	No	Switching therapy
Welch 2000[977]	Yes	Yes	No	No	No	Non-systematic review
Weller 1993[978]	Yes	Yes	No	No	No	Letter; case reports
Weller 1996[979]	No	Yes	No	No	No	Comment (letter)
Weller 1997[980]	Yes	Yes	No	No	No	Letter: response to article on NMS
Werry 1999[981]	Yes	No	No	No	No	Comment
Wetterling 1996[982]	Yes	Yes	No	No	No	German; *n* = 110; follow-up 1 year
Wetterling 2000[983]	Yes	Yes	No	No	No	German; not relevant design. Appears to be general discursive review of weight gain in neuroleptic treatments (not systematic)
Wiebe 1993[984]	Yes	Yes	No	Yes	No	*n* = 5; follow-up 16 months maximum; not case–control design
Wiholm 1989[985]	No	Yes	No	No	No	Swedish; letter
Williams 1995[986]	Yes	Yes	No	No	No	Economic review (not systematic)
Williams 2001[987]	Yes	Yes	No	No	No	Systematic review of dose of risperidone; no comparator
Wilson 1994[988]	Yes	Yes	No	No	No	*n* = 100; follow-up 18 months
Wilson 1999[989]	No	Yes	No	Yes	No	Only 165 patients, retrospective review
Wilson 2000[990]	Yes	Yes	No	Yes	No	*n* = 14; < 2 year follow-up; not case–control design
Windhaber 2000[991]	Yes	Yes	No	No	No	Comment (letter)
Wirshing 2000[992]	No	No	No	No	No	Conventional review, no original data
Wojdyslawska 1975[993]	Yes	Yes	No	No	No	Polish with English abstract; uncontrolled study of Leponex®
Wojdyslawska 1976[994]	Yes	No	No	No	No	Polish with English abstract; uncontrolled study of Leponex®
Wong 1985[995]	No	No	No	No	No	Non-systematic review; no original data

continued

Reference	Schizophrenia	Atypical	RCT	Side-effect	Economic	Reasons for exclusion
Wood 1998[996]	Yes	Yes	No	No	No	Non-systematic review
Woods 1999[997]	No	Yes	No	No	No	Comment (letter)
Yagdiran 2000[998]	Yes	Yes	No	No	No	Cohort study
Yamawaki 1990[999]	Yes	Yes	No	No	No	Not relevant design; postal survey of Japanese hospitals to identify cases of NMS
Yang 1984[1000]	Yes	Yes	No	No	No	Chinese; no English abstract
Yap 2000[1001]	No	No	No	No	No	Editorial about many different classes of drugs
Yuanguang 1998[1002]	Yes	Yes	No	No	No	No comparator drug (two doses of clozapine); unclear whether randomised
Zapletalek 1976[1003]	Yes	Yes	No	Yes	No	Czech
Zapletalek 1985[1004]	Yes	Yes	No	Yes	No	Outcome not in protocol
Zimbroff 1995[1005]	Yes	No	No	No	No	Patients swapping from clozapine to risperidone
Zimmet 2000[1006]	Yes	Yes	No	Yes	No	*n* = 110; length of follow-up variable; outcome (substance abuse) not listed in protocol
Zito 1998[1007]	Yes	Yes	No	No	No	Not full economic evaluation, non-systematic review

Appendix 11

Studies awaiting assessment

1. Beasley CM, Berg PH, Dananberg J, Kwong KC, Taylor CCM. The emergence of EEG abnormalities for clozapine and haloperidol: lack of association with treatment response and plasma levels (results of a prospective double blind study). *Biol Psychiatry* 2001;**49** suppl:121.
2. Dolnak DR, Minn K, Wieneke M, Watson C, Espinoza S, *et al.* Olanzapine versus haloperidol in the treatment of schizophrenia. Presented at 149th Annual Meeting of the American Psychiatric Association; 2000 May 4–9; New York.
3. Post HA, Sloof CJ, Wiersma D, Van Hout BA. Cost-effectiveness of olanzapine in comparison to risperidone and haloperidol. *Int J Technol Assess Health Care* 1997;**13**:134.
4. Schotte A, Van Baelen B. Treatment of the symptoms of schizophrenia: a meta-analysis comparing risperidone with other antipsychotic agents [conference poster]. *Schizophr Res* 1998;**1**.
5. Spannheimer A, Clouth J. Pharmacoeconomic evaluation of the treatment of schizophrenia in Germany: a comparison of olanzapine and haloperidol. Presented at 148th Annual Meeting of the American Psychiatric Association; 1999 15–20 May; Washington DC.
6. Taylor D. Open label extension of treatment with Seroquel for patients who have participated in the Phase III clinical trial programme. In: Cochrane Library, Issue 2, 2001. Oxford: Update Software; 2001.
7. Zelaschi NM, Rodriguez JL, Gaitan S, Panizzo S, Lopez A, *et al.* A clinical trial comparing endocrine effects of risperidone and clozapine. Presented at 150th American Psychiatric Association Annual Meeting; 2001 May 5; New Orleans.
8. Kudo Y, Nomura JI, Ikawa G, Nakajima T, Saito M, Sakai T, *et al.* Clinical evaluation of quetiapine fumarate for the treatment of schizophrenia. A double blind controlled study using mosapramine hydrochloride as a control. *Rinsho Iyaku* 2000;**16**:1807–42.
9. Lopez Ibor JJ, Ayuso JL, Gutierrez M, Guimon J, Herraiz ML, Chinchilla A, *et al.* [Risperidone in the treatment of chronic schizophrenia: multicenter study comparative to haloperidol. In Spanish]. *Actas Luso Esp Neurol Psiquiatr Cienc Afines* 1996;**24**:165–72.

Appendix 12

Cost-effectiveness

All the evidence provided by industry was commercial-in-confidence and has therefore been removed from this appendix.

Included studies

Almond S, O'Donnell O.[326] Cost analysis of the treatment of schizophrenia in the UK. A simulation model comparing olanzapine, risperidone and haloperidol. *PharmacoEconomics* 2000;**17**:383–9.

Bille A, Andersen J.[337] Risperidone Olanzapine Drug Outcomes studies in Schizophrenia (RODOS) single-centre report from an international study series. *J Eur Coll Neuropsychopharmacol* 1999;**9** Suppl 5: S286.

Blieden N, *et al.*[313] Health status and health care costs for publicly funded patients with schizophrenia started on clozapine. *Psychiatr Serv* 1998;**49**:1590–3.

Byrom BD, *et al.*[324] Influence of antipsychotic profile on cost of treatment of schizophrenia: a decision analysis approach. *Int J Psychiatry Clin Pract* 1998;**2**:129–38.

Chinchilla A, *et al.*[319] Risperidone: cost-effectiveness treatment study with schizophrenic patients. *Eur Neuropsychopharmacol* 1998;**8** Suppl 2:S231.

Coley KC, *et al.*[314] Effectiveness of antipsychotic therapy in a naturalistic setting: a comparison between risperidone, perphenazine and haloperidol. *J Clin Psychiatry* 1999;**60**:850–6.

Davies L, Lewis S.[308] Antipsychotic medication for people with first episode schizophrenia: an exploratory economic analysis of alternative treatment algorithms. Discussion Paper 178. York: Centre for Health Economics; 2000.

De Hert M, *et al.*[330] A one-year cost-effectiveness model for the treatment of chronic schizophrenia in Belgium. *Eur Neuropsychopharmacol* 2000;**10** Suppl 3:S316.

Drew LR, *et al.*[311] Clozapine in community practice: a 3-year follow-up study in the Australian Capital Territory. *Aust N Z J Psychiatry* 1999;**33**:667–75.

Duchesne I, *et al.*[336] The cost of inpatient treatment of schizophrenia: a study of two leading atypical antipsychotics. *Value in Health* 1999;**2**:355.

Edgell E, *et al.*[170] Olanzapine versus risperidone: a prospective comparison of clinical and economic outcomes in schizophrenia. *PharmacoEconomics* 2000;**18**:567–79.

Essock S, *et al.*[335] Cost-effectiveness of clozapine compared with conventional antipsychotic medication for patients in state hospitals. *Arch Gen Psychiatry* 2000;**57**:987–94.

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Gregor KJ, *et al.*[328] An economic comparison of olanzapine versus haloperidol in the treatment of schizophrenia in France. *Schizophr Res* 2000;**41**:189.

Hamilton S, *et al.*[1008] Clinical and economic outcomes of olanzapine compared with haloperidol for schizophrenia: results from a randomized clinical trial [abstract]. 11th European College of Neuropsychopharmacology Congress; 1998 31 October–4th November; Paris, France. *Eur Neuropsychopharmocology* 1998;**8** Suppl 2:P.2.075.

Hammond CM, *et al.*[327] Economic evaluation of risperidone in an outpatient population. *Ann Pharmacother* 1999;**33**:1160–6.

Iskedjian M, *et al.*[325] Cost–utility analysis of risperidone in chronic schizophrenia. *Value in Health* 1999;**2**:16–17.

Johnstone BM, *et al.*[148] To evaluate the cost-effectiveness of olanzapine compared to haloperidol for schizophrenia. Presented at 151st Annual Meeting of the American Psychiatric Association; 1998 30 May–4 June; Toronto, Ontario, Canada.

Kasper S, Duchesne I.[329] Inpatient treatment of schizophrenia: a real-life study of the two leading atypical antipsychotics. *Eur Neuropsychopharmacol* 2000; **10** Suppl 3:S316–17.

Launois R, *et al.*[321] Cost-effectiveness of sertindole versus olanzapine or haloperidol: a comprehensive model. *Int J Psychiatry Clin Pract* 1998;**2** Suppl 2:S79–86.

Loos JCM, *et al.*[331] Comparison of the costs and effects of treatment with risperidone versus olanzapine in daily practice. *Eur Neuropsychopharmacol* 2000; **10** Suppl 3:S292–3.

Martin S, Wright T.[332] Risperidone Olanzapine Drug Outcome Study (RODOS): the first English results. *Eur Neuropsychopharmacol* 2000;**10** Suppl 3:S310–11.

Obenchain RL, Johnstone BM.[320] Mixed-model imputation of cost data for early discontinuers from a randomized clinical trial. *Drug Inf J* 1999;**33**:191–209.

Oh P, Lanctot KL.[323] An economic evaluation of risperidone in chronic schizophrenia. *Eur Neuropsychopharmacol* 1999;**9** Suppl 5:S278.

Palmer CS, *et al.*[316] A cost-effectiveness clinical decision analysis model for schizophrenia. *Am J Managed Care* 1998;**4**:345–55.

Percudani M, *et al.*[309] Health care costs of therapy-refractory schizophrenic patients treated with clozapine: a study in a community psychiatric service in Italy. *Acta Psychiatr Scand* 1999;**99**:274–80.

Rosenheck R, *et al.*[115] Multiple outcomes assessment in a study of the cost-effectiveness of clozapine in the treatment of refractory schizophrenia. *Health Serv Res* 1998;**33**(5 pt 1):1237–61.

Sacristan JA, *et al.*[34] Pharmacoeconomic assessment of olanzapine in the treatment of refractory schizophrenia based on a pilot clinical study. *Clin Drug Invest* 1998;**15**:29–35.

Schiller MJ, *et al.*[310] Treatment costs and patient outcomes with use of risperidone in a public mental health setting. *Psychiatr Serv* 1999;**50**:228–32.

Tunis SL, *et al.*[315] Changes in perceived health and functioning as a cost-effectiveness measure for olanzapine versus haloperidol treatment of schizophrenia. *J Clin Psychiatry* 1999;**60** Suppl 19:38–46.

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Hamilton SH, *et al.*[334] Medical resource use and work and social outcomes for olanzapine compared with haloperidol in the treatment of schizophrenia and other psychotic disorders. Presented at 9th Biennial Winter Workshop on Schizophrenia; 1998; Davos, Switzerland.

Hong WW, *et al.*[35] Medical-claims databases in the design of a health-outcomes comparison of quetiapine ('Seroquel') and usual-care antipsychotic medication. *Schizophr Res* 1998;32:51–8.

Jolivel C, *et al.*[33] Medico-economic study of Leponex (clozapine) in the Bordeaux Charles Perrens Hospital centre. *Encephale* 1998;**24**:365–77.

Keegan DL, *et al.*[24] Long-term healthcare resource utilisation and costs before and after initiation of risperidone treatment in patients with chronic schizophrenia. *Clin Drug Invest* 1999;**18**:233–7.

Lacro J, *et al.*[26] Cost analysis of risperidone in veterans with schizophrenia or schizoaffective disorder [abstract]. Presented at annual meeting of the New Clinical Drug Evaluation Unit; 1997 May 27–30; Boca Raton. Florida, USA.

Lancon C, *et al.*[29] Sertindole: cost and effectiveness assessment. *Schizophr Res* 1999;**36**:344.

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Moore DB, *et al.*[23] Rehospitalization rates for depot antipsychotics and pharmacoeconomic implications: comparison with risperidone. *Am J Health System Pharm* 1998;**55**(24 Suppl):S17–19.

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Rabinowitz J, *et al.*[27] Comparison of cost, dosage and clinical preference for risperidone and olanzapine. *Schizophr Res* 2000;**46**:91–6.

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Shermack KM, *et al.*[882] Risperidone, haloperidol and clozapine in the South Carolina Medicaid program: a comparative analysis of utilisation and expenditure. *Dis Manage Health Outcomes* 2001;**9**:203–13.

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Tunis SL.[30] The impact of schizophrenic patient functionality on service utilization and cost. *Am J Managed Care* 1999;**5**:S583–90.

Wieselgren I, *et al.*[40] A cost-effectiveness clinical decision analysis for schizophrenia: results from Sweden. *Eur Neuropsychopharmacol* 1999;**9** Suppl 5:S289.

Validity assessment tool

Trial questions	Trial questions
Viewpoint of analysis (e.g. NHS) clearly stated? Relevant alternatives compared? Alternatives clearly described? Rationale for choosing alternatives stated? Form of economic evaluation justified?	Details of any model used given? Choice of model and key parameters justified? Time horizon of costs and benefits stated? Choice of discount rate justified? Convincing explanation given if no discounting?
Source of effectiveness data stated? Details of methods of synthesis of effectiveness data given? Primary outcome measures (e.g. life-years gained, QALY) clearly stated? Methods to value health states and other benefits clearly stated? Details of individuals from whom valuations obtained given?	Details of statistical tests and CIs given for stochastic data? Sensitivity analysis performed and described (one-way, multi-way)? Choice of variables for sensitivity analysis justified? Ranges over which variables are varied stated?
Relevance of productivity changes discussed? Productivity changes (if included) reported separately? Quantities of resources reported separately from unit costs? Methods for estimation of quantities described? Methods for estimation of unit costs described? Currency and price data reported? Details of currency or price adjustments (e.g. for inflation) included?	Incremental analysis reported? Major outcomes presented in dis-aggregated and aggregated forms? Applicable to NHS setting?

Characteristics of included studies

Study	Type	Intervention	Control	Population
Coley 1999[314]	Cost-effectiveness	Risperidone, perphenazine	Haloperidol	202 inpatients at psychiatric hospital
Drew 1999[311]	Cost-effectiveness	Post-clozapine	Pre-clozapine	Cohort of 37 patients from community practice
Tunis 1999[315]	Cost-effectiveness	Olanzapine	Haloperidol	Subsample of 1155 English-speaking patients from 17-country trial
Galvin 1999[312]	Cost-effectiveness	Clozapine, risperidone	Chlorpromazine, haloperidol	37 patients receiving services through Tarrant County Mental Health Mental Retardation Services
Blieden 1998[313]	Cost-effectiveness	Starting clozapine	6-months after starting clozapine	33 patients with schizophrenia
Palmer 1998[316]	Cost-effectiveness	Olanzapine	Haloperidol, risperidone	Patients who had experienced multiple episodes of schizophrenia
Sacristan 1998[34]	Cost-effectiveness	Olanzapine	Before olanzapine initiation	Patients from five psychiatric research units entered a 6-week pilot trial; responders entered extension phase for up to 26 weeks
Percudani 1999[309]	Cost-effectiveness	Post-clozapine	Pre-clozapine	12 patients receiving clozapine treatment for at least 1 year.
Obenchain 1999[320]	Cost-effectiveness	Olanzapine	Haloperidol	817 American patients
Schiller 1999[310]	Cost-effectiveness	Risperidone	Never received risperidone	Patients treated as outpatients
Launois 1998[321]	Cost-effectiveness	Sertindole	Olanzapine, haloperidol	Models estimated for four different healthcare systems – data presented in paper for French model

continued

Characteristics of included studies *contd*

Study	Type	Intervention	Control	Population
Hamilton 1998[1008]	Cost-effectiveness	Olanzapine	Haloperidol	Patients with DSM-II-R schizophrenia entered 6-week trial; responders eligible to enter 46-week double-blind maintenance phase
Johnstone 1998[148]	Cost-effectiveness	Olanzapine	Haloperidol	814 patients with schizophrenia in USA participating in RCT
Iskedijian 1999[325]	Cost–utility	Risperidone	Oral haloperidol, depot haloperidol, fluphenazine	Not stated
Byrom 1998[324]	Cost-effectiveness	Typical anti-psychotic drugs	Atypical anti-psychotic drugs	Patients presenting with an acute episode of chronic schizophrenia
Hammond 1999[327]	Cost-effectiveness	Post-risperidone	Pre-risperidone	Patients with severe mental disabilities schizophrenia, schizoaffective disorder, bipolar disorder
Finley 1998[317]		After risperidone initiation	Before risperidone initiation	All adult patients initiated on risperidone therapy
Davies 2000[308]	Cost–utility	Risperidone, clozapine, olanzapine	Chlorpromazine, haloperidol	Population targeted by current guidelines: first-episode schizophrenia
Almond 2000[326]	Cost-effectiveness	Olanzapine	Risperidone, haloperidol	
Chinchilla 1998[319]	Cost-effectiveness	Year with risperidone	Year before risperidone	30 patients with schizophrenia diagnosed according to DSM-IV criteria
Oh 1999[323]	Cost–utility	Risperidone	Haloperidol, haloperidol decanoate, fluphenazine decanoate	Stable patients with chronic schizophrenia
De Hert 2000[330]	Cost-effectiveness	Risperidone, olanzapine	Haloperidol	Not stated
Gregor 2000[328]	Cost-effectiveness	Olanzapine	Haloperidol	Subset of French patients (n = 275) who participated in large RCT
Kasper 2000[329]	Cost-effectiveness	Risperidone	Olanzapine	1901 patients from 61 hospitals in nine countries
Loos 2000[331]	Cost-effectiveness	Risperidone	Olanzapine	Patients within Delta Psychiatric Hospital (The Netherlands); first-episode schizophrenia
Martin 2000[332]	Cost-effectiveness	Risperidone	Olanzapine	65 newly-diagnosed patients with schizophrenia
Duchesne 1999[336]	Cost-effectiveness	Risperidone	Olanzapine	601 patients with diagnosis of schizophrenia or schizoaffective disorder
Bille 1999[337]	Cost-effectiveness	Risperidone	Olanzapine	68 patients with schizophrenia who had been hospitalised for at least 120 days or were discharged and for whom risperidone or olanzapine was drug of first choice for long-term treatment
Edgell 2000[170]	Cost-effectiveness	Olanzapine	Risperidone	150 patients with schizophrenia
Essock 2000[335]	Cost-effectiveness	Clozapine	Usual care	227 patients who had failed to respond. Patients were required to have been hospitalised for at least 4-months, with total hospitalisation for 2 of preceding 5 years
Rosenheck 1998[115]	Cost-effectiveness	Clozapine	Haloperidol	423 Veterans Affairs patients with refractory schizophrenia, who had been hospitalised for 30–364 days during year before study

Review results

Study	Currency	Cost data	Outcome data	Results
Coley 1999[314]	USA, $	Costs associated with index antipsychotic drug selection, readmission and lengths of stay during year after index hospitalisation considered	Primary efficacy measures were readmission rates and changes in antipsychotic drug treatment	Estimated yearly mean cost/patient of drug: risperidone, $2321; perphenazine, $364; haloperidol, $21
Drew 1999[311]	Australia, $	Costs of: bed occupancy, clozapine, blood monitoring, clozapine coordinator	Determined by treating psychiatrist and recorded as perceived change in clinical status	Estimated cost of psychiatric treatment for cohort: pre-clozapine – year 1, $33.40 (29.63); year 2, $30.83 (34.13) post-clozapine – year 2, bed + clozapine use $30.22 (41.21), bed costs $26.70; year 3, bed + clozapine costs $32.93 (42.42), bed costs $29.64 (42.53)
Tunis 1999[315]	USA, $	Data on utilisation collected	SF-36 completed by 1155 patients: at baseline; at end 6-week acute phase; every 8 weeks during 46-week extension phase	Results over 52 weeks: savings per one interval (point) of improvement (olanzapine – haloperidol), $1632.50 for physical health factor, $5654.74 for mental health factor
Galvin 1999[312]	USA, $	Medication, weekly clozapine blood tests, hospital services, mental health clinic services, transitional living placement costs	Severity rating of general symptoms, side-effects and focussed side-effects (tardive dyskinesia, suicidal ideation, agranulocytosis and seizures) recorded as present or absent	Actual figures not given. Large proportion of patients had fewer general symptoms and reduced costs while receiving newer antipsychotic drugs
Blieden 1998[313]	USA, $	Patients' service utilisation and residential status collected	BPRS, negative symptom assessment scale, Hamilton Rating Scale (depression), QLS	Mean total healthcare costs/person 6 months before: all $48,114 (19,901); continued $42,423 (18,576); discontinued $54,160 (20,028) Mean total healthcare costs/person 6 months after: all $44,847 (16,488); continued $36,914 (14,286); discontinued $53, 276 (14,670)
Palmer 1998[316]	USA, $	Direct medical costs based on expected use of hospital, day hospital, outpatient physician and other mental health provider services		Using all measures of effect, olanzapine versus haloperidol is cost saving; olanzapine versus risperidone is cost saving
Sacristan 1998[34]	Spain, peseta	Use of healthcare services	BPRS, PANSS and CGI-S	Mean direct medical costs/patient (SD): visits: period A, 20,532 pesetas (16,803); period B, 59,856 pesetas (99,099); $p < 0.01$ Mean improvement from baseline to 6 months after olanzapine treatment (SD): BPRS total, –15.24 (21.81); 95% CI, –6.24 to –24.24 PANSS total, –25.56 (36.70); 95% CI, –10.41 to –40.70 PANSS positive, –5.52 (9.47); 95% CI, –1.61 to –9.43 PANSS negative, –7.28 (10.25); 95% CI, –3.05 to –11.51 PANSS general, –12.76 (19.45); 95% CI, –4.73 to –20.79 CGI-S, –1.44 (1.53); 95% CI, –0.81 to –2.07

continued

Review results *contd*

Study	Currency	Cost data	Outcome data	Results
Percudani 1999[309]	Italy, lire	Costs estimated using two-step procedure: (i) recoding all healthcare costs provided to patients; (ii) assigning each service a monetary value	CGI and GAF scales	Total cost/patient for therapy: pre-clozapine, 534,085 lire (US $299.1); post-clozapine, 3,441,439 lire (US $1972.2) Total cost/patient (all services): pre-clozapine, 63,406,584 lire (US $ 35,507.7); post-clozapine, 55,521,464 lire (US $ 31,092) Mean pre-clozapine scores: CGI-I, 6.3 (SD 0.8); GAF, 20.9 (SD 7.4) Mean post-clozapine scores: CGI-I, 4.8 (SD 0.9); GAF, 43 (SD 13.4)
Obenchain 1999[320]	USA, $	Not stated	Not stated	ICER statistic (complete data using homogeneous components mixed model), –$563 per year per responder-day
Schiller 1999[310]	USA, $	Use of psychiatric services – from county mental health system or private hospitals; outpatient visits and laboratory tests – from patients' chart reviews	Monthly GAF scores used as primary measure of effectiveness; scores determined by chart reviews assessed by trained research assistants	Mean total annual costs: pre-risperidone period – risperidone $20,790; comparison $14,053; post-risperidone period – risperidone $18,695; comparison $10,907 Mixed model analysis of effect of risperidone treatment: total treatment costs/month $370.18 more for risperidone group
Launois 1998[321]	USA, $	Three sources used: (i) daily tariff charges; (ii) actual costs of professional procedures; (iii) published prices of antipsychotic drugs	Adverse events; rates of relapse; transitions from one care group to another	ICERs for different countries Sertindole versus haloperidol: France (1), sertindole dominates; France (2), sertindole more effective, more costly; Germany, sertindole dominates; UK, sertindole more effective but more costly Sertindole versus olanzapine: France (1), sertindole dominates; France (2), sertindole dominates; Germany, sertindole dominates; UK, sertindole dominates
Hamilton 1998[1008]	USA, $	Medical resource use collected	Responder days (BPRS improvement ≥ 40% or final BPRS ≤ 18) and BPRS minimal symptom days (BPRS ≤ 18)	Acute phase: mean medical costs for olanzapine patients averaged $431/month less than for haloperidol patients Maintenance phase: mean medical costs for olanzapine patients $345/ month lower than for haloperidol patients
Johnstone 1998[148]	USA, $	Not stated	Not stated	ICER = –$575
Iskedijian 1999[325]	Canada, $	Not stated	Utilities measured	Risperidone dominated all comparators with lowest expected cost, $69,885 over 1-year period Fluphenazine had highest expected cost, $82,264

continued

Review results *contd*

Study	Currency	Cost data	Outcome data	Results
Byrom 1998[324]	USA, $	Direct care costs considered. Based on unit cost data for England for 1992/93	Not stated	Atypical drugs costs: 8-week management of acute episode, $7963; 1-years' treatment following acute episode, $34,663 Typical drugs costs: 8-week management of acute episode, $8920; 1-years' treatment following acute episode, $36,900 Atypical drugs: 49% effectiveness for 8-week management of acute episode; 25.7% effectiveness after 1 year Typical drugs: 31.6% effectiveness for 8-week management of acute episode; 12.8% effectiveness after 1 year Proportion of patients achieving 40% reduction in BPRS in first 8 weeks and not suffering relapse over subsequent 1-year period doubled from 12.8% to 25.7% with atypical drug treatment
Hammond 1999[327]	USA, $			
Finley 1998[317]	USA, $	Direct care costs considered	Days hospitalised (12-month period)	Responders and non-responders: CGI-S scores; concurrent psychotropic medications Annual medication cost: responders, $49,472; non-responders, $5602; total, $55,074 Annual cost savings with reduced hospitalisation: net change in cost of hospitalisation, $203,036; annual savings associated with risperidone trial, $147,962
Davies 2000[308]	UK, £	Direct costs considered	Economic analysis used QALYs as primary outcome measure	Truncated normal distribution: chlorpromazine, all-doses versus lower dose, all-doses dominates; haloperidol (all dose) versus chlorpromazine (all dose), haloperidol dominates; haloperidol (lower dose) versus chlorpromazine (all dose), haloperidol dominates; risperidone versus chlorpromazine (lower dose), £109,935; olanzapine versus chlorpromazine (all dose), olanzapine dominates Triangular distribution: chlorpromazine, all doses versus lower dose, lower dose dominates; haloperidol (all dose) versus chlorpromazine (all dose), haloperidol dominates; haloperidol (lower dose) versus chlorpromazine (all dose), haloperidol dominates; haloperidol (lower dose) versus chlorpromazine (all dose), haloperidol dominates; risperidone versus chlorpromazine (all dose), £34,241; olanzapine versus chlorpromazine (all dose), olanzapine dominates
Almond 2000[326]	UK, £	Stated service utilisation as in previous model	BPRS scores and non-relapse rates	Cumulative and (annual) costs over 5 years (discounted at 6%): year 1 – olanzapine, £15,020; risperidone, £15,468; haloperidol, £15,414 year 2 – olanzapine, £20,734 (5714); risperidone, £21,319 (5851); haloperidol, £21,423 (6009) year 3 – olanzapine, £25,970 (5236); risperidone, £26,665 (5346); haloperidol, £26,813 (5390) year 4 – olanzapine, £30,894 (4924); risperidone, £31,688 (5023); haloperidol, £31,814 (5001)

continued

Review results *contd*

Study	Currency	Cost data	Outcome data	Results
Chinchilla 1998[319]	USA, $	Hospitalisation, outpatients visits, pharmacy cost	Effect measured by CGI	Year before: mean total cost of hospitalisation, $3.422 per patient/ per year; $102.666 for whole sample Year after: mean total cost of hospitalisation, $833 per patient/per year; $25.000 for whole sample
Oh 1999[323]	Canada, $	Costs of care	QALYs	Expected costs over 1 year: risperidone, $69,855; haloperidol, $76,365; haloperidol dec, $78,388; fluphenazine dec, $82,264 Lifetime expected cost saving of risperidone, $114,230
De Hert 2000[330]	Euro	Direct medical costs	Effectiveness measured as time with minimal symptoms and toxicity	Risperidone versus olanzapine, 451,2.46 €/time with minimal symptoms and toxicity
Gregor 2000[328]	France, franc	Mean cost/day per patient and total direct medical costs	Primary clinical measure: 'marked clinical response' taken from BPRS scores	Mean/day per patient total direct medical costs: olanzapine, F619 ± 509; haloperidol, F756 ± 478
Kasper 2000[329]	USA, $	Average total cost of inpatient drugs and average daily cost of inpatient drugs calculated	Number of patients discharged before or at day 120, average length of stay, number with effective treatment, number of days before efficacy established, number of patients discontinuing treatment	Average total cost of all inpatient drugs: risperidone, $159.9 ± 183; olanzapine, $297.5 ± 305; $p < 0.0001$
Loos 2000[331]	The Netherlands, Dfl	Medication cost per day calculated	Duration of time to efficacy, length of admission, adverse events and dose of study medication	Average daily cost of inpatient medication: risperidone, Dfl8.87; olanzapine Dfl12.34; $p < 0.03$
Martin 2000[332]	UK, £	Use and costs of all inpatients' medications	Proportion of patients discharged before 120 days, patients who discontinued or switched treatments, duration of treatment, efficacy, time to efficacy, side-effects	Mean daily cost of inpatient medication: risperidone, £3.34; olanzapine, £6.05; $p = 0.0057$
Edgell 2000[170]	USA, $	Direct healthcare costs	PANSS total score; CGI; EPS, akathisia and dyskinesia assessed with SAS, BAS and AIMS	Median total/patient costs $2843 lower in olanzapine group than in risperidone group; olanzapine patients significantly more likely to maintain response throughout trial; no difference in PANSS total scores
Rosenheck 1998[115]	USA, $	Direct healthcare and indirect costs included (e.g. administrative costs of transfer payments, disability welfare, criminal justice system, productivity and family burden)	Composite health index for schizophrenia developed using PANSS, QLS and other standard assessment instruments	Using Worst Health–Good Health scale analogous to QALYs, clozapine yielded small improvement of 0.049 units compared with 0.027 for haloperidol; average annual costs $2733 lower for clozapine (95% CI, –9220 to 3754)

continued

Review results *contd*

Study	Currency	Cost data	Outcome data	Results
Duchesne 1999[336]	USA, $	Direct medical costs	Efficacy and time to efficacy	Efficacy: risperidone, 78%; olanzapine, 77% Daily treatment costs: risperidone, $3.3; olanzapine, $6.5 Daily all-medical costs: risperidone, $4.2; olanzapine, $7.3
Bille 1999[337]	Denmark, krone	Medication costs	Efficacy and median time to efficacy	Risperidone and olanzapine had similar efficacy (77% versus 78%) Mean daily cost (krone) of inpatient medications: olanzapine, 51.6; risperidone, 22.9
Essock 2000[335]	USA, $	Direct and indirect costs	BPRS; Quality-of-Life Inventory; AIMS	If payer not willing to incur any additional costs, probability that clozapine cost-effective ~ 0.8; cost-acceptability curves presented

Validity assessment results

	Coley 1999[314]	Drew 1999[311]	Tunis 1999[315]	Galvin 1999[312]	Blieden 1998[313]	Palmer 1998[316]	Sacristan 1998[34]	Percudani 1999[309]	Obenchain 1999[320]	Schiller 1999[310]	Launois 1998[321]	Hamilton 1998[1008]	Martin 2000[332]	Bille 1998[337]	Duchesne 1999[336]	Edgell 2000[170]	Essock 2000[335]	Rosenheck 1998[115]	Johnstone 1998[148]	Iskedjian 1999[325]	Byrom 1998[324]	Hammond 1999[327]	Finley 1998[317]	Davies 2000[308]	Almond 2000[326]	Chinchilla 1998[319]	Oh 1999[323]	De Hert 2000[330]	Gregor 2000[328]	Kasper 2000[329]	Loos 2000[331]
Viewpoint	–	–	–	?	+	–	–	?	–	–	+	–	–	–	–				–	+	–	+	–	+	–	–	+	?	–	?	?
Relevant alternatives	+	+	?	+	?	+	?	+	–	?	+	?	?	?	+				?	?	–	+	?	+	?	?	–	+	?	+	?
Rationale for choice	–	+	+	+	+	–	+	+	–	–	+	–	–	–	–				–	–	–	–	+		–	?	–	–	–	–	–
Form of evaluation	–	+	–	–	–	+	–	–	+	–	+	–	–	?	–				+	–	–	+	–		–	–	+	–	–	–	–
Source of effectiveness data	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–				+	+	+	+	+	–	+	+	+	–	+	+	+
Details of synthesis	N/A	–	N/A	N/A	N/A	–	N/A	N/A	N/A	N/A	+	N/A	N/A	N/A	N/A				N/A	–	–	–		–	–	N/A	–	N/A	N/A	N/A	N/A
Primary outcome measures	+	?	+	–	+	+	–	–	+	+	–	+	–	+	–				+	+	–	+		+	+	+	+	+	+	–	–
Methods to value health states	+	+	+	+	+	+	+	+	–	+	–	+	–	N/A	–				–	+	–	–		+	–	–	–	–	+	–	–
Details of individuals	+	+	+	+	+	–	+	+	–	+	–	+	–	–/+	–				–	+	–	–		–	–	+	–	–	+	+	–
Discussion of productivity	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+				–	–	–	–		–	–	–	–	–	–	–	–
Quantities of resources reported	+	–	–	–	–	+	–	+	–	–	–	–	–	+	–				–	–	–	?		+	–	–	–	–	–	–	–
Estimation of quantities	+	+	–	+	+	+	+	+	+	+	+	+	–	–	–				–	–	–	–		+	–	+	–	–	+	+	–
Estimation of unit costs	+	+	+	–	–	+	+	+	+	+	+	–	–	–	–				–	+	–	–		+	–	–	+	–	–	–	–
Currency and price data	+	+	+	+	+	+	+	+	+	+	+	–	–	–	–				–	–	+	+		–	–	–	+	–	+	–	–
Currency and price adjustments	–	–	–	–	–	N/A	–	–	–	–	+	–	–	–	–				–	–	–	–		N/A	–	–	–	–	–	–	–
Details of modelling	N/A	N/A	+	N/A	N/A	+	N/A	N/A	+	+	–	N/A	N/A	N/A	N/A				–	–	+	–		+	+	N/A	–	+	N/A	N/A	N/A
Time horizon	+	+	+	+	+	N/A	+	+	–	+	+	+	–	–	–				+	+	+	+		N/A	+	N/A	+	+	+	N/A	N/A
Choice of discount rate	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	–	N/A	+	N/A	N/A	N/A	N/A				–	N/A	N/A	N/A		N/A	+	N/A	+	N/A	N/A	N/A	N/A
Explanation of no discounting	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	–	N/A	N/A	N/A	N/A				N/A	N/A	N/A	–		N/A	–	N/A	–	N/A	N/A	N/A	N/A
Statistical tests	N/A	N/A	+	–	N/A	N/A	N/A	–	+	–	–	N/A	–	–	–				–	–	–	+		–	–	–	–	–	N/A	N/A	–
Sensitivity analysis	–	–	+	–	–	–	–	–	+	N/A	–	–	–	–	–				+	–	–	–	–	+	–	–	–	+	–	–	–
Incremental analysis	+	–	+	+	–	+	+	–	+	+	+	+	–	–	–				+	–	–	?	+	+	?	+	+	–	–	–	–
Applicability																			?	?	?	–	?	+	+	?	?	+	?	?	?

+, Study did address this area sufficiently; –, study did not address this area sufficiently; ?, unclear; N/A, not applicable

Probabilities of key events (SD)

	Chlorpromazine	Haloperidol	Risperidone	Clozapine	Olanzapine	Quetiapine	Zotepine	Ziprasidone	Amisulpride	Sertindole
Clinical improvement	0.77 (0.23)	0.55 (0.22)	0.49 (0.20)	0.34 (0.25)	0.64 (0.22)	0.32 (0.18)	0.52 (0.23)	0.39 (0.18)	0.55 (0.17)	0.5 (0.27)
Adverse events (EPS)	0.43 (0.21)	0.26 (0.27)	0.19 (0.17)	0.18 (0.21)	0.16 (0.10)	0.19[c] (0.17)	0.05	0.04 (0.03)	0.43 (0.29)	0.04 (0.03)
Tardive dyskinesia	0.056	0.42 (0.37)	0.33 (0.28)	0.074	0.016	0.33[c] (0.28)	0.33[c] (0.28)	0.002	0.33[c] (0.28)	0.33[c] (0.28)
NMS	0.005[a]	0.005[a]	0	0	0	0	0	0	0	0
Hepatic dysfunction	0.06	0	0	0	0	0	0	0	0	0
Agranulocytosis	0	0	0.013 (0.02)	0.004 (0.07)	0	0	0	0	0	0
Therapy not acceptable/ withdrawal	0.23 (0.08)	0.25 (0.15)	0.16 (0.20)	0.24 (0.16)	0.46 (0.25)	0.39 (0.17)	0.32 (0.12)	0.09 (0.04)	0.06 (0.04)	0.29 (0.14)
Relapse – with therapy	0.13	0.34	0.05 (0.06)	0.13 (0.11)	0.03 (0.02)	0.04[b] (0.06)	0.04[b] (0.06)	0.03 (0.02)	0.2	0.04[b] (0.06)
– without therapy*	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75
Non-compliance (adequate response)*	0.09	0.09	0.09	0.09	0.09	0.09	0.09	0.09	0.09	0.09

N.B. Unless otherwise stated, probabilities taken from systematic review of clinical evidence (probabilities calculated as weighted means)

*, *estimated value (previous review)*

[a] *Thornley,* et al. *Chlorpromazine versus placebo for schizophrenia (Cochrane review). In: Cochrane Library, Issue 2, 2001. Oxford: Update Software; 2001*

[b] *Mean of ziprasidone, risperidone, olanzapine and amisulpride*

[c] *Assumed same as risperidone; rest are pooled estimates from systematic review*

Resource use associated with events

Event	Probability	Days	Total
Initial therapy			
Inpatient admission	0.6	44.93	26.96
Day-patient admission	0.4	24.00	9.60
Antipsychotic therapy	1	42.00	42.00
Maintenance therapy, no relapse (year 1)			
First-line therapy			
Community-based services	1	328.44	328.44
Antipsychotic therapy	1	323.00	323.00
Second-line therapy			
Community-based services	1	359.00	359.00
Antipsychotic therapy	1	309.00	309.00
Third-line therapy			
Community-based services	1	359.00	359.00
Antipsychotic therapy	1	309.00	309.00
Final-line therapy			
Community-based services	1	359.00	359.00
Antipsychotic therapy	1	309.00	309.00
Maintenance therapy, relapse (year 1)			
First-line therapy			
Community-based services	1	291.88	291.88
Antipsychotic therapy	1	281.00	281.00
Second-line therapy			
Community-based services	1	290.07	290.07
Antipsychotic therapy	1	267.00	267.00
Third-line therapy			
Community-based services	1	290.07	290.07
Antipsychotic therapy	1	267.00	267.00
Final-line therapy			
Community-based services	1	322.44	322.44
Antipsychotic therapy	1	267.00	267.00
Relapse			
Inpatient admission	0.6	29.4	17.64
Day-patient admission	0.4	24.0	9.6
Antipsychotic therapy	1	42	42
Change antipsychotic drug			
Clozapine			
Day-patient admission	1	14	14
Antipsychotic therapy	1	56	56
Other antipsychotic drugs			
Outpatient visits	1	6	6
Antipsychotic therapy	1	56	56
Additional treatments for adverse events/year			
EPS: anticholinergic	1	365.00	365.00
Akathisia: beta-blocker	1	365.00	365.00
Seizures: sodium valproate	1	365.00	365.00

Utilities associated with events[19]

Event	Chlorpromazine	Haloperidol	Risperidone	Clozapine	Olanzapine	Quetiapine	Zotepine	Ziprasidone	Amisulpride	Sertindole
Mild symptoms	0.86	0.86	0.89	0.91	0.89	0.89	0.89	089	0.89	0.89
Moderate/severe symptoms	0.82	0.82	0.82	0.82	0.82	0.82	0.82	0.82	0.82	0.82
Disutility of EPS/unacceptable treatment	0.07	0.07	0.07	0.07	0.07	0.07	0.07	0.07	0.07	0.07
Disutility of inpatient care	0.07	0.07	0.07	0.07	0.07	0.07	0.07	0.07	0.07	0.07

Quality-adjusted life-days of events

Utility of events	Risperidone	Clozapine	Olanzapine	Zotepine	Chlorpromazine	Haloperidol	Quetiapine	Amisulpride	Ziprasidone	Sertindole
Event										
Mild symptoms	0.89	0.91	0.89	0.89	0.86	0.86	0.89	0.89	0.89	0.89
Moderate/severe symptoms	0.82	0.82	0.82	0.82	0.82	0.82	0.82	0.82	0.82	0.82
Disutility of EPS/unacceptable treatment	–0.07	–0.07	–0.07	–0.07	–0.07	–0.07	–0.07	–0.07	–0.07	–0.07
Disutility of inpatient care	–0.07	–0.07	–0.07	–0.07	–0.07	–0.07	–0.07	–0.07	–0.07	–0.07
Initial therapy										
Inpatient admission	20.21	20.21	20.21	20.21	20.21	20.21	20.21	20.21	20.21	20.21
Day-patient admission	7.8	7.8	7.8	7.8	7.8	7.8	7.8	7.8	7.8	7.8
Total	28.09	28.09	28.09	28.09	28.09	28.09	28.09	28.09	28.09	28.09
Maintenance therapy, no relapse (year 1)										
First-line therapy	280.58	279.37	284.03	281.27	279.43	276.54	276.67	281.96	278.28	280.81
Second-line therapy	306.69	305.36	310.46	307.44	305.43	302.27	302.42	308.20	304.18	306.94
Third-line therapy	306.69	305.36	310.46	307.44	305.43	302.27	302.42	308.20	304.18	306.94
Final-line therapy	306.69	305.36	310.46	307.44	305.43	302.27	302.42	308.20	304.18	306.94
Maintenance therapy, relapse (year 1)										
First-line therapy	249.35	248.27	252.42	249.96	248.33	245.76	245.88	250.58	247.31	249.56
Second-line therapy	247.80	246.73	250.85	248.41	246.79	244.23	244.35	249.02	245.77	248.01
Third-line therapy	247.80	246.73	250.85	248.41	246.79	244.23	244.35	249.02	245.77	248.01
Final-line therapy	275.46	274.26	278.84	276.13	274.33	271.49	271.62	276.81	273.20	275.68
Relapse										
Inpatient admission	20.21	20.21	20.21	20.21	20.21	20.21	20.21	20.21	20.21	20.21
Day-patient admission	7.8	7.8	7.8	7.8	7.8	7.8	7.8	7.8	7.8	7.8
Total	28.09	28.09	28.09	28.09	28.09	28.095	28.09	28.09	28.09	28.09
Antipsychotic therapy										
Total	45.92	45.92	45.92	45.92	45.92	45.92	45.92	45.92	45.92	45.92
Additional treatment for adverse events/year										
EPS (disutility)	–25.55	–25.55	–25.55	–25.55	–25.55	–25.55	–25.55	–25.55	–25.55	–25.55

ICERs

Antipsychotic drug	Comparator	ICER
First-line therapy		
Chlorpromazine	Haloperidol	Chlorpromazine dominates
Chlorpromazine	Clozapine	98,200
Chlorpromazine	Olanzapine	10,866
Chlorpromazine	Quetiapine	8,027
Chlorpromazine	Zotepine	16,650
Chlorpromazine	Risperidone	17,514
Chlorpromazine	Ziprasidone	14,815
Chlorpromazine	Amisulpride	21,623
Chlorpromazine	Sertindole	9,850
Haloperidol	Clozapine	12,750
Haloperidol	Olanzapine	16,835
Haloperidol	Quetiapine	16,100
Haloperidol	Zotepine	46,433
Haloperidol	Risperidone	6,237
Haloperidol	Ziprasidone	8,561
Haloperidol	Amisulpride	14,885
Haloperidol	Sertindole	92,400
Clozapine	Olanzapine	16,325
Clozapine	Quetiapine	15,541
Clozapine	Zotepine	32,960
Clozapine	Risperidone	3,733
Clozapine	Ziprasidone	7,866
Clozapine	Amisulpride	15,241
Clozapine	Sertindole	59,450
Olanzapine	Quetiapine	18,675
Olanzapine	Zotepine	8,763
Olanzapine	Risperidone	12,981
Olanzapine	Ziprasidone	12,700
Olanzapine	Amisulpride	15,860
Olanzapine	Sertindole	11,100
Quetiapine	Zotepine	3,100
Quetiapine	Risperidone	11,716
Quetiapine	Ziprasidone	8,370
Quetiapine	Amisulpride	15,391
Quetiapine	Sertindole	7,622
Zotepine	Risperidone	17,200
Zotepine	Ziprasidone	15,247
Zotepine	Amisulpride	20,452
Zotepine	Sertindole	23,450
Risperidone	Ziprasidone	11,650
Risperidone	Amisulpride	26,416
Risperidone	Sertindole	15,811
Ziprasidone	Amisulpride	Ziprasidone dominates
Ziprasidone	Sertindole	1,415
Amisulpride	Sertindole	20,053

Antipsychotic drug	Comparator	ICER
Second-line therapy		
Chlorpromazine	Haloperidol	Chlorpromazine dominates
Chlorpromazine	Clozapine	Chlorpromazine dominates
Chlorpromazine	Olanzapine	4,782.35
Chlorpromazine	Quetiapine	2,166.67
Chlorpromazine	Zotepine	5,528.27
Chlorpromazine	Risperidone	20,340
Chlorpromazine	Ziprasidone	15,240
Chlorpromazine	Amisulpride	20,860
Chlorpromazine	Sertindole	Chlorpromazine dominates
Haloperidol	Clozapine	43,100
Haloperidol	Olanzapine	14,246
Haloperidol	Quetiapine	8,481.81
Haloperidol	Zotepine	33,166.67
Haloperidol	Risperidone	8,780
Haloperidol	Ziprasidone	9,160
Haloperidol	Amisulpride	14,780
Haloperidol	Sertindole	Sertindole dominates
Clozapine	Olanzapine	13,228.57
Clozapine	Quetiapine	11,366.67
Clozapine	Zotepine	35,650
Clozapine	Risperidone	160
Clozapine	Ziprasidone	4,850
Clozapine	Amisulpride	10,470
Clozapine	Sertindole	96,800
Olanzapine	Quetiapine	24,400
Olanzapine	Zotepine	4,260
Olanzapine	Risperidone	8,454.54
Olanzapine	Ziprasidone	8,655.55
Olanzapine	Amisulpride	10,737.03
Olanzapine	Sertindole	6,800
Quetiapine	Zotepine	Zotepine dominates
Quetiapine	Risperidone	6,860
Quetiapine	Ziprasidone	7,396
Quetiapine	Amisulpride	9,644
Quetiapine	Sertindole	3,600
Zotepine	Risperidone	11,950
Zotepine	Ziprasidone	11,241.18
Zotepine	Amisulpride	14,547.06
Zotepine	Sertindole	15,266.67
Risperidone	Ziprasidone	9,540
Risperidone	Amisulpride	20,780
Risperidone	Sertindole	10,844.44
Ziprasidone	Amisulpride	Ziprasidone dominates
Ziprasidone	Sertindole	10,378.57
Amisulpride	Sertindole	14,392.86

continued

ICERs *contd*

Antipsychotic drug	Comparator	ICER
Third-line therapy		
Chlorpromazine	Haloperidol	Chlorpromazine dominates
Chlorpromazine	Clozapine	Chlorpromazine dominates
Chlorpromazine	Olanzapine	5,250
Chlorpromazine	Quetiapine	2,346.15
Chlorpromazine	Zotepine	6,316.67
Chlorpromazine	Risperidone	17,516.67
Chlorpromazine	Ziprasidone	13,872.73
Chlorpromazine	Amisulpride	19,009.09
Chlorpromazine	Sertindole	Chlorpromazine dominates
Haloperidol	Clozapine	39,900
Haloperidol	Olanzapine	9,193.75
Haloperidol	Quetiapine	7,200
Haloperidol	Zotepine	16,833.33
Haloperidol	Risperidone	7,000
Haloperidol	Ziprasidone	8,127.27
Haloperidol	Amisulpride	13,272.72
Haloperidol	Sertindole	Sertindole dominates
Clozapine	Olanzapine	13,357.14
Clozapine	Quetiapine	12,136.36
Clozapine	Zotepine	46,966.67
Clozapine	Risperidone	2,625
Clozapine	Ziprasidone	3,535.71
Clozapine	Amisulpride	7,578.57
Clozapine	Sertindole	95,000
Olanzapine	Quetiapine	17,833.33
Olanzapine	Zotepine	4,610
Olanzapine	Risperidone	8,595.45
Olanzapine	Ziprasidone	8,759.25
Olanzapine	Amisulpride	10,855.55
Olanzapine	Sertindole	7,076.92
Quetiapine	Zotepine	Zotepine dominates
Quetiapine	Risperidone	7,136.84
Quetiapine	Ziprasidone	7,625
Quetiapine	Amisulpride	9,983.33
Quetiapine	Sertindole	3,850
Zotepine	Risperidone	11,916.67
Zotepine	Ziprasidone	5,317.65
Zotepine	Amisulpride	14,529.41
Zotepine	Sertindole	15,300
Risperidone	Ziprasidone	9,480
Risperidone	Amisulpride	20,800
Risperidone	Sertindole	10,788.89
Ziprasidone	Amisulpride	Ziprasidone dominates
Ziprasidone	Sertindole	11,115.38
Amisulpride	Sertindole	14,364.85

Antipsychotic drug	Comparator	ICER
Final-line therapy		
Chlorpromazine	Haloperidol	Chlorpromazine dominates
Chlorpromazine	Clozapine	Chlorpromazine dominates
Chlorpromazine	Olanzapine	5,247.06
Chlorpromazine	Quetiapine	2,660
Chlorpromazine	Zotepine	6,214.29
Chlorpromazine	Risperidone	20,860
Chlorpromazine	Ziprasidone	14,710
Chlorpromazine	Amisulpride	19,854.54
Chlorpromazine	Sertindole	725
Haloperidol	Clozapine	Haloperidol dominates
Haloperidol	Olanzapine	11,126.67
Haloperidol	Quetiapine	9,046.15
Haloperidol	Zotepine	24,240
Haloperidol	Risperidone	3,800
Haloperidol	Ziprasidone	5,783.33
Haloperidol	Amisulpride	10,823.08
Haloperidol	Sertindole	37,400
Clozapine	Olanzapine	12,720
Clozapine	Quetiapine	10,884.61
Clozapine	Zotepine	29,020
Clozapine	Risperidone	385.71
Clozapine	Ziprasidone	3,791.67
Clozapine	Amisulpride	8,984.61
Clozapine	Sertindole	49,350
Olanzapine	Quetiapine	24,650
Olanzapine	Zotepine	4,570
Olanzapine	Risperidone	8,795.45
Olanzapine	Ziprasidone	8,751.85
Olanzapine	Amisulpride	10,985.71
Olanzapine	Sertindole	7,084.61
Quetiapine	Zotepine	Zotepine dominates
Quetiapine	Risperidone	7,210
Quetiapine	Ziprasidone	7,480
Quetiapine	Amisulpride	9,934.61
Quetiapine	Sertindole	3,890.90
Zotepine	Risperidone	12,316.67
Zotepine	Ziprasidone	11,211.76
Zotepine	Amisulpride	14,550
Zotepine	Sertindole	15,466.67
Risperidone	Ziprasidone	8,560
Risperidone	Amisulpride	11,266.67
Risperidone	Sertindole	19,016.67
Ziprasidone	Amisulpride	71,300
Ziprasidone	Sertindole	10,300
Amisulpride	Sertindole	14,366.67

N.B. Since these represent CIs for ratios, they cannot be interpreted in the same way as the CIs placed around costs and QALYs; for example, an upper 95% CI indicates an intervention is dominant at the extreme values, and a lower 95% CI limit that is greater than the point estimate indicates the cost/QALY of the comparator

Appendix 13

Included RCTs

Study	Dose	Comparator	Number of participants	Duration	Blinding	Original or new
Amisulpride						
Boyer 1995[51]	100 mg/day 300 mg/day	Placebo	104	6 weeks + 6-week washout period	2	Original
Martinot 1995[52]	50 mg/day for 3 weeks; increased to 100 mg/day for next 3 weeks if not improved	Placebo	27	6 weeks + 8-day washout period	2	Original
Delcker 1990[53]	Flexible: 490–1000 mg/day	Haloperidol: flexible dose 5–40 mg/day)	41	6 weeks + 4–28-day washout period	2	Original
Hillert 1994[54]	1000 mg/day (could be adjusted to 600 mg/day)	Flupentixol, 25 mg/day (could be adjusted to 15 mg/day)	132	6 weeks + 1–9-day washout period	2	Original
Turjanski 1998 (1)[55]	400 mg/day 800 mg/day	Haloperidol, 15–20 mg/day	186	2 weeks	2	Original
Turjanski 1998 (2)[55]	400–800 mg/day	Haloperidol, 15–20 mg/day	188	2 weeks	2	Original
Puech 1998[56]	100 mg/day 400 mg/day 800 mg/day 1200 mg/day	Haloperidol, 16 mg/day	319	4 weeks + 3–7-day washout period	2	Original
Moeller 1997[57]	800 mg/day (reduced to 600 mg/day if needed)	Haloperidol, 20 mg/day, reduced to 15 mg/day if needed	191	6 weeks + 1-week washout period	2	Original
Klein 1985[58]	10 mg/kg/day for 8 days, then 5 mg/kg/day	Haloperidol, 0.5 mg/kg/day for 8 days then 0.25 mg/kg/day	19	4 weeks	2	Original
Speller 1997[59]	800 mg/day 600 mg/day 450 mg/day 300 mg/day 150 mg/day 100 mg/day – reduced every 3 months where possible	Haloperidol, 20 mg/day 16 mg/day 11.5 mg/day 8 mg/day 5 mg/day 3 mg/day – reduced every 3 months where possible	60	12 months + 3-month washout period	2	Original
Danion 1998[60]	50 mg/day 100 mg/day	Placebo	242	3 months + 1-month washout period	2	Original
Boyer 1990[61]	50–300 mg/day	Fluphenazine, 2–12 mg/day	62	6 weeks + 3-week washout period	?	Original
Fleurot 1997[62]	800 mg/day	Risperidone, 8 mg/day	228	8 weeks + 3–6-day washout period	2	Original
Loo 1997[63]	100 mg/day	Placebo	141	6 months; 12 months in responders	2	Original
Muller 1998[41]	600–1000 mg/day	Fluphenazine, 15–25 mg/day	126	6 weeks	2	New
Lecrubier 2000[43]	400–1000 mg/day	Risperidone, 4–10 mg/day	310	6 months	2	New

continued

Study	Dose	Comparator	Number of participants	Duration	Blinding	Original or new
Wetzel 1998[45]	1000 mg/day	Flupentixol, 25 mg/day	132	6 weeks + 1–9-day washout period	2	New
Carriere 2000[47]	400–1200 mg/day	Haloperidol, 10–30 mg/day	199	4 months	?	New
Colonna 2000[361] Rein 1999[50] Colonna 1998[49]	200–800 mg/day	Haloperidol, 5–20 mg/day	488	12 months	0	New (full version of original abstract)
Lecrubier 1999[42]	150 mg/day	Olanzapine, 5 mg/day 20 mg/day Placebo	244	6 months	2	New
Ziegler 1989[44]	600 mg/ day or 300–750 mg/day	Haloperidol, 12 mg/day or 2.5–22.5 mg/day	40	4 weeks + 3-day washout period	2	New
Study 128-305 (Pfizer, unpublished)	Commercial-in-confidence: data removed	Ziprasidone	Commercial-in-confidence: data	Commercial-in-confidence: data removed removed	Commercial-in-confidence: data removed	New
Clozapine						
Chiu 1976[78]	300 mg/day	Chlorpromazine, 300 mg/day	64	6 weeks + 5-day washout period	2	Original
Guirguis 1977[79]	75–450 mg/day	Chlorpromazine, 150–900 mg/day	50	7 weeks	2	Original
Xu 1985[80]	400 mg/day	Chlorpromazine, 693 mg/day	60	8 weeks	1	Original
Xu 1989[81]	50–600 mg/day	Chlorpromazine, 100–600 mg/day, or clozapine, 50–400 mg/day, + chlorpromazine, 100–400 mg/day	57	8 weeks	2	Original
Xu 1994[82]	Not stated	Thioridazine, dose not stated	40	6 weeks	2	Original
Leon 1974[83]	600 mg/day	Chlorpromazine, 600 mg/day	50	6 weeks + 3–4-year follow-up	2	Original
Gerlach 1974[84]	200 mg/day, crossover	Haloperidol, 10 mg/day, crossover	20	28 weeks, arm 1 82 days + 5–51-day washout period	Variable (depended on outcome)	Original
Gerlach 1975[85]	225 mg/day, crossover	Haloperidol, 9 mg/day, crossover	8	9 weeks, arm 1 3 weeks + 3-week washout period	2	Original
Fischer-Cornelssen 1974[86]	75–200 mg/day	Chlorpromazine, 75–200 mg/day	223	40 days + 4-day washout period	2	Original
Fischer-Cornelssen 1976a[87]	300 mg/day	Clopenthixol, 100 mg/day	74	42 days + 7-day washout period	2	Original
Fischer-Cornelssen 1976b[87]	300 mg/day	Trifluoperazine, 30 mg/day	72	42 days + 7-day washout period	2	Original
Honigfeld 1984[88]	397 mg/day	Haloperidol, 7.6 mg/day	79	40 days	2	Original
Klieser 1989[89]	400 mg/day	Haloperidol, 20 mg/day	32	6 weeks + 2-week washout period	2	Original
Klieser 1994[90]	400 mg/day	Remoxipride, 400 mg/day Haloperidol, 15 mg/day Risperidone, 4–8 mg/day Zotepine, 225 mg/day	180	28 days	2	Original

continued

Study	Dose	Comparator	Number of participants	Duration	Blinding	Original or new
***Clozapine* contd**						
Singer 1974[91]	50–300 mg/day	Chlorpromazine, 75–600 mg/day	40	40 days	2	Original
Itoh 1977[92]	Up to 500 mg/day	Haloperidol, up to 15 mg/day	91	12 weeks	2	Original
Erlandsen 1981[93]	50–400 mg/day	Haloperidol, 1–8 mg/day	40	40 days	2	Original
Ciurezu 1976[94]	100–900 mg/day	Haloperidol, 4–20 mg/day	40	40 days	2	Original
Hong 1997[95]	543 mg/day	Chlorpromazine, 1163 mg/day	40	12 weeks	2	Original
Shopsin 1979[96]	800 mg/day	Chlorpromazine, 1333 mg/day Placebo	39	5 weeks + 3–7-day washout period	2	Original
Gelenberg 1979[97]	125–525 mg/day	Chlorpromazine, 606 mg/day	15	4–8 weeks + 2-day washout period	2	Original
Claghorn 1987[98]	150–900 mg/day	Chlorpromazine, 300–1800 mg/day	151	4–8 weeks + 2-day washout period	2	Original
Kane 1988[99]	Up to 900 mg/day	Chlorpromazine, up to 1800 mg/day	268	6 weeks	2	Original
Kane 1994[100]	Not stated	Haloperidol, 10 mg/day	71	29 weeks	2	Original
Lee 1994[101]	Not stated	Various (mainly haloperidol) dose not stated	47	24 months	0	Original
Tamminga 1994[102]	294 mg/day	Haloperidol, 28.5 mg/day	43	12 months	2	Original
Essock 1996[103]	496 mg/day	'Usual care'	227	24 months	0	Original
Kumra 1996[104]	25–525 mg/day	Haloperidol, 7–27 mg/day	43	6 weeks + 4-week washout period	2	Original
Rosenheck 1997[105]	100–900 mg/day	Haloperidol, 5–30 mg/day	423	1 year	2	Original
Howanitz 1999[106]	Up to 300 mg/day	Chlorpromazine, up to 600 mg/day	42	12 weeks + 1–7-day washout period	2	Original
Buchanan 1998[107]	413 mg/day	Haloperidol, 26 mg/day	75	10 weeks	2	Original
Beasley 1999[77]	200–600 mg/day	Olanzapine, 15–25 mg/day	180	18 weeks + 2–9-day washout period	2	Original
Oliemeulen 2000[109]	Not stated	Olanzapine, dose not stated	36	8 weeks	?	Original
Klieser 1994[90]	350 mg/day	Remoxipride, 375 mg/day Haloperidol, 16 mg/day	54	4 weeks	2	Original
Bondolfi 1998[110]	150–400 mg/day	Risperidone, 3–12 mg/day	86	8 weeks	2	Original
Anand 1998[111]	200–900 mg/day	Risperidone, 2–15 mg/day	273	12 weeks	2	Original
Breier 1999[112]	200–600 mg/day	Risperidone, 2–9 mg/day	29	6 weeks	2	Original
Wahlbeck 2000[113]	Up to 600 mg/day	Risperidone, up to 10 mg/day	20	10 weeks	1	Original
Meyer-Lindenberg 1996[108]	150–450 mg/day	Zotepine, 150–450 mg/day	50	6 weeks	2	Original
Covington 2000[69]	Not stated	Haloperidol, dose not stated	82	2 years	?	New

continued

Study	Dose	Comparator	Number of participants	Duration	Blinding	Original or new
***Clozapine* contd**						
Fleming 1998[70]	200–600 mg/day	Olanzapine, 20 mg/day	18	6 weeks	2	New
HGCF 2001[201]	Not stated	Olanzapine, dose not stated	Not stated	Not stated	?	New
Chowdhury 1999[71]	250–300 mg/day	Risperidone, 6–8 mg/day	60	16 weeks	?	New
Salganik 1998[72]	Not stated; crossover	Haloperidol, dose not stated	34	10 weeks on each	2	New
Chow 2000[73]	Not stated	Usual medication	25	12 weeks	0	New
Bitter 1999[74]	150 mg/day	Olanzapine, 10 mg/day	150	18 weeks + 2–9-day washout period	?	New
Cosar 1999[75]	463 mg/day	Sulpiride, 696 mg/day Haloperidol, 35 mg/day	160	90 days	?	New
Olanzapine						
Altamura 1999[181]	5–20 mg/day	Haloperidol, 5–20 mg/day	28	14 weeks	2	Original
Beasley 1996a;[168] more information in Tollefson 1998[1009] (new)	2.5–7.5 mg/day 7.5–12.5 mg/day 12.5–17.5 mg/day	Haloperidol, 10–20 mg/day Placebo	335	6 weeks + 4–7-day washout period	2	Original
Beasley 1996b[169]	1 mg/day 10 mg/day	Placebo	152	6 weeks + 4–7-day washout period	2	Original
Beasley 1997[182]	1 mg/day 2.5–7.5 mg/day 7.5–12.5 mg/day 12.5–17.5 mg/day	Haloperidol, 10–20 mg/day	431	6 weeks + 4–7-day washout period	2	Original
Beasley 1999;[77] more information in Tollefson 2001[76] (new)	15–25 mg/day	Clozapine, 200–600 mg/day	180	18 weeks	2	Original
Conley 1998[183]	25 mg/day	Chlorpromazine, 1200 mg/day, + benztropine, 4 mg/day	84	8 weeks + 1–2-week washout period	2	Original
HGBJ (Finland) unpublished	5–20 mg/day	Perphenazine, 8–32 mg/day	46	26 weeks	2	Original
HGBL 1997 unpublished	5–20 mg/day	Flupentixol, 5–20 mg/day	33	4 weeks + 4–7-day washout period	2	Original
HGCJ (Hong Kong) unpublished	5–20 mg/day	Haloperidol, 5–20 mg/day	31	14 weeks	2	Original
HGCQ (Turkey) unpublished	Not stated	Chlorpromazine, dose not stated	30	6 weeks	2	Original
HGCU (Taiwan) unpublished	5–20 mg/day	Haloperidol, 5–20 mg/day	54	14 weeks	2	Original
HGDV (Morocco) 1999 unpublished	5–20 mg/day	Chlorpromazine, 200–800 mg/day	39	6 weeks	0	Original
HGFH (Korea) 1998 unpublished	5–20 mg/day	Haloperidol, 1.5–20 mg/day	104	6 weeks	0	Original
Jakovljevic 1999[184]	5–20 mg/day	Fluphenazine, 6–21 mg/day	60	6 weeks + 22-week extension	2	Original
Jones 1998[180]	5–20 mg/day	Risperidone, 4–10 mg/day Haloperidol, 5–20 mg/day	65	54 weeks	2	Original

continued

Study	Dose	Comparator	Number of participants	Duration	Blinding	Original or new
***Olanzapine* contd**						
Lecrubier 1999[42]	5 mg/day 20 mg/day	Amisulpride, 150 mg/day Placebo	245	6 months	2	Original
Loza 1999[185]	5–20 mg/day	Chlorpromazine, 200–800 mg/day	41	6 weeks + 2–9-day washout period	2	Original
Gureje 1998[186]	10–20 mg/day	Risperidone, 4–8 mg/day	65	30 weeks	2	Original
Tollefsen 1997;[164] more information in Tollefson 1999[165] (new), Hamilton 2000[162] (new), Kinon 2000[166] (new), Gregor 1999[163] (new), Sanger 1998[173–175]	5–20 mg/day	Haloperidol, 5–20 mg/day	1996 (778 in responder subgroup)	6 weeks + 2–9-day washout period (+ 46-week extension in responder subgroup)	2	Original
Tran 1997;[171] more information in Edgell 2000[170] (new)	10–20 mg/day	Risperidone, 4–12 mg/day	339	28 weeks + 2–9-day washout period	2	Original
Breier 2001[160]	Up to three injections in 24 hours of 2.5, 5, 7.5 or 10 mg	Haloperidol, up to three injections in 24 hours of 7.5 mg	270	24 hours	2	New
Naukkarinen 1999[147]	5–20 mg/day	Perphenazine, 8–32 mg/day	46	Not stated	2	New
Fleming 1998[70]	20 mg/day	Clozapine, 200–600 mg/day	18	6 weeks	2	New
Reams 1998[149]	5–20 mg/day	Haloperidol, 5–20 mg/day	59	6 weeks	2	New
Gomez 2001[150]	5–20 mg/day	Haloperidol, 5–20 mg/day	1658	6 weeks + 2–9-day washout period	2	New
Wright 2000[151]	Three 10-mg injections in 24 hours	Haloperidol, three 7.5-mg injections in 24 hours Placebo injection	311	2 hours?	?	New
Littrell 1999[154]	Mean 19.2 mg/day	Risperidone, mean 5.2 mg/day	24	1 year	0	New
Kolff 2000[152]	Not stated	Risperidone, dose not stated	50	6 weeks	?	New
Malyarov 1999[153]	5–15 mg/day	Risperidone, 3–6 mg/day Haloperidol, 5–20 mg/day	43	6 months	1	New
Tohen 1999[172] (subgroup of another trial, no reference)	Not stated	Haloperidol, dose not stated	177	6 weeks	2	New
Szafranski 1999[155]	5–20 mg/day	Perphenazine, 8–40 mg/day	95	18 weeks	?	New
Zhang 1999[156,157]	Not stated	Haloperidol, dose not stated	177	6 weeks	2	New
Oliemeulen 2000[109]	Not stated	Clozapine, dose not stated	36	8 weeks	?	New
HGCF 2001[201]	Not stated	Clozapine, dose not stated	?	Not stated	?	New

continued

Study	Dose	Comparator	Number of participants	Duration	Blinding	Original or new
***Olanzapine* contd**						
Ljubin 2000[158]	5–20 mg/day	Fluphenazine, 6–21 mg/day	18	22 weeks + 2–9-day washout period	1	New
Bitter 1999[74]	10 mg/day	Clozapine, 150 mg/day	150	18 weeks +2–9-day washout period	?	New
Breier 2000[159]	11.1 mg/day	Haloperidol, 10.0 mg/day	526	6 weeks	2	New
Johnstone 1998[148]	Not stated	Haloperidol, dose not stated	814	1 year	2	New
Study R-0548 (unpublished)	Commercial-in-confidence: data removed	Ziprasidone	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed	New
Conley 2001[161]	5–20 mg/day	Risperidone, 2–6 mg/day	377	8 weeks	2	New
Quetiapine						
Link 1997 (Europe-Africa 007)[215]	407 mg/day	Chlorpromazine, 384 mg/day	201	6 weeks + 1-day washout period	2	Original
Fleischhacker 1995 (Multi-country 012)[216]	450 mg/day twice daily 450 mg/day three times daily 50 mg/day	Comparison between low- and high-dose quetiapine	209	6 weeks + 2-day washout period	2	Original
Fleischhacker 1996 (Multi-country 014)[217]	50–800 mg/day	Haloperidol, 1–16 mg/day	448	6 weeks + 2-day washout period	2	Original
Purdon 2000 (Canada 2000);[212] more information in Purdon 2001[211] (new)	468 mg/day	Haloperidol, 15.5 mg/day	25	6 months + 2-day washout period	2	Original
Kudo 1999 (Japan 1999a)[218]	215 mg/day	Mosapramine, 103 mg/day	180	8 weeks	2	Original
Murasaki 1999 (Japan 1999b);[214] more information in Murasaki 2000[213] (new)	226 mg/day	Haloperidol, 6.7 mg/day	197	8 weeks	2	Original
Emsley 1999 (Multi-country 1999)[219]	600 mg/day	Haloperidol, 20 mg/day	288	8 weeks	2	Original
Arvanitis 1996 (North America 013)[220]	75 mg/day 150 mg/day 300 mg/day 600 mg/day 750 mg/day	Haloperidol, 12 mg/day Placebo	361	6 weeks + 1-week washout period	2	Original
Fabre 1995 (USA 004)[189]	250 mg/day	Placebo	12	3 weeks + 2-day washout period	2	Original
Borison 1996 (USA 006)[221]	307 mg/day	Placebo	109	6 weeks + 6–10-day washout period	2	Original
Small 1997 (USA-Europe 008)[222]	360 mg/day 209 mg/day	Placebo	286	6 weeks + 1-day washout period	2	Original
AstraZeneca 2000[1010] Reinstein 1999[209] Mullen 1999[208]	254 mg/day	Risperidone, 4.4 mg/day	751	16 weeks	0	New
Velligan 1999[210]	300 mg/day 600 mg/day	Haloperidol, 12 mg/day	58	24 weeks	2	New

continued

Study	Dose	Comparator	Number of participants	Duration	Blinding	Original or new
Risperidone						
Blin 1996[251]	Up to 12 mg/day	Haloperidol, up to 12 mg/day Methotrimeprazine, up to 125 mg/day	62	4 weeks	2	Original
Borison 1991[252]	Up to 10 mg/day	Haloperidol, up to 20 mg/day Placebo	160	6 weeks + 1-week washout period	2	Original
Bouchard 1998;[253] more information in Bouchard 2000[249] (new)	5.5 mg/day	Classical neuroleptic drugs	184	2 years	0	Original
Ceskova 1993[254]	2–20 mg/day	Haloperidol, 2–20 mg/day	62	8 weeks	2	Original
Chouinard 1993[255]	2 mg/day 6 mg/day 10 mg/day 16 mg/day	Haloperidol, 20 mg/day Placebo	135	8 weeks	2	Original
Claus 1991[256]	12 mg/day	Haloperidol, 10.3 mg/day	44	12 weeks + 1-week washout period	2	Original
Emsley 1995[257]	2–16 mg/day	Haloperidol, 1–16 mg/day	183	6 weeks	2	Original
Hoyberg 1993[258]	5–15 mg/day	Perphenazine, 16–48 mg/day	107	8 weeks	2	Original
Huttunen 1995[259]	2–20 mg/day	Zuclopenthixol, 10–100 mg/day	98	6 weeks	2	Original
Mahmoud 1998[260]	Not stated	Conventional treatment, dose not stated	684	1 year	0	Original
Marder 1994[116]	2 mg/day 6 mg/day 10 mg/day 16 mg/day	Haloperidol, 20 mg/day Placebo	388	8 weeks + 1-week washout period	2	Original
Mesotten 1991[261]	9.1 mg/day	Haloperidol, 9.4 mg/day	60	8 weeks + 1-week washout period	2	Original
Min 1993[262]	5–10 mg/day	Haloperidol, 5–10 mg/day	35	8 weeks + 1-week washout period	2	Original
Peuskens 1995[263]	1 mg/day 4 mg/day 8 mg/day 12 mg/day 16 mg/day	Haloperidol, 10 mg/day	1362	8 weeks + 1-week washout period	2	Original
Fleurot 1997[62]	8 mg/day	Amisulpride, 800 mg/day	228	8 weeks + 3–6-day washout period	2	Original
Bondolfi 1998[110]	3–12 mg/day	Clozapine, 150–400 mg/day	86	8 weeks	2	Original
Anand 1998[111]	2–15 mg/day	Clozapine, 200–900 mg/day	273	12 weeks	2	Original
Breier 1999[112]	2–9 mg/day	Clozapine, 200–600 mg/day	29	6 weeks	2	Original
Wahlbeck 2000[113]	Up to 10 mg/day	Clozapine, up to 600 mg/day	21	10 weeks	1	Original

continued

Study	Dose	Comparator	Number of participants	Duration	Blinding	Original or new
***Risperidone* contd**						
Klieser 1996[264]	4 mg/day 8 mg/day	Clozapine, 400 mg/day Zotepine, 225 mg/day Remoxipride, 400 mg/day Haloperidol, 15 mg/day	180	4 weeks	2	Original
Tran 1997;[171] more information in Edgell 2000[170]	4–12 mg/day	Olanzapine, 10–20 mg/day	339	28 weeks + 2–9-day washout period	2	Original
Jones 1998;[193] more information in Purdon 2001[211] (new)	4–10 mg/day	Olanzapine, 5–20 mg/day Haloperidol, 5–20 mg/day	65	54 weeks + 1-week washout period	2	Original
Gureje 1998[186]	4–8 mg/day	Olanzapine, 10–20 mg/day	65	30 weeks	2	Original
Chowdhury 1999[71]	6–8 mg/day	Clozapine, 250–300 mg/day	60	16 weeks	?	New
Janicak 1999[245]	Up to 10 mg/day	Haloperidol, up to 20 mg/day	150	6 weeks	2	New
Tys 1999[232]	2 mg/day	Haloperidol, 15–20 mg/day	20	2 months	?	New
Littrell 1999[154]	Mean 5.2 mg/day	Olanzapine, mean 19.2 mg/day	24	1 year	0	New
Kolff 2000[152]	Not stated	Olanzapine, dose not stated	50	6 weeks	?	New
Malyarov 1999[153]	3–6 mg/day	Olanzapine, 5–15 mg/day	43	6 months	1	New
Lecrubier 2000[43]	4–10 mg/day	Amisulpride, 400–1000 mg/day	310	6 months	2	New
Heck 2000[233]	Flexible dose	Haloperidol, flexible dose	77	6 weeks + 1 week 'dose rising'	2	New
Rabinowitz 2001[234]	4 mg	Haloperidol, 10 mg	453	8 weeks	?	New
AstraZeneca 2000[1010] Reinstein 1999[209] Mullen 1999[208]	4.4 mg/day	Quetiapine, 254 mg/day	751	16 weeks	0	New
Liu 2000[235]	Not stated	Haloperidol, dose not stated	38	12 weeks + 1-week washout period	?	New
Wirshing 1999[236]	3–15 mg/day	Haloperidol, 5–30 mg/day	67	8 weeks + 3–7-day washout period	2	New
Kern 1999[237]	Flexible dose	Haloperidol, flexible dose	64	8 weeks	2	New
Kern 1998[238]	Flexible dose	Haloperidol, flexible dose	56	8 weeks + 3–7-day washout period	2	New
Kee 1998[239]	Flexible dose	Haloperidol, flexible dose	20	8 weeks + 3–7-day washout period	?	New
Muller-Siecheneder 1998[240]	2–12 mg/day	Haloperidol Amitriptyline	123	6 weeks + 3-day washout period	2	New
Cetin 1999[241]	2 mg/day 4 mg/day 6 mg/day 8 mg/day 10 mg/day	Haloperidol, 20 mg/day	70	6 weeks + 1-week washout period	2	New

continued

Study	Dose	Comparator	Number of participants	Duration	Blinding	Original or new
***Risperidone* contd**						
Conley 2001[161]	2–6 mg/day	Olanzapine, 5–20 mg/day	377	8 weeks	2	New
Study 128-117 (Pfizer, unpublished)	Commercial-in-confidence: data removed	Ziprasidone	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed	New
Study 128-302 (Pfizer, unpublished)	Commercial-in-confidence: data removed	Ziprasidone	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed	New
Barak 2000[244]	Not stated	Haloperidol, dose not stated	51	18 months	?	New
Csernansky 2000[246,248,1012,1013]	Not stated	Haloperidol, dose not stated	365	1 year	2	New
Sertindole						
Daniel 1998[276]	24 mg/day	Haloperidol, 10 mg/day	282	1 year	2	Original
Van Kammen 1996[277]	8 mg/day 12 mg/day 20 mg/day	Placebo	205	40 days	2	Original
Hale 2000[275,1014]	8 mg/day 16 mg/day 20 mg/day 24 mg/day	Haloperidol, 10 mg/day	617	8 weeks + 3–7-day washout period	2	New
Ziprasidone						
Arato 1997[289]	40 mg/day 80 mg/day 160 mg/day	Placebo	294	1 year	2	Original
Brook 1998;[287,288] more information in Brook 2000[439] (new)	Mean 12 mg/day intramuscularly	Haloperidol, mean 5 mg/day intramuscularly	132	1 week	1	Original
Daniel 1999[290]	80 mg/day 160 mg/day	Placebo	302	6 weeks + 3–7-day washout period	2	Original
Goff 1998[291]	4 mg/day 10 mg/day 40 mg/day 160 mg/day	Haloperidol, 15 mg/day	90	4 weeks + 4–7-day washout period	2	Original
Hirsch 1999;[292] also Study 128-304e (24-week extension, new, unpublished)	80–160 mg/day	Haloperidol, 5–15 mg/day	301	28 weeks	2	Original
Keck 1998[293]	40 mg/day 120 mg/day	Placebo	139	4 weeks + 4–7-day washout period	2	Original
Swift 1998[294]	80 mg/day intramuscularly 160 mg/day intramuscularly 320 mg/day intramuscularly	Haloperidol, 10–40 mg/day intramuscularly	306	1 week	1	Original
Gunnar 1999[279]	Dose not stated; intramuscularly	Haloperidol, dose not stated; intramuscularly	8	1 week	0	New
Study 128-108 (unpublished)	Commercial-in-confidence: data removed	Haloperidol	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed	New

continued

Study	Dose	Comparator	Number of participants	Duration	Blinding	Original or new
***Ziprasidone* contd**						
Study 128-115 (unpublished)	Commercial-in-confidence: data removed	Haloperidol Placebo	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed	New
Study 128-117 (unpublished)	Commercial-in-confidence: data removed	Risperidone	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed	New
Study 128-301 (unpublished); also Study 128-301e (40-week extension), new, unpublished	Commercial-in-confidence: data removed	Haloperidol	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed	New
Study 128-302 (unpublished); also Study 128-302e (up to 44 weeks extension), new unpublished	Commercial-in-confidence: data removed	Risperidone	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed	New
Study 128-305 (unpublished)	Commercial-in-confidence: data removed	Amisulpride	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed	New
Study NY-97-001 (unpublished)	Commercial-in-confidence: data removed	Haloperidol	Commercial-in-confidence: data removed	Commercial-in- confidence: data removed	Commercial-in-confidence: data removed	New
Study R-0548 (unpublished)	Commercial-in-confidence: data removed	Olanzapine	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed	New
Study 128-104 (unpublished)	Commercial-in-confidence: data removed	Placebo	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed	New
Zotepine						
Barnas 1987[297]	94 mg/day	Haloperidol, 4 mg/day	30	6 weeks +7-day washout period	2	Original
Cooper 1999a[298]	300 mg/day	Chlorpromazine, 600 mg/day Placebo	159	8 weeks	2	Original
Cooper 1999b[299]	150–300 mg/day	Placebo	121	26 weeks	2	Original
Dieterle 1999[300]	241 mg/day	Perazine, 348 mg/day	40	4 weeks + 3–5-day washout period	2	Original
Fleischhacker 1989[301]	309 mg/day	Haloperidol, 14.5 mg/day	40	6 weeks	2	Original
Klieser 1996[302]	75 mg three times daily	Risperidone, 8 mg/day Clozapine, 400 mg/day Remoxipride, 400 mg/day Haloperidol, 15 mg/day	180	4 weeks	2	Original
Meyer-Lindenberg 1996[108]	150–450 mg/day	Clozapine, 150–450 mg/day	50	6 weeks	2	Original
Petit 1996[303]	150–300 mg/day	Haloperidol, 10–20 mg/day	126	8 weeks	2	Original
Sarai 1987[304]	75–300 mg/day	Thiothixene, 15–60 mg/day	94	8 weeks	2	Original
Wetzel 1991[305]	100–600 mg/day	Perazine, 150–900 mg/day	41	28 days	2	Original

continued

Study	Dose	Comparator	Number of participants	Duration	Blinding	Original or new
***Zotepine* contd**						
Study CTR ZT4002[295]	Commercial-in-confidence: data removed	Haloperidol	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed	New
Study BPI1201[295]	Commercial-in-confidence: data removed	Placebo	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed	Commercial-in-confidence: data removed	New
Fischer 1999[296]	Up to 225 mg/day	Placebo	77	8 weeks	2	New

Feedback

The HTA Programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (http://www.ncchta.org) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

We look forward to hearing from you.

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