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Appendices

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A systematic review and economic model of the effectiveness and cost-effectiveness of methylphenidate, dexamfetamine and atomoxetine for the treatment of attention deficit hyperactivity disorder in children and adolescents

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Appendix 1

Clinical effectiveness research

Clinical effectiveness information was identified by searching the following resources; no search filters were used.

Databases of guidelines and systematic reviews

Agency for Healthcare Research and Quality (AHRQ)
Searched: 12 July 2004 at http://www.ahrq.gov
Clinical Evidence: A compendium of the best available evidence for effective health care. Issue 10, 2003. London: BMJ Publishing Group.
Cochrane Database of Systematic Reviews (CDSR) (Cochrane Library 2004: Issue 2)
Searched: 12 July 2004 at
http://www.nelh.nhs.uk/cochrane.asp
Database of Abstracts of Reviews of Effects (DARE)
Searched: 12 July 2004 on CRD's internal database
Health Evidence Bulletins Wales
Searched: 12 July 2004 at http://hebw.uwcm.ac.uk/
Health Services Technology Assessment Text (HSTAT)
Searched: 12 July 2004 at
http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=hstat
Health Technology Assessment Database (HTA)
Searched: 12 July 2004 on CRD's internal administration database
National Coordinating Centre for Health Technology Assessment
Searched: 12 July 2004 at
http://www.hta.nhsweb.nhs.uk
National Guideline Clearinghouse
Searched: 12 July 2004 at
http://www.guidelines.gov/
National Horizon Scanning Centre (NHSC)
Searched: 12 July 2004 at
http://www.publichealth.bham.ac.uk/horizon/
National Institute for Health and Clinical Excellence (NICE) (published appraisals)
Searched: 12 July 04 at
http://www.nice.org.uk/nice-web/
Scottish Intercollegiate Guidelines Network (SIGN)
Searched: 12 July 2004 at http://www.sign.ac.uk/
Turning Research Into Practice (TRIP) Index
Searched: 12 July 2004 at
http://www.ceres.uwcm.ac.uk/framset.cfm?section=trip

Databases of RCTs and CCTs

CENTRAL (Cochrane Library 2004: Issue 2)
Searched: 17 July 2004 at
http://www.nelh.nhs.uk/cochrane.asp

Databases of all study designs

CINAHL (1982–July week 2 2004)
Searched: 14 July 2004 on OvidWeb:
http://gateway1.uk.ovid.com/ovidweb.cgi
EMBASE (1980–2004 week 28)
Searched: 14 July 2004 on OvidWeb:
http://gateway1.uk.ovid.com/ovidweb.cgi
MEDLINE (1966–July week 1 2004)
Searched: 14 July 2004 on OvidWeb:
http://gateway1.uk.ovid.com/ovidweb.cgi
MEDLINE in-process and other non-indexed citations (13 July 2004)
Searched: 14 July 2004 on OvidWeb:
http://gateway1.uk.ovid.com/ovidweb.cgi
PsycINFO (1967–July week 2 2004)
Searched: 21 July 2004 on WebSPIRS via BIDS:
http://www.bids.ac.uk/
Social Science Citation Index (SSCI) (1981–2004)
Searched: 15 July 2004 on ISI Web of Knowledge via MIMAS: http://wos.mimas.ac.uk/
Science Citation Index (SCI) (1981–2004)
Searched: 15 July 04 on ISI Web of Knowledge via MIMAS: http://wos.mimas.ac.uk/

Databases of ongoing and recently completed research

Controlled Clinical Trials
Searched: 19 July 2004 at
http://www.controlled-trials.com/
ClinicalTrials.gov
Searched: 19 July 2004 at
http://www.clinicaltrials.gov/
National Research Register (NRR) (2004: Issue 2)
Searched: 12 July 2004 at
http://www.nrr.nhs.uk/search.htm

ReFeR database
Searched: 19 July 04 at
http://http://www.info.doh.gov.uk/doh/refr_web.nsf/Home?OpenForm

Conference proceedings databases

Inside Conferences (1993–2004)
Searched: 22 September 2004 on Dialog
ISI Proceedings: Science and Technology (1990–2004)
Searched: 19 July 2004 on ISI Web of Knowledge via MIMAS: http://wos.mimas.ac.uk/
ISI Proceedings: Social Science and Humanities (1990–2004)
Searched: 19 July 2004 on ISI Web of Knowledge via MIMAS: http://wos.mimas.ac.uk/

Databases of reports, dissertations and other grey literature

Dissertation Abstracts
Searched: 16 July 2004 at
http://wwwlib.global.umi.com/dissertations/
System for Information on Grey Literature in Europe (SIGLE) (1980 December 2003)
Searched: 16 July 2004 on WebSPIRS via OVID
http://arc.uk.ovid.com/

Adverse events research

In addition to sifting the papers retrieved from the clinical effectiveness searches, adverse events information was identified by searching the following resources.
ABPI Medicines Compendium. Version 3.3. Epsom, Surrey: Datapharm Communications. July 2003.
British National Formulary (BNF). London: British Medical Association/Royal Pharmaceutical Society of Great Britain. Issue 43, March 2002.
Dukes MNG, Aronson JK. (editors). *Meylers's side effects of drugs: an encyclopedia of adverse reaction and interactions*. 14th ed. Oxford: Elsevier; 2000.
Stockley IH. *Stockley's drug interactions: a source book of interactions, their mechanisms, clinical importance and management*. 6th ed. London: Pharmaceutical Press; 2003.
Sweetman SC (editor.) *Martindale: the complete drug reference*. 33rd ed. London: Pharmaceutical Press; 2002.
TOXLINE – Toxicology Bibliographic Information (1965–Present)
Searched: 18 August20 04 at
http://toxnet.nlm.nih.gov/

Identifying guidelines and systematic reviews via internet resources and databases

Internet sites that contained only a few references were simply browsed for relevant papers. Other Internet sites were searched using a search engine/search form. The search interfaces allowed only very simple searching and in most instances the search comprised a series of terms for ADHD. Most web interfaces do not offer date restriction and none of the searches were limited by date. There was some duplication across the results.

Agency for Healthcare Research and Quality (AHRQ)
Searched: 12 July 2004 at http://www.ahrq.gov
Health Evidence Bulletins Wales
Searched: 12 July 2004 at http://hebw.uwcm.ac.uk/
Health Services Technology Assessment Text (HSTAT)
Searched; 12 July 2004 at
http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=hstat
National Coordinating Centre for Health Technology Assessment
Searched: 12 July 2004 at
http://www.hta.nhsweb.nhs.uk
National Guideline Clearinghouse
Searched: 12 July 2004 at
http://www.guidelines.gov/
National Horizon Scanning Centre (NHSC)
Searched: 12 July 2004 at
http://www.publichealth.bham.ac.uk/horizon/
National Institute for Health and Clinical Excellence (NICE) (published appraisals)
Searched: 12 July 2004 at
http://www.nice.org.uk/nice-web/
Scottish Intercollegiate Guidelines Network (SIGN)
Searched: 12 July 2004 at http://www.sign.ac.uk/
Turning Research Into Practice (TRIP) Index
Searched: 12 July 2004 at
http://www.ceres.uwcm.ac.uk/framset.cfm?section=trip

These resources were searched using the following search terms (not all the terms used retrieved records):

hyperactivity
attention deficit
minimal brain damage
minimal brain dysfunction
hyperkinetic
adhd
ad hd
addh
hkd
impulsivity
inattentive

Searches for systematic reviews in the Cochrane Database of Systematic Reviews (CDSR), the Database of Abstracts of Reviews of Effects (DARE) and the Health Technology Assessment Database (HTA)

The search strategies were limited to the ADHD terms only as these databases contain only a relatively small number of relevant records.

Cochrane Database of Systematic Reviews (CDSR) (Cochrane Library 2004: Issue 2)
Searched: 12 July 2004 at
http://www.nelh.nhs.uk/cochrane.asp

#1 BEHAVIORAL SYMPTOMS explode all trees (MeSH)
#2 hyperactiv*
#3 COGNITION DISORDERS explode all trees (MeSH)
#4 (#1 and #2)
#5 (#3 and #2)
#6 ATTENTION DEFICIT DISORDER WITH HYPERACTIVITY single term (MeSH)
#7 (attention next deficit*)
#8 (#6 or #7)
#9 (#4 or #5)
#10 (#8 or #9)
#11 (minimal next brain next damage*)
#12 (minimal next brain next dysfunction*)
#13 hyperkinetic*
#14 addh
#15 (ad next hd)
#16 hkd
#17 inattent*
#18 impulsivity
#19 adhd
#20 (#10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19)

This retrieved 45 records.

Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment Database (HTA)
Searched: 12 July 2004 on CRD's internal administration databases.
The same search strategy was used in both databases.

S behav$
S hyperactiv$
S cogniti$
S s1 and s2
S s3 and s2
S attention(w)deficit
S minimal(w)brain(w)damage$
S minimal(w)brain(w)dysfunction$
S hyperkinetic
S impulsivity
S inattent$
S adhd or ad(w)hd or addh or hkd
s s4 or s5 or s6 or s7 or s8 or s9 or s10 or s11 or s12

The search in DARE retrieved 30 records and in HTA 12 records.

Searches of databases containing all study designs

The following databases were searched for each drug in turn with the relevant cut-off date described above.

CINAHL (1982–July week 2 2004)
Searched: 14 July 2004 on OvidWeb:
http://gateway1.uk.ovid.com/ovidweb.cgi
Search strategy for atomoxetine:

1. atomoxetine.mp.
2. tomoxetine.mp.
3. ly 139602.mp.
4. ly 139603.mp.
5. ly139602.mp.
6. ly139603.mp.
7. n methyl gamma 2 methylphenoxy phenylpropylamine.mp.
8. n methyl 3 2 methylphenoxy 3 phenylpropylamine.mp.
9. n methyl 3 phenyl 3 ortho tolyloxy propylamine.mp.
10. strattera.mp.
11. or/1-10
12. exp Behavioral Symptoms/
13. hyperactiv$.mp.
14. exp Cognition Disorders/
15. 12 and 13
16. 13 and 14
17. Attention Deficit Hyperactivity Disorder/
18. attention deficit$.mp.
19. 17 or 18
20. 15 or 16
21. 19 or 20
22. minimal brain damage$.mp.
23. minimal brain dysfunction$.mp.
24. hyperkinetic$.mp.
25. ADHD.mp.
26. addh.mp.
27. ad hd.mp.
28. hkd.mp.
29. inattent$.mp.
30. impulsivity$.mp.
31. or/21-30
32. 31 and 11
33. limit 32 to yr=1981-2004

This retrieved 16 records.

CINAHL (1982–July week 2 2004)
Searched: 14 July 2004 on OvidWeb:
http://gateway1.uk.ovid.com/ovidweb.cgi

Search strategy for dexamfetamine:

1. dextroamphetamine/
2. dexamphetamine.mp.
3. dexamfetamine.mp.
4. d amphetamine.mp.
5. dexedrine.mp.
6. dextroamphetamine.mp.
7. dextro amphetamine.mp.
8. afatin.mp.
9. afettine.mp.
10. albemap.mp.
11. amfetasul.mp.
12. amitrene.mp.
13. amphedrine.mp.
14. amphex.mp.
15. amsustain.mp.
16. ardex.mp.
17. betafedrina.mp.
18. betaphedrine.mp.
19. biphetamine.mp.
20. carboxyphen.mp.
21. dadex.mp.
22. methylphenethylamin.mp.
23. d alpha methylphenethylamine sulfate.mp.
24. d amphetamine.mp.
25. daprisal.mp.
26. d beta phenylisopropylamine.mp.
27. dephadren.mp.
28. dexadrine.mp.
29. dexaline.mp.
30. dexalme.mp.
31. dexalone.mp.
32. dexamed.mp.
33. dexamphetamin.mp.
34. dexamphethamine.mp.
35. dexamphoid.mp.
36. dexamyl.mp.
37. dexaspan b.mp.
38. dexeamphetanine.mp.
39. dexoval.mp.
40. dextrostat.mp.
41. diocarb.mp.
42. diocurb.mp.
43. domafate.mp.
44. domefate.mp.
45. doxedrine.mp.
46. d 1 phenyl 2 aminopropane.mp.
47. dynaphenyl.mp.
48. evrodex.mp.
49. hetamine.mp.
50. nsc 73713.mp.
51. obesedrin.mp.
52. obesonil.mp.
53. phetadex.mp.
54. simpamina d.mp.
55. sympamin.mp.
56. /1-55
57. exp Behavioral Symptoms/
58. hyperactiv$.mp.
59. exp Cognition Disorders/
60. 57 and 58
61. 59 and 58
62. Attention Deficit Hyperactivity Disorder /
63. attention deficit$.mp.
64. 62 or 63
65. 60 or 61
66. 64 or 65
67. minimal brain damage$.mp.
68. minimal brain dysfunction$.mp.
69. hyperkinetic.mp.
70. impulsivity$.mp.
71. inattent$.mp.
72. adhd.mp.
73. ad hd.mp.
74. addh.mp.
75. hkd.mp.
76. or/66-75
77. 56 and 76
78. (200$ or 1997$ or 1998$ or 1999$).ew.
79. 77 and 78

This retrieved 20 records.

CINAHL (1982–July week 2 2004)
Searched: 14 July 2004 on OvidWeb:
http://gateway1.uk.ovid.com/ovidweb.cgi

Search strategy for methylphenidate:

1.METHYLPHENIDATE/
2. methylphenidate.mp.
3. equasym.mp.
4. centedrin.mp.
5. phenidylate.mp.
6. ritalin.mp.
7. tsentedrin.mp.
8. alpha phenyl alpha 2 piperidly acetic acid methyl ester.mp.
9. alpha phenyl 2 piperidineacetic acid methyl ester.mp.
10. c 4311 b.mp.
11. c4311 b.mp.
12. c4311b.mp.
13. centedrin.mp.
14. concerta.mp.
15. d erythro methyl phenidylacetate.mp.
16. d1 erythro methyl phenidylacetate.mp.
17. metadate.mp.
18. methylfenidate.mp.

19. methyl phenidate.mp.
20. methylphenidylacetate.mp.
21. methylphenindate.mp.
22. methylphenydate.mp.
23. methyl 2 phenyl 2 piperid 2 ylacetate.mp.
24. phenidylate.mp.
25. phenidyl hydrochloride.mp.
26. sr 20.mp.
27. attenta.mp.
28. methylin.mp.
29. ritaline.mp.
30. riphenidate.mp.
31. ritalina.mp.
32. ritaline.mp.
33. rubifen.mp.
34. tranquilyn.mp.
35. or/1-34
36. exp Behavioral Symptoms/
37. hyperactiv$.mp.
38. exp Cognition Disorders/
39. 36 and 37
40. 37 and 38
41. Attention Deficit Hyperactivity Disorder /
42. attention deficit$.mp.
43. 41 or 42
44. 39 or 40
45. 43 or 44
46. minimal brain damage$.mp.
47. minimal brain dysfunction$.mp.
48. hyperkinetic.mp.
49. impulsivity$.mp.
50. inattent$.mp.
51. adhd.mp.
52. ad hd.mp.
53. addh.mp.
54. hkd.mp.
55. or/45-54
56. 55 and 35
57. (1999$ or 200$).ew
58. 56 and 57

This retrieved 154 records

EMBASE (1980–2004 week 28)
Searched: 14 July 2004 on OvidWeb:
http://gateway1.uk.ovid.com/ovidweb.cgi

Search strategy for atomoxetine:

1. atomoxetine/
2. tomoxetine.mp. or atomoxetine.mp
3. ly 139602.mp.
4. ly 139603.mp.
5. ly139602.mp.
6. ly139603.mp.
7. n methyl gamma 2 methylphenoxy phenylpropylamine.mp.
8. n methyl 3 2 methylphenoxy 3 phenylpropylamine.mp.
9. n methyl 3 phenyl 3 ortho tolyloxy propylamine.mp.
10. strattera.mp.
11. 83015 26 3.af.
12. or/1-11
13. exp Behavior/
14. hyperactiv$.mp.
15. Cognitive Defect/
16. 13 and 14
17. 14 and 15
18. Attention Deficit Disorder/
19. attention deficit$.mp.
20. 18 or 19
21. 16 or 17
22. 20 or 21
23. minimal brain damage$.mp.
24. minimal brain dysfunction$.mp.
25. hyperkinetic$.mp.
26. ADHD.mp.
27. addh.mp.
28. ad hd.mp.
29. hkd.mp.
30. inattent$.mp.
31. impulsivity$.mp.
32. or/22-31
33. 32 and 12
34. limit 33 to yr=1981-2004

This retrieved 145 records.

EMBASE (1980–2004 week 28)
Searched: 14 July 2004 on OvidWeb:
http://gateway1.uk.ovid.com/ovidweb.cgi

Search strategy for dexamfetamine:

1. Dextroamphetamine/
2. dexamphetamine.mp.
3. dexamfetamine.mp.
4. d amphetamine.mp.
5. dexedrine.mp.
6. dextroamphetamine.mp.
7. dextro amphetamine.mp.
8. afatin.mp.
9. afettine.mp.
10. albemap.mp.
11. amfetasul.mp.
12. amitrene.mp.
13. amphedrine.mp.
14. amphex.mp.
15. amsustain.mp.
16. ardex.mp.
17. betafedrina.mp.
18. betaphedrine.mp.
19. biphetamine.mp.

20. carboxyphen.mp.
21. dadex.mp.
22. methylphenethylamin.mp.
23. d alpha methylphenethylamine sulfate.mp.
24. d amphetamine.mp.
25. daprisal.mp.
26. d beta phenylisopropylamine.mp.
27. dephadren.mp.
28. dexadrine.mp.
29. dexaline.mp.
30. dexalme.mp.
31. dexalone.mp.
32. dexamed.mp.
33. dexamphetamin.mp.
34. dexamphethamine.mp.
35. dexamphoid.mp.
36. dexamyl.mp.
37. dexaspan b.mp.
38. dexeamphetanine.mp.
39. dexoval.mp.
40. dextrostat.mp.
41. diocarb.mp.
42. diocurb.mp.
43. domafate.mp.
44. domefate.mp.
45. doxedrine.mp.
46. d 1 phenyl 2 aminopropane.mp.
47. dynaphenyl.mp.
48. evrodex.mp.
49. hetamine.mp.
50. nsc 73713.mp.
51. obesedrin.mp.
52. obesonil.mp.
53. phetadex.mp.
54. simpamina d.mp.
55. sympamin.mp.
56. 51 64 9.rn.
57. or/1-56
58. exp Behavior/
59. hyperactiv$.mp.
60. Cognitive Defect/
61. 58 and 59
62. 59 and 60
63. Attention Deficit Disorder/
64. attention deficit$.mp.
65. 63 or 64
66. 61 or 62
67. 65 or 66
68. minimal brain damage$.mp.
69. minimal brain dysfunction$.mp.
70. hyperkinetic.mp.
71. impulsivity$.mp.
72. inattent$.mp.
73. adhd.mp.
74. ad hd.mp.
75. addh.mp.
76. hkd.mp.
77. or/67-76
78. 57 and 77
79. (200$ or 1997$ or 1998$ or 1999$).ed.
80. 78 and 79

This retrieved 521 records.

EMBASE (1980–2004 week 28)
Searched: 14 July 2004 on OvidWeb:
http://gateway1.uk.ovid.com/ovidweb.cgi

Search strategy for methylphenidate:

1. METHYLPHENIDATE/
2. 113 45 1.rn.
3. methylphenidate.mp.
4. equasym.mp.
5. centedrin.mp.
6. phenidylate.mp.
7. ritalin.mp.
8. tsentedrin.mp.
9. alpha phenyl alpha 2 piperidly acetic acid methyl ester.mp.
10. alpha phenyl 2 piperidineacetic acid methyl ester.mp.
11. c 4311 b.mp.
12. c4311 b.mp.
13. c4311b.mp.
14. centedrin.mp.
15. concerta.mp.
16. d erythro methyl phenidylacetate.mp.
17. d1 erythro methyl phenidylacetate.mp.
18. metadate.mp.
19. methylfenidate.mp.
20. methyl phenidate.mp.
21. methylphenidylacetate.mp.
22. methylphenindate.mp.
23. methylphenydate.mp.
24. methyl 2 phenyl 2 piperid 2 ylacetate.mp.
25. phenidylate.mp.
26. phenidyl hydrochloride.mp.
27. sr 20.mp.
28. attenta.mp.
29. methylin.mp.
30. ritaline.mp.
31. riphenidate.mp.
32. ritalina.mp.
33. ritaline.mp.
34. rubifen.mp.
35. tranquilyn.mp.
36. or/1-35
37. exp Behavior/
38. hyperactiv$.mp.
39. Cognitive Defect/
40. 37 and 38
41. 38 and 39
42. Attention Deficit Disorder/

43. attention deficit$.mp.
44. 42 or 43
45. 40 or 41
46. 44 or 45
47. minimal brain damage$.mp.
48. minimal brain dysfunction$.mp.
49. hyperkinetic.mp.
50. impulsivity$.mp.
51. inattent$.mp.
52. adhd.mp.
53. ad hd.mp.
54. addh.mp.
55. hkd.mp.
56. or/44-55
57. 56 and 36
58. (1999$ or 200$).ew
59. 57 and 58

This retrieved 1174 records.

MEDLINE (1966–July week 1 2004)
Searched: 14 July 2004 on OvidWeb:
http://gateway1.uk.ovid.com/ovidweb.cgi

Search strategy for atomoxetine:

1. atomoxetine.mp.
2. tomoxetine.mp.
3. ly 139602.mp.
4. ly 139603.mp.
5. ly139602.mp.
6. ly139603.mp.
7. n methyl gamma 2 methylphenoxy phenylpropylamine.mp.
8. n methyl 3 2 methylphenoxy 3 phenylpropylamine.mp.
9. n methyl 3 phenyl 3 ortho tolyloxy propylamine.mp.
10. strattera.mp.
11. 83015 26 3.rn.
12. or/1-11
13. exp Behavioral Symptoms/
14. hyperactiv$.mp.
15. exp Cognition Disorders/
16. 13 and 14
17. 14 and 15
18. Attention Deficit Disorder with hyperactivity/
19. attention deficit$.mp.
20. 18 or 19
21. 16 or 17
22. 20 or 21
23. minimal brain damage$.mp.
24. minimal brain dysfunction$.mp.
25. hyperkinetic$.mp.
26. ADHD.mp.
27. addh.mp.
28. ad hd.mp.
29. hkd.mp.
30. inattent$.mp.
31. impulsivity$.mp.
32. or/22-31
33. 32 and 12
34. limit 33 to yr=1981-2004

This retrieved 55 records.

MEDLINE (1966–July Week 1 2004)
Searched: 14 July 2004 on OvidWeb:
http://gateway1.uk.ovid.com/ovidweb.cgi

Search strategy for dexamphetamine:

1. Dextroamphetamine/
2. dexamphetamine.mp.
3. dexamfetamine.mp.
4. d amphetamine.mp.
5. dexedrine.mp.
6. dextroamphetamine.mp.
7. dextro amphetamine.mp.
8. afatin.mp.
9. afettine.mp.
10. albemap.mp.
11. amfetasul.mp.
12. amitrene.mp.
13. amphedrine.mp.
14. amphex.mp.
15. amsustain.mp.
16. ardex.mp.
17. betafedrina.mp.
18. betaphedrine.mp.
19. biphetamine.mp.
20. carboxyphen.mp.
21. dadex.mp.
22. methylphenethylamin.mp.
23. d alpha methylphenethylamine sulfate.mp.
24. d amphetamine.mp.
25. daprisal.mp.
26. d beta phenylisopropylamine.mp.
27. dephadren.mp.
28. dexadrine.mp.
29. dexaline.mp.
30. dexalme.mp.
31. dexalone.mp.
32. dexamed.mp.
33. dexamphetamin.mp.
34. dexamphethamine.mp.
35. dexamphoid.mp.
36. dexamyl.mp.
37. dexaspan b.mp.
38. dexeamphetanine.mp.
39. dexoval.mp.
40. dextrostat.mp.
41. diocarb.mp.
42. diocurb.mp.

43. domafate.mp.
44. domefate.mp.
45. doxedrine.mp.
46. d 1 phenyl 2 aminopropane.mp.
47. dynaphenyl.mp.
48. evrodex.mp.
49. hetamine.mp.
50. nsc 73713.mp.
51. obesedrin.mp.
52. obesonil.mp.
53. phetadex.mp.
54. simpamina d.mp.
55. sympamin.mp.
56. 51 64 9.rn.
57. or/1-56
58. exp Behavioral Symptoms/
59. hyperactiv$.mp.
60. exp Cognition Disorders/
61. 58 and 59
62. 59 and 60
63. Attention Deficit Disorder with Hyperactivity/
64. attention deficit$.mp.
65. 63 or 64
66. 61 or 62
67. 65 or 66
68. minimal brain damage$.mp.
69. minimal brain dysfunction$.mp.
70. hyperkinetic.mp.
71. impulsivity$.mp.
72. inattent$.mp.
73. adhd.mp.
74. ad hd.mp.
75. addh.mp.
76. hkd.mp.
77. or/67-76
78. 57 and 77
79. (200$ or 1997$ or 1998$ or 1999$).ed.
80. 78 and 79

This retrieved 136 records.

MEDLINE (1966–July week 1 2004)
Searched: 14 July 2004 on OvidWeb:
http://gateway1.uk.ovid.com/ovidweb.cgi

Search strategy for methylphenidate:

1. METHYLPHENIDATE/
2. 113 45 1.rn.
3. methylphenidate.mp.
4. equasym.mp.
5. centedrin.mp.
6. phenidylate.mp.
7. ritalin.mp.
8. tsentedrin.mp.
9. alpha phenyl alpha 2 piperidly acetic acid methyl ester.mp.
10. alpha phenyl 2 piperidineacetic acid methyl ester.mp.
11. c 4311 b.mp.
12. c4311 b.mp.
13. c4311b.mp.
14. centedrin.mp.
15. concerta.mp.
16. d erythro methyl phenidylacetate.mp.
17. d1 erythro methyl phenidylacetate.mp.
18. metadate.mp.
19. methylfenidate.mp.
20. methyl phenidate.mp.
21. methylphenidylacetate.mp.
22. methylphenindate.mp.
23. methylphenydate.mp.
24. methyl 2 phenyl 2 piperid 2 ylacetate.mp.
25. phenidylate.mp.
26. phenidyl hydrochloride.mp.
27. sr 20.mp.
28. attenta.mp.
29. methylin.mp.
30. ritaline.mp.
31. riphenidate.mp.
32. ritalina.mp.
33. ritaline.mp.
34. rubifen.mp.
35. tranquilyn.mp.
36. or/1-35
37. exp Behavioral Symptoms/
38. hyperactiv$.mp.
39. exp Cognition Disorders/
40. 37 and 38
41. 38 and 39
42. Attention Deficit Disorder with Hyperactivity/
43. attention deficit$.mp.
44. 42 or 43
45. 40 or 41
46. 44 or 45
47. minimal brain damage$.mp.
48. minimal brain dysfunction$.mp.
49. hyperkinetic.mp.
50. impulsivity$.mp.
51. inattent$.mp.
52. adhd.mp.
53. ad hd.mp.
54. addh.mp.
55. hkd.mp.
56. or/44-55
57. 56 and 36
58. (1999$ or 200$).ed and 57

This retrieved 635 records.

MEDLINE in-process and other non-indexed citations (13 July 2004)
Searched: 14 July 2004 on OvidWeb:
http://gateway1.uk.ovid.com/ovidweb.cgi

Search strategy for atomoxetine:

1. atomoxetine.ti,ab.
2. tomoxetine.ti,ab.
3. ly 139602.ti,ab.
4. ly 139603.ti,ab.
5. ly139602.ti,ab.
6. ly139603.ti,ab.
7. n methyl gamma 2 methylphenoxy phenylpropylamine.ti,ab.
8. n methyl 3 2 methylphenoxy 3 phenylpropylamine.ti,ab.
9. n methyl 3 phenyl 3 ortho tolyloxy propylamine.ti,ab.
10. strattera.ti,ab.
11. or/1-10
12. attention deficit$.ti,ab.
13. minimal brain damage$.ti,ab.
14. minimal brain dysfunction$.ti,ab.
15. hyperkinetic$.ti,ab.
16. ADHD.ti,ab.
17. addh.ti,ab.
18. ad hd.ti,ab.
19. hkd.ti,ab.
20. inattent$.ti,ab.
21. impulsivity$.ti,ab.
22. or/12-21
23. 22 and 11

This retrieved 13 records.

MEDLINE in-process and other non-indexed citations (13 July 2004)
Searched: 14 July 2004 on OvidWeb:
http://gateway1.uk.ovid.com/ovidweb.cgi

Search strategy for dexamfetamine:

1. dexamphetamine.ti,ab.
2. dexamfetamine.ti,ab.
3 d amphetamine.ti,ab.
4. dexedrine.ti,ab.
5. dextroamphetamine.ti,ab.
6. dextro amphetamine.ti,ab.
7. afatin.ti,ab.
8. afettine.ti,ab.
9. albemap.ti,ab.
10. amfetasul.ti,ab.
11. amitrene.ti,ab.
12. amphedrine.ti,ab.
13. amphex.ti,ab.
14. amsustain.ti,ab.
15. ardex.ti,ab.
16. betafedrina.ti,ab.
17. betaphedrine.ti,ab.
18. biphetamine.ti,ab.
19. carboxyphen.ti,ab.
20. dadex.ti,ab.
21. methylphenethylamin.ti,ab.
22. d alpha methylphenethylamine sulfate.ti,ab.
23. d amphetamine.ti,ab.
24. daprisal.ti,ab.
25. d beta phenylisopropylamine.ti,ab.
26. dephadren.ti,ab.
27. dexadrine.ti,ab.
28. dexaline.ti,ab.
29. dexalme.ti,ab.
30. dexalone.ti,ab.
31. dexamed.ti,ab.
32. dexamphetamin.ti,ab.
33. dexamphethamine.ti,ab.
34. dexamphoid.ti,ab.
35. dexamyl.ti,ab.
36. dexaspan b.ti,ab.
37. dexeamphetanine.ti,ab.
38. dexoval.ti,ab.
39. dextrostat.ti,ab.
40. diocarb.ti,ab.
41. diocurb.ti,ab.
42. domafate.ti,ab.
43. domefate.ti,ab.
44. doxedrine.ti,ab.
45. d 1 phenyl 2 aminopropane.ti,ab.
46. dynaphenyl.ti,ab.
47. evrodex.ti,ab.
48. hetamine.ti,ab.
49. nsc 73713.ti,ab.
50. obesedrin.ti,ab.
51. obesonil.ti,ab.
52. phetadex.ti,ab.
53. simpamina d.ti,ab.
54. sympamin.ti,ab.
55. or/1-54
56. attention deficit$.ti,ab.
57. minimal brain damage$.ti,ab.
58. minimal brain dysfunction$.ti,ab.
59. hype59rkinetic$.ti,ab.
60. ADHD.ti,ab.
61. addh.ti,ab.
62. ad hd.ti,ab.
63. hkd.ti,ab.
64. inattent$.ti,ab.
65. impulsivity$.ti,ab.
66. or/56-65
67. 66 and 55

This retrieved eight records.

MEDLINE in-process and other non-indexed citations (13 July 2004)
Searched: 14 July 2004 on OvidWeb:
http://gateway1.uk.ovid.com/ovidweb.cgi

Search strategy for methylphenidate:

1. methylphenidate.ti,ab.
2. equasym.ti,ab.
3. centedrin.ti,ab.
4. phenidylate.ti,ab.
5. ritalin.ti,ab.
6. tsentedrin.ti,ab.
7. alpha phenyl alpha 2 piperidly acetic acid methyl ester.ti,ab.
8. alpha phenyl 2 piperidineacetic acid methyl ester.ti,ab.
9. c 4311 b.ti,ab.
10. c4311 b.ti,ab.
11. c4311b.ti,ab.
12. centedrin.ti,ab.
13. concerta.ti,ab.
14. d erythro methyl phenidylacetate.ti,ab.
15. d1 erythro methyl phenidylacetate.ti,ab.
16. metadate.ti,ab.
17. methylfenidate.ti,ab.
18. methyl phenidate.ti,ab.
19. methylphenidylacetate.ti,ab.
20. methylphenindate.ti,ab.
21. methylphenydate.ti,ab.
22. methyl 2 phenyl 2 piperid 2 ylacetate.ti,ab.
23. phenidylate.ti,ab.
24. phenidyl hydrochloride.ti,ab.
25. sr 20.ti,ab.
26. attenta.ti,ab.
27. methylin.ti,ab.
28. ritaline.ti,ab.
29. riphenidate.ti,ab.
30. ritalina.ti,ab.
31. ritaline.ti,ab.
32. rubifen.ti,ab.
33. tranquilyn.ti,ab.
34. or/1-33
35. attention deficit$.ti,ab.
36. minimal brain damage$.ti,ab.
37. minimal brain dysfunction$.ti,ab.
38. hype59rkinetic$.ti,ab.
39. ADHD.ti,ab.
40. addh.ti,ab.
41. ad hd.ti,ab.
42. hkd.ti,ab.
43. inattent$.ti,ab.
44. impulsivity$.ti,ab.
45. or/35-44
46. 34 and 45

This retrieved 42 records.

PsycINFO (1967–July 2004)
Searched: 21 July 2004 on WebSPIRS via BIDS:
http://www.bids.ac.uk/

Search strategy for atomoxetine:

1981–2004
#1 atomoxetine or tomoxetine or ly 139602 or ly 139603 or ly139602 or ly139603 or n methyl gamma 2 methylphenoxy phenylpropylamine or n methyl 3 2 methylphenoxy 3 phenylpropylamine or n methyl 3 phenyl 3 ortho tolyloxy propylamine or strattera
#2 Behavio* symptom* and hyperactiv*
#3 Cognition* and hyperactiv*
#4 attention deficit* or minimal brain damage* or minimal brain dysfunction* or hyperkinetic or adhd or ad hd or addh or hkd or impulsivity or inattent*
#5 #2 or #3 or #4
#6 #1 and #5

The retrieved 34 records.

PsycINFO (1967–July 2004)
Searched: 21 July 04 on WebSPIRS via BIDS:
http://www.bids.ac.uk/

Search strategy for dexamfetamine:

1997–2004

#1 dexamphetamine or dexamfetamine or d amphetamine or Dexedrine or dextroamphetamine or dextro amphetamine or afatin or afettine or albemap or amfetasul or amitrene or amphedrine or amphex or amsustain or ardex or betafedrina or betaphedrine biphetamine carboxyphen dadex or methylphenethylamin or d alpha methylphenethylamine sulfate or d amphetamine or daprisal or d beta phenylisopropylamine
#2 dephadren or dexadrine or dexaline or dexalme or dexalone or dexamed or dexamphetamin or dexamphethamine or dexamphoid or dexamyl or dexaspan b or dexeamphetanine or dexoval or dextrostat or diocarb or diocurb or domafate or domefate or doxedrine or d 1 phenyl 2 aminopropane or dynaphenyl or evrodex or hetamine or nsc 73713 or obesedrin or obesonil or phetadex or simpamina d or sympamin
#3 Behavio* symptom* and hyperactiv*
#4 Cognition* and hyperactiv*
#5 attention deficit* or minimal brain damage* or .minimal brain dysfunction* or hyperkinetic or adhd or ad hd or addh or hkd or impulsivity or inattent*
#6 #1 or #2
#7 #3 or #4 or #5
#8 #6 and #7

This retrieved 88 records.

PsycINFO (1967–July 2004)
Searched: 21 July 2004 on WebSPIRS via BIDS: http://www.bids.ac.uk/

Search strategy for methylphenidate:

#1 113 45 1 or methylphenidate or equasym or centedrin or phenidylate or Ritalin or tsentedrin or alpha phenyl alpha 2 piperidly acetic acid methyl ester or alpha phenyl 2 piperidineacetic acid methyl ester or c 4311 b or c4311 b or c4311b centedrin or concerta or d erythro methyl phenidylacetate or d1 erythro methyl phenidylacetate or metadate or methylfenidate or methyl phenidate or methylphenidylacetate or methylphenindate or methylphenydate or methyl 2 phenyl 2 piperid 2 ylacetate or phenidylate or phenidyl hydrochloride or .sr 20 or attenta or methylin or ritaline or riphenidate or ritalina or ritaline or rubifen or tranquilyn
#2 Behavio* symptom* and hyperactiv*
#3 Cognition* and hyperactiv*
#4 attention deficit* or minimal brain damage* or .minimal brain dysfunction* or hyperkinetic or adhd or ad hd or addh or hkd or impulsivity or inattent*
#5 #2 or #3 or #4
#6 #1 and #5

This retrieved 357 records.

Social Science Citation Index (SSCI) (1981–2004)
Searched: 15 July 2004 on ISI Web of Knowledge via MIMAS: http://wos.mimas.ac.uk/
Science Citation Index (SCI) (1981–2004)
Searched: 15 July 2004 on ISI Web of Knowledge via MIMAS: http://wos.mimas.ac.uk/

Search strategy for atomoxetine:

1981–2004
#1 atomoxetine or tomoxetine or ly 139602 or ly 139603 or ly139602 or ly139603 or n methyl gamma 2 methylphenoxy phenylpropylamine or n methyl 3 2 methylphenoxy 3 phenylpropylamine or n methyl 3 phenyl 3 ortho tolyloxy propylamine or strattera
#2 Behavio* symptom* and hyperactiv*
#3 Cognition* and hyperactiv*
#4 attention deficit* or minimal brain damage* or minimal brain dysfunction* or hyperkinetic or adhd or ad hd or addh or hkd or impulsivity or inattent*
#5 #2 or #3 or #4
#6 #1 and #5

This retrieved 75 records in SCI and 31 records in SSCI

Social Science Citation Index (SSCI) (1981–2004)
Searched: 15 July 2004 on ISI Web of Knowledge via MIMAS: http://wos.mimas.ac.uk/
Science Citation Index (SCI) (1981–2004)
Searched: 15 July 2004 on ISI Web of Knowledge via MIMAS: http://wos.mimas.ac.uk/

Search strategy for dexamfetamine:

1997–2004
#1 dexamphetamine or dexamfetamine or d amphetamine or Dexedrine or dextroamphetamine or dextro amphetamine or afatin or afettine or albemap or amfetasul or amitrene or amphedrine or amphex or amsustain or ardex or betafedrina or betaphedrine biphetamine carboxyphen dadex or methylphenethylamin or d alpha methylphenethylamine sulfate or d amphetamine or daprisal or d beta phenylisopropylamine
#2 dephadren or dexadrine or dexaline or dexalme or dexalone or dexamed or dexamphetamin or dexamphethamine or dexamphoid or dexamyl or dexaspan b or dexeamphetanine or dexoval or dextrostat or diocarb or diocurb or domafate or domefate or doxedrine or d 1 phenyl 2 aminopropane or dynaphenyl or evrodex or hetamine or nsc 73713 or obesedrin or obesonil or phetadex or simpamina d or sympamin
#3 Behavio* symptom* and hyperactiv*
#4 Cognition* and hyperactiv*
#5 attention deficit* or minimal brain damage* or .minimal brain dysfunction* or hyperkinetic or adhd or ad hd or addh or hkd or impulsivity or inattent*
#6 #1 or #2
#7 #3 or #4 or #5
#8 #6 and #7

This retrieved 161 records in SCI and 123 in SSCI.

Social Science Citation Index (SSCI) (1981–2004)
Searched: 15 July 2004 on ISI Web of Knowledge via MIMAS: http://wos.mimas.ac.uk/
Science Citation Index (SCI) (1981–2004)
Searched: 15 July 2004 on ISI Web of Knowledge via MIMAS: http://wos.mimas.ac.uk/

Search strategy for methylphenidate:

1999–2004

#1 113 45 1. or methylphenidate or equasym or centedrin or phenidylate or Ritalin or tsentedrin or alpha phenyl alpha 2 piperidly acetic acid methyl ester or alpha phenyl 2 piperidineacetic acid methyl ester or c 4311 b or c4311 b or c4311b centedrin or concerta or d erythro methyl phenidylacetate or d1 erythro methyl phenidylacetate or metadate or methylfenidate or methyl phenidate or methylphenidylacetate or methylphenindate or methylphenydate or methyl 2 phenyl 2 piperid 2 ylacetate or phenidylate or phenidyl hydrochloride or .sr 20 or attenta or methylin or ritaline or riphenidate or ritalina or ritaline or rubifen or tranquilyn
#2 Behavio* symptom* and hyperactiv*
#3 Cognition* and hyperactiv*
#4 attention deficit* or minimal brain damage* or .minimal brain dysfunction* or hyperkinetic or adhd or ad hd or addh or hkd or impulsivity or inattent*
#5 #2 or #3 or #4
#6 #1 and #5

This retrieved 678 records in SCI and 398 in SSCI.

CENTRAL (2004: Issue 2)
Searched: 12 July 2004 at
http://www.nelh.nhs.uk/cochrane.asp

Search strategy for atomoxetine:

#1 BEHAVIORAL SYMPTOMS explode all trees (MeSH)
#2 hyperactiv*
#3 COGNITION DISORDERS explode all trees (MeSH)
#4 (#1 and #2)
#5 (#3 and #2)
#6 ATTENTION DEFICIT DISORDER WITH HYPERACTIVITY single term (MeSH)
#7 (attention next deficit*)
#8 (#6 or #7)
#9 (#4 or #5)
#10 (#8 or #9)
#11 (minimal next brain next damage*)
#12 (minimal next brain next dysfunction*)
#13 hyperkinetic*
#14 addh
#15 (ad next hd)
#16 hkd
#17 inattent*
#18 impulsivity
#19 adhd
#20 (#10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19)
#21 tomoxetine
#22 (n next methyl next gamma next methylphenoxy next phenylpropylamine)
#23 (n next methyl next methylphenoxy next phenylpropylamine)
#24 (n next methyl next phenyl next ortho next tolyloxy next propylamine)
#25 strattera
#26 atomoxetine
#27 (#21 or #22 or #23 or #24 or #25 or #26)
#28 (#27 and #20) (1981 to current date)

This retrieved 17 records.

CENTRAL (2004: Issue 2)
Searched: 12 July 2004 at
http://www.nelh.nhs.uk/cochrane.asp

Search strategy for dexamfetamine:

#1 BEHAVIORAL SYMPTOMS explode all trees (MeSH)
#2 hyperactiv*
#3 COGNITION DISORDERS explode all trees (MeSH)
#4 (#1 and #2)
#5 (#3 and #2)
#6 ATTENTION DEFICIT DISORDER WITH HYPERACTIVITY single term (MeSH)
#7 (attention next deficit*)
#8 (#6 or #7)
#9 (#4 or #5)
#10 (#8 or #9)
#11 (minimal next brain next damage*)
#12 (minimal next brain next dysfunction*)
#13 hyperkinetic*
#14 addh
#15 (ad next hd)
#16 hkd
#17 inattent*
#18 impulsivity
#19 adhd
#20 (#10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19)
#21 DEXTROAMPHETAMINE single term (MeSH)
#22 (dephadren or dexadrine or dexaline or dexalme or dexalone or dexamed or dexamphetamin or dexamphethamine or dexamphoid or dexamyl or (dexaspan next b) or dexeamphetanine or dexoval or dextrostat or diocarb or diocurb or domafate or domefate or doxedrine or (d next phenyl

next aminopropane) or dynaphenyl or evrodex or hetamine or obesedrin or obesonil or phetadex or (simpamina next d) or sympamin)
#23 (dexamphetamine or dexamfetamine or (d next amphetamine) or dexedrine or dextroamphetamine or (dextro next amphetamine) or afatin or afettine or albemap or amfetasul or amitrene or amphedrine or amphex or amsustain or ardex or betafedrina or (betaphedrine next biphetamine next carboxyphen next dadex) or methylphenethylamin or (d next alpha next methylphenethylamine next sulfate) or (d next amphetamine) or daprisal or (d next beta next phenylisopropylamine))
#24 (#21 or #22 or #23)
#25 (#20 and #24) (1997 to current date)

This retrieved 33 records.

CENTRAL (2004: Issue 2)
Searched: 12 July 2004 at
http://www.nelh.nhs.uk/cochrane.asp

Search strategy for methylphenidate:

#1 BEHAVIORAL SYMPTOMS explode all trees (MeSH)
#2 hyperactiv*
#3 COGNITION DISORDERS explode all trees (MeSH)
#4 (#1 and #2)
#5 (#3 and #2)
#6 ATTENTION DEFICIT DISORDER WITH HYPERACTIVITY single term (MeSH)
#7 (attention next deficit*)
#8 (#6 or #7)
#9 (#4 or #5)
#10 (#8 or #9)
#11 (minimal next brain next damage*)
#12 (minimal next brain next dysfunction*)
#13 hyperkinetic*
#14 addh
#15 (ad next hd)
#16 hkd
#17 inattent*
#18 impulsivity
#19 adhd
#20 (#10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19)
#21 (methylphenidate or equasym or centedrin or phenidylate or ritalin or tsentedrin or (alpha next phenyl next alpha next piperidly next acetic next acid next methyl next ester) or (alpha next phenyl next piperidineacetic next acid next methyl next ester) or centedrin or concerta or (d next erythro next methyl next phenidylacetate) or (d1 next erythro next methyl next phenidylacetate) or metadate or methylfenidate or (methyl next phenidate) or methylphenidylacetate or methylphenindate or methylphenydate or (methyl next phenyl next piperid next ylacetate) or phenidylate or (phenidyl next hydrochloride) or attenta or methylin or ritaline or riphenidate or ritalina or ritaline or rubifen or tranquilyn)
#22 METHYLPHENIDATE single term (MeSH)
#23 (#21 or #22)
#24 (#20 and #23) (1999 to current date)

This retrieved 115 records.

Searches for ongoing and recently completed research

The following databases were searched for papers relating to ADHD and an initial sift for relevance was carried out by the information officer.
Controlled Clinical Trials
Searched: 19 July 2004 at http://www.controlled-trials.com/
ClinicalTrials.gov
Searched: 19 July 2004 at
http://www.clinicaltrials.gov/
ReFeR database
Searched: 19 July 2004 at
http://http://www.info.doh.gov.uk/doh/refr–web.nsf/Home?OpenForm

The following search terms were used in these databases;

hyperactivity
attention deficit
minimal brain damage
minimal brain dysfunction
hyperkinetic
adhd
ad hd
addh
hkd
impulsivity
inattentive

National Research Register (NRR) (2004: Issue 2)
Searched: 12 July 2004 at
http://www.nrr.nhs.uk/search.htm

#1 BEHAVIORAL SYMPTOMS explode all trees (MeSH)
#2 hyperactiv*

#3 COGNITION DISORDERS explode all trees (MeSH)
#4 (#1 and #2)
#5 (#3 and #2)
#6 ATTENTION DEFICIT DISORDER WITH HYPERACTIVITY single term (MeSH)
#7 (attention next deficit*)
#8 (#6 or #7)
#9 (#4 or #5)
#10 (#8 or #9)
#11 (minimal next brain next damage*)
#12 (minimal next brain next dysfunction*)
#13 hyperkinetic*
#14 addh
#15 (ad next hd)
#16 hkd
#17 inattent*
#18 impulsivity
#19 adhd
#20 (#10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19)

Searches for conference proceedings

ISI Proceedings: Science and Technology (1990–2004) and ISI Proceedings: Social Science and Humanities (1990–2004)
Searched: 19 July 2004 on ISI Web of Knowledge via MIMAS at http://wos.mimas.ac.uk/

Search strategy for atomoxetine:

1990–2004
#1 atomoxetine or tomoxetine or ly 139602 or ly 139603 or ly139602 or ly139603 or n methyl gamma 2 methylphenoxy phenylpropylamine or n methyl 3 2 methylphenoxy 3 phenylpropylamine or n methyl 3 phenyl 3 ortho tolyloxy propylamine or strattera
#2 hyperactiv* or attention deficit* or minimal brain damage* or .minimal brain dysfunction* or hyperkinetic or adhd or ad hd or addh or hkd or impulsivity or inattent*
#3 #1 and #2

This retrieved 23 records in ISI Proceedings: Science and Technology and five in ISI Proceedings: Social Science and Humanities.

ISI Proceedings: Science and Technology (1990–2004) and ISI Proceedings: Social Science and Humanities (1990–2004)
Searched: 19 July 2004 on ISI Web of Knowledge via MIMAS at http://wos.mimas.ac.uk/

Search strategy for dexamfetamine:

1997–2004
#1 (dephadren or dexadrine or dexaline or dexalme or dexalone or dexamed or dexamphetamin or dexamphethamine or dexamphoid or dexamyl or (dexaspan next b) or dexeamphetanine or dexoval or dextrostat or diocarb or diocurb or domafate or domefate or doxedrine or (d next phenyl next aminopropane) or dynaphenyl or evrodex or hetamine or obesedrin or obesonil or phetadex or (simpamina next d) or sympamin)
#2 (dexamphetamine or dexamfetamine or (d next amphetamine) or dexedrine or dextroamphetamine or (dextro next amphetamine) or afatin or afettine or albemap or amfetasul or amitrene or amphedrine or amphex or amsustain or ardex or betafedrina or (betaphedrine next biphetamine next carboxyphen next dadex) or methylphenethylamin or (d next alpha next methylphenethylamine next sulfate) or (d next amphetamine) or daprisal or (d next beta next phenylisopropylamine))
#3 hyperactiv* or attention deficit* or minimal brain damage* or minimal brain dysfunction* or hyperkinetic or adhd or ad hd or addh or hkd or impulsivity or inattent*
#4 #1 or #2
#5 #3 and #4

This retrieved 27 records in ISI Proceedings: Science and Technology and six in ISI Proceedings: Social Science and Humanities.

ISI Proceedings: Science and Technology (1990–2004) and ISI Proceedings: Social Science and Humanities (1990–2004)
Searched: 19 July 2004 on ISI Web of Knowledge via MIMAS at http://wos.mimas.ac.uk/

Search strategy for methylphenidate:

1999–2004
#1 113 45 1 or methylphenidate or equasym or centedrin or phenidylate or Ritalin or tsentedrin or alpha phenyl alpha 2 piperidly acetic acid methyl ester or alpha phenyl 2 piperidineacetic acid methyl ester or c 4311 b or c4311 b or c4311b centedrin or concerta or d erythro methyl phenidylacetate or d1 erythro methyl phenidylacetate or metadate or methylfenidate or methyl phenidate or methylphenidylacetate or methylphenindate or methylphenydate or methyl 2 phenyl 2 piperid 2 ylacetate or phenidylate or phenidyl hydrochloride or .sr 20 or attenta or methylin

or ritaline or riphenidate or ritalina or ritaline or rubifen or tranquilyn
#2 hyperactiv* or attention deficit* or minimal brain damage* or minimal brain dysfunction* or hyperkinetic or adhd or ad hd or addh or hkd or impulsivity or inattent*
#3 #1 and #2

This retrieved 85 records in ISI Proceedings: Science and Technology and 22 in ISI Proceedings: Social Science and Humanities.

Inside Conferences (1993–2004)
Searched 22 September 04 on Dialog
All three drugs were searched in the same strategy to save on the costs of downloading records:

S behavio?ral(w)symptom?
S hyperactiv?
S cognition(w)disorder?
S s1 AND s2
S s3 AND s2
S attention(w)deficit
S minimal(w)brain(w)damage?
S minimal(w)brain(w)dysfunction?
S hyperkinetic
S impulsivity
S inattent?
S adhd OR ad(w)hd OR addh OR hkd
s s4:s12
s atomoxetine
s tomoxetine
s ly(w)139602
s ly139603
s ly139602
s ly139603
s n(w)methyl(w)gamma(w)2(w)methylphenoxy(w)phenylpropylamine
s n(w)methyl(w)3(w)2(w)methylphenoxy(w)3(w)phenylpropylamine
s n(w)methyl(w)3(w)phenyl(w)3(w)ORtho(w)tolyloxy(w)propylamine
s 83015(w)26(w)3
s strattera
s 113(w)45(w)1
s methylphenidate
s equasym
s centedrin
s phenidylate
s Ritalin
s tsentedrin
s alpha(w)phenyl(w)alpha(w)2(w)piperidly(w)acetic(w)acid(w)methyl(w)ester
s alpha(w)phenyl(w)2(w)piperidineacetic(w)acid(w)methyl(w)ester
s c(w)4311(w)b
s c4311(w)b
s c4311b
s centedrin
s concerta
s d(w)erythro(w)methyl(w)phenidylacetate
s d1(w)erythro(w)methyl(w)phenidylacetate
s metadate
s methylfenidate
s methyl(w)phenidate
s methylphenidylacetate
s methylphenindate
s methylphenidate
s methyl(w)2(w)phenyl(w)2(w)piperid(w)2(w)ylacetate
s phenidylate
s phenidyl(w)hydrochlORide
s sr(w)20
s attenta
s methylin
s ritaline
s riphenidate
s ritalina
s ritaline
s rubifen
s tranquilyn
s dexamphetamine
s dexamfetamine
s d(w)amphetamine
s Dexedrine
s dextroamphetamine
s dextro(w)amphetamine
s afatin
s afettine
s albemap
s amfetasul
s amitrene
s amphedrine
s amphex
s amsustain
s ardex
s betafedrina
s betaphedrine
s biphetamine
s carboxyphen
s dadex
s methylphenethylamin
s d(w)alpha(w)methylphenethylamine(w)sulphate
s d(w)amphetamine
s daprisal
s d(w)beta(w)phenylisopropylamine
s dephadren
s dexadrine
s dexaline
s dexalme
s dexalone
s dexamed
s dexamphetamine

s dexamphethamine
s dexamphoid
s dexamyl
s dexaspan(w)b
s dexeamphetanine
s dexoval
s dextrostat
s diocarb
s diocurb
s domafate
s domefate
s doxedrine
s d(w)1(w)phenyl(w)2(w)aminopropane
s dynaphenyl
s evrodex
s hetamine
s nsc(w)73713
s obesedrin
s obesonil
s phetadex
s simpamina(w)d
s sympamin
s 51(w)64(w)9
s s14:s50
s s51:s90
s s91:s113
s s114:s116
s s117 and s13

This retrieved 35 records.

Searches for reports, dissertations and other grey literature

Dissertation Abstracts
Searched: 16 July 2004 at
http://wwwlib.global.umi.com/dissertations/
This database has a simple query interface so the search strategy was limited to ADHD terms only.

hyperactiv? or attention deficit? or minimal brain damage? or .minimal brain dysfunction? or hyperkinetic or adhd or ad hd or addh or hkd or impulsivity or inattent?

This retrieved 195 records.

System for Information on Grey Literature in Europe (SIGLE) (1980–December 2003)
Searched: 16 July 2004 on WebSPIRS via OVID at
http://arc.uk.ovid.com/

Search strategy for atomoxetine:

1990–2004
#1 atomoxetine or tomoxetine or ly 139602 or ly 139603 or ly139602 or ly139603 or n methyl gamma 2 methylphenoxy phenylpropylamine or n methyl 3 2 methylphenoxy 3 phenylpropylamine or n methyl 3 phenyl 3 ortho tolyloxy propylamine or strattera
#2 hyperactiv* or attention deficit* or minimal brain damage* or .minimal brain dysfunction* or hyperkinetic or adhd or ad hd or addh or hkd or impulsivity or inattent*
#3 #1 and #2

This retrieved no records

System for Information on Grey Literature in Europe (SIGLE) (1980–December 2003)
Searched: 16 July 2004 on WebSPIRS via OVID at
http://arc.uk.ovid.com/

Search strategy for dexamfetamine:

1997–2004
#1 (dephadren or dexadrine or dexaline or dexalme or dexalone or dexamed or dexamphetamin or dexamphethamine or dexamphoid or dexamyl or (dexaspan next b) or dexeamphetanine or dexoval or dextrostat or diocarb or diocurb or domafate or domefate or doxedrine or (d next phenyl next aminopropane) or dynaphenyl or evrodex or hetamine or obesedrin or obesonil or phetadex or (simpamina next d) or sympamin)
#2 (dexamphetamine or dexamfetamine or (d next amphetamine) or dexedrine or dextroamphetamine or (dextro next amphetamine) or afatin or afettine or albemap or amfetasul or amitrene or amphedrine or amphex or amsustain or ardex or betafedrina or (betaphedrine next biphetamine next carboxyphen next dadex) or methylphenethylamin or (d next alpha next methylphenethylamine next sulfate) or (d next amphetamine) or daprisal or (d next beta next phenylisopropylamine))
#3 hyperactiv* or attention deficit* or minimal brain damage* or minimal brain dysfunction* or hyperkinetic or adhd or ad hd or addh or hkd or impulsivity or inattent*
#4 #1 or #2
#5 #3 and #4

This retrieved no records

System for Information on Grey Literature in Europe (SIGLE) (1980–December 2003)
Searched: 16 July 2004 on WebSPIRS via OVID at http://arc.uk.ovid.com/

Search strategy for methylphenidate:

1999–2004
#1 113 45 1 or methylphenidate or equasym or centedrin or phenidylate or Ritalin or tsentedrin or alpha phenyl alpha 2 piperidly acetic acid methyl ester or alpha phenyl 2 piperidineacetic acid methyl ester or c 4311 b or c4311 b or c4311b centedrin or concerta or d erythro methyl phenidylacetate or d1 erythro methyl phenidylacetate or metadate or methylfenidate or methyl phenidate or methylphenidylacetate or methylphenindate or methylphenydate or methyl 2 phenyl 2 piperid 2 ylacetate or phenidylate or phenidyl hydrochloride or .sr 20 or attenta or methylin or ritaline or riphenidate or ritalina or ritaline or rubifen or tranquilyn
#2 hyperactiv* or attention deficit* or minimal brain damage* or minimal brain dysfunction* or hyperkinetic or adhd or ad hd or addh or hkd or impulsivity or inattent*
#3 #1 and #2

This retrieved three records.

Search strategies and databases used to retrieve papers on adverse events

In addition to sifting the results of the clinical effectiveness searches for adverse events papers, searches on specialist databases TOXLINE were carried out.
TOXLINE – Toxicology Bibliographic Information (1965–Present)
Searched: 18/08/04 at http://toxnet.nlm.nih.gov/

Search strategy for atomoxetine:
atomoxetine tomoxetine strattera ly139602 ly139603

This retrieved seven records.

TOXLINE – Toxicology Bibliographic Information (1965–Present)
Searched: 18 August 2004 at http://toxnet.nlm.nih.gov/

Search strategy for dexamfetamine:

dexamphetamine dexamfetamine amphetamine Dexedrine dextroamphetamine dextro amphetamine afatin afettine albemap amfetasul amitrene amphedrine amphex amsustain ardex betafedrina betaphedrine biphetamine carboxyphen dadex methylphenethylamin methylphenethylamine amphetamine daprisal phenylisopropylamine dephadren dexadrine dexaline dexalme dexalone dexamed dexamphetamin dexamphethamine dexamphoid dexamyl dexaspan dexeamphetanine dexoval dextrostat diocarb diocurb domafate domefate doxedrine aminopropane dynaphenyl evrodex hetamine 73713 obesedrin obesonil phetadex simpamina sympamin

This retrieved 33 records.

TOXLINE – Toxicology Bibliographic Information (1965–Present)
Searched: 18 August 2004 at http://toxnet.nlm.nih.gov/

Search strategy for methylphenidate:

methylphenidate equasym centedrin phenidylate Ritalin tsentedrin centedrin concerta metadate methylfenidate methylphenidylacetate methylphenindate methylphenydate attenta ritaline riphenidate ritalina ritaline rubifen tranquilyn

This retrieved 432 records.

Appendix 2

Economic evaluations and health-related quality of life research

Economic evaluations

In addition to sifting the papers retrieved from the clinical effectiveness searches, economic evaluations were identified by searching the following resources.
Health Economic Evaluations Database (HEED)(Issue: July 2004)
Searched: 22 July 2004 on CD-ROM
NHS Economic Evaluation Database (NHS EED)
Searched: 22 July 2004 on CRD's internal administration database

Health-related quality of life research

HRQoL research was sought by searching the following resources.
CINAHL (1982–June week 2 2004)
Searched: 18 June 2004 on OvidWeb at http://gateway1.uk.ovid.com/ovidweb.cgi
Database of Abstracts of Reviews of Effects (DARE)
Searched 22 June 2004 on CRD's internal administration database
EMBASE (1980–2004 week 11)
Searched: 18 June 2004 on OvidWeb at http://gateway1.uk.ovid.com/ovidweb.cgi
Health Economic Evaluations Database (HEED) (Issue: June 2004)
Searched 22 June 2004 on CD-ROM
Health Technology Assessment Database (HTA)
Searched 22 June 2004 on CRD's internal administration database
MEDLINE (1966–March week 2 2004)
Searched: 18 June 2004 on OvidWeb at http://gateway1.uk.ovid.com/ovidweb.cgi
MEDLINE in-process and other non-indexed citations (18 June 2004)
Searched: 22 June 2004 on OvidWeb at http://gateway1.uk.ovid.com/ovidweb.cgi
NHS Economic Evaluation Database (NHS EED)
Searched 22 June 2004 on CRD's internal administration database
PsycINFO (1967–June week 1 2004)
Searched: 23 June 2004 on WebSPIRS via BIDS at http://www.bids.ac.uk/
Social Science Citation Index (SSCI) (1981–2004)
Searched: 22 June 2004 on ISI Web of Knowledge via MIMAS at http://wos.mimas.ac.uk/
Science Citation Index (SCI) (1981–2004)
Searched: 22 June 2004 on ISI Web of Knowledge via MIMAS at http://wos.mimas.ac.uk/

Search strategies and databases used to retrieve economic evaluations

In addition to sifting the results of the clinical effectiveness searches for economic evaluations and cost studies, searches on specialist databases were carried out. The economic evaluations databases were searched using ADHD terms only.
Health Economic Evaluations Database (HEED) (Issue: July 2004)
Searched: 22 July 2004 in CD-ROM
attention deficit
minimal brain damage
minimal brain dysfunction
hyperkinetic
adhd
ad hd
addh
hkd
impulsivity
inattent
Hyperactiv* and behav*
Hyperactiv* and cognit*

This retrieved 12 records.

NHS Economic Evaluation Database (NHS EED)
Searched: 22 July 2004 on CRD's internal administration database

S behav$
S hyperactiv$
S cogniti$
S s1 and s2
S s3 and s2
S attention(w)deficit
S minimal(w)brain(w)damage$
S minimal(w)brain(w)dysfunction$

S hyperkinetic
S impulsivity
S inattent$
S adhd or ad(w)hd or addh or hkd
s s4 or s5 or s6 or s7 or s8 or s9 or s10 or s11 or s12

This retrieved 35 records.

Search strategies used to retrieve health-related quality of life research

Separate searches were conducted for HRQoL research and these searches were conducted with ADHD and QoL terms only.

Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment Database (HTA)
Searched 22 June 2004 on CRD's internal administration databases

s Behav$
s hyperactiv$
s Cogniti$
s s1 and s2
s s2 and s3
s adhd
s attention(w)deficit$
s s6 or s7
s s4 or s5
s s8 or s9
s minimal(w)brain(w)damage$
s minimal(w)brain(w)dysfunction$
s hyperkinetic$
s conduct(w)disorder$
s oppositional(w)defiant
s impulsivity
s inattent$
s s10 or s11 or s12 or s13 or s14 or s15 or s16 or s17
s eq5d or eq 5d or euroqol or short(w)form(w)36 or shortform(w)36 or sf(w)thirtysix or sf(w)thirty(w)six or shortform(w)thirtysix or shortform(w)thirty(w)six or short(w)form(w)thirtysix or short(w)form(w)thirty(w)six or hrql or hrqol or qol or hql or hqol or hye or hyes or health$(w)year$(w)equivalent$ or health(w)utilit$ or rosser
s person(w)trade(w)off$ or person(w)tradeoff$ or standard(w)gamble$ or time(w)trade(w)off or time(w)tradeoff or tto or willingness(2w)pay or disutilities or disutility or daly or disability(w)adjusted(w)life or qaly$ or qualy$ or quality(w)adjusted(w)life or quality(2w)life or qwb
s quality(2w)wellbeing or quality(2w)well(w)being or index(2w)well(w)being or index(2w)wellbeing or factor(w)analysis or preference(w)based or health(w)status or health(w)state$ or state(2w)(value or values or valuing or valued) or hspv
s quality(w)adjusted(w)life(w)year or Sickness(w)Impact(w)Profile or utilit$(w)approach$ or health(w)gain or hui or hui2 or hui(w)2 or hui3 or hui(w)3 or categor$(w)scal$ or linear(w)scal$ or linear(w)analog$(w)scal$ or visual(w)scal$ or magnitude(w)estimat$ or multiattribute$(w)health or multi(w)attribute$(w)health
s health(w)measurement$ or health(w)survey(w)questionnaire$ or general(w)health(w)questionnaire$ or ghq or multiattribute$(w)theor$ or multi(w)attribute$(w)theor$ or multiattribute$(w)analys$ or multi(w)attribute$(w)analys$
s classification(w)illness(w)state$ or health(w)utilit$ or multiattribute$(w)utilit$ or multi(w)attribute$(w)utilit$ or theory(w)utilit$
s s19 or s20 or s21 or s22 or s23 or s24
s s18 and s25

This retrieved nine records in DARE and one record in the HTA database

NHS Economic Evaluation Database (NHS EED)
Searched 22 June 2004 on CRD's internal administration database

s Behav$
s hyperactiv$
s Cogniti$
s s1 and s2
s s2 and s3
s adhd
s attention(w)deficit$
s s6 or s7
s s4 or s5
s s8 or s9
s minimal(w)brain(w)damage$
s minimal(w)brain(w)dysfunction$
s hyperkinetic$
s conduct(w)disorder$
s oppositional(w)defiant
s impulsivity
s inattent$
s s10 or s11 or s12 or s13 or s14 or s15 or s16 or s17

This retrieved 34 records.

Health Economic Evaluations Database (HEED)
Searched 22 June 2004. Issue: June 2004 on CD-ROM

(Behav* and hyperactiv*) OR (Cogniti$ and hyperactiv*) OR adhd OR attention deficit* OR minimal(w)brain(w)damage* OR minimal(w)brain(w)dysfunction*. OR hyperkinetic* OR conduct(w)disorder* OR oppositional(w)defiant OR impulsivity OR inattent$

This retrieved 18 records.

CINAHL (1982–June week 2 2004)
Searched: 18 June 2004 on OvidWeb at http://gateway1.uk.ovid.com/ovidweb.cgi

1. exp Behavioral Symptoms/
2. hyperactiv$.ti,ab.
3. exp Cognition Disorders/
4. 1 and 2
5. 2 and 3
6. Attention Deficit Hyperactivity Disorder/
7. (attention deficit$ or adhd).ti,ab.
8. 6 or 7
9. 4 or 5
10. 8 or 9
11. minimal brain damage$.ti,ab.
12. minimal brain dysfunction$.ti,ab.
13. hyperkinetic$.ti,ab.
14. conduct disorder$.ti,ab.
15. oppositional defiant.ti,ab.
16. impulsivity.ti,ab.
17. inattent$.ti,ab.
18. (sf36 or sf 36).ti,ab.
19. (eq5d or eq 5d or euroqol).ti,ab.
20. (short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform or thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti,ab.
21. (hrql or hrqol or qol or hql or hqol).ti,ab.
22. (hye or hyes or health$ year$ equivalent$ or health utilit$).ti,ab.
23. rosser.ti,ab.
24. (person trade off$ or person tradeoff$ or standard gamble$ or time trade off or time tradeoff or tto).ti,ab.
25. (disutilities or disutility or daly or disability adjusted life).ti,ab.
26. (qaly$ or qualy$ or quality adjusted life or quality of life or life quality).ti,ab.
27. qwb.ti,ab.
28. (quality of wellbeing or quality of well being or index of well being or index of wellbeing).ti,ab.
29. factor analysis.ti,ab.
30. preference based.ti,ab.
31. (health status or health state$).ti,ab.
32. (state adj2 (value or values or valuing or valued)).ti,ab
33. hspv.ti,ab.
34. exp "Quality of Life"/
35. exp Health Status/
36. Health Status Indicators/
37. Sickness Impact Profile/
38. (utilit$ approach$ or health gain or hui or hui2 or hui 2 or hui3 or hui 3).ti,ab.
39. (categor$ scal$ or linear scal$ or linear analog$ scal$ or visual scal$ or magnitude estimat$).ti,ab.
40. (multiattribute$ health or multi attribute$ health).ti,ab.
41. health measurement$.ti,ab.
42. health survey questionnaire$.ti,ab.
43. (general health questionnaire$ or ghq).ti,ab.
44. (multiattribute$ theor$ or multi attribute$ theor$ or multiattribute$ analys$ or multi attribute$ analys$).ti,ab.
45. classification illness state$.ti,ab.
46. (health adj2 utilit$).ti,ab.
47. (multiattribute$ utilit$ or multi attribute$ utilit$).ti,ab.
48. willingness pay.ti,ab.
49. theory utilit$.ti,ab.
50. animal/ not (animal/ and human/)
51. or/10-17
52. or/18-49
53. 51 and 52

This retrieved 40 records.

EMBASE (1980–2004 week 11)
Searched: 18 June 2004 on OvidWeb at http://gateway1.uk.ovid.com/ovidweb.cgi

1. exp Behavior/ or exp behavior disorder/
2. hyperactiv$.ti,ab.
3. Cognitive Defect/
4. 1 and 2
5. 2 and 3
6. Attention Deficit Disorder/
7. (attention deficit$ or adhd).ti,ab.
8. 6 or 7
9. 4 or 5
10. 8 or 9
11. minimal brain damage$.ti,ab.
12. minimal brain dysfunction$.ti,ab.
13. hyperkinetic$.ti,ab.
14. conduct disorder$.ti,ab.
15. oppositional defiant.ti,ab.
16. impulsivity.ti,ab.
17. inattent$.tia,b.
18. (sf36 or sf 36).ti,ab.

19. (eq5d or eq 5d or euroqol).ti,ab.
20. (short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti,ab.
21. (hrql or hrqol or qol or hql or hqol).ti,ab.
22. (hye or hyes or health$ year$ equivalent$ or health utilit$).ti,ab.
23. rosser.ti,ab.
24. (person trade off$ or person tradeoff$ or standard gamble$ or time trade off or time tradeoff or tto).ti,ab.
25. (disutilities or disutility or daly or disability adjusted life).ti,ab.
26. (qaly$ or qualy$ or quality adjusted life or quality of life or life quality).ti,ab.
27. qwb.ti,ab.
28. (quality of wellbeing or quality of well being or index of well being or index of wellbeing).ti,ab.
29. factor analysis.ti,ab.
30. preference based.ti,ab.
31. (health status or health state$).ti,ab.
32. (state adj2 (value or values or valuing or valued)).ti,ab.
33. hspv.ti,ab.
34. quality adjusted life year/
35. "Quality of Life"/
36. Health Status/
37. health survey/
38. (hui or hui2 or hui 2 or hui3 or hui 3).ti,ab.
39. (utilit$ approach$ or health gain).ti,ab.
40. (categor$ scal$ or linear scal$ or linear analog$ scal$ or visual scal$ or magnitude estimat$).ti,ab.
41. (multiattribute$ health or multi attribute$ health).ti,ab.
42. health measurement$.ti,ab.
43. health survey questionnaire$.ti,ab.
44. (general health questionnaire$ or ghq).ti,ab.
45. (multiattribute$ theor$ or multi attribute$ theor$ or multiattribute$ analys$ or multi attribute$ analys$).ti,ab.
46. classification illness state$.ti,ab.
47. (health adj2 utilit$).ti,ab.
48. (multiattribute$ utilit$ or multi attribute$ utilit$).ti,ab.
49. willingness pay.ti,ab.
50. theory utilit$.ti,ab.
51. or/18-50
52. animal/ not (animal/ and human/)
53. or/10-17
54. 51 and 53
55. 54 not 52
56. limit 54 to yr=1981 – 2004

This retrieved 364 records.

MEDLINE (1966–March week 2 2004)
Searched: 18 June 2004 on OvidWeb at http://gateway1.uk.ovid.com/ovidweb.cgi

1. exp Behavioral Symptoms/
2. hyperactiv$.ti,ab.
3. exp Cognition Disorders/
4. 1 and 2
5. 2 and 3
6. exp "Attention Deficit and Disruptive Behavior Disorders"/
7. (attention deficit$ or adhd).ti,ab.
8. 6 or 7
9. 4 or 5
10. 8 or 9
11. minimal brain damage$.ti,ab.
12. minimal brain dysfunction$.ti,ab.
13. hyperkinetic$.ti,ab.
14. conduct disorder$.ti,ab.
15. oppositional defiant.ti,ab.
16. impulsivity.ti,ab.
17. inattent$.ti,ab.
18. (sf36 or sf 36).ti,ab.
19. (eq5d or eq 5d or euroqol).ti,ab.
20. (short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti,ab.
21. (hrql or hrqol or qol or hql or hqol).ti,ab.
22. (hye or hyes or health$ year$ equivalent$ or health utilit$).ti,ab.
23. rosser.ti,ab.
24. (person trade off$ or person tradeoff$ or standard gamble$ or time trade off or time tradeoff or tto).ti,ab.
25. (disutilities or disutility or daly or disability adjusted life).ti,ab.
26. (qaly$ or qualy$ or quality adjusted life or quality of life or life quality).ti,ab.
27. qwb.ti,ab.
28. (quality of wellbeing or quality of well being or index of well being or index of wellbeing).ti,ab.
29. factor analysis.ti,ab.
30. preference based.ti,ab.
31. (health status or health state$).ti,ab.
32. (state adj2 (value or values or valuing or valued)).ti,ab.
33. hspv.ti,ab.
34. quality adjusted life year/
35. "Quality of Life"/
36. Health Status/
37. Health Status Indicators/
38. Sickness Impact Profile/
39. (utilit$ approach$ or health gain or hui or hui2 or hui 2 or hui3 or hui 3).ti,ab.
40. (categor$ scal$ or linear scal$ or linear analog$ scal$ or visual scal$ or magnitude estimat$).ti,ab.

41. (multiattribute$ health or multi attribute$ health).ti,ab.
42. health measurement$.ti,ab.
43. health survey questionnaire$.ti,ab.
44. (general health questionnaire$ or ghq).ti,ab.
45. (multiattribute$ theor$ or multi attribute$ theor$ or multiattribute$ analys$ or multi attribute$ analys$).ti,ab.
46. classification illness state$.ti,ab.
47. (health adj2 utilit$).ti,ab.
48. (multiattribute$ utilit$ or multi attribute$ utilit$).ti,ab.
49. willingness pay.ti,ab.
50. theory utilit$.ti,ab.
51. or/18-50
52. animal/ not (animal/ and human/)
53. or/10-17
54. 51 and 53
55. 54 not 52
56. limit 55 to yr=1981 – 2004

This retrieved 259 records.

MEDLINE in-process and other non-indexed citations (18 June 2004)
Searched: 22 June 2004 on OvidWeb at http://gateway1.uk.ovid.com/ovidweb.cgi

1. (attention deficit$ or adhd).ti,ab.
2. minimal brain damage$.ti,ab.
3. minimal brain dysfunction$.ti,ab.
4. hyperkinetic$.ti,ab.
5. conduct disorder$.ti,ab.
6. oppositional defiant.ti,ab.
7. impulsivity.ti,ab.
8. inattent$.ti,ab.
9. (sf36 or sf 36).ti,ab.
10. (eq5d or eq 5d or euroqol).ti,ab.
11. (short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti,ab.
12. (hrql or hrqol or qol or hql or hqol).ti,ab.
13. (hye or hyes or health$ year$ equivalent$ or health utilit$).ti,ab.
14. rosser.ti,ab.
15. (person trade off$ or person tradeoff$ or standard gamble$ or time trade off or time tradeoff or tto or willingness to pay).ti,ab.
16. (disutilities or disutility or daly or disability adjusted life).ti,ab.
17. (qaly$ or qualy$ or quality adjusted life or quality of life or life quality).ti,ab.
18. qwb.ti,ab.
19. (quality of wellbeing or quality of well being or index of well being or index of wellbeing).ti,ab.
20. factor analysis.ti,ab.
21. preference based.ti,ab.
22. (health status or health state$).ti,ab.
23. (state adj2 (value or values or valuing or valued)).ti,ab.
24. hspv.ti,ab.
25. (utilit$ approach$ or health gain or hui or hui2 or hui 2 or hui3 or hui 3).ti,ab.
26. (categor$ scal$ or linear scal$ or linear analog$ scale$ or visual scal$ or magnitude estimat$).ti,ab.
27. (multiattribute$ health or multi attribute$ health).ti,ab.
28. health measurement$.ti,ab.
29. health survey questionnaire$.ti,ab.
30. (general health questionnaire$ or ghq).ti,ab.
31. (multiattribute$ theor$ or multi attribute$ theor$ or multiattribute$ analys$ or multi attribute$ analys$).ti,ab.
32. classification illness state$.ti,ab.
33. (health adj2 utilit$).ti,ab.
34. (multiattribute$ utilit$ or multi attribute$ utilit$).ti,ab.
35. willingness pay.ti,ab.
36. theory utilit$.ti,ab.
37. or/1-8
38. or/9-36
39. 37 and 38

This retrieved 10 records.

PsycINFO (1967–June week 1 2004)
Searched: 23 June 2004 on WebSPIRS via BIDS at http://www.bids.ac.uk/

1. (Behav* and Hyperactiv*) in ti,ab,de,kc,mj,mn
2. (Cogniti* and Hyperactiv*) in ti,ab,de,kc,mj,mn
3. adhd in ti,ab,de,kc,mj,mn
4. attention deficit* in ti,ab,de,kc,mj,mn
5. minimal brain damage* in ti,ab,de,kc,mj,mn
6. minimal brain dysfunction* in ti,ab,de,kc,mj,mn
7. hyperkinetic* in ti,ab,de,kc,mj,mn
8. conduct disorder* in ti,ab,de,kc,mj,mn
9. oppositional defiant in ti,ab,de,kc,mj,mn
10. impulsivity in ti,ab,de,kc,mj,mn
11. inattent* in ti,ab,de,kc,mj,mn
12. #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11
13. (eq5d or eq 5d or euroqol or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six or hrql or hrqol or qol or hql or hqol or hye or hyes or health* year* equivalent* or health utilit* or rosser) in ti,ab,de,kc,mj,mn

14. (person trade off* or person tradeoff* or standard gamble* or time trade off or time tradeoff or tto or willingness pay or disutilities or disutility or daly or disability adjusted life or qaly* or qualy* or quality adjusted life or quality life) in ti,ab,de,kc,mj,mn
15. (life quality or qwb or quality wellbeing or quality well being or index well being or index wellbeing or factor analysis or preference based or health status or health state*) in ti,ab,de,kc,mj,mn
16. (state near (value or values or valuing or valued)) in ti,ab,de,kc,mj,mn
17. (sickness Impact Profile or hspv or quality adjusted life year or utilit* approach* or health gain or hui or hui2 or hui 2 or hui3 or hui 3) in ti,ab,de,kc,mj,mn
18. (categor* scal* or linear scal* or linear analog* scal* or visual scal* or magnitude estimat* or multiattribute* health) in ti,ab,de,kc,mj,mn
19. (multi attribute* health or health measurement* or health survey questionnaire* or general health questionnaire* or ghq or multiattribute* theor* or multi attribute* theor* or multiattribute* analys* or multi attribute* analys* or classification illness state* or health utilit* or multiattribute* utilit* or multi attribute* utilit* or theory utilit*) in ti,ab,de,kc,mj,mn
20. #13 or #14 or #15 or #16 or #17 or #18
21. #19 and #12

This retrieved 69 records.

Social Science Citation Index (SSCI) (1981–2004) and Science Citation Index (SCI) (1981–2004)
Searched: 22 June 2004 on ISI Web of Knowledge via MIMAS at http://wos.mimas.ac.uk/

#1 TS=((Behav* and Hyperactiv*) OR (Cogniti* and Hyperactiv*) OR adhd OR attention deficit* OR Minimal brain damage* OR minimal brain dysfunction* OR hyperkinetic* OR conduct disorder* OR oppositional defian* OR impulsivity OR inattent*)
#2 TS=(sf 36 or sf 36 or eq5d or eq 5d or euroqol or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six or hrql or hrqol or qol or hql or hqol
#3 TS=(health status or health state* or sickness Impact Profile or hspv or quality adjusted life year or utilit* approach* or health gain or hui or hui2 or hui 2 or hui3 or hui 3 or categor* scal* or linear scal* or linear analog* scal* or visual scal* or magnitude estimat* or multiattribute* health)
#4 TS=(hye or hyes or health* year* equivalent* or rosser or person trade off* or person tradeoff* or standard gamble* or time trade off or time tradeoff or tto or willingness pay or disutilities or disutility or daly or disability adjusted life or qaly* or qualy* or quality adjusted life or quality life or life quality or qwb or quality wellbeing or quality well being or index well being or index wellbeing or preference based)
#5 TS=(multi attribute* health or health measurement* or health survey questionnaire* or general health questionnaire* or ghq or multiattribute* theor* or multi attribute* theor* or multiattribute* analys* or multi attribute* analys* or classification illness state* or multiattribute* utilit* or multi attribute* utilit* or theory utilit*)
#6 TS=state same (value or values or valuing or valued)
#7 TS=(health same utilit*)
#8 #2 or #3 or #4 or #5 or #6 or #7
#9 #1 and #8

This retrieved 49 records.

Appendix 3

Excluded studies from the updated search (after the first screening) (*n* = 115)

Reference	Reason for exclusion
Aggarwal and Lillystone, 2000[160]	Inappropriate population: co-morbid disorder
Akhondzadeh *et al.*, 2003[161]	Unlicensed comparator/no placebo
Akhondzadeh *et al.*, 2004[162]	Inadequate data presentation
Allen, *et al.*, 2001[163]	Abstract only
Allen, *et al.*, 2002[164]	Abstract only
Aman and Langworthy, 2000[165]	Inappropriate population: co-morbid disorder
Aman *et al.*, 2003[166]	Inappropriate population: co-morbid disorder
Baren *et al.*, 2000[167]	Abstract only
Bedard, 2002[168]	No relevant outcomes
Bedard *et al.*, 2004[169]	No relevant outcomes
Berman, 1998[170]	Inadequate trial duration
Berman *et al.*, 1999[171]	Inadequate trial duration
Biederman, 2003[172]	Inadequate trial duration
Biederman, 2003[173]	Abstract only
Biederman *et al.*, 2003[174]	Inadequate trial duration
Caballero and Nahata, 2003[175]	Primary studies assessed for inclusion
Chen *et al.*, 2002[176]	Unlicensed comparator/no placebo
Chronis *et al.*, 2003[177]	No relevant outcomes
Connor, 2002[178]	Primary studies assessed for inclusion
Connor *et al.*, 2000[179]	Inadequate data presentation
Cox *et al.*, 2004[180]	No relevant outcomes
Davidovitch *et al.*, 1999[181]	Inappropriate population: co-morbid disorder
Denney and Rapport, 1999[182]	No relevant outcomes
Ding *et al.*, 2002[183]	Translation required
Donnelly *et al.*, 1989[184]	Inadequate data presentation
Duggan *et al.*, 2000[185]	Inadequate data presentation
Ebell, 2002[186]	Abstract only
Eiland and Guest, 2004[187]	Primary studies assessed for inclusion
Firestone *et al.*, 1998[188]	Delayed receipt of paper
Francis *et al.*, 2001[189]	No relevant outcomes
Gadow *et al.*, 1990[190]	Inappropriate population: co-morbid disorder
Gadow *et al.*, 1999[191]	Inappropriate population: co-morbid disorder
Gadow *et al.*, 2002[192]	Inappropriate population: co-morbid disorder
Gilmore and Milne, 2001[123]	Primary studies assessed for inclusion
Goldberg, 2002[193]	Inappropriate population: co-morbid disorder
Goldberg, 2002[194]	Inappropriate population: co-morbid disorder
Grcevich, 2003[195]	Abstract only
Greenhill, 2000[196]	Abstract only
Greenhill, 2000[197]	Abstract only
Greenhill *et al.*, 1999[198]	Inadequate data presentation (data not presented by drug)
Greenhill *et al.*, 2002[199]	Inadequate data presentation (data not presented by drug)
Gross-Tsur *et al.*, 2002[200]	Inappropriate population: co-morbid disorder
Handen *et al.*, 2000[201]	Inappropriate population: co-morbid disorder
Heiligenstein *et al.*, 2002[202]	Abstract only
Heiligenstein *et al.*, 2001[203]	Abstract only
Heiligenstein *et al.*, 2001[204]	Abstract only
Heiligenstein *et al.*, 2001[205]	Abstract only
Hoffman *et al.*, 2003[206]	Abstract only
Jadad *et al.*, 2000[207]	Primary studies assessed for inclusion
Kent, 1999[208]	No relevant outcomes

continued

Reference	Reason for exclusion
Klein *et al.*, 2002[209]	No relevant outcomes
Kollins *et al.*, 2001[210]	Inappropriate outcomes/predominantly adult or non-human population
Konrad *et al.*, 2004[211]	No relevant outcomes
Kurlan and Goldberg, 2002[212]	Inappropriate population: co-morbid disorder.
Lewis *et al.*, 2003[213]	Inappropriate population: co-morbid disorder
Li and Chen, 1999[214]	Required translation
Lieberman and Christophersen, 2000[215]	Abstract only
Loo *et al.*, 2003[216]	No relevant outcomes
Lopez *et al.*, 2003[217]	Inadequate trial duration
Malone *et al.*, 2002[218]	No relevant outcomes
Mannuzza *et al.*, 2003[219]	Inappropriate population: alternative condition
Manos *et al.*, 2000[220]	Abstract only
McBurnett, 2003[221]	Inadequate trial duration
Michelson *et al.*, 2001[222]	Abstract only
Michelson *et al.*, 2001[223]	Abstract only
Mohammadi *et al.*, 2004[224]	Unlicensed comparator/no placebo
Montiel Nava *et al.*, 2002[225]	Delayed receipt of paper
Newcorn, 2003[226]	Abstract only
Nolan *et al.*, 1999[227]	Inappropriate population: co-morbid disorder
Overtoom *et al.*, 2003[228]	No relevant outcomes
Palumbo and Starr, 2003[229]	Abstract only
Pearson *et al.*, 2003[230]	Inappropriate population: co-morbid disorder
Pearson *et al.*, 2004[231]	Inappropriate population: co-morbid disorder
Pearson *et al.*, 2004[232]	Inappropriate population: co-morbid disorder
Pelham *et al.*, 2002[233]	Inadequate data presentation
Rapport *et al.*, 2002[234]	No relevant outcomes
Rhodes, *et al.*, 2003[235]	Abstract only
Riyad *et al.*, 2002[236]	Inappropriate outcomes/inappropriate comparators
Rubia *et al.*, 2003[237]	No relevant outcomes
Schachter *et al.*, 2001[238]	Primary studies assessed for inclusion
Scheres *et al.*, 2003[239]	No relevant outcomes
Sharp *et al.*, 1999[149]	Inadequate data presentation
Sharp *et al.*, 2003[240]	Delayed receipt of paper
Shaughnessy, 1999[241]	Abstract only
Smith *et al.*, 2000[242]	Primary studies assessed for inclusion
Smith *et al.*, 2004[243]	No relevant outcomes
Spencer, 2004[244]	Inappropriate population: co-morbid disorder
Sunohara, 1999[245]	No relevant outcomes
Swanson *et al.*, 2000[246]	Abstract only
Swanson, 2000[247]	Abstract only
Swanson *et al.*, 1998[248]	Inadequate data presentation
Swanson *et al.*, 1998[249]	Inadequate data presentation
Swanson *et al.*, 2002[250]	Inadequate trial duration
Swanson *et al.*, 1999[251]	Inadequate trial duration
Swanson *et al.*, 2000[252]	Abstract only
Swanson *et al.*, 2002[253]	Abstract only
Szobot *et al.*, 2003[254]	No relevant outcomes
Tenreiro, 2001[255]	No relevant outcomes
The Tourette's Syndrome Study Group 2002[256]	Inappropriate population: co-morbid disorder
Tillery *et al.*, 2000[257]	Inappropriate population: co-morbid disorder
van der Meere *et al.*, 1999[258]	No relevant outcomes
Weiss *et al.*, 2003[144]	Abstract only
Wernicke *et al.*, 2001[259]	Abstract only
Wernicke *et al.*, 2001[260]	Abstract only
Wernicke *et al.*, 2001[261]	Abstract only
Whalen *et al.*, 1989[262]	No relevant outcomes
Wigal, 2002[263]	Abstract only
Wigal *et al.*, 1998[264]	No relevant outcomes
Wigal *et al.*, 2003[265]	Delayed receipt of paper

continued

Reference	Reason for exclusion
Wigal *et al.*, 2002[266]	Abstract only
Wigal *et al.*, 1999[267]	Inadequate data presentation (data not presented by drug)
Wilens, 2000[268]	Abstract only
Wilens *et al.*, 2003[269]	Inadequate data presentation (data not presented by drug)
Wilens *et al.*, 2004[270]	No relevant outcomes
Wolraich, 2000[271]	Abstract only

Appendix 4

Excluded studies from NICE, CCOHTA and AHRQ reviews (n = 28)

Reference	Source	Reason for exclusion
Amery *et al.*, 1984[272]	CCOHTA Report	Not randomised
Barrickman *et al.*, 1995[273]	AHRQ Report	Inappropriate comparator
Castellanos *et al.*, 1997[274]	AHRQ Report	Co-morbid condition
Donnelly *et al.*, 2002[275]	CCOHTA Report	Abstract only
Gadow *et al.*, 1990[190]	AHRQ Report	Irrelevant outcomes
Gadow *et al.*, 1992[276]	AHRQ Report	Co-morbid condition
Gadow *et al.*, 1995[277]	AHRQ Report	Co-morbid condition
Gadow *et al.*, 1995[278]	AHRQ Report	Co-morbid condition
Gadow *et al.*, 1995[279]	AHRQ Report	Co-morbid condition
Garfinkel *et al.*, 1981[280]	AHRQ Report	Inadequate data presentation
Gittelman-Klein *et al.*, 1988[281]	AHRQ Report	Inadequate data presentation
Handen *et al.*, 1991[282]	AHRQ Report	Co-morbid condition
Hinshaw *et al.*, 1984[283]	AHRQ Report	Inadequate duration
Hinshaw *et al.*, 1989[284]	AHRQ Report	Irrelevant outcomes
Hinshaw *et al.*, 1989[285]	AHRQ Report	Irrelevant outcomes
Klein *et al.*, 1997[286]	AHRQ Report	Inadequate data presentation
Long *et al.*, 1193[287]	AHRQ Report	Effectiveness data for MPH
Lufi *et al.*, 1997[288]	NICE Report	Not randomised
Matochik *et al.*, 1994[289]	AHRQ Report	Adult sample
McBride, 1988[290]	CCOHTA Report	Inadequate data presentation
Pelham *et al.*, 1997[291]	NICE Report	Irrelevant outcomes
Quinn *et al.*, 1975[292]	AHRQ Report	Not randomised
Rapport *et al.*, 1993[293]	AHRQ Report	Irrelevant outcomes
Solanto *et al.*, 1997[294]	AHRQ Report	Irrelevant outcomes
Spencer *et al.*, 1995[295]	AHRQ Report	Adult sample
Wender *et al.*, 1985[296]	AHRQ Report	Adult sample
Winsberg *et al.*, 1974[297]	AHRQ Report	Co-morbid condition
Zametkin *et al.*, 1985[298]	CCOHTA Report	Inappropriate comparator

Appendix 5

Quality assessment questions used for clinical effectiveness studies (as modified from CRD Report No. 4[31])

1. Was the method used to assign participants to the treatment groups really random, or if the study used a crossover design, was the sequence of treatments really random?

If authors used computer-generated random numbers or random number tables, the study was classified as 'good'. If the authors did not fully and clearly report the method of randomisation, the study was classified as 'poor'. If the authors used inadequate methods, such as alternation, case record numbers, birth dates or week days, it was excluded from the review.

2. Was the sequence of randomisation concealed?

The study was classified as 'good' if the authors employed any of the following concealment methods: centralised real-time or pharmacy-controlled randomisation; serially numbered identical containers; on-site computer-based systems where the randomisation sequence is unreadable until after allocation; other approaches with robust methods to prevent foreknowledge of the allocation sequence to clinicians and patients. The study was classified as 'poor' if the authors did not report concealment of treatment allocation, if the reporting was unclear or if the following inadequate methods were employed: alternation, case record numbers, birth dates, week days, open random number lists, serially numbered envelopes even if opaque.

3. Was blinding carried out?

Where the authors explicitly reported that they did not blind, this question was answered as 'no'. Where authors reported blinding, whatever the level of detail, this question was answered as 'yes'. If the authors did not mention blinding, reviewers answered this question with 'unclear'.

4. Who was blinded?

Those blinded to treatment allocation, whether patients, physicians, outcome assessors or others involved in the trial, were listed. If not reported, this was noted (e.g. if a study was simply described as double-blind, with no further detail). Similarly, if it was unclear who was blinded, this was noted.

5. Was blinding successful?

Where authors assessed the blinding procedure and found it to be successful, the study was scored as 'yes'. Where the authors assessed the blinding procedure and found it to be unsuccessful, the study was scored as 'no'. When authors did not report assessment, reported that they did not carry out assessment or where their assessment reached no definitive conclusion, the study was scored as 'unclear'.

6. Was an ITT analysis performed?

When authors reported analysing the data on an ITT basis and it was clear from the results that this occurred, reviewers answered this question with 'yes'. Where the authors reported ITT analysis, but it was clear from the results that this had not been carried out, reviewers answered this question with 'no'. If the authors did not report using ITT analysis or it was unclear whether it had been performed, reviewers answered this question with 'unclear'.

7. Was a complete description of any withdrawals given?

Where authors detailed numbers of withdrawals per treatment arm together with reasons for withdrawal, this was deemed a complete description. Where either numbers or reasons were reported, this was considered a partial description. Where it appeared that withdrawals had occurred, but the authors reported no detail, reviewers answered this question with 'no'. Where it was clear that there was full compliance, either through explicit reporting by the authors or by examination of the numbers, the question was marked as 'not applicable'. If it was unclear whether there were any withdrawals, reviewers answered this question with 'unclear'.

8. Was the statistical analysis appropriately presented?

Numbers of participants per treatment arm should be clear. Mean scores, presented as before/after scores or change scores, should be reported together with measures of variance, either standard errors or standard deviations of the mean scores. Analysis of data from two period-two treatment crossover trials should use a method specific to paired data.

9. Was an association with industry reported by the authors?

Where reported, reviewers noted an association with industry. Otherwise, this question was marked as 'no'.

In addition, reviewers highlighted any further issues that might have impacted on the reliability of study results.

Appendix 6

Economic evaluation quality assessment checklist

Cost-effectiveness	References							
	123, 124	4	128	30, 127	129	154	156	155
Study question								
Were costs and effects examined?	✓	✓	✓	✓	✓	✓	✓	✓
Alternatives compared?	✓	✓	✓	✓	✓	✓	✓	✓
Viewpoint(s) clearly stated?	✓	✓	✓	✓	✓	✓	✓	✓
Selection of alternatives								
All relevant alternatives compared?	P	P	P	P	✓	×	✓	✓
All relevant alternatives clearly described?	P	✓	✓	✓	✓	✓	✓	✓
Rationale for choosing the alternative programmes compared is stated?	×	✓	✓	✓	✓	U	U	U
Form of evaluation								
Choice of form of economic evaluation is justified in relation to questions addressed?	✓	✓	P	✓	✓	✓	✓	✓
If a cost-minimisation analysis is chosen, have equivalent outcomes been adequately demonstrated?	NA	NA	NA	NA	NA	NA	NA	NA
Effectiveness data								
The source of effectiveness estimates used are stated?	✓	✓	✓	✓	✓	✓	✓	P
Effectiveness data from RCT or review of RCTs?	✓	✓	×	✓	✓	✓	✓	✓
Details of method of synthesis or meta-analysis of estimates are given?	✓	✓	✓	✓	✓	✓	✓	NA
Costs								
All the important and relevant resource use included?	✓	✓	✓	✓	P	✓	✓	✓
All the important and relevant resource use measured accurately?	P	✓	✓	✓	U	✓	✓	✓
Unit costs reported separately from resource use data?	✓	✓	✓	✓	✓	✓	✓	✓
Productivity costs treated separately from other costs?	NA	NA	NA	NA	NA	NA	NA	NA
The year and country to which unit costs apply is stated with appropriate adjustments for inflation and/or currency conversion?	✓	✓	✓	✓	✓	✓	✓	✓
Benefit measurement and valuation								
The primary outcome measure for the economic evaluation is clearly stated?	✓	✓	NA	✓	NA	✓	✓	✓
Methods to value health states and other benefits are stated?	✓	NA	NA	NA	NA	✓	✓	✓
Details of the individuals from whom valuations were obtained are given?	×	NA	NA	NA	NA	✓	✓	NA
Decision modelling								
Details of any model used are given?	NA	NA	✓	✓	✓	✓	✓	✓
The choice of model used and the key input parameters on which it is based are adequately detailed and justified?	NA	NA	✓	✓	✓	P	✓	P
All model outputs described adequately?	NA	NA	✓	✓	✓	✓	×	✓
Discounting								
Discount rate used for both costs and benefits?	NA	NA	NA	NA	NA	NA	NA	NA
Do discount rates accord with NHS guidance?	NA	NA	NA	NA	NA	NA	NA	NA
Allowance for uncertainty								
Stochastic analysis of patient-level data								
Uncertainty around cost-effectiveness estimates expressed?	NA	✓	NA	×	✓	✓	×	✓
Sensitivity analysis of decision models								
Are all appropriate input parameters included with uncertainty?	NA	NA	NA	NA	✓	P	U	P
Is second-order uncertainty (uncertainty in means) included rather than first order uncertainty (uncertainty between patients)?	NA	NA	NA	NA	✓	✓	P	✓

continued

Cost-effectiveness	References							
	123, 124	4	128	30, 127	129	154	156	155
Are the probability distributions adequately detailed and appropriate?	NA	NA	NA	NA	✓	✓	NA	✓
Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs) and analytic decisions (e.g. methods to handle missing data)?	NA	NA	NA	NA	✓	✓	✓	✓
Deterministic analysis								
The approach to sensitivity analysis is given?	✓	X	✓	✓	NA	NA	NA	NA
The choice of variables for sensitivity analysis is justified?	X	P	✓	✓	NA	NA	NA	NA
The ranges over which the variables are varied are stated?	✓	X	✓	✓	NA	NA	NA	NA
Presentation of results								
Incremental analysis is reported using appropriate decision rules?	P	✓	NA	✓	NA	✓	X	✓
Major outcomes are presented in a disaggregated as well as aggregated form?	✓	✓	X	✓	✓	✓	✓	✓

✓, Yes; X, no; NA, not applicable; P, partial; U, uncertain.

Appendix 7

Economic evaluation data extraction forms

Gilmore and colleagues, 2001[123] data extraction form

Authors	Gilmore *et al*.
Date	2001
Type of economic evaluation	Cost–utility analysis
Currency used	£
Years to which costs apply	1997
Perspective	NHS
Study population	Children aged 6–12 years. Children diagnosed using DSM Criteria for Pervasive ADHD/ADD-H or Barkleys Research Criteria who are otherwise normal. The authors state that these criteria are very similar to ICD criteria for HKDs and that the children in the studies can be considered representative of those treated in the UK. Studies of children with conduct disorder, oppositional defiant or learning disorders were included but studies with data on children with co-morbid anxiety were excluded
Intervention 1	IR-MPH
Intervention 2	Placebo
Source of effectiveness data	Review of randomised controlled or crossover trials with sample sizes of >15 and clear entry criteria
Clinical outcomes measured and methods of valuation used	Absolute response rate of MPH, the response rate in comparison with placebo, side-effects and discontinuation rates
Cost data handled appropriately?	Yes. Unit costs and their sources were reported separately from quantities of resources used. The expert opinion of five child psychiatrists was used to assess the average number of outpatient clinics attended per year and MPH dosages, the latter of which was supplemented by the literature. Data on children's weights, used to calculate dosages, were taken from the percentile charts. Drug costs were obtained from MIMs. The costs of child/adolescent psychiatry and family therapy outpatient clinics were obtained from fund-holding tariffs of four NHS trusts and the average of these costs was used. The perspective of the costing was the NHS and the costs included were consistent with this. Mean costs were reported
Modelling summary	Not undertaken
Outcome measures used in economic evaluations	QALYs were calculated using data from the literature review and expert opinion and the IHRQoL. A quality of life improvement of 0.086 per patient per year was assumed. Some 6% of children were assumed to discontinue treatment owing to severe side effects and the response rate was assumed to be 70%
Direction of result with appropriate quadrant location	The cost per QALY of MPH fell in the north-east quadrant
Statistical analysis for patient-level stochastic data?	No
Appropriateness of statistical analysis?	No
Uncertainty around cost-effectiveness expressed?	No

continued

Appropriateness of method of dealing with uncertainty around cost-effectiveness?	No
Sensitivity analysis?	Multi-way sensitivity analysis was conducted to test the robustness of the findings to response rates, changes in QoL and costs. The sensitivity analysis suggested a range of £4691–28,191 per QALY gained
Modelling inputs and techniques appropriate?	No
Authors' conclusions	MPH is of reasonable cost-effectiveness when considering short-term and long-term benefits with an estimated cost per QALY of £7446–9177

Lord and Paisley, 2000[4] data extraction form

Authors	Lord and Paisley
Date	2000
Type of economic evaluation	Cost-effectiveness analysis
Currency used	£
Years to which costs apply	1999
Perspective	NHS
Study population	Children
Intervention 1	Combined therapy (IR-MPH) and BT
Intervention 2	BT
Source of effectiveness data	Meta-analysis of MTA SNAP hyperactivity/impulsiveness index results
Clinical outcomes measured and methods of valuation used	SNAP hyperactivity/impulsiveness index results based on teacher report
Cost data handled appropriately?	Yes, unit costs were reported separately from resource use
Modelling summary	Not undertaken
Outcome measures used in economic evaluations	SNAP-IV
Direction of result with appropriate quadrant location	North-east when comparing combination therapy with BT
Statistical analysis for patient-level stochastic data?	No
Appropriateness of statistical analysis?	Appropriate
Uncertainty around cost-effectiveness expressed	Yes
Appropriateness of method of dealing with uncertainty around cost-effectiveness?	OK
Sensitivity analysis?	Two-way sensitivity analyses varying costs and effects. Assumptions not tested
Modelling inputs and techniques appropriate?	No
Authors' conclusions	The best estimate of the ICER for combined therapy compared with behavioural therapy was about £1600 per one SD in the SNAP hyperactivity/impulsiveness index

Zupancic and colleagues 1998[126] data extraction form

Authors	Zupancic *et al.* Canadian Coordinating Office of Health Technology Assessment (CCOHTA). Shukla and Otten[127] conducted a technology overview based on this work (CCOHTA)
Date	1998
Type of economic evaluation	Cost-effectiveness analysis
Currency used	Can$
Years to which costs apply	1997
Perspective	Third-party payers (public and private)
Study population	Children 0–18 years with a diagnosis of ADD, ADD-H or ADHD
Intervention 1	MPH
Intervention 2	DEX
Intervention 3	BT
Intervention 4	Combined therapy (BT and MPH)
Intervention 5	No treatment was used as the initial treatment comparator
Intervention 6	PEM (low dose, high dose). Results were calculated both including and excluding pemoline. The report below is based on their analysis excluding pemoline as this is of most relevance in the UK
Source of effectiveness data	A meta-analysis using various behavioural rating scales including the Abbreviated CTRS
Clinical outcomes measured and methods of valuation used	Treatment outcomes were expressed in mean scores of various behavioural rating scales as completed by parents or teachers
Cost data handled appropriately?	Direct costs included medication, physician visits and hospitalisation. Information on typical resource use was obtained from three expert panels. Patients on MPH were assumed to have two specialist visits and four GP visits over 1 year along with two complete blood count tests (at baseline and 1 year). Patients on DEX were assumed to have two specialist visits and three GP visits. Patients on BT were assumed to have 16 hours of child counselling, 8 hours of parent training and 2 hours of teacher training. Patients receiving combined therapy received MPH and BT. Patients not receiving any treatment were assumed to have four extra visits to their GP per year. Costs of severe side-effects were included but not mild and moderate
Modelling summary	A decision-analytic model was used based on a decision tree
Outcome measures used in economic evaluations	The magnitude of clinical effects was estimated from a CCOHTA meta-analysis using the CTRS. Economic outcomes were expressed as the weighted mean difference in CTRS. A six-point change on the CTRS is approximately one SD and was thought to be a 'clinically relevant' effect size. Based on a survey of treatment practice in British Columbia, they estimated 35% of children started on MPH would continue to be treated at 6 months and 15% at 1 year
Direction of result with appropriate quadrant location	In the analysis excluding PEM, MPH was found to be the most cost-effective treatment, the result being located in the north-east quadrant
Statistical analysis for patient-level stochastic data?	No
Appropriateness of statistical analysis?	Yes
Uncertainty around cost-effectiveness expressed?	Yes
Appropriateness of method of dealing with uncertainty around cost-effectiveness?	Appropriate

continued

Sensitivity analysis?	Extensive one-way sensitivity analyses were undertaken. The use of a generic band of MPH, worst case analysis, change in physician and psychologist fees, compliance and lower or higher body weight for drug dose calculation were tested but these did not alter the conclusions
Modelling inputs and techniques appropriate?	Yes
Authors' conclusions	The ICER of MPH compared with no treatment was Can$64 for every point gained on the CTRS or Can$386 for a six-point gain, that is, one SD

Marchetti and colleagues, 2001[128] data extraction form

Authors	Marchott, *et al*.
Date	2001
Type of economic evaluation	Total expected cost analysis
Currency used	Can$
Years to which costs apply	2001
Perspective	Third-party payer (although in-school costs are calculated also)
Study population	Children and/or adolescents with ADHD with no co-morbidities
Intervention 1	MPH IR/ER
Intervention 2	MPH IR
Intervention 3	Metadate CD (branded IR/ER MPH)
Intervention 4	Concerta (branded ER MPH)
Intervention 5	Ritalin (branded IR MPH)
Intervention 6 in the UK	Adderall (a combination of DEX and amphetamine salts) – not licensed
Source of effectiveness data	Response rates based on pooled estimates from the literature and on author assumption
Clinical outcomes measured and methods of valuation used	As above only
Cost data handled appropriately?	Direct costs included medication, office visits (physician, psychiatrist and psychologist) and laboratory tests. Human and material resources associated with ADHD care were estimated based on a survey and national and published data. Additionally, time spent by school personnel on administering in-school drug doses was included from a sample of four schools
Modelling summary	Effect sizes were combined across studies using a random effects model. Information from the clinical assessment and meta-analysis were used to populate a decision-analytic model to compute total expected cost for each comparator
Outcome measures used in economic evaluations	Response rates used to calculate the cost of pathways of care
Direction of result with appropriate quadrant location	Not applicable as not compared with relative effects. Metadate CD had the lowest total expected cost relative to the other five interventions assessed
Statistical analysis for patient-level stochastic data?	Not undertaken
Appropriateness of statistical analysis	The approach to estimating the response rate for each comparator was unusual in the sense that the results of different outcome measures to assess response rate were pooled
Uncertainty around cost-effectiveness expressed	Not undertaken

continued

Appropriateness of method of dealing with uncertainty around cost-effectiveness?	No
Sensitivity analysis?	One-way sensitivity analyses were conducted to test the robustness of the results to changes in the drug acquisition cost per tablet and the cost of in-school dosing. Threshold analyses for drug acquisition costs and response rates were also undertaken. The rank ordering of results remained fairly robust to these tests
Modelling inputs and techniques appropriate?	Yes
Authors' conclusions	Metadate CD had the lowest total expected cost relative to the other five interventions compared

Vanoverbeke and colleagues, 2003[129] data extraction form

Authors	Vanoverbeke *et al*.
Date	2003
Type of economic evaluation	Total expected cost analysis
Currency used	£
Years to which costs apply	2001
Perspective	NHS
Study population	Children aged 6–16 years
Intervention 1	MPH IR
Intervention 2	Concerta ER (branded MPH ER)
Intervention 3	BT
Source of effectiveness data	Response rates based on trial data
Clinical outcomes measured and methods of valuation used	A Delphi Panel of eight psychiatrists and paediatricians. Two-stage process to obtain estimates of treatment patterns and healthcare utilisation
Cost data handled appropriately?	Direct costs included medication, consultations (physician, psychiatrist and psychologist and staff involved in BT) and laboratory tests. Unit costs were obtained from the published literature and national databases
Modelling summary	A decision tree. Information from the clinical assessment and clinical trials were used to populate a decision-analytic model to compute total cost based on treatment initiated with each treatment
Outcome measures used in economic evaluations	Response rates used to calculate the cost of pathways of care
Direction of result with appropriate quadrant location	Not applicable as not compared with relative effects. The cost of starting treatment with IR-MPH was marginally lower than with Concerta ER (£1332 and £1362, respectively) and BT was the most costly treatment to start with (£2147). The probability of treatment success was highest for Concerta ER (77.8%), then IR-MPH (55.6%), followed by BT (33.8%)
Statistical analysis for patient-level stochastic data?	Not undertaken
Appropriateness of statistical analysis?	Appropriate
Uncertainty around cost-effectiveness expressed?	Not undertaken
Appropriateness of method of dealing with uncertainty around cost-effectiveness?	No

continued

Sensitivity analysis?	A probabilistic sensitivity analysis was undertaken which showed that results were sensitive to treatment success and the proportion of patients with co-morbidities. Although the sensitivity analysis did not alter the results, the response rates used in the model may be questioned
Modelling inputs and techniques appropriate?	Unclear
Authors' conclusions	UK treatment costs over 1 year appear comparable whether patients were first treated with IR-MPH or Concerta ER. Treating patients first with BT and then adding stimulant medication if needed resulted in higher overall annual treatment costs

Appendix 8

All possible treatment strategies

The main analysis considers a subset of all the possible treatment strategies. This was chosen to improve the interpretability of the model results, but is methodologically incorrect. There are in fact 38 treatment strategies with drug monotherapy and no treatment. The results of this full analysis are shown in *Table 105*. All but strategies 35 (first-line DEX, second-line IR-MPH then no treatment) and 13 (first-line DEX, second-line IR-MPH, third-line ATX) are dominated. The cost per QALY gained with strategy 13 compared with strategy 35 is £11,739, so strategy 13 appears to be the optimal treatment strategy.

TABLE 105 *Results of analysis including all possible treatment strategies (excluding combination therapy)*

Strategy	Order of treatments received	Cost (£)	QALY	ICER (£)
1	IR-MPH – ATX – DEX – no treatment	1,233	0.8279	D
2	ER-MPH8 – ATX – DEX – no treatment	1,470	0.8273	D
3	ER-MPH12 – ATX – DEX – no treatment	1,479	0.8278	D
4	ATX – IR-MPH – DEX – no treatment	1,480	0.8278	D
5	ATX – ER-MPH8 – DEX – no treatment	1,550	0.8277	D
6	ATX – ER-MPH12 – DEX – no treatment	1,563	0.8274	D
7	IR-MPH – DEX – ATX – no treatment	1,140	0.8283	D
8	ER-MPH8 – DEX – ATX – no treatment	1,336	0.8277	D
9	ER-MPH12 – DEX – ATX – no treatment	1,410	0.8284	D
10	ATX – DEX – IR-MPH– no treatment	1,466	0.8281	D
11	ATX – DEX – ER-MPH8 –no treatment	1,485	0.8281	D
12	ATX – DEX – ER-MPH12 – no treatment	1,488	0.8278	D
13	DEX – IR-MPH – ATX – no treatment	1,098	0.8289	11,739
14	DEX – ER-MPH8 – ATX – no treatment	1,157	0.8287	D
15	DEX – ER-MPH12 – ATX – no treatment	1,159	0.8287	D
16	DEX – ATX – IR-MPH – no treatment	1,158	0.8288	D
17	DEX – ATX – ER-MPH8 – no treatment	1,177	0.8288	D
18	DEX– ATX – ER-MPH12 – no treatment	1,180	0.8285	D
19	No treatment	1,223	0.7727	D
20	ATX – no treatment	1,517	0.8093	D
21	IR-MPH – no treatment	1,158	0.8112	D
22	ER-MPH8 – no treatment	1,360	0.8053	D
23	ER-MPH12 – no treatment	1,427	0.8140	D
24	DEX – no treatment	1,090	0.8172	D
25	IR-MPH – no treatment	1,250	0.8218	D
26	ER-MPH8 – ATX – no treatment	1,489	0.8209	D
27	ER-MPH12 – ATX – no treatment	1,495	0.8214	D
28	ATX – IR-MPH – no treatment	1,497	0.8217	D
29	ATX – ER-MPH8 – no treatment	1,569	0.8212	D
30	ATX – ER-MPH12 – no treatment	1,580	0.8210	D
31	IR-MPH – DEX – no treatment	1,113	0.8261	D
32	ER-MPH8 – DEX – no treatment	1,303	0.8243	D
33	ER-MPH12 – DEX – no treatment	1,388	0.8270	D
34	ATX – DEX – no treatment	1,469	0.8253	D
35	DEX – IR-MPH – no treatment	1,072	0.8266	–
36	DEX – ER-MPH8 – no treatment	1,124	0.8253	D
37	DEX – ER-MPH12 – no treatment	1,139	0.8273	D
38	DEX – ATX – no treatment	1,161	0.8260	D

D, dominates.

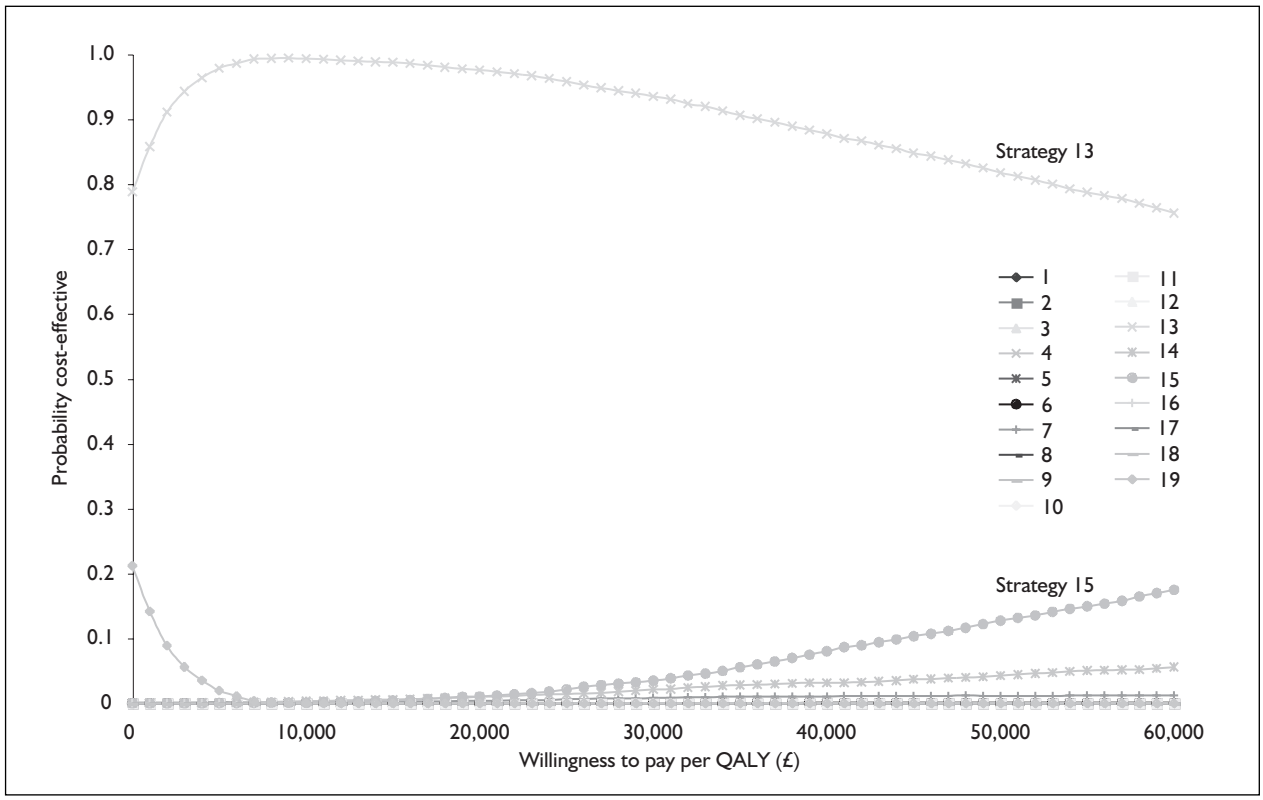

FIGURE 28 *CEACs for all possible treatment strategies (excluding combination therapy)*

TABLE 106 *Cost per QALY gained with single-drug strategies compared with no treatment*

	Cost per QALY gained compared with no treatment (£)				
Scenario	**IR-MPH**	**ER-MPH8**	**ER-MPH12**	**ATX**	**DEX**
Base case	D	4,183	4,917	8,004	D
Alternative utility estimates	D	5,294	6,612	6,660	D
Long-term extrapolation	11,462	19,020	16,590	20,534	8,416
All response, CGI-I baseline	D	4,211	4,963	8,341	D
All response, ADHD-RS baseline	D	4,022	4,881	8,049	D

D, dominates

Table 106 reports the cost per QALY gained for each individual treatment compared with no treatment under various scenarios explored in the main analysis.

Provided that the societal willingness to pay per QALY exceeds £20,534, a treatment strategy with three active drugs would be recommended. If the societal willingness to pay per QALY were below £20,534, then ATX does not look favourable in comparison with no treatment in the long-term extrapolation model, so a three-drug strategy may not be recommended.

Appendix 9

WinBUGS code

```
#Baseline shift random effects model for response
model {for (i in 1:18) { r(i) ~ dbin(p(study(i),trt(i)),n(i))
        #Binomial distribution using observed data, r and n
        logit(p(study(i),trt(i))) <- mu(study(i)) + delta(study(i),b(i),trt(i)) }
        #Random treatment effects
for (j in 1:9) {mu(j) ~ dnorm(mu.m,tau.m)       # Random effects for study baseline
        for (c in 1:4) { delta(j,c,c) <-0
                for (k in (c+1):9) { delta(j,c,k) ~ dnorm(dshift(c,k),tau) }
                }
        }
for (k in 2:9) {d(k) ~ dnorm(0,.001) }
d(1)<-0
mu.m ~ dnorm(0,.0001)
tau.m <- 1/pow(sd.m,2)
sd.m ~ dunif(0,10)

for (c in 1:4) { for (k in (c+1):9) {dshift(c,k) <- d(k) - d(c) }}
for (i in 1:3) {mu1(i) <- mu(i)}
for (i in 1:2) {mu1(i+3) <- mu(i+5) }
m <- mean(mu1())
tau <- 1/pow(sd,2)
sd ~ dunif(0,10)

for(k in 1:9) { logit(T(k)) <- m + d(k)       # Treatment effects on the natural scale
                diff(k) <- T(k) - T(1) }
                # difference between treatment effects and placebo effect
}
```

The first 500,000 iterations were discarded. Subsequently, 5000 iterations were collected by taking every 100th iteration (i.e. the chain was thinned by 100). This was necessary to overcome autocorrelation in the model results that was not eliminated by altering the initial values.

Appendix 10

Health state descriptions used to elicit standard gamble utility estimates from parents of children with ADHD[156]

Health state	Responder to ATX, no side-effects	Responder to ATX, side-effects	Non-responder to ATX, no side-effects	Non-responder to ATX, side-effects
Behaviour throughout the day	In the early morning, your child has little or no difficulty getting ready. He/she tends not to struggle and is rarely overly argumentative During the school day, your child can focus on his/her schoolwork for most of the time and is achieving his/her academic potential. He/she is not disruptive in class Throughout the late afternoon and evening, your child is a little inattentive and distracted, needs occasional reminders to do things but tends to play quietly At night, your child rarely complains about getting ready for bed. He/she does not usually have much difficulty falling asleep and is likely to sleep through the night without waking and being disruptive	In the early morning, your child has little or no difficulty getting ready. He/she tends not to struggle and is rarely overly argumentative During the school day, your child can focus on his/her schoolwork for most of the time and is achieving his/her academic potential. He/she is not disruptive in class Throughout the late afternoon and evening, your child is a little inattentive and distracted, needs occasional reminders to do things but tends to play quietly. At night, your child rarely complains about getting ready for bed. He/she does not usually have much difficulty falling asleep and is likely to sleep through the night without waking and being disruptive	In the early morning, your child has slight to moderate difficulty getting ready. He/she tends to struggle and may be overly argumentative During the school day, your child has difficulty focusing on his/her schoolwork which interferes with his/her academic performance. He/she is frequently disruptive in class Throughout the late afternoon and evening, your child is moderately inattentive and easily distracted, needs multiple reminders to do things and has some difficulty playing quietly At night, your child complains about getting ready for bed. However, he/she does not usually have much difficulty falling asleep but may wake several times and behave disruptively	In the early morning, your child has slight to moderate difficulty getting ready. He/she tends to struggle and may be overly argumentative During the school day, your child has difficulty focusing on his/her schoolwork which interferes with his/her academic performance. He/she is frequently disruptive in class Throughout the late afternoon and evening, your child is moderately inattentive and easily distracted, needs multiple reminders to do things and has some difficulty playing quietly At night, your child complains about getting ready for bed. However, he/she does not usually have much difficulty falling asleep but may wake several times and behave disruptively
Social well-being	Your child feels reasonably satisfied with his/her own abilities at school, sport and getting on with friends and family	Your child feels reasonably satisfied with his/her own abilities at school, sport and getting on with friends and family	Your child feels neither satisfied nor dissatisfied with his/her own abilities at school, sport and getting on with friends and family	Your child feels neither satisfied nor dissatisfied with his/her own abilities at school, sport and getting on with friends and family
Medication attributes	Your child receives medication for ADHD once per day	Your child receives medication for ADHD once per day	Your child receives medication for ADHD once per day	Your child receives medication for ADHD once per day

continued

Health state	Responder to ATX, no side-effects	Responder to ATX, side-effects	Non-responder to ATX, no side-effects	Non-responder to ATX, side-effects
Adverse events	Your child is not experiencing any side-effects from his/her medication	Your child is experiencing one or more of the following medication-related side-effects: Slight drowsiness or lethargy A slightly upset stomach A small chance of vomiting (which may be avoided by taking tablets with food) Loss of appetite These side-effects do not require your child to be withdrawn from medication	Your child is not experiencing any side-effects from his/her medication	Your child is experiencing one or more of the following medication-related side-effects: Slight drowsiness or lethargy A slightly upset stomach A small chance of vomiting (which may be avoided by taking tablets with food) Loss of appetite These side-effects do not require your child to be withdrawn from medication

Health state	Responder to IR-MPH, no side-effects	Responder to IR-MPH, side-effects	Non-responder to IR-MPH, no side-effects	Non-responder to IR-MPH, side-effects
Behaviour throughout the day	In the early morning, your child has slight to moderate difficulty getting ready. He/she tends to struggle and may be overly argumentative During the school day, your child can focus on his/her schoolwork for most of the time and is achieving his/her academic potential. He/she is not disruptive in class As the evening progresses, your child becomes more inattentive and easily distracted, needs increasing reminders to do things and becomes less able to play quietly At night, your child complains about getting ready for bed. However, he/she does not usually have much difficulty falling asleep but may wake several times and behave disruptively	In the early morning, your child has slight to moderate difficulty getting ready. He/she tends to struggle and may be overly argumentative During the school day, your child can focus on his/her schoolwork for most of the time and is achieving his/her academic potential. He/she is not disruptive in class As the evening progresses, your child becomes more inattentive and easily distracted, needs increasing reminders to do things and becomes less able to play quietly At night, your child complains about getting ready for bed. He/she may have some difficulty falling asleep and may wake several times and behave disruptively	In the early morning, your child has slight to moderate difficulty getting ready. He/she tends to struggle and may be overly argumentative During the school day, your child has difficulty focusing on his/her schoolwork and this interferes with his/her academic performance. He/she is frequently disruptive in class Throughout the late afternoon and evening, your child is moderately inattentive and easily distracted, needs multiple reminders to do things and has some difficulty playing quietly At night, your child complains about getting ready for bed. However, he/she does not usually have much difficulty falling asleep but may wake several times and behave disruptively	In the early morning, your child has slight to moderate difficulty getting ready. He/she tends to struggle and may be overly argumentative During the school day, your child has difficulty focusing on his/her schoolwork and this interferes with his/her academic performance. He/she is frequently disruptive in class Throughout the late afternoon and evening, your child is moderately inattentive and easily distracted, needs multiple reminders to do things and has some difficulty playing quietly At night, your child complains about getting ready for bed. He/she may have some difficulty falling asleep and may wake several times and behave disruptively
Social well-being	Your child feels reasonably satisfied with his/her own abilities at school, sport and getting on with friends and family	Your child feels reasonably satisfied with his/her own abilities at school, sport and getting on with friends and family	Your child feels neither satisfied nor dissatisfied with his/her own abilities at school, sport and getting on with friends and family	Your child feels neither satisfied nor dissatisfied with his/her own abilities at school, sport and getting on with friends and family
Medication attributes	Your child receives medication for ADHD two or three times per day. One of these doses is given at school Your child's behaviour may be subject to swings throughout the day as each tablet takes effect and then wears off	Your child receives medication for ADHD two or three times per day. One of these doses is given at school Your child's behaviour may be subject to swings throughout the day as each tablet takes effect and then wears off	Your child receives medication for ADHD two or three times per day. One of these doses is given at school	Your child receives medication for ADHD two or three times per day. One of these doses is given at school

continued

Health state	Responder to IR-MPH, no side-effects	Responder to IR-MPH, side-effects	Non-responder to IR-MPH, no side-effects	Non-responder to IR-MPH, side-effects
Adverse events	Your child is not experiencing any side-effects from his/her medication	Your child is experiencing one or more of the following medication-related side-effects: Insomnia A mildly upset stomach Headache Loss of appetite Be slightly nervous or jumpy These side-effects do not require your child to be withdrawn from medication	Your child is not experiencing any side-effects from his/her medication	Your child is experiencing one or more of the following medication-related side-effects: Insomnia A mildly upset stomach Headache Loss of appetite Be slightly nervous or jumpy These side-effects do not require your child to be withdrawn from medication

Health state	Responder to ER-MPH, no side-effects	Responder to ER-MPH, side-effects	Non-responder to ER-MPH, no side-effects	Non-responder to ER-MPH, side-effects
Behaviour throughout the day	In the early morning, your child has slight to moderate difficulty getting ready. He/she tends to struggle and may be overly argumentative During the school day, your child can focus on his/her schoolwork for most of the time and is achieving his/her academic potential. He/she is not disruptive in class As the evening progresses, your child becomes more inattentive and easily distracted, needs increasing reminders to do things and becomes less able to play quietly At night, your child complains about getting ready for bed. However, he/she does not usually have much difficulty falling asleep but may wake several times and behave disruptively	In the early morning, your child has slight to moderate difficulty getting ready. He/she tends to struggle and may be overly argumentative During the school day, your child can focus on his/her schoolwork for most of the time and is achieving his/her academic potential. He/she is not disruptive in class As the evening progresses, your child becomes more inattentive and easily distracted, needs increasing reminders to do things and becomes less able to play quietly At night, your child complains about getting ready for bed. He/she may have some difficulty falling asleep and may wake several times and behave disruptively	In the early morning, your child has slight to moderate difficulty getting ready. He/she tends to struggle and may be overly argumentative During the school day, your child has difficulty focusing on his/her schoolwork and this interferes with his/her academic performance. He/she is frequently disruptive in class Throughout the late afternoon and evening, your child is moderately inattentive and easily distracted, needs multiple reminders to do things and has some difficulty playing quietly At night, your child complains about getting ready for bed. However, he/she does not usually have much difficulty falling asleep but may wake several times and behave disruptively	In the early morning, your child has slight to moderate difficulty getting ready. He/she tends to struggle and may be overly argumentative During the school day, your child has difficulty focusing on his/her schoolwork and this interferes with his/her academic performance. He/she is frequently disruptive in class Throughout the late afternoon and evening, your child is moderately inattentive and easily distracted, needs multiple reminders to do things and has some difficulty playing quietly At night, your child complains about getting ready for bed. He/she may have some difficulty falling asleep and may wake several times and behave disruptively
Social well-being	Your child feels reasonably satisfied with his/her own abilities at school, sport and getting on with friends and family	Your child feels reasonably satisfied with his/her own abilities at school, sport and getting on with friends and family	Your child feels neither satisfied nor dissatisfied with his/her own abilities at school, sport and getting on with friends and family	Your child feels neither satisfied nor dissatisfied with his/her own abilities at school, sport and getting on with friends and family
Medication attributes	Your child receives medication for ADHD once per day	Your child receives medication for ADHD once per day	Your child receives medication for ADHD once per day.	Your child receives medication for ADHD once per day

continued

Health state	Responder to ER-MPH, no side-effects	Responder to ER-MPH, side-effects	Non-responder to ER-MPH, no side-effects	Non-responder to ER-MPH, side-effects
Adverse events	Your child is not experiencing any side-effects from his/her medication	Your child is experiencing one or more of the following medication-related side-effects: Insomnia A mildly upset stomach Headache Loss of appetite Be slightly nervous or jumpy These side-effects do not require your child to be withdrawn from medication	Your child is not experiencing any side-effects from his/her medication	Your child is experiencing one or more of the following medication-related side-effects: Insomnia A mildly upset stomach Headache Loss of appetite Be slightly nervous or jumpy These side-effects do not require your child to be withdrawn from medication

Health state	No medication 'responder'	No medication 'non-responder'
Behaviour throughout the day	In the early morning, your child has little or no difficulty getting ready. He/she tends not to struggle and is rarely overly argumentative During the school day, your child can focus on his/her schoolwork for most of the time and is achieving his/her academic potential. He/she is not disruptive in class As the evening progresses, your child becomes more inattentive and easily distracted, needs increasing reminders to do things and becomes less able to play quietly At night, your child complains about getting ready for bed. However, he/she does not usually have much difficulty falling asleep but may wake several times and behave disruptively	In the early morning, your child has slight to moderate difficulty getting ready. He/she tends to struggle and may be overly argumentative During the school day, your child has difficulty focusing on his/her schoolwork and this interferes with his/her academic performance. He/she is frequently disruptive in class Throughout the late afternoon and evening, your child is moderately inattentive and easily distracted, needs multiple reminders to do things and has some difficulty playing quietly At night, your child complains about getting ready for bed. However, he/she does not usually have much difficulty falling asleep but may wake several times and behave disruptively
Social well-being	Your child feels reasonably satisfied with his/her own abilities at school, sport and getting on with friends and family	Your child feels neither satisfied nor dissatisfied with his/her own abilities at school, sport and getting on with friends and family
Adverse events	Your child receives no medication for ADHD	Your child receives no medication for ADHD
Medication attributes	Your child is not experiencing any side-effects	Your child is not experiencing any side-effects

Appendix 11

WinBUGS code for extended MTC model

```
#Baseline shift random effects model for response
model {


for (i in 1:10) { r1[i] ~ dbin(p1[study[i],trt[i]],n1[i])
                  logit(p1[study[i],trt[i]]) <- mucgii[study[i]] + delta[study[i],b[i],trt[i]] }
for (i in 1:8)   { r1[i+16] ~ dbin(p1[study[i+16],trt[i+16]],n1[i+16])
                  logit(p1[study[i+16],trt[i+16]]) <- mucgii[study[i+16]] +
delta[study[i+16],b[i+16],trt[i+16]]  }

for (i in 1:2)   { r2[i+4] ~ dbin(p2[study[i+4],trt[i+4]],n2[i+4])
                  logit(p2[study[i+4],trt[i+4]]) <- mucgii[study[i+4]] +
delta[study[i+4],b[i+4],trt[i+4]] + cgis[study[i+4]] }
for (i in 1:8) { r2[i+10] ~ dbin(p2[study[i+10],trt[i+10]],n2[i+10])
                  logit(p2[study[i+10],trt[i+10]]) <- mucgii[study[i+10]] +
delta[study[i+10],b[i+10],trt[i+10]] + cgis[study[i+10]]}

for (j in 1:12) {mucgii[j] ~ dnorm(mu.cgii,tau.cgii)
for (c in 1:4)  { delta[j,c,c] <-0
                  for (k in (c+1):9) { delta[j,c,k] ~ dnorm(dshift[c,k],tau) }
                  }
                  cgis[j] ~ dnorm(0,.0001)
                  }
for (k in 2:9) {d[k] ~ dnorm(0,.001) }
d[1]<-0
mu.cgii ~ dnorm(0,.0001)
tau.cgii <- 1/pow(sd.cgii,2)
sd.cgii ~ dunif(0,10)

for (c in 1:4) { for (k in (c+1):9) {dshift[c,k] <- d[k] - d[c] }}
for (i in 1:8) {mu1[i] <- mucgii[i]}
m <- mean(mu1[])
tau <- 1/pow(sd,2)
sd ~ dunif(0,10)

for(k in 1:9)      { logit(T[k]) <- m + d[k]
                  diff[k] <- T[k] - T[1] }
}
```

The first 500,000 iterations were discarded. Subsequently, 5000 iterations were collected by taking every 100th iteration (i.e. the chain was thinned by 100). This was necessary to overcome autocorrelation in the model results that was not eliminated by altering the initial values.

Appendix 12

Data extraction tables of clinical effectiveness studies

Study	Intervention	Participants	Outcomes
Reference Ahmann *et al.*, 1993[35] **Source** AHRQ Report **Setting** USA (tertiary care clinic) **Design** Crossover trial **Duration** Each treatment was given for 7 days over a 4-week period. **Purpose** To assess the frequency of side-effects of Ritalin therapy in children with ADHD	**Arm 1** MPH 0.3 mg/kg; administered three times daily (Individual administering medication not reported) **Arm 2** MPH 0.5 mg/kg; administered three times daily (Individual administering medication not reported) **Arm 3** Placebo Administered three times daily (Individual administering medication not reported)	**Inclusion criteria** At least three of the following criteria had to be met: 1. ACTeRS Attention Score = 25th percentile 2. ACTeRS Hyperactivity Score = 25th percentile 3. CTRS-28 Inattention/Passivity Scale two or more SD above the mean 4. CTRS-28 Hyperactivity Index two or more SD above the mean 5. CPRS-48 Hyperactivity Index two or more SD above the mean In addition: 6. No history of seizures, mental retardation, Tourette's syndrome or other significant neurological history **Diagnostic criteria** DSM-III-R **Number** Total randomised = 234 (male = 189) Total withdrawals = 28 Reasons for withdrawals: Adverse events: $n = 4$ Randomisation procedure: Randomisation was conducted for MPH 0.3 mg/kg and placebo, and then again after 2 weeks for MPH 0.5 mg/kg and placebo **Age** 5–15 years (range) **IQ** Not reported **Co-morbid disorders** Not reported **Diagnostic subtypes** Not reported **Additional information** No relevant information reported	**Core symptoms** Not reported **Co-existent problems** Not reported **Educational performance** Not reported **Psychological function** Not reported **Depression or anxiety** Not reported **Quality of life** Not reported **Adverse events** Barkley Side Effects Questionnaire (BSEQ) **Additional outcomes** Not reported

Core symptoms	Educational performance	Quality of life	Adverse events
Not reported	Not reported	Not reported	Side-effects that increased in frequency with Ritalin therapy were reported by the authors

% of participants reporting under each treatment arm (n=206) (reported by parents);

	Baseline	0.3 mg/kg per dose	Placebo	OR (95% CI)
Insomnia	37.7	58.8	36.7	5.40 (2.92 to 9.99)
Decreased appetite	29.3	55.7	25.4	7.10 (3.99 to 12.63)
Stomach ache	35.0	33.8	18.4	4.10 (2.12 to 7.92)
Headache	37.4	30.4	21.4	2.00 (1.11 to 3.60)
Dizziness	10.7	12.5	4.5	4.2 (1.61, 10.93)

	Baseline	0.5 mg/kg per dose	Placebo	OR (95% CI)
Insomnia	37.7	53.2	35.3	3.13 (1.80 to 5.42)
Decreased appetite	29.3	64.2	26.3	19.00 (9.18 to 39.31)
Stomach ache	35.0	35.8	16.8	7.00 (3.29 to 14.89)
Headache	37.4	33.9	18.0	5.29 (2.51 to 11.15)
Dizziness	10.7	9.5	2.7	7.50 (1.93 to 29.13)

Conclusions

Authors' conclusions: The frequency of side-effects significantly increased with Ritalin therapy: insomnia, decreased appetite, stomach ache, headache and dizziness, even at a relatively low dose (0.3 mg/kg per dose). The BSEQ proved to be clinically effective in tracking Ritalin side-effects and should be incorporated into the routine evaluation and monitoring of ADHD patients for whom stimulants are prescribed

Reviewer's comments: No comments noted

Study	Intervention	Participants	Outcomes
Reference Arnold *et al.*, 1976[36] **Source** AHRQ Report **Setting** USA **Design** Crossover trial **Duration** Treatment periods: 4 weeks per treatment condition. Total treatment time: 12 weeks **Purpose** To compare placebo, dextroamphetamine and levoamphetamine in children with minimal brain dysfunction	**Arm 1** DEX Ascending dosage schedule beginning with one tablet the first morning to maximum benefit or intolerable side-effects; mean daily dose 21.75 mg (? unclear) (Administered by parent) **Arm 2** Levoamphetamine Ascending dosage schedule beginning with one tablet the first morning to maximum benefit or intolerable side-effects; mean daily dose 24.25 mg (? unclear) (Administered by parent) **Arm 3** Placebo Ascending dosage schedule beginning with one tablet the first morning to maximum benefit or intolerable side-effects; mean daily dose 26.25 mg (? unclear) (Administered by parent)	**Inclusion criteria** 1. Diagnosable minimal brain dysfunction with such signs and symptoms as hyperactivity, distractability, short attention span, incorrigibility, lability, explosiveness, incoordination, perceptual motor dysfunction, and other minor neurological signs 2. A total score = 24 on the first six items of the Davids' Hyperkinetic Ratings Scale 3. Aged ≤ 12 years 4. Enrolment in some sort of school setting (in order to obtain teachers' ratings) 5. No psychoactive medication for the preceding month 6. Parental and child's consent **Diagnostic criteria** See inclusion criteria **Number** Total randomised = 31 (male = 26) Total withdrawals reported **Age** 8 years (mean), $4^{1}/_{2}$–12 years (range) **IQ** Not reported **Co-morbid disorders** Not reported **Diagnostic subtypes** Hyperkinetic n = 13; overanxious n = 8; unsocialised aggressive n = 10 **Additional information** Previous medication: 21/31 had never previously received medication for their behaviour problems. Participants were required to be (psychoactive) medication free for the month preceding the trial	**Core symptoms** Parents' Behaviour Checklist: inattentive unproductiveness, hyperactivity Conners' Teachers' Behaviour Checklist: daydreaming-inattentive, hyperactivity Davids' Hyperkinetic Rating Scale (teachers, parents): hyperactivity, short attention span, impulsiveness Target Symptom Assessment **Co-existent problems** Parents' Behaviour Checklist: unsocialised aggression, sociopathy Conners' Teachers' Behaviour Checklist: defiance and aggressive misconduct Davids' Hyperkinetic Rating Scale (teachers, parents): variability, irritability, explosiveness **Educational performance** Davids' Hyperkinetic Rating Scale (teachers, parents): school work **Psychological function** Not reported **Depression or anxiety** Parents' Behaviour Checklist: withdrawal-depression Conners' Teachers' Behaviour Checklist: anxious-fearful **Quality of life** Global ratings (clinicians) **Adverse events** Parents' Behaviour Checklist: somatic complaints Conners' Teachers' Behaviour Checklist: lack of health **Additional outcomes** Weight Blood pressure

Core symptoms	Educational performance	Quality of life	Adverse events
Parents' Behaviour Checklist: overall (mean raw scores with SD at end of treatment periods) Baseline: 187.13 (36.10); placebo: 166.81 (43.48); DEX: 148.32 (47.30) *p*-Values not reported. Parents' Behaviour Checklist: overall (mean standardised scores at 4 weeks) Baseline: 2.31; placebo: 2.06; DEX: 1.83 DEX > placebo, $p < 0.01$ Parents' Behaviour Checklist: inattentive unproductiveness (mean, SD) Baseline: 17.48 (3.78); placebo: 14.65 (4.79); DEX: 11.90 (5.09) *p*-Values not reported Parents' Behaviour Checklist: hyperactivity (mean, SD) Baseline: 23.74 (5.60); placebo: 20.81 (6.83); DEX: 16.68 (6.59) *p*-Values not reported Conners' Teachers' Behaviour Checklist: overall (mean raw scores with SD at end of treatment periods) Baseline: 92.03, 18.53; placebo: 86.77, 23.07; DEX: 72.27, 20.41 *p*-Values not reported Conners' Teachers' Behaviour Checklist: overall (mean standardised scores at 4 weeks) Baseline: 2.36; placebo: 2.22; DEX 1.85 DEX > placebo, $p < 0.01$ Conners' Teachers' Behaviour Checklist: daydreaming-inattentive (mean, SD) Baseline: 16.57 (4.00); placebo: 15.33 (3.83); DEX: 12.40 (4.26) *p*-Values not reported Conners' Teachers' Behaviour Checklist: hyperactivity (mean, standard deviation) Baseline: 22.43 (5.42); placebo: 21.27 (5.63); DEX: 16.80 (5.54) *p*-Values not reported Davids' Hyperkinetic Rating Scale: overall (parents; mean raw scores at end of treatment periods) Baseline: 34.9 (5.92); placebo: 32.42 (5.58); DEX: 27.52 (8.56) *p*-Values not reported	Davids' Hyperkinetic Rating Scale: school work (mean raw scores with SD at end of treatment periods) Baseline: 5.03 (1.50); placebo: 4.67 (1.60); DEX: 4.20 (1.81) (teacher) Baseline: 5.19 (1.42); placebo: 4.45 (1.61); DEX: 3.90 (1.72) (parent) *p*-Values not reported. Davids' Hyperkinetic Rating Scale: school work (mean standardised scores at 4 weeks) Baseline: 5.03; placebo: 4.67; DEX: 4.20 DEX > placebo, $p < 0.05$	Global ratings: Total no. in whom DEX efficacious: 22/31 ('efficacious' = rating better than placebo and 1, 2, 3 on nine-point scale) Baseline: 5.00; placebo: 4.89; DEX: 3.11 (mean standardised scores at 4 weeks) Placebo vs DEX: $p < 0.01$	Poor appetite: (mean) (1 = not at all, 4 = very much) Baseline: 1.42; placebo: 1.39, DEX: 2.06 DEX vs placebo: $p < 0.01$, DEX vs baseline: $p < 0.01$ Awake at night: (mean) (1 = not at all, 4 = very much) Baseline: 1.68; placebo: 1.68; DEX: 1.65 Headaches: (mean) (1 = not at all, 4 = very much) Baseline: 1.61; placebo: 1.42; DEX: 1.32 Tummy aches: (mean) (1 = not at all, 4 = very much) Baseline: 1.77; placebo: 1.45; DEX: 1.45 Side-effects of medicine: (mean) (1 = not at all, 4 = very much) Baseline: 1.19; placebo: 1.29; DEX: 1.68 DEX vs baseline: $p < 0.05$; DEX vs placebo: $p < 0.05$ Conners' Teachers' Behaviour Checklist: lack of health (mean, SD) Baseline: 8.67, 3.27; placebo: 8.57, 3.32; DEX: 7.40, 2.75 Parent's Behaviour Checklist: somatic complaints (mean, SD) Baseline: 7.13, 2.77; placebo: 6.35, 2.44; DEX: 6.06, 2.42

continued

Core symptoms	Educational performance	Quality of life	Adverse events
Davids' Hyperkinetic Rating Scale: overall (teachers; mean raw scores at end of treatment periods) Baseline: 32.60 (6.23); placebo: 31.30 (6.31); DEX: 25.37 (8.25) *p*-Values not reported Davids' Hyperkinetic Rating Scale: overall (parents; mean standardised scores at 4 weeks) (Baseline: 4.99); placebo: 4.63; DEX: 3.93 DEX > placebo, $p > 0.001$ Davids' Hyperkinetic Rating Scale: overall (teachers; mean standardised scores at 4 weeks) Baseline: 4.66; placebo: 4.47; DEX: 3.62 DEX > placebo, $p > 0.001$ Davids' Hyperkinetic Rating Scale: hyperactivity (mean, SD) Baseline: 5.10 (1.14); placebo: 4.58 (1.26); DEX: 3.97 (1.40) (parents) Baseline: 4.57 (1.76); placebo: 4.90 (1.30); DEX: 3.70, (1.49) (teachers) *p*-Values not reported Davids' Hyperkinetic Rating Scale: short attention span (mean, SD) Baseline: 5.13 (1.28); placebo: 4.52 (1.29); DEX: 3.84 (1.53) (parents) Baseline: 5.10 (1.49); placebo: 4.73 (1.55); DEX: 3.83 (1.62) (teachers) *p*-Values not reported. Davids' Hyperkinetic Rating Scale: impulsiveness (mean, SD) Baseline: 4.90 (1.42); placebo: 4.87 (1.02); DEX: 4.06 (1.46) (parents) Baseline: 4.87 (1.14); placebo: 4.60 (1.30); DEX: 3.77 (1.41) (teachers) Target Symptom Assessment Baseline: 5.00; Placebo: 4.89 (1.22); DEX: 3.11 (1.52)			
Conclusions	**Authors' conclusions:** Both isomers showed significantly more benefit than placebo but were not significantly different from each other **Reviewer's comments:** No comments noted		

Study	Intervention	Participants	Outcomes
Reference Arnold *et al.*, 1978[37] **Source** AHRQ Report **Setting** USA **Design** Crossover trial **Duration** Placebo washout period 2 weeks; treatment period 3 weeks **Purpose** The authors do not explicitly state the purpose of their study but appear to include the caffeine treatment arm owing to 'the potential value of a non-prescription remedy considered by some "safer" than the prescription stimulants'	**Arm 1** MPH 10-mg capsules administered once or twice daily (a.m., noon); ascending dosage schedule, with individualised adjustments made by telephone consultation; mean optimum daily dose 1.25 ± 0.51 mg/kg (Individual administering medication not reported) **Arm 2** DEX 5-mg capsules administered once or twice daily (a.m., noon); ascending dosage schedule, with individualised adjustments made by telephone consultation; mean optimum daily dose 0.63 ± 0.24 mg/kg (Individual administering medication not reported) **Arm 3** Caffeine 80-mg capsules administered once or twice daily (a.m., noon); ascending dosage schedule, with individualised adjustments made by telephone consultation; mean optimum daily dose 12.1 ± 4.2 mg/kg (Individual administering medication not reported)	**Inclusion criteria** 1. Diagnosed with minimal brain dysfunction, with such signs and symptoms as hyperactivity, short attention span, distractibility, irritability, variability, explosiveness, aggression, inability to keep friends or function in a group, underachievement, visual-motor dysfunction and poor coordination or other minor neurological signs 2. Total score = 24 on first six items of Davids' Hyperkinetic Rating Scale by parents and teacher 3. Indication for stimulant treatment as determined by psychiatrist 4. 5–12 years old 5. Attending school 6. No psychoactive treatment in preceding month 7. Parents' and child's consent 8. Insufficient benefit from an initial 2-week 'placebo washout' to be maintained without active drug **Diagnostic criteria** See inclusion criteria **Number** Total randomised = 29 (male = 22) No withdrawals reported **Age** 8 years (mean) **IQ** Not reported **Co-morbid disorders** Not reported **Diagnostic subtypes** Fish categories: 308.0 hyperkinetic: $n = 18$; 308.2 overanxious: $n = 5$; 308.4 unsocialised aggressive: $n = 6$ **Additional information** Previous medication: 19/29 children had never received psychoactive treatment. 10/29 had tried MPH, amphetamine, anticonvulsants or some combination previously. Participants were required not to have been receiving psychoactive treatment in the month preceding the trial	**Core symptoms** Problem Behaviour Checklist (parents): total, inattentive unproductiveness; hyperactivity Conners' Teachers' Behaviour Problem Checklist: total, day-dreaming and inattention, hyperactivity Davids' Hyperkinetic Rating Scale (parents, teachers): total, hyperactivity; short attention span, impulsiveness Arnold target symptom assessment (parents, psychiatrists) **Co-existent problems** Problem Behaviour Checklist (parents): unsocialised aggression; sociopathy Conners' Teachers' Behaviour Problem Checklist: aggressive misconduct Davids' Hyperkinetic Rating Scale (parents, teachers): variability, irritability, explosiveness **Educational performance** Davids' Hyperkinetic Rating Scale (parents, teachers): poor schoolwork **Psychological function** Not reported **Depression or anxiety** Problem Behaviour Checklist (parents): withdrawal-depression Conners' Teachers' Behaviour Problem Checklist: anxious and fearful **Quality of life** Not reported **Adverse events** Problem Behaviour Checklist (parents): side-effects, somatic complaints Conners' Teachers' Behaviour Problem Checklist: lack of health Weight loss **Additional outcomes** Physiological outcomes: blood pressure, pulse Global rating of the value of the 3 drugs on a 9-point scale (benefits and side effects) (psychiatrists)

Core symptoms	Educational performance	Quality of life	Adverse events
Problem Behaviour Checklist (parents): total score (mean, SD) Before drug: 190.07 (37.91) MPH: 152.28 (34.79) DEX: 146.97 (36.63) MPH = DEX, not significant Problem Behaviour Checklist (parents): hyperactivity Before drug: 24.31 (4.66) MPH: 18.21 (5.61) DEX: 17.21 (5.45) Significance of difference not reported Problem Behaviour Checklist (parents): inattentive unproductiveness Before drug: 15.83 (4.32) MPH: 11.83 (3.79) DEX: 11.38 (3.39) Significance of difference not reported Conners' Teachers' Behaviour Problem Checklist: total score Before drug: 91.52 (16.70) MPH: 73.55 (22.35) DEX: 70.26 (18.33) MPH = DEX, not significant Conners' Teachers' Behaviour Problem Checklist: hyperactivity Before drug: 23.10 (4.50) MPH: 16.83 (5.50) DEX: 16.17 (4.64) Significance of difference not reported Conners' Teachers' Behaviour Problem Checklist: day-dreaming and inattention Before drug: 14.97 (3.27) MPH: 12.10 (3.53) DEX: 12.03 (3.94) Significance of difference not reported Davids' Hyperkinetic Rating Scale (parents): total score Before drug: 30.76 (3.40) MPH: 25.41 (5.19) DEX: 25.31 (5.57) MPH = DEX, not significant	Davids' Hyperkinetic Rating Scale (parents): poor schoolwork Before drug: 4.62 (1.29) MPH: 3.69 (1.28) DEX: 3.79 (1.18) Significance of difference not reported Davids' Hyperkinetic Rating Scale (teachers): poor schoolwork Before drug: 4.62 (1.29) MPH: 3.83 (1.28) DEX: 3.93 (1.33) MPH = DEX, not significant	Not reported	Problem Behaviour Checklist (parents): side-effects (Mean, SD) (1 = not at all; 4 = very much) Scores for: poor appetite/awake at night/headaches/ 'tummyaches'/'side-effects of drugs' Before drug: 1.48 (0.87)/1.79 (1.01) /1.79 (0.73) /1.93 (1.80)/1.34 (0.81) MPH: 1.83 (0.97)/1.76 (0.91) /1.52 (0.51) /1.62 (0.62)/1.59 (0.78) DEX: 1.93 (1.03)/1.86 (0.92) /1.52 (0.78) /1.52 (0.57)/1.59 (0.87) Poor appetite: placebo > MPH, $p < 0.05$; placebo > DEX, $p < 0.01$ 'Tummyaches': DEX > placebo, $p < 0.05$

continued

Core symptoms	Educational performance	Quality of life	Adverse events
Davids' Hyperkinetic Rating Scale (parents): hyperactivity Before drug: 5.24 (0.91) MPH: 4.31 (1.23) DEX: 4.28 (1.07) Significance of difference not reported Davids' Hyperkinetic Rating Scale (parents): short attention span Before drug: 5.14 (0.99) MPH: 3.90 (1.01) DEX: 4.21 (0.94) Significance of difference not reported. Davids' Hyperkinetic Rating Scale (parents): impulsiveness Before drug: 5.38 (0.78) MPH: 4.10 (1.21) DEX: 4.17 (1.04) Significance of difference not reported Davids' Hyperkinetic Rating Scale (teachers): total score Before drug: 29.03 (5.14) MPH: 23.14 (7.08) DEX: 22.38 (7.20) MPPH = DEX, not significant Davids' Hyperkinetic Rating Scale (teachers): hyperactivity Before drug: 5.28 (1.03) MPH: 3.83 (1.49) DEX: 3.90 (1.54) Significance of difference not reported Davids' Hyperkinetic Rating Scale (teachers): short attention span Before drug: 4.86 (1.41) MPH: 3.97 (1.18) DEX: 3.79 (1.35) Significance of difference not reported Davids' Hyperkinetic Rating Scale (teachers): impulsiveness Before drug: 5.03 (1.12) MPH: 3.93 (1.28) DEX: 3.90 (1.42) Significance of difference not reported			

continued

Core symptoms	Educational performance	Quality of life	Adverse events
Arnold target symptom assessment (psychiatrists) Before drug: 5.00 (0.00) – by definition MPH: 3.38 (1.36) DEX: 3.13 (1.47) MPH = DEX, not significant			
Conclusions	**Authors' conclusions:** MPH and DEX were significantly better than placebo and caffeine, but not significantly different from each other in the treatment of minimal brain dysfunction **Reviewer's comments:** Placebo treatment was administered prior to randomisation and therefore is not a relevant comparator – results for placebo have not been extracted		

Study	Intervention	Participants	Outcomes
Reference Arnold *et al.*, 1989[38] and Arnold *et al.*, 2000[299] **Source** CCOHTA Report **Setting** USA **Design** Crossover trial **Duration** Treatment period: 3 months (1 month per treatment). **Purpose** To test γ-linolenic Acid with placebo control in comparison with a standard stimulant treatment	**Arm 1** D-Amphetamine 10–15 mg/day time-release capsules administered once daily (morning); placebo administered once daily (afternoon) (Individual administering medication not reported) **Arm 2** γ-Linolenic Acid 500 mg evening primrose oil capsules including 13 IU of vitamin E; administered twice daily (morning, afternoon) (Individual administering medication not reported) **Arm 3** Placebo administered twice daily (morning, afternoon) (Individual administering medication not reported)	**Inclusion criteria** 1. 6–12 years old 2. Normal intelligence 3. Diagnosis of attention deficit disorder with hyperactivity by DSM-II criteria 4. Score = 18 on Conners' Hyperactivity Index 5. Sum = 24 on first six items of Davids' Hyperkinetic Rating Scale 6. No psychoactive treatment in preceding week 7. No history of seizures **Diagnostic criteria** DSM-III **Number** Total randomised = 18 (male = 18) No withdrawals reported **Age** 9 years (mean) 6–12 years **IQ** Not reported **Co-morbid disorders** Not reported **Diagnostic subtypes** Not reported **Additional information** Previous medication: no subjects were given psychoactive treatment in the week preceding the trial	**Core symptoms** Conners' Teacher Rating Scale: total score Conners' Teacher Rating Scale: hyperactivity index **Co-existent problems** Not reported **Educational performance** Not reported **Psychological function** Not reported **Depression or anxiety** Not reported **Quality of life** Global ratings (psychiatrist) **Adverse events** Weight **Additional outcomes** Haemodynamics

Core symptoms	Educational performance	Quality of life	Adverse events
Conners' Teacher Rating Scale: total score (mean, SD) Placebo: 1.59 (0.39) DEX: 1.11 (0.57) Efamol: .39 (0.58) At 4 weeks: DEX > placebo, $p < 0.05$ Conners' Teacher Rating Scale: Hyperactivity Index Placebo: 2.10 (0.47) DEX: 1.39 (0.76) Efamol: 1.81 (0.67) At 4 weeks: DEX > Efamol > placebo, $p < 0.05$	Not reported	Global ratings (psychiatrist) (SD not reported) Placebo: 3.78 DEX: 2.67 Efamol: 3.17 DEX > placebo, $p < 0.05$	Weight: mean (SD) Placebo: 70.6 lb (18) DEX: 68.1 lb (18) Efamol: 69.5 lb (19) DEX < placebo, $p < 0.05$
Conclusions	**Authors' conclusions:** γ-Linolenic acid supplementation should be considered to be an experimental treatment for ADHD **Reviewer's comments:** No comments noted		

Study	Intervention	Participants	Outcomes
Reference Barkley *et al.*, 1990[39] **Source** AHRQ Report **Setting** USA **Design** Crossover trial **Duration** Treatment periods: 7–10 days **Purpose** To assess the frequency and severity of side-effects associated with two therapeutic doses of MPH in children with ADHD	**Arm 1** MPH 0.3 mg/kg/dose; administered twice daily (a.m. and noon) (Individual administering medication not reported) **Arm 2** MPH 0.5 mg/kg/dose; administered twice daily (a.m. and noon) (Individual administering medication not reported) **Arm 3** Placebo (Individual administering medication not reported)	**Inclusion criteria** 1. IQ > 80 (Peabody Picture Vocabulary) 2. Parental and/or teacher complaints of significant problems with inattention, overactivity and impulsivity 3. Placement at the 93rd percentile on the hyperactivity scales using the Child Behaviour Checklist 4. Appearance of symptoms before age 7 years 5. Symptoms persisting for at least 12 months 6. No gross sensory or motor disabilities, epilepsy, autism, psychosis, tic disorders or Tourette syndrome, or significant cardiac problems **Diagnostic criteria** See inclusion criteria **Number** Total randomised = 83 (male = 71) Total withdrawals = 3 Reasons for withdrawals: 3 children were unable to complete the drug protocol owing to serious adverse reactions. **Age** 8.2 years (mean), 5–13 years (range), 2.2 years (SD) **IQ** 105.1 (mean) **Co-morbid disorders** Not reported **Diagnostic subtypes** Not reported **Additional information** No relevant information reported	**Core symptoms** Not reported **Co-existent problems** Not reported **Educational performance** Not reported **Psychological function** Not reported **Depression or anxiety** Not reported **Quality of life** Not reported **Adverse events** Stimulant Drug Side Effects Questionnaire: 17-item list **Additional outcomes** Not reported

Core symptoms	Educational performance	Quality of life	Adverse events
Not reported	Not reported	Not reported	Withdrawals: Nervous facial tic, dizziness and headache: $n = 1$ Dizziness, headache and increased hyperactivity: $n = 1$ Excessive speech and disjointed thinking: $n = 1$ Parent reports: % severe side-effects ($n = 82$): Low dose, high dose, placebo Decreased appetite: 7, 13, 1 (significant difference between high dose and placebo) Insomnia: 18, 18, 7 (significant difference between high dose and placebo) Stomach aches: 1, 6, 0 Headaches: 1, 4, 0 Prone to crying: 16, 10, 10 Tics/nervous movements: 4, 7, 5 Dizziness: 0, 1, 0 Drowsiness: 2, 1, 1 Nail biting: 4, 9, 7 Talks less: 1, 2, 1 Anxiousness: 9, 7, 12 Disinterested in others: 1, 2, 0 Euphoria: 4, 7, 9 Irritable: 15, 13, 18 Nightmares: 0, 3, 0 Sadness: 6, 8, 5 Staring: 4, 1, 2 Parent reports: % side-effects ($n = 82$): Low dose, high dose, placebo: Decreased appetite: 52, 56, 15 (no significant differences between treatment arms) Insomnia: 62, 68, 40 (no significant differences between treatment arms) Stomach aches: 39. 35, 18 (no significant differences between treatment arms) Headaches: 26, 21, 11 (no significant differences between treatment arms) Prone to crying: 59, 54, 49 (significant difference between low dose and placebo) ($p < 0.05$) Tics/nervous movements: 18, 28, 18 (significant difference between high dose and placebo) ($p < 0.05$) Dizziness: 10, 7, 4 (no significant differences between treatment arms) Drowsiness: 23, 20, 18 (no significant differences between treatment arms) Nail biting: 26, 29, 22 (no significant differences between treatment arms) Talks less: 20, 22, 16 (no significant differences between treatment arms) Anxiousness: 58, 52, 58 (no significant differences between treatment arms) Disinterested in others: 18, 15, 18 (no significant differences between treatment arms)

continued

Core symptoms	Educational performance	Quality of life	Adverse events
			Euphoria: 34, 43, 41 (no significant differences between treatment arms) Irritable: 65, 66, 72 (no significant differences between treatment arms) Nightmares: 20, 21, 20 (no significant differences between treatment arms) Sadness: 48, 41, 43 (no significant differences between treatment arms) Staring: 38, 38, 40 (no significant differences between treatment arms) The authors also presented incidence data of side-effects reported by teachers and mean severity ratings reported by both parents and teachers
Conclusions	**Authors' conclusions:** Parent ratings indicated that decreased appetite, insomnia, stomach aches and headaches increased significantly in frequency and severity during the two active medication doses compared with placebo. Stimulant medications, when given in therapeutic doses, are generally safe and produce only minor degrees of side effects in most children with ADHD **Reviewer's comments:** No comments noted		

Study	Intervention	Participants	Outcomes
Reference Barkley *et al.*, 2000[40] **Source** Updated search **Setting** USA **Design** Crossover trial **Duration** Treatment: 5 weeks (1 week per treatment arm) **Purpose** To compare the treatment effectiveness of MPH and Adderall using systematic assessments of stimulant medication response in teenagers with ADHD as it may occur in routine outpatient clinical practice	**Arm 1** MPH 5-mg MPH capsule twice daily, morning and noon, for 1 week (Administered by parent and teacher) **Arm 2** MPH 10-mg MPH capsule twice daily, morning and noon, for 1 week (Administered by parent and teacher) **Arm 3** Adderall 5-mg capsule twice daily, morning and noon, for 1 week (Administered by parent and teacher) **Arm 4** Adderall 10-mg capsule twice daily, morning and noon, for 1 week (Administered by parent and teacher)	**Inclusion criteria** 1. Diagnosis of ADHD 2. No history of motor or vocal tics or Tourette's Syndrome 3. No history of cardiac surgery, high blood-pressure or cerebral vascular accident 4. No history of adverse reactions to stimulant medications 5. No history of hyperthyroidism 6. No pregnancy or lactation **Diagnostic criteria** DSM-IV **Number** Total randomised = 38 (male = 30/35) Total withdrawals = 3 Reasons for withdrawals: Family problems: $n = 2$ Low IQ: $n = 1$ (57) Randomisation procedure: Lower dose of each active medication always preceded the higher dose **Age** 14 years (mean), 12–17 years (range) **IQ** 103.9 (mean) **Co-morbid disorders** Not reported **Diagnostic subtypes** Not reported **Additional information** No relevant information reported	**Core symptoms** Teacher (English and maths) rating of ADHD Parent rating of ADHD Co-existent problems Teacher rating of ODD Parent rating of ODD Self-rating of ODD **Educational performance** Not reported **Psychological function** Conners' Continuous Performance Test (CPT) Stroop Word–Colour Association Test **Depression or anxiety** Not reported **Quality of life** Not reported **Adverse events** Side effects: number and severity (teacher, parent, self) **Additional outcomes** Not reported

Core symptoms	Educational performance	Quality of life	Adverse events
ADHD total parent rating: [complete data for $n = 31/35$ (89%)] Placebo 21.9 (12.5) MPH 5 mg 21.01 (11.4) MPH 10 mg 16.8 (9.7) Adderall 5 mg 21.3 (8.7) Adderall 10 mg 19.0 (9.2) $F = 2.05$, p = NS	Not reported	Not reported	Number of side-effects: parent rating [complete data for $n = 31/35$ (89%)] Placebo 5.1 (3.7) MPH 5 mg 5.4 (4.8) MPH 10 mg 5.5 (3.6) Adderall 5 mg 4.8 (3.4) Adderall 10 mg 5.1 (3.8) $F = 0.23$, p = NS
ADHD total English teacher rating: [complete data for $n = 13/35$ (37%)] Placebo 22.5 (14.0) MPH 5 mg 17.9 (14.8) MPH 10 mg 21.5 (14.1) Adderall 5 mg 21.9 (13.1) Adderall 10 mg 18.1 (11.6) $F = 1.02$, p = NS			Number of side-effects: English teacher rating [complete data for $n = 13/35$ (37%)] Placebo 3.8 (4.4) MPH 5 mg 3.2 (3.2) MPH 10 mg 3.6 (4.2) Adderall 5 mg 2.9 (2.6) Adderall 10 mg 3.1 (3.9) $F = 0.59$, p = NS
ADHD total Maths teacher rating [complete data $n = 15/35$ (43%)] Placebo 17.7 (13.8) MPH 5 mg 12.2 (13.7) MPH 10 mg 14.0 (12.3) Adderall 5 mg 17.5 (14.2) Adderall 10 mg 16.4 (15.2) $F = 1.78$, p = NS			Number of side-effects: maths teacher rating [complete data $n = 15/35$ (43%)] Placebo 3.2 (2.4) MPH 5 mg 1.9 (2.6) MPH 10 mg 3.1 (2.5) Adderall 5 mg 3.1 (2.4) Adderall 10 mg 3.9 (3.0) $F = 1.73$, p = NS
			Number of side-effects: self-rating Placebo 4.6 (3.6) MPH 5 mg 4.3 (4.1) MPH 10 mg 4.8 (4.1) Adderall 5 mg 4.7 (3.8) Adderall 10 mg 4.7 (3.3) $F = 0.17$, p = NS

continued

Core symptoms	Educational performance	Quality of life	Adverse events
			Severity of side-effects: parent rating [complete data for $n = 31/35$ (89%)] Placebo 2.9 (2.1) MPH 5 mg 3.0 (1.9) MPH 10 mg 2.9 (1.9) Adderall 5 mg 3.1 (1.6) Adderall 10 mg 2.8 (1.6) $F = 0.18$, p = NS Severity of side-effects: English teacher rating [complete data for $n = 13/35$ (37%)] Placebo 1.9 (1.7) MPH 5 mg 3.4 (2.1) MPH 10 mg 2.7 (2.1) Adderall 5 mg 3.3 (2.4) Adderall 10 mg 1.9 (1.7) $F = 3.25$, $p = 0.01$ Severity of side effects: maths teacher rating [complete data for $n = 15/35$ (43%)] Placebo 2.2 (1.8) MPH 5 mg 1.5 (2.0) MPH 10 mg 2.4 (2.0) Adderall 5 mg 2.6 (2.6) Adderall 10 mg 2.3 (2.0) $F = 0.98$, p = NS Severity of side-effects: self-rating Placebo 2.7 (1.6) MPH 5 mg 3.3 (2.3) MPH 10 mg 2.9 (2.2) Adderall 5 mg 2.5 (1.9) Adderall 10 mg 2.4 (1.4) $F = 2.42$, $p = 0.05$
Conclusions	**Authors' conclusions:** Both Adderall and MPH appear to be clinically effective in the treatment of ADHD in teenagers, based on clinician's global impressions (data not presented). No significant medication effects could be detected on parent or teacher ratings. Only teen self-reported ratings of side-effects revealed a significant drug effect, suggesting less severe side-effects on the 10-mg Adderall dose than the 5-mg MPH dose **Reviewer's comments:** Authors' conclusions on relative clinical effectiveness of MPH and Adderall are based on unblinded investigator judgement (data not presented). Incomplete data limited the power to detect significance		

Study	Intervention	Participants	Outcomes
Reference Brown *et al.*, 1985[41] **Source** AHRQ Report **Setting** USA **Design** Parallel trial **Duration** Cognitive training programme: 12 weeks; MPH treatment: 6 months; follow-up assessment: 3 months after end of study **Purpose** To compare systematically the effects of a programme of cognitive behaviour training, MPH and the combined effects of both therapies on school-aged hyperactive boys with academic difficulties	**Arm 1** MPH 0.3 mg/kg/day administered in two doses (morning, lunch); dosage range 5–15 mg/day (Individual administering medication not reported) **Arm 2** Cognitive training 24 individual cognitive training sessions; 1 hour; twice weekly (Administered by trainer) **Arm 3** MPH plus cognitive training 0.3 mg/kg/day administered in two doses (morning, lunch); dosage range 5–15 mg/day 24 individual cognitive training sessions; 1 hour; twice weekly (Administered by trainer)	**Inclusion criteria** 1. Demonstration of serious and persistent symptoms associated with ADD-H identified by both parents and teachers 2. Symptoms not appearing to stem from stress at home or inconsistent child management practices 3. No major diseases or obvious physical defects 4. No gross neurological, sensory, or motor impairment or psychosis 5. Symptoms demonstrated from infancy or early childhood for a duration of at least 12 months prior to referral 6. Reading deficit of at least two grade levels **Diagnostic criteria** Not reported **Number** Total = 30 (male = 30) Arm 1 = 10 Arm 2 = 10 Arm 3 = 10 No withdrawals reported Randomisation procedure: comparisons were also made with a non-randomised control group of 10 children **Age** 11.36 years (mean): 6 years 4 months–11 years 9 months (range); 1.44 (SD) **IQ** 101.92 (mean) **Co-morbid disorders** Not reported **Diagnostic subtypes** Not reported **Additional information** Previous medication: no child was receiving treatment at time of selection	**Core symptoms** CPRS Abbreviated CTRS Teacher ratings of attention Teacher ratings of impulsivity Self-ratings of impulsivity **Co-existent problems** Not reported. **Educational performance** Wide Range Achievement Test (WRAT): Arithmetic and Reading Subtests Durrell Analysis of Reading Difficulty: Listening Comprehension Subtest Detroit Tests of Learning Aptitude: Attention Subtests[71,287,296] Children's Checking Task (CCT) Matching Familiar Figures Test (MFFT) Children's Embedded Figures Test (CEFT) Attention–Concentration Factor of WISC-R: Arithmetic, Digit Span and Coding Subtests **Psychological function** Not reported **Depression or anxiety** Not reported **Quality of life** Not reported **Adverse events** Not reported **Additional outcomes** Not reported

Core symptoms	Educational performance	Quality of life	Adverse events
CPRS: pre-, post- and delayed post-test means (SDs) MPH: 17.40 (4.4), 7.40 (5.8), 9.10 (5.9) Cognitive: 16.50 (5.1), 13.10 (4.1), 13.20 (3.4) Combined: 16.60 (2.3), 7.50 (2.6), 10.50 (4.9) Abbreviated CTRS: pre-, post- and delayed post-test means (SDs) MPH: 20.70 (5.1), 15.00 (3.1), 15.90 (5.1) Cognitive: 18.90 (5.9), 15.70 (2.9), 16.90 (4.5) Combined: 20.60 (6.1), 15.10 (4.6), 15.60 (5.7) Teacher ratings of attention MPH: 56.90 (6.4), 48.20 (10.4), 43.60 (7.5) Cognitive: 55.90 (6.5), 51.40 (9.1), 49.80 (7.1) Combined: 56.30 (15.0), 46.60 (7.5), 44.50 (9.2) Teacher ratings of impulsivity MPH: 68.90 (7.4), 61.60 (7.3), 68.00 (5.3) Cognitive: 68.50 (7.2), 61.20 (9.0), 62.40 (4.5) Combined: 68.00 (5.3), 61.60 (8.1), 57.50 (9.1) Self-ratings of impulsivity MPH: 74.60 (4.5), 67.90 (4.2), 63.80 (3.7) Cognitive: 74.40 (3.0), 67.40 (5.8), 65.00 (2.8) Combined: 74.80 (4.5), 71.80 (12.5), 72.00 (2.9)	WISC-R: pre-, post- and delayed post-test means (SDs) Arm 1: 55.00 (11.5), 69.50 (11.5), 70.80 (8.2) Arm 2: 57.20 (9.7), 70.60 (11.9), 67.40 (11.3) Arm 3: 54.50 (3.9), 72.80 (21.5), 65.80 (13.0)	Not reported	Not reported

Conclusions	
	Authors' conclusions: Only those children in the two medication treatment conditions demonstrated improvement in attentional deployment and behavioural ratings. In the cognitive therapy condition, there were changes only on measures of attentional deployment. The data did not provide evidence indicating that the combined medication and cognitive therapy condition was any more effective than that condition involving medication alone
	Reviewer's comments: No analyses were performed to compare effects across treatment arms

Study	Intervention	Participants	Outcomes
Reference Brown *et al.*, 1986[42] **Source** AHRQ Report **Setting** USA **Design** Parallel trial **Duration** Treatment programme: 3 months; follow-up: 3 months after termination of treatment programme **Purpose** To investigate the efficacy of methylphenidate and an adjunctive cognitive behavioural management programme	**Arm 1** MPH plus attention control 0.3 mg/kg/dose administered twice daily; mean dosage 20.08 mg/day (10–40 mg/day); 22 1-hour sessions [Administered by trainer (attention control)] **Arm 2** Placebo plus cognitive therapy 22 1-hour sessions twice weekly on an individual basis [Administered by trainer (cognitive therapy)] **Arm 3** MPH plus cognitive therapy 0.3 mg/kg/dose administered twice daily; mean dosage 20.08 mg/day (10–40 mg/day); 22 1-hour sessions twice weekly on an individual basis [Administered by trainer (cognitive therapy)] **Arm 4** Placebo plus attention control 22 1-hour sessions [Administered by trainer (attention control)]	**Inclusion criteria** 1. CTRS or CPRS score of at least 15 **Diagnostic criteria** DSM-III **Number** Total randomised = 40 (male = 28/33) Arm 1 = 7 Arm 2 = 10 Arm 3 = 9 Arm 4 = 7 Total withdrawals = 7 40 children began the study. Baseline characteristics and results are given only for the 33 who completed the study and for whom follow-up indicators are available **Age** 9 years 1 month (mean); 5 years 8 months–13 years 1 month (range); 1 year 10 months (SD) **IQ** 96.73 (mean) **Co-morbid disorders** Conduct disorder: 16% **Diagnostic subtypes** ADD: 8 children; ADD-H: 25 children **Additional information** No relevant information reported	**Core symptoms** CPRS: hyperactivity index ACTeRs: attention and hyperactivity Abbreviated Conners' Rating Scale (ACRS) (teachers) Teacher ratings: attention and impulsivity **Co-existent problems** ACTeRS: oppositional and social skills Humphrey scale: self-control **Educational performance** WRAT: Reading, Arithmetic and Spelling Durell Analysis of Reading Difficulty: listening comprehension **Psychological function** Weschler Intelligence Scale for Children – Revised: Freedom from Distractibility Factor (WISC-R, FFD) Matching Familiar Figures Test (MFFT) Children's Checking Test (CCT) Detroit Tests of Learning Ability: three attention subtests[49,71,296] **Depression or anxiety** Not reported **Quality of life** Not reported **Adverse events** Not reported **Additional outcomes** Not reported

Core symptoms	Educational performance	Quality of life	Adverse events
CPRS: Hyperactivity Index. Unadjusted means (SD) at baseline/post-treatment (3m)/3m follow-up Arm 1: 20.25 (6.20)/15.88 (6.36)/14.71 (4.47); *n* = 7 Arm 2: 20.20 (6.83)/21.10 (5.65)/14.50 (5.31); *n* = 10 Arm 3: 18.22 (6.04)/13.78 (8.14)/15.33 (5.79); *n* = 9 Arm 4: 21.38 (5.00)/17.25 (7.50)/17.71 (4.15); *n* = 7 ACTeR: attention. Unadjusted means (SD) at baseline/post-treatment (3m)/3m follow-up Arm 1: 20.63 (4.17)/22.00 (2.45)/22.20 (1.48); *n* = 7 Arm 2: 15.30 (5.01)/15.90 (6.01)/17.00 (7.24); *n* = 10 Arm 3: 17.55 (6.00)/16.33 (5.57)/17.29 (7.23); *n* = 9 Arm 4: 18.75 (4.30)/19.50 (5.47)/19.43 (5.71); *n* = 7 ACTeR: hyperactivity. Unadjusted means (SD) at baseline/post-treatment (3m)/3m follow-up Arm 1: 18.25 (5.50)/14.25 (5.60)/17.00 (5.79); *n* = 7 Arm 2: 18.80 (2.35)/19.60 (2.63)/16.83 (2.23); *n* = 10 Arm 3: 16.11 (4.88)/14.33 (4.66)/16.43 (5.88); *n* = 9 Arm 4: 17.38 (4.50)/17.50 (4.41)/19.71 (3.15); *n* = 7 Abbreviated CTRS. Unadjusted means (SD) at baseline/post-treatment (3m)/3m follow-up Arm 1: 13.50 (6.16)/9.88 (3.18)/10.80 (7.09); *n* = 7 Arm 2: 16.90 (3.31)/16.50 (5.38)/15.50 (5.54); *n* = 10 Arm 3: 14.00 (7.50)/12.56 (4.07)/12.00 (7.23); *n* = 9 Arm 4: 14.38 (6.26)/13.63 (6.26)/14.57 (4.54); *n* = 7 Teacher ratings: impulsivity. Unadjusted means (SD) at baseline/post-treatment (3m)/3m follow-up Arm 1: 3.46 (0.29)/3.28 (0.49)/3.09 (1.43); *n* = 7 Arm 2: 3.53 (0.25)/3.47 (0.18)/3.05 (1.19); *n* = 10 Arm 3: 3.21 (0.82)/3.30 (0.70)/3.19 (0.64); *n* = 9 Arm 4: 3.34 (0.37)/3.21 (0.52)/3.16 (0.49); *n* = 7 Teacher ratings: attention. Unadjusted means (SD) at baseline/post-treatment (3m)/3m follow-up Arm 1: 50.25 (8.73)/45.38 (3.20)/44.40 (12.78); *n* = 7 Arm 2: 51.70 (4.11)/51.60 (7.93)/49.00 (9.25); *n* = 10 Arm 3: 51.56 (9.77)/47.00 (6.08)/47.14 (8.63); *n* = 9 Arm 4: 51.88 (6.92)/48.00 (8.23)/52.29 (8.14); *n* = 7	WRAT: Reading. Mean (SD) at baseline/post-treatment (3 months)/3-month follow-up Arm 1: 60.00 (10.68)/61.88 (13.25)/65.57 (11.05) Arm 2: 57.70 (17.58)/59.20 (16.54)/59.60 (16.46) Arm 3: 53.78 (19.92)/56.56 (20.02)/54.33 (23.60) Arm 4: 45.88 (15.56)/47.75 (10.19)/51.86 (11.70) WRAT: Arithmetic. Mean (SD) at baseline/post-treatment (3 months)/3-month follow-up Arm 1: 30.13 (5.06)/35.00 (9.47)/30.43 (5.53) Arm 2: 26.40 (4.50)/29.40 (5.80)/29.10 (5.07) Arm 3: 25.00 (5.39)/28.33 (5.63)/27.67 (8.51) Arm 4: 20.50 (5.63)/24.75 (5.60)/25.14 (5.67) WRAT: Spelling. Mean (SD) at baseline/post-treatment (3 months)/3-month follow-up Arm 1: 38.88 (7.16)/40.13 (7.28)/41.29 (6.47) Arm 2: 34.90 (8.24)/36.10 (8.60)/38.60 (8.37) Arm 3: 35.11 (11.90)/37.89 (12.29)/35.78 (14.18) Arm 4: 27.13 (6.42)/30.00 (8.28)/30.14 (7.31) Durell Listening Comprehension. Mean (SD) at baseline/post-treatment (3 months)/3-month follow-up Arm 1: 27.25 (10.87)/33.00 (9.29)/30.14 (10.81) Arm 2: 25.10 (9.79)/ 25.50 (11.65)/28.50 (7.49) Arm 3: 18.00 (14.33)/24.44 (15.56)/20.89 (14.70) Arm 4: 20.00 (13.35)/19.00 (6.50)/26.57 (12.96)	Not reported	Not reported
Conclusions	**Authors' conclusions:** The results of this study, except for the marginal trend on a single laboratory measure, failed to support the efficacy of such treatment combinations **Reviewer's comments:** No comments noted		

Study	Intervention	Participants	Outcomes
Reference Brown and Sexton, 1988[43] **Source** CCOHTA Report **Setting** USA **Design** Crossover trial **Duration** Total treatment period: 8 weeks (2 weeks per treatment arm) **Purpose** 1. To examine the efficacy of MPH, with ADD-H black adolescents 2. To examine differential responses on laboratory and behavioural measures according to varying dosages 3. To examine side-effects according to varying dosages 4. To examine the effect of MPH on academic performance	**Arm 1** MPH 0.15 mg/kg/dose administered twice daily (8 a.m., 12 p.m.); mean dose 4.38 mg/dose (Administered by parent/teacher/clinic staff) **Arm 2** MPH 0.30 mg/kg/dose administered twice daily (8 a.m., 12 p.m.); mean dose 12.55 mg/dose (Administered by parent/teacher/clinic staff) **Arm 3** MPH 0.50 mg/kg/dose administered twice daily (8 a.m., 12 p.m.); mean dose 21.28 mg/dose (Administered by parent/teacher/clinic staff) **Arm 4** Placebo Administered twice daily (8 a.m., 12 p.m.) (Administered by parent/teacher/clinic staff)	**Inclusion criteria** 1. Sexual maturity rating = 3 on Tanner's scale. 2. Long history of symptoms associated with attention deficit disorder 3. Score = 15 on Abbreviated CTRS 4. No mental retardation or gross neurological disorders **Diagnostic criteria** DSM-III **Number** Total randomised = 11 (male = 11) No withdrawals reported **Age** 13 years 7 months (mean); 12 years 10 months – 14 years 10 months (range) **IQ** 92.91 (mean) **Co-morbid disorders** Conduct disorder, socialised aggressive: 5/11 (DSM-III) **Diagnostic subtypes** Not reported **Additional information** Previous medication: none of the participants had been treated with stimulants in the preceding year	**Core symptoms** CPRS-R: impulsive-hyperactive Teacher Hyperactivity Index (ATR) ACTeRS: attention, hyperactivity **Co-existent problems** CPRS-R: conduct problems ACTeRS: oppositional behaviour, social skills, peer acceptance, dependence on and solicitation from teacher **Educational performance** CPRS-R: learning problems Arithmetic task: no. of questions attempted, no. of questions completed correctly, accuracy score, time spent **Psychological function** MFFT Gordon Diagnostic System (GDS) **Depression or anxiety** CPRS-R: anxiety **Quality of life** Not reported **Adverse events** SERS: (parents) **Additional outcomes** Cardiovascular measures Weight

Core symptoms	Educational performance	Quality of life	Adverse events
CPRS-R: total score (mean, SD) Placebo: 39.66 (3.61) MPH (0.15): 28.83 (9.82) MPH (0.30): 31.50 (5.85) MPH (0.50): 36.50 (3.20), 0.15/0.30 > placebo: $p < 0.05$ CPRS-R: hyperactivity index (mean, SD) Placebo: 12.66 (4.13) MPH (0.15): 9.33 (4.32) MPH (0.30): 9.00 (3.16) MPH (0.50): 9.33 (2.06) No significant differences CPRS-R: impulsivity (mean, SD) Placebo: 8.33 (3.20) MPH (0.15): 4.83 (0.98) MPH (0.30): 4.83 (0.75) MPH (0.50): 3.00 (2.44) 0.50 > placebo: $p < 0.05$ Conners' Teacher Hyperactivity Index (ATR) (mean, SD) Placebo: 24.50 (2.81) MPH (0.15): 22.16 (3.12) MPH (0.30): 18.33 (3.07) MPH (0.50): 17.33 (3.72) 0.30/0.50 > placebo: $p < 0.05$; 0.30/0.50 > 0.15: $p < 0.05$ ACTeRS: hyperactivity (mean, SD) Placebo: 8.00 (0.63) MPH (0.15): 13.66 (6.97) MPH (0.30): 9.50 (5.04) MPH (0.50): 10.00 (6.69) 0.30/0.50 > 0.15: $p < 0.05$ ACTeRS: attention Placebo: 7.16 (0.75) MPH (0.15): 5.83 (0.40) MPH (0.30): 5.83 (1.47) MPH (0.50): 7.32 (3.50) No significant differences	CPRS-R: learning problems (mean, SD) Placebo: 7.50 (2.94) MPH (0.15): 5.00 (1.26) MPH (0.30): 4.66 (2.33) MPH (0.50): 6.00 (4.51) 0.15/0.30 > placebo: $p < 0.05$ Arithmetic task: no. of questions attempted (mean, SD) Placebo: 44.50 (8.09) MPH (0.15): 48.00 (4.00) MPH (0.30): 49.66 (0.81) MPH (0.50): 50.00 (0.00) No significant differences Arithmetic task: no. of questions completed correctly (mean, SD) Placebo: 28.66 (16.26) MPH (0.15): 31.83 (14.35) MPH (0.30): 34.33 (15.78) MPH (0.50): 37.16 (15.76) 0.30/0.50 > placebo: $p < 0.05$; 0.50 > 0.15: $p < 0.05$; 0.50 > 0.30: $p < 0.05$ Arithmetic task: accuracy score (mean, SD) Placebo: 62.33 (28.99) MPH (0.15): 66.00 (28.53) MPH (0.30): 68.83 (31.21) MPH (0.50): 74.33 (31.53) 0.50 > placebo: $p < 0.05$; 0.50 > 0.15: $p < 0.05$; 0.50 > 0.30: $p < 0.05$ Arithmetic task: time spent (mean, SD) Placebo: 26.00 (6.78) MPH (0.15): 33.33 (16.02) MPH (0.30): 32.66 (11.09) MPH (0.50): 29.33 (3.55) 0.15/0.30 > placebo: $p < 0.05$; 0.50 > 0.15: $p < 0.05$	Not reported	SERS (parents), no. of side effects out of list of 17 (mean, SD) Placebo: 12.50 (6.56) MPH (0.15): 8.66 (4.71) MPH (0.30): 10.16 (2.85) MPH (0.50): 12.00 (4.42) 0.50 > 0.15: $p < 0.05$ Weight (mean, SD) Placebo: 102.16 (4.40) MPH (0.15): 103.33 (3.32) MPH (0.30): 104.40 (4.24) MPH (0.50): 103.66 (4.63) No significant differences
Conclusions	**Authors' conclusions:** The authors conclude that MPH is an effective adjunct to the treatment of ADD in adolescents **Reviewer's comments:** No comments noted		

Study	Intervention	Participants	Outcomes
Reference Buitelaar *et al.*, 1996[44] **Source** CCOHTA Report **Setting** The Netherlands **Design** Parallel trial **Duration** Referral period: August 1990–June 1993; treatment period: 4 weeks **Purpose** To compare the efficacy and side-effects of pindolol and MPH in children with attention-deficit/hyperactivity disorder	**Arm 1** Pindolol During first 3 days, participants received a single dose of 20 mg (a.m.); thereafter they were treated with two doses of 20 mg administered at breakfast and noon (Individual administering medication not reported) **Arm 2** MPH During first 3 days, participants received a single dose of 10 mg (a.m.); thereafter they were treated with two doses of 10 mg administered at breakfast and noon (Individual administering medication not reported) **Arm 3** Placebo Administered twice daily (breakfast, noon) (Individual administering medication not reported)	**Inclusion criteria** 1. Diagnosis according to DSM-III-R criteria 2. Scores in the clinical range on both CBCL and CTRS hyperactivity factors 3. Deficits in attention performance on either a reaction-time task or a continuous performance task in the neuropsychological testing 4. No previous treatment with psychotropic medication 5. Clinical indication for drug treatment 6. No diagnosis or family history of tic disorder 7. No pervasive developmental disorder 8. No contraindications for treatment with beta-blockers **Diagnostic criteria** DSM-III-R **Number** Total randomised = 32 (male = 30) Arm 1 = 11 Arm 2 = 10 Arm 3 = 11 Total withdrawals = 0 **Age** 109.8 months (mean); 6–13 years (range); 20.2 months (SD) **IQ** 93.2 (mean) **Co-morbid disorders** Conduct disorder: *n* = 20; depressive disorder: *n* = 8 (15%); anxiety disorder: *n* = 22 (42%); epilepsy: *n* = 1 (NB: numbers for whole sample of 52) **Diagnostic subtypes** Not reported **Additional information** Previous medication: Participants in the trial were required not to have previously received psychotropic medication	**Core symptoms** Abbreviated Conners' Rating Scale (ACRS); parents, teachers, clinic **Co-existent problems** Not reported **Educational performance** Not reported **Psychological function** Not reported **Depression or anxiety** Not reported **Quality of life** Not reported **Adverse events** Stimulant Drug Side Effects Rating Scale (modified version): frequency and severity (parents, psychiatrist) **Additional outcomes** Pulse Blood pressure

Core symptoms	Educational performance	Quality of life	Adverse events	
Data presented in graphs cannot be extracted. The authors stated that no significant difference was detected between MPH and placebo	Not reported	Not reported	Frequency (%):	MPH, placebo treatment
			Insomnia	38, 25%
			Anorexia	24, 25%
			Incoherent speech	15%, 18
			Stomach pain	12, 25
			Nausea	16, 17
			Tiredness	18, 8
			Headache	20, 25
			Sedation	8, 8
			Anxiety	16, 16
			Irritability	29, 27
			Moodiness	33, 27
			Tics	10, 0
			Social isolation	8, 0
			Nightmares	8, 8
			Hallucinations	4, 0
			Paresthesias	0, 0
			Severity (%):	MPH, placebo treatment
			No distress:	84, 83
			Distress:	12, 17
			Considerable distress:	4, 0
			Sum (median, range) of adverse events:	2.0 (0–10), 2.5 (0–7)
			There was poor compliance in two subjects owing to side-effects; they were nonetheless included in the analysis. Adjustment of MPH dosage was necessary in four subjects owing to increased agitation, restlessness and insomnia	
Conclusions	**Authors' conclusions:** Pindolol was modestly effective in the treatment of ADHD. Safety concerns on troubling side effects clearly limit the use of it **Reviewer's comments:** No comments noted			

Study	Intervention	Participants	Outcomes
Reference Conners *et al.*, 1972[45] **Source** AHRQ Report **Setting** USA **Design** Parallel trial **Duration** Total treatment period: 8 weeks **Purpose** To compare the efficacy, side-effects and safety of magnesium PEM (Cylert) and dextroamphetamine (Dexedrine) compared with placebo	**Arm 1** Cylert 25 mg/day increasing to mean dosage of 82 mg/day (25–125 mg/day); administered before breakfast and a placebo before lunch (from day 4) (Administered by parent and teacher) **Arm 2** Dexedrine 5 mg/day increasing to a mean dosage of 20 mg/day (5–40 mg/day); administered before breakfast and before lunch (from day 4) (Administered by parent and teacher) **Arm 3** Placebo Administered before breakfast and before lunch (from day 4) (Administered by parent and teacher)	**Inclusion criteria** 1. 6–12 years old 2. IQ 80 3. No severe neurotic, psychotic or neurological symptoms 4. No history of family psychopathology sufficient to account of current behaviour symptoms 5. One or more of the following indications of 'minimal brain dysfunction': (a) significant history of complications of pregnancy, parturition, delivery or perinatal complications (b) delayed or otherwise abnormal developmental milestones (c) early onset of severe hypermotility (d) soft neurological signs (e) abnormal EEG of a non-epileptic type (f) visual or auditory perceptual impairment (g) a significant discrepancy between actual school achievement and learning potential **Diagnostic criteria** See inclusion criteria **Number** Total randomised = 84 (male = 74) Arm 1 = 28 Arm 2 = 28 Arm 3 = 28 Total withdrawals = 3 Arm 1 = 1 Arm 2 = 1 Arm 3 = 1 **Age** 98.99 months (mean); 6–12 years (range); 17.95 months (SD) **IQ** Not reported	**Core symptoms** Symptom Checklist: inattentiveness and hyperactivity Parent Questionnaire: impulsiveness and hyperactivity **Co-existent problems** Symptom Checklist: defiance, sociability Parent Questionnaire: conduct disorder, immaturity, psychosomatic, obsessive and antisocial **Educational performance** Teacher global ratings of classroom performance WRAT: reading, spelling and arithmetic Gates Diagnostic Reading Test: comprehension, speed and accuracy Gray Oral Reading Test Illinois Test of Psycholinguistic Abilities (ITPA) **Psychological function** WISC: full scale, verbal IQ, performance IQ, information, comprehension, arithmetic, similarities, vocabulary, digit span, picture completion, picture arrangement, block design, object assembly and coding Harris Goodenough Draw-a-Man Test Bender Visual Motor Gestalt Test Porteus Mazes: test quotient and qualitative Frostig Test of Developmental Visual Perception: Perceptual Quotient, Eye Motor Coordination, Figure Ground, Constancy of Shape, Position in Space and Spatial Relationships Continuous Performance Test (CPT) Paired Associate Learning (PAL) task

continued

Study	Intervention	Participants	Outcomes
		Co-morbid disorders Behaviour and academic problems at referral: 59/84; primarily academic problems at referral: 6/84; history of febrile seizures: 10% **Diagnostic subtypes** Not reported **Additional information** No additional information reported	**Depression or anxiety** Symptom Checklist: anxiety Parent Questionnaire: anxiety **Quality of life** Clinical global improvement Teacher global ratings of overall behaviour **Adverse events** No specific scale reported **Additional outcomes** Lincoln–Oseretsky Test of Motor Development: selected items (not specified) Measure of hand–arm steadiness Physiological measures Psychiatric examination

Core symptoms	Educational performance	Quality of life	Adverse events
Symptom Checklist: inattentiveness, factor scores at 0/4/8 weeks (mean, SD not reported) Arm 1: 11.5/8.9/7.7 (n = 20) Arm 2: 11.1/7.1/6.4 (n = 23) Arm 3: 11.1/9.3/9.8 (n = 20) $F(4,132) = 3.64$, $p = 0.008$ Symptom Checklist: hyperactivity, factor scores at 0/4/8 weeks (mean, SD not reported) Arm 1: 16.5/11.2/9.8 (n = 20) Arm 2: 15.4/6.9/6.2 (n = 23) Arm 3: 16.4/12.7/13.3 (n = 20) $F(4,132) = 5.52$, $p = 0.001$ Parent Questionnaire: impulsiveness , factor scores at 0/4/8 weeks (mean, SD not reported) Arm 1: 22.9/15.3/13.2 (n = 25) Arm 2: 22.5/11.2/11.0 (n = 27) Arm 3: 21.4/18.5/19.1 (n = 27) $F(4,152) = 7.65$, $p = 0.001$	Teacher global ratings of classroom performance (% much worse; worse; same; improved; much improved) Arm 1: 0.0; 11.5; 38.5; 46.2; 3.8 (n = 26) (4 weeks) 4.5; 9.1; 22.7; 50.0; 13.6 (n = 22) (8 weeks) Arm 2: 0.0; 0.0; 7.7; 73.1; 19.2 (n = 26) (4 weeks) 4.8; 4.8; 14.3; 42.9; 33.3 (n = 21) (8 weeks) Arm 3: 3.8; 11.5; 38.5; 46.2; 0.0 (n = 26) (4 weeks) 8.7; 17.4; 39.1; 34.8; 0.0 (n = 23) (8 weeks)	Clinical global improvement (clinician; % much worse; worse; unchanged; improved; much improved) Arm 1: 0.0; 11.5; 23.1; 57.7; 7.7 (n = 26) (4 weeks) 0.0; 7.4; 14.8; 59.3; 18.5 (n = 27) (8 weeks) Arm 2: 0.0; 0.0; 11.1; 77.8; 11.1 (n = 27) (4 weeks) 0.0; 0.0; 3.7; 63.0; 33.3 (n = 27) (8 weeks) Arm 3: 0.0; 7.4; 63.0; 29.6; 0.0 (n = 27) (4 weeks) 0.0; 3.7; 66.7; 29.6; 0.09 (n = 27) (8 weeks)	The major side-effects of both drugs were insomnia and anorexia. Insomnia: At day 28, insomnia in DEX and Cylert group was significantly worse than in the placebo group. At 8 weeks, < 5% of patients were experiencing moderate or severe insomnia on DEX Anorexia (range): At day 14, 14% of participants on DEX were suffering from severe anorexia. At day 56, 4% of participants on either drug were suffering from severe anorexia Sadness and irritability: Participants suffered significantly more sadness and irritability on DEX than on placebo. However incidence was low

continued

Core symptoms	Educational performance	Quality of life	Adverse events
Parent Questionnaire: hyperactivity, factor scores at 0/4/8 weeks (mean, SD not reported) Arm 1: 15.4/10.6/10.0 (n = 25) Arm 2: 17.1/10.4/10.6 (n = 27) Arm 3: 16.8/13.4/13.4 (n = 27) $F(4,152) = 1.79$, $p = 0.135$		Teacher global rating of overall behaviour (% much worse; worse; same; improved; much improved) Arm 1: 0.0; 0.0; 50.0; 42.3; 7.7 (n = 26) (4 weeks) 0.0; 4.5; 31.8; 50.0; 13.6 (n = 22) (8 weeks) Arm 2: 0.0; 0.0; 11.5; 65.4; 23.1 (n = 26) (4 weeks) 4.5; 4.5; 13.6; 40.9; 36.4 (n = 22) (8 weeks) Arm 3: 0.0; 11.5; 50.0; 34.6; 3.8 (n = 26) (4 weeks) 13.0; 17.4; 39.1; 30.4; 0.0 (n = 23) (8 weeks)	Withdrawals: No withdrawals due to side-effects, although some had dosage adjustments
Conclusions	**Authors' conclusions:** Significant improvement was found for both active drugs and few differences between drugs were obtained. Side-effects were similar for the two drugs and a laboratory battery showed no toxic effects. It is concluded that magnesium pemoline offers a good alternative for treatment of this syndrome **Reviewer's comments:** No comments noted		

Study	Intervention	Participants	Outcomes
Reference Conners and Taylor, 1980[46] **Source** AHRQ Report **Setting** USA **Design** Parallel trial **Duration** Treatment period: 8 weeks; Study length: 10 weeks **Purpose** To examine the clinical efficacy, side-effects and toxicity of PEM and to compare it with MPH	**Arm 1** PEM 37.5 mg/day up to a maximum of 112.5 mg/day or when side-effects necessitate stabilisation; administered once per day (a.m.). Final mean dosage of 2.25 mg/kg/day or 60.4 mg/day; placebo administered once per day (p.m.) (Administered by parent) **Arm 2** MPH 10 mg/day up to a maximum of 60 mg/day or when side effects necessitated stabilisation; administered in two evenly divided doses (a.m., p.m. 30 minutes before evening meal). Final mean dosage of 0.82 mg/kg/day or 22.0 mg/day (Administered by parent) **Arm 3** Placebo Dummy tablets administered twice per day (a.m., p.m.) (Administered by parent)	**Inclusion criteria** 1. Between 6 years and 11 years 6 months 2. IQ = 80 (full scale, performance or verbal) 3. Physician-diagnosed hyperkenesis due to minimal brain dysfunction 4. Visual and auditory acuity sufficient for normal learning process 5. Stable family 6. No obsessive, compulsive or phobic behaviour 7. Normal laboratory values in relation to established paediatric norms 8. No current medical illness or history that contraindicates prescribed drug therapy 9. All prior therapy for hyperkinesis discontinued for a minimum of 8 days prior to study (patients receiving phenothiazines within the previous 6 months were excluded) 10. No demonstrable or suspected need for antiseizure medications 11. No concurrent therapy for chronic illness 12. Moderate to severe symptoms of restlessness, inattentiveness, impulsivity, emotional liability and distractibility reported by parent and school 13. Family physician or paediatrician consent **Diagnostic criteria** Process involving documentation of family history, past developmental and medical status, neurological and psychological function, behaviour in a structured psychiatric examination and symptom ratings from parent and teacher **Number** Total randomised = 60 (male = 57) Arm 1 = 19 Arm 2 = 20 Arm 3 = 21 Total withdrawals = 2 Arm 1 = 2 Arm 2 = 0 Arm 3 = 0	**Core symptoms** Conners' Parent Questionnaire: hyperactivity, impulsivity Conners' Teacher Questionnaire: inattentive–passive, hyperactivity **Co-existent problems** Conners' Parent Questionnaire: conduct problem, antisocial Conners' Teacher Questionnaire: conduct problem, sociability **Educational performance** Wide Range Achievement: reading; spelling; arithmetic **Psychological function** WISC Porteus Maze Test Harris–Goodenough Draw-a-Man Test Kagan's Matching Familiar Figures Test Minnesota Percepto-Diagnostic Test Continuous performance task Goldman–Fristoe–Woodcock Test for Auditory Discrimination **Depression or anxiety** Conners' Parent Questionnaire: anxiety Conners' Teacher Questionnaire: anxiety **Quality of life** Global judgements of improvement (parents, teachers, staff) **Adverse events** Physician's Rating Sheet for Side Effects Standardised form (parents): 50-item checklist Conners' Parent Questionnaire: psychosomatic

continued

Study	Intervention	Participants	Outcomes
		Age 7 years 11 months (mean); 6 to 11 years 1 month (range) **IQ** Arm 1: 93.72 (mean); Arm 2: 97.20 (mean); Arm 3: 95.90 (mean) **Co-morbid disorders** High level of perinatal and developmental anomalies reported Learning problems: 81%. **Diagnostic subtypes** Not reported **Additional information** Previous medication: 13% had received prior analeptic therapy. Participants were required to be medication free for 8 days preceding trial. Participants receiving phenothiazines were not included Concurrent medication: no participant receiving concurrent therapy for chronic illness was included in the trial	**Additional outcomes** Weight Pulse Blood pressure Additional laboratory findings Activity level Conners' Parent Questionnaire: immaturity, obsessional

Core symptoms	Educational performance	Quality of life	Adverse events
Conners' Parent Questionnaire: hyperactivity: mean (SD) MPH: baseline 0.99 (0.36) ($n = 20$), 8 weeks 0.46 (0.23) ($n = 20$) Placebo: baseline 0.98 (0.36) ($n = 21$), 8 weeks 0.75 (0.36) ($n = 20$) Not significant, $p = 0.069$ Conners' Parent Questionnaire: impulsivity: mean (SD) MPH: baseline 1.53 (0.56) ($n = 20$), 8 weeks 0.69 (0.52) ($n = 20$) Placebo: baseline 1.45 (0.51) ($n = 21$), 8 weeks 1.31 (0.57) ($n = 20$) MPH > Placebo, $p < 0.001$ Conners' Teacher Questionnaire: inattentive–passive: mean (SD) MPH: baseline 1.86 (0.49) ($n = 20$), 8 weeks 1.20 (0.73), ($n = 19$) Placebo: baseline 1.65 (0.80) ($n = 21$), 8 weeks 1.25 (0.73) ($n = 19$) Not significant, p-value not reported Conners' Teacher Questionnaire: hyperactivity: mean (SD) MPH: baseline 2.24 (0.55) ($n = 20$), 8 weeks 1.28 (0.67) ($n = 19$) Placebo: baseline 1.90 (0.50) ($n = 21$), 8 weeks 1.45 (0.63) ($n = 19$) MPH > Placebo, $p = 0.039$	Wide Range Achievement: reading: mean (SEM) MPH: baseline 2.33 (0.25) ($n = 20$), 8 weeks 2.66 (0.25) ($n = 20$) Placebo: baseline 2.35 (0.26) ($n = 20$), 8 weeks 2.56 (0.26) ($n = 20$) No significant differences Wide Range Achievement: spelling: mean (SEM) MPH: baseline 2.09 (0.19) ($n = 20$), 8 weeks 2.37 (0.24) ($n = 20$) Placebo: baseline 2.07 (0.20) ($n = 20$), 8 weeks 2.14 (0.20) ($n = 20$) No significant differences. Wide Range Achievement: arithmetic: mean (SD) MPH: baseline 2.24 (0.17) ($n = 20$), 8 weeks 2.58 (0.17) ($n = 20$) Placebo: baseline 1.93 (0.19) ($n = 20$), 8 weeks 2.22 (0.22) ($n = 20$) No significant differences	Parent global judgements of improvement (how serious a problem does your child have? no/minor/serious problem): At week 8, % responding 'serious problem': PEM: 17.6%; MPH: 27.8%; PLA: 50% ($\chi^2=6.67$, $p < 0.155$) Parent rating of problems compared with peers (much worse, worse, same, better, much better) at baseline no differences between groups: at 8 weeks % 'same or better': PEM: 71%; MPH: 90%; PLA: 37% ($\chi^2=18.422$, $p < 0.019$) Teacher rating of problems compared with peers (much worse, worse, same, better, much better): at 8 weeks no significant difference between groups	Physician Rating Sheet: incidence (MPH, placebo) Insomnia and sleep problems: 3, 5 Anorexia and appetite problems: 8, 5 Increased crying: 10, 5 Stomach ache: 9, 7 Headache: 5, 2 Increased irritability: 2, 0 Increased nervousness: 1, 1 Nausea: 1, 2 Dizziness: 1, 2 Rash: 0, 3 Moodiness: 2, 0 Temper tantrums: 0, 0 Thirsty: 1, 0 Itching: 2, 0 Depression: 1, 1 Increased appetite: 1, 1 Glassy eyed: 1, 1 Nose bleed: 1, 1 Enuresis: 0, 2 Argumentative: 0, 0 Sensitive to light: 0, 0 Night terrors: 0, 0 Stares glassily: 0, 0 Fine tremors: 0, 0 Dilated pupils: 0, 0 Leg cramps: 0, 0 Odd mannerism of mouth: 0, 0 Bad dreams: 0, 0 Increased sensitivity: 0, 0 Diarrhoea: 0, 0 Palpitations: 1, 0 Stuttering: 1, 0 Negativism: 1, 0 Nocturnal fears: 1, 0 Eyes reddened: 1, 0 Speech incoherent: 1, 0 Eating erratic: 0, 1 Grouchy: 0, 1

continued

Core symptoms	Educational performance	Quality of life	Adverse events
			Pains in ribs: 0, 1 Sluggishness: 0, 1 No. of different side-effects: 65, 42 No. of patients with side-effects: 20, 14 Little difference between groups overall
Conclusions	**Authors' conclusions:** Both drugs produced improvement in all areas except the achievement measures **Reviewer's comments:** No comments noted		

Study	Intervention	Participants	Outcomes
Reference Conrad *et al.*, 1971[47] **Source** AHRQ Report **Setting** USA **Design** Parallel trial **Duration** DEX treatment period: 4–6 months; tutoring: average of 20 weeks **Purpose** 1. To evaluate the relatively long-term (4–6 months) effects of dextroamphetamine on the behaviour, achievement and perceptual–cognitive functioning of hyperkinetic children 2. To compare the effects of dextroamphetamine and prescriptive perceptual–cognitive tutoring	**Arm 1** Placebo 5 mg/day; daily dosage increased by 5 mg at weekly intervals until undesirable side-effects or maximum positive response achieved; majority maintained on 10–20 mg/day (Administered by parent) **Arm 2** Placebo plus prescriptive tutoring 5 mg/day; daily dosage increased by 5 mg at weekly intervals until undesirable side–effects or maximum positive response achieved; majority maintained on 10–20 mg/day Tutoring sessions twice per week; average of 39.2 tutorial sessions (Administered by parent and tutor) **Arm 3** DEX 5 mg/ day; daily dosage increased by 5 mg at weekly intervals until undesirable side-effects or maximum positive response achieved; majority maintained on 10–20 mg/day (Administered by parent) **Arm 4** DEX plus prescriptive tutoring 5 mg/day; daily dosage increased by 5 mg at weekly intervals until undesirable side-effects or maximum positive response achieved; majority maintained on 10–20 mg/day Tutoring sessions twice per week; average of 39.9 tutorial sessions (Administered by parent and tutor)	**Inclusion criteria** 1. Rated hyperactive (19th percentile or lower) on Schenectady Hyperkinetic Scale (SHS). 2. Significant evidence of perceptual–cognitive impairment, defined as any of the following: (a) a perceptual age on the Bender–Gestalt ≥ 1 year or below the chronological age of the child (b) a Frostig Perceptual Quotient of ≤90 (c) three or more errors on the Bender Gestalt (d) a discrepancy between Verbal IQ and Performance IQ on the WISC of ≥ 5 points (e) variability among subscores on the WISC of ≥6 points 3. Not currently receiving medication 4. Parental consent 5. Able to be contacted **Diagnostic criteria** SHS **Number** Total randomised = 81 (male/female split not reported) Arm 1 = 18 Arm 2 = 17 Arm 3 = 17 Arm 4 = 16 Total withdrawals = 13 Details are only given for the 68 children who completed the study **Age** Children were of kindergarten, first and second grade age **IQ** Not reported **Co-morbid disorders** Not reported **Diagnostic subtypes** All included participants were hyperkinetic **Additional information** Previous/concurrent medication: To be included in the trial, individuals were not to be currently receiving medication	**Core symptoms** Behaviour ratings (teacher, parent) SHS Judgements of distractibility Judgements of motor activity **Co-existent problems** Not reported **Educational performance** WISC: Information, Comprehension, Arithmetic, Similarities, Digit Span, Picture Completion, Picture Arrangement, Block Design, Object Assembly, Coding; Verbal IQ, Performance IQ, Full Scale IQ Temporal Order test Recall test WRAT: Arithmetic and Reading Subtests Bender–Gestalt Visual Motor Test Frostig Developmental Test of Visual Perception: I-V, PQ and Stars **Psychological function** Not reported **Depression or anxiety** Not reported **Quality of life** Not reported **Adverse events** Not reported **Additional outcomes** Judgements of motor coordination Judgements of visual tracking Spatial orientation test Motor pattern repetition test

Core symptoms	Educational performance	Quality of life	Adverse events
SHS score (no variance reported): Arm 1: ?2.28, Arm 2: ?5.59, Arm 3: ?9.29, Arm 4: ?6.25 *F* ratio: 2.44; $p = 0.08$ Behaviour rating by teacher: Arm 1: ?3.00, Arm 2: ?2.77, Arm 3: ?2.59, Arm 4: 2.19 *F* ratio: 5.74, $p = 0.001$ Behaviour rating by parent: Arm 1: ?2.94, Arm 2: ?2.77, Arm 3: ?2.06, Arm 4: ?1.94 *F* ratio=10.23, $p = 0.001$ Judgements of distractibility: Arm 1: ?0.22, Arm 2: ?0.35, Arm 3: ?0.59, Arm 4: ?0.44 *F* ratio: 0.67; $p > 0.50$ Judgements of motor activity: Arm 1: ?–0.06, Arm 2: ?0.18, Arm 3: ?0.65, Arm 4: ?0.69 *F* ratio: 4.17; $p = 0.01$	WISC – Information Subtest: Arm 1: ?–1.17, Arm 2: ?0.88, Arm 3: ?-0.06, Arm 4: ?1.06 *F* ratio: 4.49, $p = 0.005$ WISC – Other subtests: No significant differences. WISC – Full Scale IQ: Arm 1: ?2.11, Arm 2: ?4.41, Arm 3: ?6.24, Arm 4: ?7.43 *F* ratio: 2.10, $p = 0.12$ WISC – other IQ scores: No significant differences	Not reported	Not reported
Conclusions	**Authors' conclusions:** DEX contributed to a reduction of hyperkinetic behavioural symptoms and to improvement in performance on various measures of perceptual motor and cognitive development. Tutoring resulted in gains on some WISC subtests but was clearly not as effective as medication. Neither experimental condition significantly influenced academic achievement **Reviewer's comments:** The authors' conclusions regarding reduction in hyperkinetic behaviour are based primarily on behaviour ratings made by parents and teachers on a four-point scale: dramatic improvement, definite improvement, no change and worse		

Study	Intervention	Participants	Outcomes
Reference Dopfner *et al.*, 2003[48] **Source** Updated search **Setting** Germany **Design** Parallel trial **Duration** Treatment periods: 4 weeks. **Purpose** To test the efficacy and safety of MPH during school-time in children with ADHD	**Arm 1** MPH 2 × 5-mg immediate-release capsules for first 2 days; subsequent dose began at 20-mg sustained-release capsules (for children of 20–30 kg) and could be increased to a maximum of 60 mg; children of heavier weights began at higher dosages and could be increased to a maximum of 60 mg (20–30 kg: max. 20 mg; 31–50 kg: max. 40 mg; >50 kg: max 60 mg); once daily (a.m.) (Individual administering medication not reported) **Arm 2** Placebo No details reported (Individual administering medication not reported)	**Inclusion criteria** 1. Boys and girls 6–16 years old 2. Attending school 3. IQ = 85 4. Body weight = 20 kg 5. No strong depressive disorder or anxiety disorder 6. No tic or Tourette's disorder 7. No familial tic disorder 8. No profound developmental disorder or psychosis 9. No previous seizures and no indication of seizure potential on EEG 10. No MPH or other psychostimulant treatment in the 3 weeks preceding trial 11. Sufficient knowledge of German **Diagnostic criteria** DSM-IV **Number** Total randomised = 85 (male/female split not reported.) Arm 1 = 43 Arm 2 = 42 Total withdrawals = 7 Arm 1 = 3 Arm 2 = 4 Reasons for withdrawals: Arm 1: treatment not effective *n* = 1, unforeseen circumstances *n* = 2 Arm 2: treatment not effective *n* = 3 In addition, one patient was not included in the final analysis; it appears that this was because s/he was receiving treatment for depression (imipramine) Randomisation procedure: Participants were randomised across four strata: age, sex, severity of disorder and centre **Age** Arm 1: 9.8 years (mean); Arm 2: 9.8 years (mean); Arm 1: 2.4 (SD); Arm 2: 2.1 (SD)	**Core symptoms** Peer Assessment for Hyperkinetic Disorders (FBB/HKS) (teachers) 5-point effectiveness scale (parents, physicians) **Co-existent problems** Not reported **Educational performance** Not reported **Psychological function** Not reported **Depression or anxiety** Not reported **Quality of life** Not reported **Adverse events** No specific scale reported **Additional outcomes** EEG Blood pressure Heart rate Biochemical levels

continued

Study	Intervention	Participants	Outcomes
		IQ Arm 1: 104.8 (mean); Arm 2: 102.7 (mean) **Co-morbid disorders** Arm 1: ODD: *n* = 21/43; social behaviour disorder: *n* = 2/43; other social behavioural disorders: *n* = 2/43; dysthymia: *n* = 0/43 Arm 2: ODD: *n* = 23/42; social behaviour disorder: *n* = 6/42; other social behavioural disorders: *n* = 1/42; dysthymia: 1/42 **Diagnostic subtypes** Arm 1: hyperactive/impulsive subtype: *n* = 32/43; inattentive subtype: *n* = 11/43 Arm 2: Hyperactive/impulsive subtype: *n* = 31/42; inattentive subtype: n=10/42; unknown subtype: *n* = 1/42 **Additional information** Previous medication: Arm 1: 16/43 had previously received treatment for ADHD Arm 2: 11/42 had previously received treatment for ADHD Participants were required to be free of MPH or other psychostimulant treatment in the 3 weeks preceding the trial	

Core symptoms	Educational performance	Quality of life	Adverse events
FBB/HKS: mean (SD) Week 0: Arm 1: 1.82 (0.49), Arm 2: 1.87 (0.59); effect size: 0.09 Week 1: Arm 1: 1.25 (0.64), Arm 2: 1.69 (0.59); effect size: 0.80 Week 2: Arm 1: 1.00 (0.61), Arm 2: 1.66 (0.69); effect size: 0.98 Week 3: Arm 1: 0.92 (0.58), Arm 2: 1.69 (0.71); effect size: 1.22 Week 4: Arm 1: 0.85 (0.62), Arm 2: 1.64 (0.69); effect size: 1.20 5-point effectiveness scale: parents Missing: Arm 1: *n* = 1/43; Arm 2: *n* = 0/42 Very good: Arm 1: *n* = 10/43; Arm 2: *n* = 0/42 Good: Arm 1: *n* = 16/43; Arm 2: *n* = 2/42 Average: Arm 1: *n* = 7/43; Arm 2: *n* = 8/42 Poor: Arm 1: *n* = 7/43; Arm 2: *n* = 15/42 Very poor: Arm 1: *n* = 2/43; Arm 2: *n* = 17/42 ?2 *p*-value <0.001 5-point effectiveness scale: physicians Missing: Arm 1: *n* = 2/43; Arm 2: *n* = 0/42 Very good: Arm 1: *n* = 11/43; Arm 2: *n* = 0/42 Good: Arm 1: *n* = 17/43; Arm 2: *n* = 4/42 Average: Arm 1: *n* = 6/43; Arm 2: *n* = 5/42 Poor: Arm 1: *n* = 5/43; Arm 2: *n* = 23/42 Very poor: Arm 1: *n* = 2/43; Arm 2: *n* = 10/42 ?2 *p*-value <0.001	Not reported	Not reported	Physician's ratings: Arm 1: 84% well or very well tolerated Arm 2: 90% well or very well tolerated Parent ratings: Arm 1: 88% well or very well tolerated Arm 2: 90% well or very well tolerated
Conclusions	**Authors' conclusions:** The drug showed very good clinical efficacy and safety in children with ADHD. Its two-step galenic release of MPH seems to be appropriate for a once-a-day (morning) stimulant in schoolchildren **Reviewer's comments:** No comments noted		

Study	Intervention	Participants	Outcomes
Reference DuPaul and Rapport, 1993[49] **Source** CCOHTA Report **Setting** USA **Design** Crossover trial **Duration** 6 weeks; Each dosage was given for 6 days, followed by one washout day **Purpose** To examine the degree to which a wide range of MPH dosages affect classroom behaviour and academic functioning in children with ADD	**Arm 1** MPH 5 mg administered once daily (Administered by parent) **Arm 2** MPH 10 mg (Administered by parent) **Arm 3** MPH 15 mg (Administered by parent) **Arm 4** MPH 20 mg (Administered by parent) **Arm 5** Placebo (Administered by parent)	**Inclusion criteria** 1. Diagnosis using DSM-III criteria 2. Problem behaviours in at least 50% of situations on the Home Situations Questionnaire 3. Two SDs above the mean on the Werry–Weiss–Peters Activity Scale 4. Abbreviated CTRS >15 5. Performance on the Matching Familiar Figures Test characteristic of a 'fast–inaccurate' responder 6. Absence of any gross neurological, sensory or motor impairment **Diagnostic criteria** DSM-III **Number** Total randomised = 31 (male = 26) No withdrawals reported The study also involved a normal control group of 25 children **Age** 8.12 years (mean); 6–11 years (range); 1.18 years (SD) **IQ** Not reported **Co-morbid disorders** Not reported **Diagnostic subtypes** Not reported **Additional information** No relevant information reported	**Core symptoms** Abbreviated CTRS: total score On-task behaviour **Co-existent problems** Not reported **Educational performance** Academic efficiency score **Psychological function** Not reported **Depression or anxiety** Not reported **Quality of life** Not reported **Adverse events** Not reported **Additional outcomes** Not reported

Core symptoms	Educational performance	Quality of life	Adverse events
Abbreviated CTRS: total score Baseline: 20.68 (4.21) Arm 1: 12.55 (5.16) Arm 2: 9.16 (4.72) Arm 3: 8.22 (4.18) Arm 4: 7.16 (5.0) Placebo: 15.84 (5.06) (Arm 2 > Arm 1, $p < 0.05$; Arm 3 > Arm 1, $p < 0.01$; Arm 4 > Arm 1, $p < 0.01$; All MPH conditions > placebo, p = not clear) On-task behaviour: Baseline: 55.74 (16.56) Arm 1: 67.81 (19.65) Arm 2: 77.87 (9.62) Arm 3: 78.10 (12.74) Arm 4: 81.58 (10.90) Placebo: 53.84 (18.71) (Arm 2 > Arm 1, $p < 0.05$; Arm 3 > Arm 1, $p < 0.01$; Arm 4 > Arm 1, $p < 0.01$; all MPH conditions > placebo, p <0.01)	Academic efficiency score: Baseline: 50.39 (23.48) Arm 1: 67.74 (19.3) Arm 2: 75.87 (13.99) Arm 3: 75.19 (18.66) Arm 4: 75.68 (17.46) Placebo: 48.16 (21.03) (all MPH conditions > placebo, $p < 0.01$)	Not reported	Not reported
Conclusions	**Authors' conclusions:** MPH exerted a remarkable and highly significant effect on children's attention (on-task), and academic efficiency, while simultaneously improving teacher ratings (Abbreviated CTRS) of classroom conduct **Reviewer's comments:** No comments noted		

Study	Intervention	Participants	Outcomes
Reference Efron *et al.*, 1997;[50] Efron *et al.*, 1997;[143] Efron *et al.*, 1997[300] and Efron *et al.*, 1998[301] **Source** AHRQ Report **Setting** Australia **Design** Crossover trial **Duration** Total treatment time: 4 weeks; Treatment periods: 2 weeks per treatment arm with 24-hour washout **Purpose** 1. To compare MPH and DEX in a sample of children with ADHD 2. To compare the side-effect profiles of MPH and DEX in children with ADHD and to determine which symptoms are genuine adverse effects of stimulant medication, as opposed to aspects of the child's underlying behaviour phenotype	**Arm 1** MPH Gradual build-up to target of 0.3 mg/kg/dose administered after breakfast and lunch (Individual administering medication not reported) **Arm 2** DEX Gradual build-up to target of 0.15 mg/kg/dose administered after breakfast and lunch (Individual administering medication not reported)	**Inclusion criteria** 1. Aged between 5 and 15 years 2. Satisfy DSM-IV criteria for ADHD 3. T score of at least 1.5 SD units above the mean on the attention problems scale of the CBCL or Teacher Report Form (TRF) 4. No history of intellectual disability, gross neurological abnormality or Tourette's syndrome 5. Decision made to undertake stimulant medication trial on clinical grounds **Diagnostic criteria** DSM-IV **Number** Total randomised = 125 (male = 114) No withdrawals reported **Age** 104.8 months (mean); 60–179 months (range) 27.6 months (SD) **IQ** 98.9 (mean) **Co-morbid disorders** Not reported **Diagnostic subtypes** ADHD mixed type: 101 (80.8%) ADHD predominantly inattentive type: 22 (17.6%) ADHD predominantly hyperactive/impulsive type: 2 (1.6%) **Additional information** No relevant information reported	**Core symptoms** CPRS-R: impulsive-hyperactive factor and composite hyperactivity index CTRS-R: hyperactivity factor, inattentive–passive factor and hyperactivity index Parental Global Perceptions Questionnaire: concentration, activity **Co-existent problems** CPRS-R: conduct problems CTRS-R: conduct problems **Educational performance** CPRS-R: learning problems **Psychological function** Continuous Performance Test (CPT) **Depression or anxiety** CPRS-R: anxiety **Quality of life** Parental Global Perceptions Questionnaire: overall perceptions Child Global Perceptions Questionnaire **Adverse events** SERS (parents) **Additional outcomes** CPRS-R: psychosomatic

Core symptoms	Educational performance	Quality of life	Adverse events
CPRS-R: composite hyperactivity index Baseline: 84.63 (10.19) MPH: 64.28 (13.46) DEX: 64.89 (13.74) Difference in treatment effect (MPH – DEX, 95% CI): 1.03 (–2.03 to 4.10), $p = 0.51$ CPRS-R: impulsive-hyperactive factor Baseline: 73.46 (9.85) MPH: 57.39 (10.53) DEX: 57.33 (11.22) Difference in treatment effect (MPH – DEX, 95% CI): 0.21 (–2.18 to 2.61), $p = 0.87$ CTRS-R: hyperactivity index Baseline: 71.46 (11.45) MPH: 56.14 (10.17) DEX: 58.76 (10.57) Difference in treatment effect (MPH – DEX, 95% CI): 2.60 (0.69 to 4.51), $p < 0.01$ CTRS-R: hyperactivity factor Baseline: 71.26 (13.24) MPH: 56.20 (11.02) DEX: 58.88 (11.08) Difference in treatment effect (MPH – DEX, 95% CI): 2.78 (0.70 to 4.86), $p < 0.01$ CTRS-R: inattentive-passive factor Baseline: 64.87 (8.80) MPH: 54.09 (7.61) DEX: 55.69 (8.90) Difference in treatment effect (MPH – DEX, 95% CI) 1.61 (0.30, 2.92), $p = 0.02$ Parental Global Perceptions Questionnaire: concentration MPH: 74.2% DEX: 70.4% $p = 0.59$	Not reported	Parental Global Perceptions Questionnaire: overall perceptions MPH: 72.6% DEX: 68.8% $p = 0.60$ Global ratings of response: 64/102 children on MPH rated themselves as responders 38/102 children on MPH rated themselves as non-responders 75/102 parents of children on MPH rated their child as a responder 27/102 parents of children on MPH rated their child as a non-responder There was a significant difference between parent and child ratings: $\chi^2 = 3.70$, $p = 0.05$. This was a discrepancy of 26.5% 56/102 children on DEX rated themselves as responders 48/102 children on DEX rated themselves as non-responders 72/102 parents of children on DEX rated their child as a responder 29/102 parents of children on DEX rated their child as a non-responder There was a significant difference between parent and child ratings: $\chi^2 = 6.25$, $p = 0.01$. This was a discrepancy of 35.6%	Barkley SERS[50] 1. Many symptoms commonly considered to be side effects of stimulant medication were present at baseline 2. DEX was associated with a significantly greater severity of side-effects than MPH, particularly negative emotional side-effects (e.g. irritability, tearfulness, anxiety)[143] Total side-effects: Mean number (SD): Baseline: 8.19 (3.97); DEX: 7.64 (3.83); MPH: 7.19 (3.82) $F = 3.72$; $p = 0.03$; baseline vs MPH pairwise contrast also significant ($p < 0.01$) Mean severity (of those reported) (SD): Baseline: 4.08 (1.56); DEX: 3.73 (1.68); MPH: 3.24 (1.46) $F = 15.98$; $p < 0.01$; baseline vs MPH and DEX vs MPH pairwise contrasts also significant ($p < 0.01$) Individual side-effects: Prevalence: no (%) (significant difference in proportions using χ^1): Trouble sleeping: DEX: 88 (70); MPH: 79 (640) Poor appetite: DEX: 74 (59); MPH: 69 (56) Irritable: DEX: 102 (82); MPH: 100 (80) Proneness to crying: DEX: 95 (76); MPH: 89 (71) Anxiousness: DEX: 85 (68); MPH: 76 (61) Sadness/unhappiness: DEX: 74 (59); MPH: 69 (56) Headaches: DEX: 38 (30); MPH: 30 (24) Stomach aches: DEX: 50 (40); MPH: 40 (32) Nightmares: DEX: 35 (28); MPH: 26 (21) Daydreams: DEX: 78 (62); MPH: 77 (62)

continued

Core symptoms	Educational performance	Quality of life	Adverse events
Parental Global Perceptions Questionnaire: activity MPH: 37.9% DEX: 41.6%; $p = 0.57$			Talking little with others: DEX: 37 (30); MPH: 35 (28) Uninterested in others: DEX: 43 (34); MPH: 39 (31) Drowsiness: DEX: 23 (18); MPH: 22 (18) Biting fingernails: DEX: 50 (40); MPH: 56 (45) Unusually happy: DEX:33 (26); MPH: 35 (28) Dizziness: DEX: 18 (14); MPH: 15 (12) Tics or nervous movements: DEX: 32 (26); MPH: 35 (28) Mean severity (*F*-statistic and related *p*-value) (statistically significant pairwise contrasts: $p < 0.01$: Trouble sleeping: DEX: 3.61; MPH: 2.69 (12.9, <0.01) (DEX vs MPH) Poor appetite: DEX: 2.74; MPH: 2.12 (19.9, <0.01) Irritable: DEX: 3.65; MPH: 2.94 (21.0, <0.01) (DEX vs MPH) Proneness to crying: DEX: 3.4; MPH: 2.7 (4.9, <0.01) (DEX vs MPH) Anxiousness: DEX: 2.71; MPH: 2.07 (30.9, <0.01) (DEX vs MPH) Sadness/unhappiness: DEX: 2.43; MPH: 1.69 (15.5), <0.01) (DEX vs MPH) Headaches: DEX: 0.83; MPH: 0.65 (4.8, 0.01) Stomach aches: DEX: 1.42; MPH: 1.14 (1.8, 0.16) Nightmares: DEX: 0.79; MPH: 0.48 (10.6, <0.01) (DEX vs MPH) Daydreams: DEX: 1.76; MPH: 1.94 (19.2, <0.01) Talking little with others: DEX: 1.15; MPH: 0.77 (2.1, 0.13) Uninterested in others: DEX: 1.08; MPH: 0.99 (0.8, 0.47) Drowsiness: DEX: 0.64; MPH: 0.45 (1.4, 0.24) Biting fingernails: DEX: 1.84; MPH: 2.02 (12.9, <0.01)

continued

Core symptoms	Educational performance	Quality of life	Adverse events
			Unusually happy: DEX: 0.83; MPH: 0.94 (2.9, 0.6) Dizziness: DEX: 0.36; MPH: 0.26 (0.61, 0.54) Tics or nervous movements: DEX: 0.83; MPH: 0.81 (6.9, <0.01) Withdrawals: 4 subjects (3.2%) discontinued particular trial periods owing to severe adverse effects: 2 boys on DEX: one boy became overfocused, extra sensitive and increasingly anxious. The other because agitated and uncharacteristically aggressive. Both tolerated MPH 1 boy and 1 girl on MPH: the boy became extremely aggressive and tearful. The girl suffered severe headaches. Both tolerated DEX
Conclusions	**Authors' conclusions:** 1. Most children with ADHD improve significantly on both MPH and DEX. There was a slight advantage to MPH on most measures 2. Several behaviours commonly considered to be adverse effects of stimulant medication were reported more frequently before commencing the trial. DEX was associated with more severe adverse effects than MPH, although very few subjects had severe side-effects on either drug; the role of DEX as an alternative medication for children with ADHD is supported providing equivalent efficacy is demonstrated **Reviewer's comments:** The analysis focused on examining changes from baseline scores		

Study	Intervention	Participants	Outcomes
Reference Elia *et al.*, 1991;[51] Castellanos *et al.*, 1996[302] **Source** AHRQ Report **Setting** USA (day hospital) **Design** Crossover trial **Duration** Hospital programme: 11 weeks; treatment period: 9 weeks (3 weeks per treatment); baseline assessment period: 1 week **Purpose** To compare the clinical effects of DEX and MPH in a sample of children with ADHD	**Arm 1** MPH plus non-drug intervention Mean dose 0.9 mg/kg/day (week 1), 1.5 mg/kg/day (week 2), 2.5 mg/kg/day (week 3) administered in two doses (9 a.m., 1 p.m.); complemented by multidisciplinary behaviour modification programme and low monoamine diet (Individual administering medication not reported) **Arm 2** DEX plus non-drug intervention Mean dose 0.4 mg/kg/day (week 1), 0.9 mg/kg/day (week 2), 1.3 mg/kg/day (week 3) administered in two doses (9 a.m., 1 p.m.); complemented by multidisciplinary behaviour modification programme and low-monoamine diet (Individual administering medication not reported) **Arm 3** Placebo plus non-drug intervention Administered twice daily (9 a.m., 1 p.m.); complemented by multidisciplinary behaviour modification programme and low-monoamine diet (Individual administering medication not reported) **Additional information** Where side-effects were severe, dosages were held at current level, partially increased or decreased; this occurred for 19/48 participants (7 on MPH, 7 on DEX, 5 during both drug phases)	**Inclusion criteria** 1. Fulfils DSM-III criteria for attention deficit disorder with hyperactivity in at least two settings 2. Score = 2 SDs above age norms on CTRS: Factor IV (hyperactivity) 3. Full-scale IQ score = 80 on WISC-R 4. No evidence of medical or neurological diseases 5. No other Axis I psychiatric disorder except conduct, oppositional, mild overanxious or specific developmental disorders **Diagnostic criteria** DSM-III **Number** Total randomised = 48 (male = 48) No withdrawals reported **Age** 8.6 years (mean); 1.7 years (SD); 6–12 years (range) **IQ** 105.6 (mean) **Co-morbid disorders** CD: *n* = 10/48; ODD: *n* = 12/48; specific developmental disorders: *n* = 11; dysthymic disorder: *n* = 1 **Diagnostic subtypes** Not reported **Additional information** Previous medication: 18/48 had received no previous stimulant treatment. 5/48 had previously taken stimulant treatment. 24/48 were on stimulants at time of screening: 20/24 MPH; 2/24 PEM; 2/24 DEX. 1/48 was receiving imipramine at time of screening. (The authors attempted to recruit children who were stimulant drug non-responders, but this was not successful)	**Core symptoms** CTRS: hyperactivity Conners' Parent Questionnaire (CPQ): hyperactivity **Co-existent problems** Not reported **Educational performance** Not reported **Psychological function** Visual Continuous Performance Test Palwin Paired Associate Learning Task **Depression or anxiety** Not reported **Quality of life** CGI (physician) C-GAS **Adverse events** STESS (physician, parents) Children's Psychiatric Rating Scale: nervous mannerism **Additional outcomes** Truncal motor activity Blood and urine samples

Core symptoms	Educational performance	Quality of life	Adverse events
CTRS, Hyperactivity Results presented in graphs MPH > placebo, DEX > placebo, $p < 0.05$ CPQ, Hyperactivity Results presented in graphs MPH > placebo, DEX > placebo, $p < 0.05$	Not reported	CGI Scale (physician) Results presented in graphs MPH > placebo, DEX > placebo, $p < 0.05$ C-GAS Results presented in graphs MPH > placebo, DEX > placebo, $p < 0.05$	STESS (parents and physican) Decreased appetite ($n = 48$), %, mild/moderate/severe: MPH: 40/35/10 DEX: 40/42/13 PLA: 0/0/0 MPH/DEX > PLA, $p < 0.01$ Sleep difficulties ($n = 48$): MPH: 40/31/8 DEX: 31/40/10 PLA: 23/4/0 MPH/DEX > PLA, $p < 0.01$ Overly meticulous ($n = 33$): MPH: 30/3/0 DEX: 18/12/6 PLA: 0/0/0 MPH > PLA, $p < 0.05$; DEX > PLA, $p < 0.01$ Not happy ($n = 48$): MPH: 27/35/6 DEX: 25/33/4 PLA: 31/15/2 MPH > PLA, $p < 0.01$; DEX > PLA, $p < 0.05$ Children's Psychiatric Rating Scale: nervous mannerisms ($n = 34$): MPH: 26/21/3 DEX: 35/9/0 PLA: 15/0/0 MPH > PLA, $p < 0.01$
Conclusions	**Authors' conclusions:** The authors concluded that both drugs were highly and equally efficacious for the group as a whole, and frequently one drug or the other was superior for an individual child, or adverse effects occurred only on one of the stimulants. They further note that non-response appears to be extremely rare when both stimulants and a wide range of doses are given **Reviewer's comments:** No comments noted		
PLA, placebo.			

Study	Intervention	Participants	Outcomes
Reference Fine and Johnston, 1993[52] **Source** AHRQ Report **Setting** Canada **Design** Crossover trial **Duration** 3 weeks **Purpose** To examine the nature and frequency of side-effects of low- and high-dose MPH compared with placebo. The authors also were interested in finding out whether the side-effects were similar to the symptoms of ADHD reported by the parents	**Arm 1** MPH 0.3 mg/kg; administered twice daily (Individual administering medication not reported) **Arm 2** MPH 0.6 mg/kg; administered twice daily (Individual administering medication not reported) **Arm 3** Placebo Administered twice daily (Individual administering medication not reported)	**Inclusion criteria** A minimum of eight symptoms were required to confirm a diagnosis of ADHD **Diagnostic criteria** DSM-III-R **Number** Total randomised = 12 (male = not reported) Total withdrawals = 0 Randomisation procedure: Two doses of MPH and placebo were randomly assigned across days **Age** 6–10 years (range) **IQ** Not reported **Co-morbid disorders** Not reported **Diagnostic subtypes** Not reported **Additional information** No relevant information reported	**Core symptoms** Not reported **Co-existent problems** Not reported **Educational performance** Not reported **Psychological function** Not reported **Depression or anxiety** Not reported **Quality of life** Not reported **Adverse events** Side Effects Questionnaire **Additional outcomes** Not reported

Core symptoms	Educational performance	Quality of life	Adverse events
Not reported	Not reported	Not reported	Mean severity rating by parents (17 side effects): *Low-dose MPH* / *High-dose MPH* / *Placebo* Trouble sleeping 2.89 (2.33) / 2.61 (2.45) / 1.69 (2.68) NS Nightmares 0.39 (0.60) / 0.43 (0.88) / 0.33 (0.77) NS Stares/daydreams 1.72 (1.43) / 1.07 (1.33) / 1.09 (1.33) NS Talks less with others 0.80 (0.81) / 1.27 (1.53) / 1.17 (2.38) NS Interested in others 0.52 (0.74) / 1.34 (1.34) / 0.76 (1.23) NS Decreased appetite 2.23 (1.34) / 3.09 (3.09) / 1.33 (1.38) $F = 13.0$, $p = 0.002$ Irritable 3.71 (2.19) / 2.98 (2.85) / 2.69 (2.39) NS Stomach ache 0.81 (1.68) / 2.32 (3.35) / 1.06 (2.25) NS Headache 0.17 (0.30) / 1.39 (2.55) / 0.81 (1.64) NS Drowsiness 0.24 (0.30) / 0.73 (0.99) / 0.63 (1.62) Sad 1.52 (1.56) / 2.77 (3.12) / 1.65 (1.98) NS Crying 2.11 (2.16) / 3.30 (3.54) / 1.97 (2.21) NS Anxious 2.91 (2.37) / 3.16 (3.46) / 3.26 (2.97) NS Bites nails 0.67 (1.71) / 1.27 (2.34) / 0.63 (1.82) NS Euphoric 0.78 (1.19) / 1.21 (1.56) / 1.35 (1.63) NS Dizziness 0.11 (0.28) / 0.91 (1.26) / 0.28 (0.71) NS
Conclusions	**Authors' conclusions:** Several side-effects appeared equally often on placebo as on active medication and the parents' reports of side-effects are significantly related to reports of ADHD symptomology **Reviewer's comments:** No comments noted		

Study	Intervention	Participants	Outcomes
Reference Firestone *et al.*, 1986[53] **Source** AHRQ Report **Setting** Canada **Design** Parallel trial **Duration** Trial length: 3 months; follow-up: 2 years. **Purpose** Not explicitly stated. The authors examine long-term outcomes (2 years) of a 3-month trial that compared stimulant medication alone, stimulant medication plus parents trained in behaviour modification and placebo plus parent training	**Arm 1** MPH plus non-drug intervention Average of 22 mg/day with a maximum of 30 mg and minimum of 10 mg; administered twice daily (a.m., noon). Parent training involved sessions and group meetings on child management and learning how to cooperate efficiently with school personnel (Administered by parent and medical personnel) **Arm 2** Placebo plus non-drug intervention Parent training (Administered by parent and medical personnel) **Arm 3** MPH Average of 22 mg/day with a maximum of 30 mg and minimum of 10 mg; administered twice daily (a.m., noon). (Administered by parent)	**Inclusion criteria** 1. 5–9 years of age 2. Demonstration of symptoms before 3 years old 3. A rating of 1.5 on the Teachers Hyperactivity Index 4. IQ of ≥ 85 or greater (Peabody Picture Vocabulary) 5. No signs of brain damage, epilepsy or psychosis **Diagnostic criteria** DSM-III **Number** Total randomised = 134 (male/female split not reported) Numbers in each arm not reported Total analysed at post-test (3 months) = 73 Arm 1 = 22 Arm 2 = 21 Arm 3 = 30 Total with follow-up data (2 years) = 52 Total analysed at follow-up = 30 Arm 1 = 10 Arm 2 = 9 Arm 3 = 11 (22 had switched from their original treatment condition) **Age** 5–9 years (range) **IQ** Not reported **Co-morbid disorders** Not reported **Diagnostic subtypes** Not reported **Additional information** No relevant information reported	**Core symptoms** CTRS: Hyperactivity Index **Co-existent problems** Quay–Peterson Behaviour Problem Checklist: conduct problem **Educational performance** Gates–MacGinitie Reading Test Vocabulary Grade (GMVG) **Psychological function** Mean reaction time **Depression or anxiety** Not reported **Quality of life** Not reported **Adverse events** Not reported **Additional outcomes** Not reported

Core symptoms	Educational performance	Quality of life	Adverse events
CTRS Hyperactivity Index: (at post test) mean (SD) Arm 1: pre-test: 1.85 (0.31); post-test: 0.89 (0.49) ($n = 22$) Arm 2: pre-test: 1.93 (0.35); post-test: 1.37 (0.57) ($n = 21$) Arm 3: pre-test: 1.96 (0.37); post-test: 0.91 (0.58) ($n = 30$) Arm 1 > Arm 2, $p < 0.05$; Arm 3 > Arm 2, $p < 0.05$	Vocabulary Grade: (at post test) mean (SD) Arm 1: pre-test: 2.95 (1.33); post-test: 3.44 (1.65) ($n = 21$) Arm 2: pre-test: 2.81 (2.27); post-test: 3.23 (2.47) ($n = 20$) Arm 3: pre-test: 2.64 (1.81); post-test: 3.34 (2.23) ($n = 29$) No significant differences between treatment arms	Not reported	Not reported
CTRS: Hyperactivity Index: (at 1 year) mean (SD) Arm 1: pre-test: 1.87 (0.34); post-test: 0.98 (0.51); 1 year: 0.96 (0.43) ($n = 16$) Arm 2: pre-test: 1.86 (0.33); post-test: 1.21 (0.52); 1 year: 1.27 (0.62) ($n = 13$) Arm 3: pre-test: 1.97 (0.37); post-test: 0.88 (0.61), 1 year: 0.96 (0.54) ($n = 22$) No significant differences between treatment arms	Vocabulary Grade: (at 1-year follow-up) mean (SD) Arm 1: pre-test: 2.94 (0.95); post-test: 3.47 (1.14); 1 year: 3.96 (1.22) ($n = 15$) Arm 2: pre-test: 3.16 (2.32); post-test: 3.56 (2.50); 1 year: 3.97 (2.39) ($n = 12$) Arm 3: pre-test: 2.64 (1.72); post-test: 3.26 (1.82); 1 year: 3.46 (1.98) ($n = 22$) No significant differences between treatment arms		
CTRS: Hyperactivity Index: (at 2 years) mean (SD) Arm 1: pre-test: 1.81 (0.38); post-test: 1.03 (0.46); 1 year: 0.92 (0.36); 2 years: 1.06 (0.59) ($n = 10$) Arm 2: pre-test: 1.83 (0.28); post-test: 1.12 (0.56); 1 year: 1.07 (0.55); 2 years: 1.09 (0.63) ($n = 9$) Arm 3: pre-test: 2.03 (0.39); post-test: 0.81 (0.44); 1 year: 0.96 (0.59); 2 years: 1.09 (0.60) ($n = 11$) No significant differences between treatment arms	Vocabulary Grade: (at 2-year follow-up) mean (SD) Arm 1: pre-test: 0.95 (3.47); post-test: 3.46 (1.22); 1 year: 3.97 (1.34); 2 years: 5.14 (1.92) ($n = 9$) Arm 2: pre-test: 2.42 (1.96); post-test: 2.51 (1.62); 1 year: 3.23 (2.16); 2 years: 4.29 (2.74) ($n = 8$) Arm 3: pre-test: 2.51 (1.35); post-test: 3.42 (1.54); 1 year: 3.56 (1.62); 2 years: 4.56 (1.70) ($n = 10$) No significant differences between treatment arms		

Conclusions	
	Authors' conclusions: This study supports previous short-term studies which suggested that stimulant medication is superior to parent training, and long-term studies which found no differences between the two interventions
	Reviewer's comments: There is a high level of attrition in this study which may impact upon results. When the data were analysed based on 'pure groups' alone, i.e. without those participants who switched treatment, no evidence was found for even a short-term advantage of MPH

Study	Intervention	Participants	Outcomes
Reference Fischer and Newby, 1991[54] **Source** CCOHTA Report **Setting** USA **Design** Crossover trial **Duration** Treatment period: 1 week per treatment **Purpose** The authors used a refined multimethod clinical protocol to assess stimulant drug response in clinic-referred ADHD children. The utility and any placebo/practice effect of the dependent measures was also evaluated	**Arm 1** MPH 0.2 mg/kg twice daily; modal dose 7.5 mg twice daily (daily: 15 mg) (Individual administering medication not reported) **Arm 2** MPH 0.4 mg/kg twice daily; modal dose 12.5 mg twice daily (daily: 25 mg) (Individual administering medication not reported) **Arm 3** Placebo Lactose placebo (Individual administering medication not reported)	**Inclusion criteria** 1. Diagnosis according to diagnostic criteria detailed 2. No history of mental retardation 3. No gross brain damage, gross sensory deficits, or severe emotional disturbance 4. No history of tic disorders or Tourette's syndrome, cardiovascular problems 5. No previous poor response to MPH after 5 years of age **Diagnostic criteria** 1. Parent and/or teacher complaints of poor sustained attention, impulsivity and restlessness 2. Behaviour problems for at least 12 months 3. Onset of problems by 6 years of age 4. Scores of 1.5 SDs above mean for same age, normal children: (a) on one of two factors: CPRS-R: impulsivity–hyperactivity factor or Achenbach CBCL: hyperactive factor; (b) and/or two of four factors: CTRS-R: hyperactivity factor; CTRS-R: inattention-passivity factor; Achenbach CBCL – Teacher Report Form (TRF): inattentive factor; Achenbach CBCL-TRF: nervous overactive factor **Number** Total randomised = 161 (male = 141) Total withdrawals = 7 Reasons for withdrawal: These children did not complete the entire protocol: parents changed mind about trial: $n = 2$; parents desired open trial: $n = 1$; experienced marked side effects: $n = 3$; parent noncompliant/possibly abusing medication: $n = 1$ **Age** 8.9 years (mean); 2.4–17.2 years (range); 2.9 years (SD) **IQ** Not reported **Co-morbid disorders** Elevated scores on CBCL: aggression and delinquency factors (mean = 69.0 and 65.8, respectively) are indicative of conduct problems **Diagnostic subtypes** Not reported **Additional information** No relevant information reported	**Core symptoms** Home Situations Questionnaire (parents): total number of problematic settings, mean severity score CPRS-R: hyperactivity index, impulsivity–hyperactivity CBCL (parents) School Situations Questionnaire (teachers): number of problem settings, mean severity ratings CTRS-R: hyperactivity index, hyperactivity, inattention–passivity CBCL-TRF **Co-existent problems** CPRS-R: conduct problems CTRS-R: conduct problems **Educational performance** Not reported **Psychological function** GDS Vigilance Task Restricted Academic Task: total, off-task, fidgeting, vocalising, playing with objects out of seat **Depression or anxiety** CPRS-R: anxiety **Quality of life** **Adverse events** CPRS-R: psychosomatic SERS (parents, teachers): number of side-effects, mean severity rating **Additional outcomes** Reaction time

Core symptoms	Educational performance	Quality of life	Adverse events
CPRS-R: total problems (mean, SD) Baseline: 53.3 (19.9), *n* = 161, range: 7–96 MPH 0.2: 34.9 (19.9) MPH 0.4: 33.6 (20.4) Placebo: 42.2 (21.2); *F* = 18.88, *p* < 0.001. Pairwise comparison: L/H > Placebo (*p* = placebo, L = low dose, H = high dose) CPRS-R: hyperactivity index Baseline: 17.8 (6.0), *n* = 161, range: 2–30 MPH 0.2: 11.7 (6.4) MPH 0.4: 11.1 (6.7) Placebo: 14.3 (6.8) *F* = 21.13, *p* < 0.001. L/H > P CPRS-R: impulsivity–hyperactivity Baseline: 7.8 (3.2), *n* = 161, range: 0–17 MPH 0.2: 5.1 (3.0) MPH 0.4: 4.8 (3.1) Placebo: 6.6 (3.4) *F* = 28.16, *p* < 0.001. Pairwise comparison: L/H > P CTRS-R: total problems Baseline: 39.2 (16.8), *n* = 161, range: 5–81 MPH 0.2: 25.7 (16.3) MPH 0.4: 21.3 (14.7) Placebo: 34.0 (19.4) *F* = 40.62, *p* < 0.001. Pairwise comparison: L/H > P, H > L CTRS-R: hyperactivity index Baseline: 16.4 (7.2), *n* = 161, range: 0–31 MPH 0.2: 9.9 (6.6) MPH 0.4: 8.4 (6.3) Placebo: 13.7 (7.6) *F* = 44.47, *p* < 0.001. Pairwise comparison: H/L > P	Not reported	Not reported	SERS (parents): number of side-effects MPH 0.2: 5.7 (3.5) MPH 0.4: 5.8 (3.5) Placebo: 5.7 (3.7) *F* = 0.20, NS SERS (parents): mean severity rating MPH 0.2: 3.2 (1.7) MPH 0.4: 3.3 (1.8) Placebo: 3.5 (1.8) *F* = 1.77, NS SERS (teachers): number of side-effects MPH 0.2: 4.2 (2.8) MPH 0.4: 4.1 (3.0) Placebo: 4.5 (2.9) *F* = 1.15, NS SERS (teachers): mean severity rating MPH 0.2: 3.3 (1.9) MPH 0.4: 3.1 (1.9) Placebo: 3.8 (2.0) *F* = 7.74, *p* < 0.001. Pairwise comparison: H/L > P

continued

Core symptoms	Educational performance	Quality of life	Adverse events
CTRS-R: hyperactivity Baseline: 11.8 (6.2), $n = 161$, range: 0–21 MPH 0.2: 7.1 (5.5) MPH 0.4: 6.0 (4.9) Placebo: 9.5 (5.8) $F = 32.33$, $p < 0.001$. Pairwise comparison: H/L > P, H > L			
CTRS-R: inattention-passivity Baseline: 13.2 (5.4), $n = 161$, range: 1–24 MPH 0.2: 9.1 (5.2) MPH 0.4: 7.7 (5.3) Placebo: 11.0 (5.7) $F = 31.88$, $p < 0.001$. Pairwise comparison: H/L > P, H > L			
Home Situations Questionnaire (parents): total number of problematic settings Baseline: 9.3 (4.1), $n = 161$, range: 0–16 MPH 0.2: 7.9 (4.5) MPH 0.4: 7.4 (4.5) Placebo: 8.7 (4.4) $F = 11.61$, $p < 0.001$. Pairwise comparison: H/L > P			
Home Situations Questionnaire (parents): mean severity score Baseline: 4.3 (1.7), $n = 161$, range: 0–9 MPH 0.2: 3.3 (1.8) MPH 0.4: 3.1 (1.8) Placebo: 4.1 (2.0) $F = 23.23$, $p < 0.001$. Pairwise comparison: H/L > P			
School Situations Questionnaire (teachers): number of problem settings Baseline: 6.9 (3.6), $n = 161$, range: 0–12 MPH 0.2: 4.8 (3.2) MPH 0.4: 4.7 (3.6) Placebo: 5.8 (3.4) $F = 14.59$, $p < 0.001$. Pairwise comparison: H/L > P			

continued

Core symptoms	Educational performance	Quality of life	Adverse events
School Situations Questionnaire (teachers): mean severity ratings Baseline: 4.3 (1.9), $n = 161$, range: 0–7.6 MPH 0.2: 3.1 (2.0) MPH 0.4: 2.7 (1.9) Placebo: 4.0 (2.3) $F = 32.14$, $p < 0.001$. Pairwise comparison: H/L > P			
Conclusions	**Authors' conclusions:** The authors conclude that the data indicate a statistically significant medication reponse on most measures, in addition to a significant difference between the low and moderate doses on some measures **Reviewer's comments:** No comments noted		

Study	Intervention	Participants	Outcomes
Reference Fitzpatrick *et al.*, 1992[55] **Source** AHRQ Report **Setting** USA **Design** Crossover trial **Duration** Total treatment period: 8 weeks (2 weeks per treatment arm) **Purpose** The authors compared the relative effectiveness of standard and sustained-release MPH and investigated the hypothesis that a combined regimen is superior to either individual preparation	**Arm 1** MPH <30 kg: 2 capsules (a.m.): 1 × 7.5 mg standard MPH, 1 x placebo matching sustained-release MPH; 1 capsule (p.m.): 1 × 7.5 mg standard MPH >30 kg: 2 capsules (a.m.): 1 × 10 mg standard MPH, 1 x placebo matching sustained-release MPH; 1 capsule (p.m.): 1 × 10 mg standard MPH Mean dose 0.6 ± 0.08 mg/kg/day (Administered by parent and school nurse) **Arm 2** MPH 2 capsules (a.m.): 1 × 20 mg sustained-release MPH, 1 × placebo matching standard MPH; 1 capsule (p.m.): 1 x placebo matching standard MPH Mean dose 0.7 ± 0.14 mg/kg/day (Administered by parent and school nurse) **Arm 3** MPH <30 kg: 2 capsules (a.m.): 1 × 5 mg standard MPH; 1 × 20 mg sustained-release MPH; 1 capsule (p.m.): 1 x 5 mg standard MPH >30 kg: 2 capsules (a.m.): 1 × 7.5 mg standard MPH; 1 x 20 mg sustained-release MPH; 1 capsule (p.m.): 1 × 7.5 mg standard MPH Mean dose 0.4 ± 0.07 mg/kg/day for standard MPH, 0.7 ± 0.14 mg/kg/day for sustained-release MPH (Administered by parent and school nurse) **Arm 4** Placebo 2 capsules (a.m.): 1 × matching standard MPH, 1 × matching sustained-release MPH; 1 capsule (p.m.): matching standard MPH (Administered by parent and school nurse)	**Inclusion criteria** Fulfils criteria for diagnosis of ADD **Diagnostic criteria** DSM-III **Number** Total randomised = 19 (male = 17) No withdrawals reported **Age** 8.71 years (mean); 6.9–11.5 years (range); 1.33 years (SD) **IQ** 114.11 (mean) **Co-morbid disorders** Oppositional disorder: *n* = 12/19; CD and ODD: *n* = 1/19; enuresis: *n* = 2/19: encopresis: *n* = 2/19; phobia: *n* = 1/19; overanxious disorder: *n* = 1/19; adjustment disorder: *n* = 1/19. **Diagnostic subtypes** ADD with hyperactivity: *n* = 16/19; ADD without hyperactivity: *n* = 3/19 (cut-off defined as at least 2 positive responses to eight DICA questions on hyperactivity) **Additional information** Previous medication: 18/19 participants had never received psychotropic medication Intervention medication: 4 participants had slightly adjusted dosage schedules	**Core symptoms** Conners' Hyperactivity Index (parents, teacher) IOWA Inattention/Overactivity Scale (parents, teacher) TOTS: Hyperactivity, Attention **Co-existent problems** IOWA Aggression/Noncompliance Scale (parents, teacher) TOTS: Aggression Child Psychiatric Scale: silly/inappropriate, negative/resistant/uncooperative, loud voice, low voice **Educational performance** Not reported **Psychological function** Continuous Performance Test (CPT) Paired-associate Learning Test (PAL) **Depression or anxiety** Child Psychiatric Scale: withdrawn/unspontaneous, crying **Quality of life** Parent and teacher comments ratings Parent improvement rankings **Adverse events** STESS (parents) Weight **Additional outcomes** EEG and EOG (electroculograph) readings

Core symptoms	Educational performance	Quality of life	Adverse events
Conners' Hyperactivity Index (parents) (?mean, ?SD) (range 0–3, lower scores = better behaviour) MPH, standard: 0.96 (0.50) MPH, sustained release (SR): 0.98 (0.72) MPH, standard + SR: 0.81 (0.46) Placebo: 1.75 (0.67) Wilcoxon pairwise comparisons did not identify significant differences among MPH conditions, but indicated that placebo was ranked lower than all of the active conditions (all $p < 0.006$) Conners' Hyperactivity Index (teacher) (range 0–3, lower scores = better behaviour) MPH, standard: 0.73 (0.65) MPH, SR: 0.77 (0.63) MPH, standard + SR: 0.58 (0.40) Placebo: 1.36 (0.80) Conners' Hyperactivity: $F(3,42) = 21.96$, $p < 0.0001$ (Patients were rated by both teachers and parents behaving better in all MPH conditions than placebo, but MPH conditions did not differ from one another) IOWA Inattention/Overactivity Scale (parents) (range 0–3, lower scores = better behaviour) MPH, standard: 1.01 (0.46) MPH, SR: 0.98 (0.61) MPH, standard + SR: 0.79 (0.48) Placebo: 1.90 (0.63) IOWA Inattention/Overactivity Scale (teacher) (range 0–3, lower scores = better behaviour) MPH, standard: 0.87 (0.63) MPH, SR: 0.92 (0.68) MPH, standard + SR: 0.70 (0.56) Placebo: 1.65 (0.90) IOWA Inattention/Overactivity Scale: $F(3,42) = 23.82$, $p < 0.0001$ (Patients were rated by both teachers and parents as behaving better in all MPH conditions than placebo, but MPH conditions did not differ from one another)	Not reported	Parent comments ratings MPH, standard: 0.17 (0.44) MPH, SR: –0.05 (0.55) MPH, standard + SR: 0.18 (0.41) Placebo: –0.43 (0.42) Teacher comments ratings MPH, standard: 0.19 (0.48) MPH, SR: 0.20 (0.44) MPH, standard + SR: 0.40 (0.37) Placebo: –0.40 (0.54) TOTS Attention: $F(3,42) = 17.19$, $p < 0.0001$ (Patients were rated by both teachers and parents as behaving better in all MPH conditions than placebo, but MPH conditions did not differ from one another) Parent improvement rankings MPH, standard: 2.18 (0.78) MPH, SR: 2.16 (1.09) MPH, standard + SR: 1.87 (0.86) Placebo: 3.79 (0.38) $\chi^2(3) = 25.97$, $p < 0.0001$ (No differences among MPH conditions, but placebo ranked lower than all active conditions: all $p < 0.006$)	STESS (parents) Frequency (%) for sleep problem/appetite decrease/crying/sadness/unhappiness/anger/headaches/increased thirst/dry mouth/nausea/stomach aches/shakiness: MPH, standard: 41.1/15.8/15.8/10.5/5.3/10.5/10.5/0.0/0.0/5.3/5.3/0.0 MPH, SR: 36.8/36.8/21.0/0.0/21.0/31.6/10.5/5.3/0.0/0.0/0.0/0.0 MPH, standard + SR: 63.2/26.3/26.3/0.0/15.8/26.3/5.3/0.0/0.0/0.0/0.0/5.3 Placebo: 15.8/5.3/31.6/5.3/26.3/42.1/10.5/10.5/0.0/0.0/0.0/0.0 Sleep problems increased with MPH: $F(93,42) = 5.38$, $p < 0.01$ (only significant for combined versus placebo) No significant differences for other side-effects Weight (kg) MPH, standard: 31.41 (6.82) MPH, SR: 31.59 (7.25) MPH, standard + SR: 31.33 (7.00) Placebo: 31.94 (7.39) $F(3,41) = 10.29$, $p < 0.0006$ (Placebo weights significantly higher than combined and standard)

continued

Core symptoms	Educational performance	Quality of life	Adverse events
TOTS: Hyperactivity (parents) (range 0–3, lower scores = better behaviour) MPH, standard: 0.20 (0.31) MPH, SR: 0.22 (0.50) MPH, standard + SR: 0.18 (0.49) Placebo: 0.70 (0.48) TOTS: Attention (parents) (range 0–3, higher scores = better behaviour) MPH, standard: 0.81 (0.41) MPH, SR: 0.72 (0.38) MPH, standard + SR: 0.91 (0.44) Placebo: 0.36 (0.41) TOTS: Hyperactivity (teacher) (range 0–3, lower scores = better behaviour) MPH, standard: –0.16 (0.44) MPH, SR: –0.12 (0.51) MPH, standard + SR: –0.29 (0.56) Placebo: 0.36 (0.69) TOTS, Hyperactivity: $F(3,42) = 16.56$, $p < 0.0001$ (Patients were rated by both teachers and parents as behaving better in all MPH conditions than placebo, but MPH conditions did not differ from one another) TOTS: Attention (teacher) (range 0–3, higher scores = better behaviour) MPH, standard: 1.01 (0.57) MPH, SR: 0.88 (0.62) MPH, standard + SR: 1.05 (0.52) Placebo: 0.67 (0.62) TOTS, Attention: $F(3,42) = 11.12$, $p < 0.0001$ (Patients were rated by both teachers and parents as behaving better in all MPH conditions than placebo, but MPH conditions did not differ from one another)			
Conclusions	**Authors' conclusions:** The authors conclude that the MPH conditions were superior to placebo and comparable to each other. They state that the findings suggest comparable effectiveness for sustained-release and standard preparations of MPH **Reviewer's comments:** No comments noted		

Study	Intervention	Participants	Outcomes
Reference Gillberg *et al.*, 1997[56] **Source** AHRQ Report **Setting** Sweden **Design** Parallel trial **Duration** Treatment period: 15 months **Purpose** To evaluate the effects of amphetamine sulphate on behaviour and cognition, and adverse effects during 15 months of treatment	**Arm 1** Amphetamine sulphate Dosage was titrated from 5 mg twice daily (breakfast, lunch) to a max. of 45 mg/day. Mean dose 0.52 mg/kg/day (0.20–1.10). (Individual administering medication not reported) **Arm 2** Placebo All children received amphetamine for the first 3 months of the study (titration phase); at 3 months they were randomised to DEX or placebo. Those in the placebo group had the active drug withdrawn gradually over a 2-week period (Individual administering medication not reported)	**Inclusion criteria** 1. 6–11 years of age 2. Met at least 8 of the 14 DSM-III-R criteria for ADHD 3. IQ > 50 4. No chronic medical conditions 5. No receipt of ongoing medication (except antiepileptic drug) 6. No substandard height (below –2 SD of the norm) 7. No major psychosocial problems 8. No history of alcohol or drug abuse themselves or of their principal caretaker **Diagnostic criteria** DSM-III-R **Number** Total randomised = 62 (male = 51) Arm 1 = 32 Arm 2 = 30 Total withdrawals = 30 Arm 1 = 8 Arm 2 = 22 Randomisation procedure: Randomisation was balanced within each site and stratified for age **Age** 9 years (mean); 6–11 years (range); 1.6 (SD) **IQ** 51–72 (range) **Co-morbid disorders** Autistic disorder (1); mild mental retardation (10); ODD (8); CD (3); separation anxiety disorder (2); tics or Tourette syndrome (3). 32/62 had academic problems or special educational needs **Diagnostic subtypes** Not reported **Additional information** Previous/concurrent medication: All participants had interventions prior to the study: 2 had amphetamine therapy, 8 had been taking other drugs (neuroleptics, γ-linolenic–butyric acid and folic acid); 3 were taking carbamazepine and 1 was taking volproic acid throughout study. Participants were not to receive ongoing medication (except antiepileptic drug) during the trial	**Core symptoms** CPRS: impulsivity/hyperactivity CTRS: inattentive–passive; hyperactivity CPRS: total score CTRS: total score **Co-existent problems** CPRS: conduct problems CTRS: conduct problems **Educational performance** CPRS: inattention/learning problems CTRS: inattention/learning problems **Psychological function** WISC-R **Depression or anxiety** CTRS: anxious–fearful Birleson Depression Self-report Scale McGrath Test **Quality of life** Not reported **Adverse events** Incidence of 20 adverse events **Additional outcomes** Height, weight, pulse, blood pressure

Core symptoms	Educational performance	Quality of life	Adverse events
CPRS: impulsivity/hyperactivity (DEX > placebo, $p < 0.001$) CTRS: inattentive–passive; hyperactivity (DEX > placebo, $p < 0.01$ for both) Results were presented in graph form and actual scores could not be extracted; no SDs presented CPRS: total score (DEX > placebo, $p < 0.001$) CTRS: total score (DEX > placebo, $p < 0.01$) Results were presented in graph form and actual scores could not be extracted; no SDs presented	Not reported	CPRS: total score (DEX > placebo, $p < 0.001$) CTRS: total score (DEX > placebo, $p < 0.01$) Results were presented in graph form and actual scores could not be extracted; no SDs presented	Withdrawals: severe tics and hallucinations ($n = 1$), hallucinations only ($n = 2$) Adverse events (patients reporting as occasionally or often) baseline/6 months for amphetamine ($n = 40$)/placebo ($n = 16$) (No. (%): Difficulty falling asleep: 18 (33%)/14 (35%)/3 (19%) Early awakenings: 13 (25%)/6 (15%)/4 (25%) Disturbed sleep: 15 (28%)/9 (23%)/2 (12%) Increased need to sleep: 6 (11%)/1 (2%)/2 (12%) Headache: 7 (13%)/10 (25%)/3 (19%)a Abdominal pain: 9 (17%)/5 (12%)/1 (6%) Diarrhoea: 3 (6%)/1 (2%)/1 (6%) Constipation: 3 (6%)/1 (2%)/0 (0%) Dry mouth: 4 (7%)/5 (12%)/1 (6%) Nausea, vomiting: 3 (6%)/5 (12%)/1 (6%) Tics: 9 (17%)/8 (20%)/5 (31%) Stereotypes: 2 (4%)/5 (12%)/1 (6%) Anxiety, nervousness: 18 (33%)/11 (28%)/7 (44%) Dysthymia: 4 (7%)/9 (23%)/2 (13%) Euphoria, hypomania: 22 (41%)/4 (10%)/4 (25%) Palpitation: 0 (0%)/2 (5%)/0 (0%)

continued

Core symptoms	Educational performance	Quality of life	Adverse events
			Dizziness: 0 (0%)/1 (2%)/0 (0%) Decreased appetite: 2 (4%)/17 (42%)/2 (12%); placebo > amphetamine, $p < 0.05$ Increased appetite: 7 (13%)/4 (10%)/2 (12%) Hallucinations, delusions: 0 (0%)/1 (2%)/0 (0%) (All comparisons NS except for decreased appetite)
Conclusions	**Authors' conclusions:** Amphetamine was superior to placebo in improving behaviour **Reviewer's comments:** No comments noted		

Study	Intervention	Participants	Outcomes
Reference Gittelman-Klein *et al.*, 1976[57] **Source** AHRQ Report **Setting** USA **Design** Parallel trial **Duration** Drug treatment periods: 12 weeks each; placebo treatment period: 4 weeks **Purpose** To evaluate the relative efficacy of a stimulant and a phenothiazine in the treatment of hyperkinetic children	**Arm 1** MPH Fixed dose for first 4 weeks to a maximum dosage of 60 mg/day unless noticeable side-effects occurred; MPH twice daily (a.m., lunch) and placebo once daily (night) Mean dosages (at 12 weeks) 1.66 mg/kg/day (0.83–3.08 mg/kg/day) (Individual administering medication not reported) **Arm 2** Thioridazine hydrochloride Fixed dose for first 4 weeks to a maximum dosage of 300 mg/day unless noticeable side-effects occurred; placebo twice daily (a.m., lunch) and thioridazine hydrochloride once daily (night) Mean dosage 4.54 mg/kg/day (0.99–14.38 mg/kg/day) (Individual administering medication not reported) **Arm 3** MPH and thioridazine hydrochloride Fixed dose for first 4 weeks to a maximum dosage of 60 mg/day and 300 mg/day, respectively, unless noticeable side-effects occurred; dosages to be equal for each drug; MPH twice daily (a.m., lunch) and thioridazine hydrochloride once daily (night) Mean dosage 1.59 mg/kg/day MPH (25–60 mg/day) and 3.94 mg/kg/day thioridazine hydrochloride (25–300 mg/day) (Individual administering medication not reported) **Arm 4** Placebo Three times daily (a.m., lunch, night) (Individual administering medication not reported)	**Inclusion criteria** 1. 6–12 years old 2. Attending school 3. Free of neurological disease, such as epilepsy, hemiparesis, cerebral palsy, microcephaly 4. Non-psychotic 5. WISC IQ of ≥ 80 and a sub-IQ of ≥ 85 6. A parent or responsible adult willing to come for weekly visits 7. Home telephone 8. Family fluent in English 9. No previous history of psychopharmacological treatment (more than a daily dose of 5 mg DEX or 10 mg MPH for a 2-month period). **Diagnostic criteria** DSM-II CTRS, Home Hyperactivity Scale (parents), Test Behaviour Scale (psychologists, psychiatrists) were used for diagnosis **Number** Total randomised = 166 (male = 140/155) Arm 1 = 41 Arm 2 = 41 Arm 3 = 42 Arm 4 = 42 Total withdrawals = 11 Arm 1 = 2 Arm 2 = 5 Arm 3 = 3 Arm 4 = 1 Reasons for withdrawals: Arm 1: 1/2 dropped out owing to poor family motivation; 1/2 dropped out owing to sleep difficulties Arm 2: 2/5 had extreme drowsiness, 1/5 had nosebleeds, 1/5 parents dissatisfied with lack of improvement, 1/5 did not follow prescription and stopped attending appointments	**Core symptoms** Not reported **Co-existent problems** Not reported **Educational performance** Not reported **Psychological function** Not reported **Depression or anxiety** Not reported **Quality of life** Not reported **Adverse events** Side-effects standardised form: severity and consistency **Additional outcomes** Not reported

continued

Study	Intervention	Participants	Outcomes
		Arm 3: 3/3 had substantial side-effects; 2/3 took medication irregularly and were referred elsewhere; 1/3 stopped attending appointments Arm 4: 1/1 received medication irregularly and stopped attending appointments **Age** 102.59 months (mean); 24.25 months (SD) **IQ** Not reported **Comorbid disorders** Not reported **Diagnostic subtypes** Not reported **Additional information** Previous medication: participants with a previous history of psychopharmacological treatment were excluded	

Core symptoms	Educational performance	Quality of life	Adverse events
Not reported	Not reported	Not reported	Side-effects (%) (at 4 weeks): mild effects for 1–3 days of previous week/4–7 days of previous week, moderate effects for 1–3 days of previous week/4–7 days of previous week Dizziness: placebo: 5/2; 0/0; MPH: 0/3, 0/0 Headache: placebo: 5/2, 0/0; MPH: 0/3, 0/0 Other cardiovascular: placebo: 0/0, 0,0; MPH: 0/0, 0/0 Abdominal pain: placebo: 2/0, 0/0; MPH: 5/0, 0/0 Appetite decrease: placebo: 0/2, 0/0; MPH: 8/31, 0/15 Appetite increase: placebo: 0/5, 0/0; MPH: 0/5, 0/3 Heartburn: placebo: 0/0, 0/0; MPH: 0/0, 0/0 Nausea: placebo: 0/0, 0/0; MPH: 0/3, 0/0 Vomiting: placebo: 0/0, 0/0; MPH: 0/0, 0/0 Other gastrointestinal: placebo: 0/0, 0/0; MPH: 0/0, 3/0 Difficulty falling asleep: placebo: 2/10, 0/5; MPH: 15/31, 0/21 Difficulty arousing: placebo: 2/2, 0/0; MPH: 8/15, 0/0 Drowsiness: placebo: 2/0, 0/0; MPH: 3/0, 0/0 Mask-like facial expression: placebo: 0/0, 0/0; MPH: 0/0, 0/0 Monotonous speech: placebo: 0/0, 0/0; MPH: 0/0, 0/0 Pallor: placebo: 0/0, 0/0; MPH: 0/0, 0/0 Slurred speech: placebo: 0/0, 0/0; MPH: 0/0, 0/3 Sweating: placebo: 0/0, 0/0; MPH: 0/0, 0/0 Tremor: placebo: 0/0, 0/0; MPH: 0/3, 0/0 Depression: placebo: 0/0, 0/0; MPH: 0/0, 0/0 Lethargy: placebo: 2/0, 0/0; MPH: 3/3, 0/3 Irritability: placebo: 10/7, 0/0; MPH: 15/3, 0/0 Outbursts of anger: placebo: 10/5, 0/2; MPH: 8/3, 3/0 Sadness: placebo: 5/0, 0/0; MPH: 10/3, 0/3 Sensitivity: placebo: 0/0, 0/0; MPH: 3/3, 0/10 Blurring: placebo: 0/0, 0/0; MPH: 0/3, 0/0 Other ocular: placebo: 0/0, 0/0; MPH: 0/3, 0/0 Respiratory other: placebo: 0/0, 0/0; MPH: 0/3, 0/0 Dry mouth: placebo: 0/0, 0/0; MPH: 3/3, 0/5 Nasal congestions: placebo: 0/0, 0/0; MPH: 3/0, 0/0 Other mouth and nose: placebo: 0/0, 0/0; MPH: 0/0, 0/0 Enuresis: placebo: 2/0, 0/0; MPH: 3/3, 0/0 Other genito-urinary: placebo: 0/0, 0/0; MPH: 0/3, 0/0 Rash: placebo: 0/0, 0/0; MPH: 3/3, 0/0 Other dermatology: placebo: 0/0, 0/0; MPH: 0/3, 0/0 Muscle skeletal: placebo: 0/0, 0/0; MPH: 0/0, 0/0

continued

Core symptoms	Educational performance	Quality of life	Adverse events
			No child treated with placebo or MPH had severe side-effects. See Additional information above for information on withdrawals due to side-effects
Conclusions	**Authors' conclusions:** Significant clinical improvement was obtained in a variety of settings – all treatments were superior to placebo on ratings filled out by parents, teacher and clinic staff **Reviewer's comments:** No comments noted		

Study	Intervention	Participants	Outcomes
Reference Greenberg *et al.*, 1972[58] **Source** AHRQ Report **Setting** USA **Design** Parallel trial **Duration** Treatment period: 8 weeks **Purpose** To determine the clinical efficacy of three commonly prescribed medications: chlorpromazine, dextroamphetamine and hydroxyzine, in the treatment of hyperactive children	**Arm 1** DEX Gradual titration using 5-mg capsules administered twice daily (with breakfast and mid-afternoon); dosage increased until side effects necessitated lower dose; mean dosage 25 mg/day during 4–8th weeks (Individuals administering medication not reported) **Arm 2** Chlorpromazine Gradual titration using 35-mg capsules administered twice daily (with breakfast and mid-afternoon); dosage increased until side-effects necessitated lower dose; mean dosage 125 mg/day during 4–8th weeks (Individuals administering medication not reported) **Arm 3** Hydroxyzine Gradual titration using 25-mg capsules administered twice daily (with breakfast and mid-afternoon); dosage increased until side-effects necessitated lower dose; mean dosage 150 mg/day during 4–8th weeks (Individuals administering medication not reported) **Arm 4** Placebo Twice daily (with breakfast and mid-afternoon) (Individuals administering medication not reported)	**Inclusion criteria** No explicit inclusion criteria **Diagnostic criteria** Diagnostic conference undertaken with staff paediatrician, parents and child **Number** Total randomised = 76 (male = 76) Numbers by arm not reported Total analysed = 61 Arm 1 = 17 Arm 2 = 17 Arm 3 = 17 Arm 4 = 10 Total withdrawals = 14.4% **Age** 8.7 years (mean); 6 years 6 months–11 years (range) **IQ** Full scale: 85 (mean) **Co-morbid disorders** Not reported **Diagnostic subtypes** Not reported **Additional information** No relevant information reported	**Core symptoms** Not reported **Co-existent problems** Not reported **Educational performance** Not reported **Psychological function** Not reported **Depression or anxiety** Not reported **Quality of life** Not reported **Adverse events** Incidence of side-effects (no specific scale reported) **Additional outcomes** Weight

Core symptoms	Educational performance	Quality of life	Adverse events
Not reported	Not reported	Not reported	Percentage reporting adverse events: Sleepiness: placebo: 30%; DEX: 35% No significant difference Increased appetite: placebo: 10%; DEX: 16% No significant difference Decreased appetite: placebo: 20%; DEX: 76% No significant difference Insomnia: placebo: 10%; DEX: 53% No significant difference Increased depression: placebo: 10%; DEX: 49% No significant difference Irritability: placebo: 0%; DEX: 29% No significant difference Dizziness: placebo: 0%; DEX: 23% No significant difference Headache: placebo: 10%; DEX: 41% No significant difference Stomach ache: placebo: 0%; DEX: 41% No significant difference Psychosis: placebo: 0%; DEX: 6% (n = 1; improved upon withdrawal of medication) No significant difference
Conclusions	**Authors' conclusions:** Dextroamphetamine was associated with both strongly favourable and strongly unfavourable observations, although fewer of the latter. The frequent physical and psychiatric side-effects necessitated many dosage manipulations **Reviewer's comments:** It is unclear whether side-effects were examined systematically. Data for QoL were inadequately presented to be extracted; measures of variance were not given		

Study	Intervention	Participants	Outcomes
Reference Greenhill *et al.*, 2002[59] **Source** Updated search **Setting** USA **Design** Parallel trial **Duration** 3 weeks **Purpose** To compare the efficacy, safety and tolerability of once-daily administration of modified-release MPH with placebo in children with ADHD	**Arm 1** MPH (Metadate CD): mean dose at week 3 was 40.7 mg/day (1.28 mg/kg/day); once daily (a.m.) (range from 20 to 60 mg) (Administered by parent) **Arm 2** Placebo (Administered by parent)	**Inclusion criteria** 1. 6–16 years of age 2. No co-morbid psychiatric diagnosis; history of seizure or tic disorder or a family history of Tourette's syndrome 3. IQ > 80 4. Children had to understand study instruction 5. No females who had undergone menarche 6. No use of amphetamines, PEM or an investigational drug within 30 days of study entry; concomitant use of clonidine, anticonvulsant drugs or medications known to affect blood pressure, heart rate or CNS function 7. No hyperthyroidism or glaucoma or any concurrent chronic or acute illness 8. No prior non-reponse to a trial of stimulants for ADHD 9. No previous requirement for a third daily dose in the afternoon or evening 10. No documented allergy or intolerance to MPH 11. Not currently living with anyone with a substance abuse disorder **Diagnostic criteria** DSM-IV **Number** Total randomised = 321 (male = 257?) Arm 1 = 158 Arm 2 = 163 Total withdrawals = 45 Arm 1 = 17 Arm 2 = 28 314 children were included in the ITT efficacy population (MPH: n = 155, placebo; n = 159) **Age** 9 years (mean); 5–15 years (range) **IQ** Not reported	**Core symptoms** Not reported **Co-existent problems** Not reported **Educational performance** Not reported **Psychological function** Not reported **Depression or anxiety** Not reported **Quality of life** Conners' Global Index: teacher; parent CGI-ratings **Adverse events** Teacher and Parent Side-Effect Questionnaires **Additional outcomes** Not reported

continued

Study	Intervention	Participants	Outcomes
		Co-morbid disorders Not reported **Diagnostic subtypes** Not reported **Additional information** Previous medication: There was a 1-week placebo wash-out period before study. 64% of children in both groups had been treated previously with medications for ADHD Participants were required to be medication free (amphetamines, PEM or investigational drug) in the 30 days preceding study entry Concurrent medication: Concomitant use of clonidine, anticonvulsant drugs or medications known to affect blood pressure, heart rate or CNS function excluded individuals from the trial	

Core symptoms	Educational performance	Quality of life	Adverse events
Not reported	Not reported	Conners' Global Index: teacher MPH: baseline 12.7 (7.24); 3 weeks 4.9 (4.7) Placebo: baseline 11.5 (7.35); 3 weeks 10.3 (6.9) MPH > placebo, $p < 0.001$, 95% CI: 5.26 to 8.09 Conners' Global Index: parent MPH: baseline 13.6 (6.6); 3 weeks 7.4 (5.9) Placebo: baseline 12.9 (7.6); 3 weeks 10.1 (6.7) MPH > placebo, $p < 0.001$; 95% CI: 1.7 to 4.9 CGI-Improvement ratings: CGI efficacy scores in the moderately improved range or better: MPH: 64% (98/154) Placebo: 27% (98/154) CGI-I Scores: MPH: 81% (125/154) Placebo: 50% (78/156)	2 children (MPH) discontinued treatment owing to adverse events. 52% of 155 children in the MPH group and 38% of 161 children in the placebo group spontaneously reported one or more adverse events ($p = 0.01$) Teacher scores: MPH placebo / MPH placebo Parent scores: Appetite loss: 42 (27%) / 17 (11%); 73 (47%) / 33 (20%) Dull, tired, listless: 47 (30%) / 45 (28%); 48 (31%) / 41 (26%) Crabby, irritable: 34 (22%) / 48 (30%); 70 (45%) / 79 (49%) Tearful, sad, depressed: 28 (18%) / 33 (20%); 44 (28%) / 37 (23%) Worried, anxious: 41 (26%) / 43 (27%); 36 (23%) / 39 (24%) Motor tics: 20 (13%) / 26 (16%); 11 (7%) / 8 (5%) Buccal-lingual movements: 17 (11%) / 22 (14%); 9 (6%) / 7 (4%) Picking at finger or skin, nail-biting, lip or cheek chewing: 32 (21%) / 34 (21%); 37 (24%) / 38 (24%) Stomach aches: 19 (12%) / 8 (5%); 36 (23%) / 25 (16%) Headaches: 18 (12%) / 7 (4%); 33 (21%) / 29 (18%) Trouble sleeping: Not evaluated / Not evaluated; 50 (32%) / 38 (24%) No differences between treatments were found in physical examinations performed at the end of the treatment period
Conclusions	**Authors' conclusions:** Modified-release MPH administered once daily in the morning is effective and safe in controlling ADHD symptoms throughout the day **Reviewer's comments:** No comments noted		

Study	Intervention	Participants	Outcomes
References Handen *et al.*, 1999;[60] Handen *et al.*, 2003[303] **Source** Updated search **Setting** USA **Design** Crossover trial **Duration** 3 weeks (+ 1 week baseline measures) **Purpose** To extend knowledge of safety and efficacy of MPH among preschool children with developmental disabilities as a first step towards establishing guidelines for use. To examine the rate of positive responding to MPH among the group of children	**Arm 1** MPH 0.3 mg/kg dose (up to 3 times daily) for 1 week (Individual administering medication not reported) **Arm 2** MPH 0.6 mg/kg dose (up to 3 times daily) for 1 week (Individual administering medication not reported) **Arm 3** Placebo 1 week (Individual administering medication not reported)	**Inclusion criteria** 1. No diagnosis of autism/pervasive development disorder 2. No previously prescribed stimulant medication **Diagnostic criteria** DSM-III **Number** Total randomised = 11 (male = 9) Total withdrawals = 1 Reasons for withdrawals: One child experienced significant adverse side-effects and was not given a 0.6 mg/kg dose Randomisation procedure: Seven children received two doses, two children received a third MPH dose in mid-afternoon. Lower dose always preceded higher dose **Age** 58.9 months (mean); 4–5.11 years (range) **IQ** 60 (mean) **Co-morbid disorders** ODD: *n* = 2/9 (9/11 met criteria for ADHD) **Diagnostic subtypes** Not reported **Additional information** No individuals having previously received stimulant medication were included in the trial	**Core symptoms** CTRS: conduct problems, hyperactivity, inattention–passivity, hyperactivity index Preschool Behaviour Questionnaire: Hyperactive–distractible **Co-existent problems** Preschool Behaviour Questionnaire: hostile–aggressive, anxious **Educational performance** Not reported **Psychological function** Not reported **Depression or anxiety** Not reported **Quality of life** Not reported **Adverse events** Side-effects checklist administered to preschool teachers and parents. Mean severity rating 0–6 **Additional outcomes** Waiting task Resistance to temptation Play session Compliance task Clean-up task

Core symptoms	Educational performance	Quality of life	Adverse events
CTRS: mean (SD) for placebo,0.3 mg/kg, 0.6 mg/kg Hyperactivity 14.0 (3.7), 9.0 (5.1), 6.2 (3.4), p =0.001 (*post hoc*: 0.6 mg/kg > placebo, $p < 0.05$) Inattention–Passivity 12.8 (4.3), 9.9 (3.9), 8.9 (3.7), $p = 0.03$ (*post hoc*: 0.6 mg/kg > placebo, $p < 0.05$) Hyperactivity Index 17.4 (6.0), 11.9 (5.7), 9.2 (3.8), $p = 0.006$ (*post hoc*: 0.6 mg/kg > Placebo, $p < 0.05$) Preschool Behaviour Questionnaire: mean (SD) for placebo, 0.3 mg/kg, 0.6 mg/kg Hyperactive–distractible 7.0 (1.5), 4.7 (2.5), 3.8 (1.5), $p = 0.001$ (*post hoc*: 0.6 mg/kg > placebo, $p < 0.05$)	Not reported	Not reported	Teacher-rated side-effects: mean (SD) and number of subjects experiencing adverse side-effects for placebo, 0.3 mg/kg, 0.6 mg/kg Repetitive tongue movements 0.3 (1.0) 1, 0.3 (0.7) 2, 0.4 (1.0) 2 Motor or vocal twitches 0.3 (1.0) 1, 0.3 (0.7) 2, 0.2 (0.6) 1 Nervous movements 0.4 (1.0) 2, 0.6 (1.1) 3, 0.2 (0.4) 2 Tearful, prone to crying 0.8 (1.5) 3, 0.7 (1.6) 3, 0.1 (0.3) 1 Dull, not alert 0.4 (0.7) 3, 1.5 (1.7) 6, 2.2 (2.0) 7 Sad, unhappy, depressed 0.2 (0.4) 2, 0.5 (1.6) 1, 0.6 (1.1) 3 Staring, daydreaming 1.8 (2.1) 6, 2.0 (1.6) 7, 1.7 (2.2) 5 Social withdrawal, talks less 0.4 (1.0) 2, 1.3 (1.9) 6, 2.1 (2.4) 5 Irritable 0.6 (1.0) 4, 0.9 (1.5) 3, 1.2 (1.9) 4 Poor appetite 0.1 (0.3) 1, 1.9 (2.4) 5, 3.2 (2.9) 6 Dizzy, balance unstable 0.0 (0.0) 0, 0.2 (0.7) 2, 0.0 (0.0) 0 Anxiety 0.0 (0.0) 0, 0.1 (0.3) 1, 0.3 (0.5) 3 Headaches 0.0 (0.0) 0, 0.1 (0.3) 1, 0.0 (0.0) 0 Stomach aches, nausea 0.0 (0.0) 0, 0.1 (0.3) 1, 0.0 (0.0) 0 Restless, high activity level 5.0 (1.1) 9, 3.0 (1.6) 6, 1.1 (1.6) 5 Crabby, touchy, whiny 1.0 (1.4) 4, 1.0 (1.7) 3, 0.7 (1.3) 4 Excessive talking 2.8 (2.4) 7, 1.0 (1.2) 5, 0.6 (1.1) 3 Drowsiness 0.0 (0.0) 0, 1.1 (1.8) 3, 0.6 (0.8) 4

continued

Core symptoms	Educational performance	Quality of life	Adverse events
			Number reported: 4.6 (2.1), 6.1 (4.5), 5.5 (2.7), p = NS Severity rating: 14.1 (7), 15.8 (14.6), 15 (8.7), p = NS
Conclusions	**Authors' conclusions:** Results suggest that preschool children with developmental disabilities and ADHD respond to MPH at rates similar to those of school-age children with mental retardation and ADHA. However, this population appears to be especially susceptible to adverse drug side-effects **Reviewer's comments:** The authors do not report family measures, as most families observed their children on medication for only relatively short periods (4–8 hours each Saturday/Sunday) and there was variation in the exposure of family observers		

Study	Intervention	Participants	Outcomes
Reference Hoeppner *et al.*, 1997[61] **Source** NICE Report **Setting** USA **Design** Crossover trial **Duration** Trial length: 4 weeks **Purpose** To evaluate the results of a double-blind placebo clinical protocol designed to aid practitioners in their analysis of the cognitive and behavioural effects of MPH response in children with ADHD	**Arm 1** MPH 0.15 mg/kg/dose; administered twice daily; 1 unmedicated week followed by 1 week on specified dose (Administered by parent and teacher) **Arm 2** MPH 0.3 mg/kg/dose; administered twice daily; 1 unmedicated week followed by 1 week on specified dose (Administered by parent and teacher) **Arm 3** Placebo Administered twice daily; 1 unmedicated week followed by 1 week on specified dose (Administered by parent and teacher)	**Inclusion criteria** 1. DSM-IIIR ADHD diagnosis or DSM-III ADD diagnosis or DSM-III ADD/H diagnosis 2. Score on CPRS or CTRS of 1.5 SDs above norm **Diagnostic criteria** DSM-III **Number** Total = 50 (male = 39) No withdrawals reported **Age** 115.6 months (mean); 73–218 months (range); 31.7 months (SD) **IQ** Not reported **Co-morbid disorders** Not reported **Diagnostic subtypes** DSM-III ADD/H: *n* = 25/50 DSM-III ADD no hyperactivity: *n* = 5/50 DSM-IIIR ADHD: *n* = 20/50 **Additional information** Previous/concurrent medication: Participants had either never been prescribed stimulant medication or received an appropriate washout period before the trial	**Core symptoms** CPRS: Hyperactivity Index CTRS: Hyperactivity Index **Co-existent problems** Not reported **Educational performance** Not reported **Psychological function** Children's Selective Reminding Test Cancellation of Rapidly Recurring Target Figures Go No-Go Test GDS Delay Task GDS Vigilance Task **Depression or anxiety** Not reported **Quality of life** Not reported **Adverse events** Not reported **Additional outcomes** Not reported

Core symptoms	Educational performance	Quality of life	Adverse events
CPRS: Hyperactivity Index. Mean (SD) at baseline for total group and post-test scores: Placebo: 12.16 (6.78)/8.40 (6.59) Low dose: 12.16 (6.78)/7.91 (7.21) High dose: 12.16 (6.78)/7.13 (6.37) L/H > placebo. *p*-Values not reported for direct comparisons CTRS: Hyperactivity Index. Mean (SD) at baseline for total group and post-test scores: Placebo: 14.23 (8.31)/13.54 (8.66) Low dose: 14.23 (8.31)/8.48 (7.42) High dose: 14.23 (8.31)/8.20 (6.85) L/H > placebo. *p*-Values not reported for direct comparisons.	Not reported	Not reported	Not reported
Conclusions	**Authors' conclusions:** The authors drew conclusions regarding the sensitivity of measuring instruments rather than on the effectiveness of MPH **Reviewer's comments:** No comments noted		

Study	Intervention	Participants	Outcomes
Reference James *et al.*, 2001[62] **Source** Updated search **Setting** USA (research school) **Design** Crossover trial **Duration** 8 weeks double-blind followed by 2 weeks open treatment optimisation **Purpose** To compare the efficacy and time course of single morning doses of Adderall and extended-release and immediate-release dextroamphetamine sulfate	**Arm 1** Adderall plus non-drug intervention 5–30 mg/kg in two doses, one each week for 2 weeks. Doses based on age, weight, prior medication experience and symptom severity. See additional information (Administered by parent) **Arm 2** DEX plus non-drug intervention Extended release; 5–30 mg/kg in two doses, one each week for 2 weeks. Doses based on age, weight, prior medication experience and symptom severity. See additional information (Administered by parent) **Arm 3** DEX plus non-drug intervention Immediate release; 5–30 mg/kg in two doses, one each week for 2 weeks. Doses based on age, weight, prior medication experience and symptom severity. See additional information (Administered by parent) **Arm 4** Placebo plus non-drug intervention See additional information (Administered by parent) Overall mean low dose was 7.8 mg (range 5–25 mg, 0.24 mg/kg), and the mean high dose was 12.8 mg (range 10–30 mg, 0.39 mg/kg)	**Inclusion criteria** 1. History of severe hyperactivity, impulsivity and inattention who meet DSM-IV criteria for combined-type ADHD 2. Full-scale IQ >80 on WISC-III 3. No chronic medical or neurological disease including Tourette's disorder, chronic tic disorder, pervasive developmental disorders and mood or anxiety disorders requiring current treatment **Diagnostic criteria** DSM-IV **Number** Total randomised = 35 (male = 21) Total withdrawals = 0 **Age** 9.1 years (mean); 6.9–12.2 years (range); 1.5 years (SD) **IQ** 99.8 (mean) **Co-morbid disorders** ODD: *n* = 10, anxiety disorder: *n* = 12; enuresis: *n* = 3; dysthymic disorder: *n* = 2; and learning disorder: *n* = 6 **Diagnostic subtypes** All participants had combined-type ADHD **Additional information** Previous medication: 15 subjects were naïve to stimulant treatment prior to participation All psychotropic medications were discontinued prior to beginning the study with 3-week medication-free observation period	**Core symptoms** CTRS: Hyperactive/Impulsive Children's Psychiatric Rating Scale: Hyperactivity (recreation therapist rated) CPRS: Hyperactive/Impulsive (for 28 most recently enrolled subjects) **Co-existent problems** Not reported **Educational performance** 5-minute timed maths task (arithmetic problems) **Psychological function** Not reported **Depression or anxiety** Not reported **Quality of life** Not reported **Adverse events** Stimulant SERS (nurse) Barkley SERS (parent) **Additional outcomes** Weight

Core symptoms	Educational performance	Quality of life	Adverse events
CTRS: hyperactivity (9 a.m. to 12.30 p.m.): mean (SD) for Adderall/DEX-ER/DEX-IR/placebo: 50.6 (5.6)/53.7 (9.1)/50.5 (5.4)/63.1(12.6), $F = 15.7$, $p < 0.001$ DEX-IR, which did not differ significantly from Adderall, decreased teacher-rated hyperactivity significantly more than DEX-ER ($p = 0.025$). Higher doses were significantly more effective than lower doses for all three medications [$F(1,34) = 5.38$, $p = 0.03$] Conners' Psychiatric Rating Scale: hyperactivity between (1 and 3 p.m.): Mean (SD) for Adderall/DEX-ER/DEX-IR/placebo: 2.8 (1.0)/2.3 (1.0)/2.5 (1.1)/3.8 (1.1), $F = 35$, $p < 0.001$ Across doses, all three active drugs were significantly more effective than placebo ($p < 0.001$) A higher dose was significantly more effective than a lower dose [$F(1,31) = 8.65$, $p = 0.006$] DEX-ER decreased hyperactive behaviour significantly more than Adderall ($p = 0.04$) CPRS Hyperactivity score (between 4 p.m. and 7 p.m.): Mean (SD) for Adderall/DEX-ER/DEX-IR/placebo: 58.3 (13.1)/60 (15.6)/60.5 (14.7)/68, (14.5), $F = 5.8$ $p = 0.01$ DEX-ER and Adderall showed significant improvement over placebo ($p = 0.007$ and 0.03 respectively)	Total attempted maths problems: mean (SD) for Adderall/DEX-ER/DEXs-IR/placebo 171.6 (56.4)/187.0 (60.9)/177.4 (42.9)/147.7 (50.7), $F = 6.3$, $p = 0.002$. Stimulants significantly increased the number of maths problems attempted. DEX-IT and DEX-ER both significantly increased the number of problems attempted relative to placebo ($p = 0.01$ and 0.003, respectively) Total correct maths problems: mean (SD) for Adderall/DEX-ER/DEX-IR/placebo 164.6(55.9)/177.6(61.1)/167.6(41.2)/140.2 (51.3) $F = 5.6$, $p = 0.003$. DEX-IR and DEX-ER significantly increased the number of problems done correctly compared with placebo ($p = 0.02$ and 0.003, respectively)	Not reported	Barkley's SERS (nurse): number of side effects: Mean (SD) for Adderall/DEX-ER/DEX-IR/placebo 3.3(2.0)/2.9(1.8)/2.6(1.8)/2.0(1.9), $F(3,23) = 3.94$, $p = 0.02$ Nurse ratings revealed a significantly increased number of adverse effects. Adderall had significantly greater number of adverse effects than placebo ($p = 0.04$) Barkley's SERS (nurse) severity of reported adverse effects: Mean (SD) for Adderall/DEX-ER/DEX-IR/placebo 2.7(1.5)/3.1(2.0)/2.7(1.7)/1.8(1.2), $F = 3.6$, $p = 0.03$ Nurse ratings revealed a greater mean severity of reported adverse effects, $F(3,23) = 3.56$, $p = 0.03$. DEX-ER had significantly greater severity of reported adverse effects compared with placebo ($p = 0.02$) Barkley's SERS (parent) Number of side effects: Mean (SD) for Adderall/DEX-ER/DEX-IR/placebo 6.3(2.7)/6.7(2.9)/6.4(3.5)/5.9(3.2), $F = 0.3$, $p = $ NS Barkley's SERS (parent) severity of reported side effects: Mean (SD) for Adderall/DEX-ER/DEX-IR/placebo 3.2(1.2)/3.7(1.5)/3.2(1.6)/2.8(1.5), $F = 2.2$, $p = $ NS Mean magnitude of adverse effects rated by parents and staff nurse for Adderall/DEX-ER/DEX-IR/placebo Trouble sleeping, nightmares, daydreams, talks less with others, uninterested in others, irritable, stomach aches, headaches, drowsiness, sadness/happiness, prone to crying, anxiousness, bites fingernails, euphoric, dizziness, tics, $p = $ NS Poor appetite, $p = <0.001$. All three stimulants significantly decreased body weight [$F(3,32) = 13.42$, $p < 0.001$]
Conclusions	**Authors' conclusions:** All three drugs exhibited robust efficacy versus placebo on nearly all measures. The effects of DEX-ER were less robust in the morning, particularly compared with Adderall, but they lasted 3–6 hours longer, depending on the measure. Although parent behaviour ratings and locomotor activity showed improvements up to 12 hours after single doses of all three drugs, the number of maths problems attempted and completed correctly 4 hours after dosing were only robustly increased by DEX-ER. Both immediate-release amphetamines (DEX-IR and Adderall) demonstrated earlier onset of effects, but DEX-ER showed more sustained effects that were present on a wider range of measures **Reviewer's comments:** No comments noted		

Study	Intervention	Participants	Outcomes
Reference Kelsey *et al.*, 2004[63] **Source** Updated search **Setting** USA **Design** Parallel trial **Duration** 8 weeks **Purpose** To assess the efficacy of once-daily ATX therapy in the evening and early morning among children with ADHD	**Arm 1** ATX Mean final dose was 1.3 (0.3) mg/kg/day (44.5 mg/day); administered once daily (a.m.) (range 10–89 mg/day) (Administered by parent) **Arm 2** Placebo (Individual administering medication not reported)	**Inclusion criteria** 1. 6–12 years 2. Symptom severity score at least 1.5 SDs above age and gender normative values 3. No serious medical illness 4. No history of psychosis or bipolar disorder 5. No alcohol or drug abuse within the past 3 months 6. No ongoing use of psychoactive medications other than the study drug **Diagnostic criteria** DSM-IV **Number** Total randomised = 197 (male = 139) Arm 1 = 133 Arm 2 = 64 Total withdrawals = 43 Arm 1 = 26 Arm 2 = 17 Reasons for withdrawals: Adverse events: Arm 1: *n* = 6 Arm 2: *n* = 1 **Age** 9.5 years (mean); 1.8 years (SD) **IQ** Not reported **Co-morbid disorders** ODD: 35%; CD: 4% **Diagnostic subtypes** Combined: 69%; hyperactive/impulsive: 4%; inattentive: 27% **Additional information** Previous medication: All participants underwent a minimum 5-day, medication-free evaluation period before randomisation. 52% of the participants had previous stimulant treatment Concurrent medication: Participants were not to be in receipt of any psychoactive medications other than the study drug during the trial	**Core symptoms** ADHD-RS: total score; inattentive subscore; hyperactive/impulsive subscore (investigator rated) Conners' Global Index: Parent-Evening: total score; restless–impulsive **Co-existent problems** Conners' Global Index: Parent-Evening: (GIPE): emotional liability **Educational performance** Not reported **Psychological function** Not reported **Depression or anxiety** Not reported **Quality of life** Clinical Global Impressions-ADHD-Severity (CGI-ADHD-S) **Adverse events** Vital signs, electrocardiograms, adverse events collected with open-ended questioning and clinical laboratory tests **Additional outcomes** Daily Parent Ratings of Evening and Morning Behaviour – Revised: total score; evening subscore; problems with homework/tasks; difficulty sitting through dinner; difficulty playing quietly in p.m.; inattentive and distractable in p.m.; difficulty transitioning; arguing or struggling in p.m.; difficulty settling at bedtime; difficulty falling asleep; morning subscore; difficulty getting out of bed; difficulty getting ready; arguing or struggling in a.m.

Core symptoms	Educational performance	Quality of life	Adverse events
Not reported	Not reported	Clinical Global Impressions-ADHD-Severity (baseline/end-point/change) ATX (n = 126): 5.0 (0.8)/3.5 (1.3)/–1.6 (1.4) Placebo (n = 60): 5.0 (0.8)/4.3 (1.0)/–0.7 (1.1) (ATX > placebo, $p < 0.05$), 95% CI for difference from placebo: –1.2 to 5	Withdrawals: Six ATX-treated participants, and 1 placebo-treated participant discontinued because of adverse events Treatment-emergent adverse events report by ≥5% of participants in either group

	ATX (n = 131)	Placebo (n = 63)
Decreased appetite PLA > ATX, p = 0.05	23 (17.6%)	4 (6.3%)
Abdominal pain	20 (15.3)	4 (6.3)
Nausea	15 (11.5)	5 (7.9)
Somnolence PLA > ATX, p = 0.05	19 (14.5)	1 (1.6)
Headache	9 (6.9)	9 (14.3)
Fatigue PLA > ATX, p = 0.05	13 (9.9)	1 (1.6)
Dyspepsia	8 (6.1)	1 (1.6)
Vomiting	8 (6.1)	1 (1.6)
Diarrhoea	2 (1.5)	4 (6.3)

Conclusions	**Authors' conclusions:** The authors state that once-daily administration of ATX in the morning provided safe, rapid, continuous symptom relief that lasted into the evening hours and also into the morning hours. ATX treatment was safe and well tolerated **Reviewer's comments:** No comments reported

Study	Intervention	Participants	Outcomes
Reference Kemner *et al.*, 2004[99]		**[Confidential information removed]**	

Core symptoms	Educational performance	Quality of life	Adverse events
[Confidential information removed]			
Conclusions	**Authors' conclusions: [Confidential information removed]** **Reviewer's comments: [Confidential information removed]**		

Study	Intervention	Participants	Outcomes
Reference Klein and Abikoff, 1997[65] **Source** AHRQ report **Setting** USA **Design** Parallel trial **Duration** Treatment period:12 weeks **Purpose** To assess, in hyperactive children: 1. Relative efficacy of behaviour therapy, MPH and their combination 2. Effects of MPH withdrawal after combined treatment 3. Normalisation effects of the combination	**Arm 1** MPH Gradual titration to a maximum of 60 mg/day for optimal efficacy provided no significant side-effects occurred; mean dosage (for first 8 weeks) 1.55 mg/kg/day (Individual administering medication not reported) **Arm 2** MPH plus non-drug intervention Gradual titration to a maximum of 60 mg/day for optimal efficacy provided no signficant side-effects occurred; mean dosage (for first 8 weeks) 1.48 mg/kg/day; MPH for 8 weeks then 4 weeks of placebo BT included parent and teacher education, individualised assessment of child, reinforcement via contract. No formal programme weeks 9–12. (Administered by parent, therapist, teacher) **Arm 3** Placebo and non-drug intervention Behavioural intervention incorporated parent and teacher education, individualised assessment of child, reinforcement via contract. No formal programme weeks 9–12. (Administered by parent, therapist, teacher)	**Inclusion criteria** 1. 6 to 12 years 2. Attending elementary school 3. Free of neurological, tic and psychotic disorders plus no CD 4. Verbal IQ or performance IQ of at least 85 on the WISC-R 5. Parental consent 6. No current or past psychostimulant treatment 7. Meeting severity criteria for hyperactivity (1.8–3.0) Hyperactivity factor score on CTRS and parental reports of behavioural problems at home or observation in clinic) **Diagnostic criteria** Other Clinical psychiatric examinations to confirm pervasive ADHD symptoms carried out with child and parent; school history taken into account **Number** Total randomised = 86 (male = 81) Arm 1 = 29 Arm 2 = 29 Arm 3 = 28 Total withdrawals = 3 [The dropouts are not included in the analyses or sample information (i.e. 89 began the trial)] **Age** 7.8 years (mean); 1.4 years (SD) **IQ** Not reported **Co-morbid disorders** 'Relatively free' of co-morbid anxiety, depression and CD (see Inclusion criteria) **Diagnostic subtypes** Not reported **Additional information** Previous medication: Note that included subjects were required not to have been on stimulant treatment in the past 4 weeks	**Core symptoms** CTRS: overall severity, inattention and hyperactivity Hillside Behaviour Scale: concentration, interest in tasks, impulse control and gross motor activity (teachers, mothers, psychologists, blinded observers) CPRS: impulsivity and hyperactivity Home Hyperactivity Scale (parents) Children's Psychiatric Rating Scale: fidgetiness, hyperactivity and distractibility Classroom Code: off-task, minor and gross motor activity, out of chair (blinded observers) Overall Severity Index (blinded observers) **Co-existent problems** CTRS: conduct problems, sociability Hillside Behaviour Scale: frustration tolerance, initiating aggressive behaviour with peers, joining aggressive activities, cooperation, attitude towards work, attention seeking behaviour and popularity (teachers, mothers, psychologists, blinded observers) CPRS: conduct problems, immaturity, psychosomatic, obsessional and antisocial Children's Psychiatric Rating Scale: angry affect, temper outbursts, negative and pressure of speech Classroom Code: aggression, verbal aggression, interference, non-compliance and solicitation (blinded observers) **Educational performance** WRAT: Reading, Arithmetic, Spelling **Psychological function** MFFT Paired-Associate Test **Depression or anxiety** CTRS: anxiety CPRS: anxiety **Quality of life** CGI (teachers, mothers and psychiatrists) **Adverse events** No specific scale **Additional outcomes** WISC-R: verbal IQ, performance IQ, full-scale IQ

Core symptoms	Educational performance	Quality of life	Adverse events
CTRS: overall severity. Adjusted mean (SD) factor scores before/after treatment (12 weeks) Arm 1: 2.7 (0.5)/1.2 (1.0), $n = 29$ Arm 2: 2.7 (0.6)/0.9 (0.8), $n = 29$ Arm 3: 2.9 (0.4)/2.1 (0.9), $n = 28$ MPH > BT ($t = 3.57$, $p = 0.003$); comb > BT ($t = 5.32$, $p = 0.001$); MPH vs comb (not significant) CTRS: inattention. Adjusted mean (SD) factor scores before/after treatment (12 weeks) Arm 1: 1.7 (0.6)/0.9 (0.5), $n = 29$ Arm 2: 1.7 (0.5)/0.7 (0.5), $n = 29$ Arm 3: 1.7 (0.6)/1.2 (0.6), $n = 28$ Comb > BT ($t = 3.77$, $p = 0.001$); other comparisons not significant CTRS: hyperactivity. Adjusted mean (SD) factor scores before/after treatment (12 weeks) Arm 1: 2.5 (0.4)/1.1 (0.4), $n = 29$ Arm 2: 2.3 (0.3)/0.8 (0.4), $n = 29$ Arm 3: 2.3 (0.4)/1.5 (0.6), $n = 28$ MPH > BT ($t = 3.02$, $p = 0.01$); comb > BT ($t = 5.28$, $p = 0.001$); MPH vs comb (not significant) CPRS: impulsivity. Adjusted mean (SD) factor scores before/after treatment (12 weeks) Arm 1: 1.1 (0.6)/0.7 (0.8), $n = 28$ Arm 2: 1.0 (0.4)/0.5 (0.5), $n = 28$ Arm 3: 1.4 (0.7)/0.8 (0.7), $n = 27$ No significant differences CPRS: hyperactivity. Adjusted mean (SD) factor scores before/after treatment (12 weeks) Arm 1: 1.2 (0.2)/0.7 (0.5), $n = 28$ Arm 2: 1.1 (0.1)/0.6 (0.3), $n = 28$ Arm 3: 1.1 (0.2)/0.8 (0.4), $n = 27$ No significant differences Hillside Behaviour Scale: concentration (teachers). Adjusted mean (SD) factor scores before/after treatment (12 week) Arm 1: 3.3 (0.8)/2.2 (0.8), $n = 25$ Arm 2: 3.2 (0.7)/1.8 (0.6), $n = 23$ Arm 3: 3.1 (0.7)/2.6 (0.8), $n = 25$ Comb > BT ($t = 3.89$, $p = 0.001$); other comparisons not significant	Wide Range Achievement Test: Reading: mean (SD) scores before/after treatment Arm 1: 3.40 (1.6)/3.9 (1.9) Arm 2: 3.1 (1.9)/3.7 (2.0) Arm 3: 3.4 (1.6)/3.73 (1.8) No significant differences Wide Range Achievement Test: Arithmetic: mean (SD) scores before/after treatment Arm 1: 3.0 (1.2)/3.3 (1.1) Arm 2: 2.7 (1.3)/3.2 (1.4) Arm 3: 2.8 (0.9)/3.12 (1.0) No significant differences Wide Range Achievement Test: Spelling: mean (SD) scores before/after treatment Arm 1: 3.0 (1.6)/3.3 (1.6) Arm 2: 2.7 (2.0)/3.1 (1.8) Arm 3: 2.8 (1.3)/3.05 (1.2) No significant differences	CGI (teacher/mothers/psychiatrists). Improvement rates [n (%)] after 8 weeks of treatment Arm 1: 20 (69%)/22 (76%)/23 (79%), $n = 29$ Arm 2: 27 (93%)/27 (93%)/28 (97%), $n = 29$ Arm 3: 18 (57%)/18 (64%)/14 (50%), $n = 28$	Not reported

continued

Core symptoms	Educational performance	Quality of life	Adverse events
Hillside Behaviour Scale: interest in tasks (teachers). Adjusted mean (SD) factor scores before/after treatment (12 weeks) Arm 1: 3.2 (1.0)/2.2 (0.7), $n = 25$ Arm 2: 3.1 (0.8)/2.1 (0.8), $n = 23$ Arm 3: 3.0 (0.6)/2.9 (0.9), $n = 25$ MPH > BT ($t = 3.07$, $p = 0.01$); comb > BT ($t = 3.24$, $p = 0.006$); MPH vs comb (not significant)			
Hillside Behaviour Scale: impulse control (teachers). Adjusted mean (SD) factor scores before/after treatment (12 weeks) Arm 1: 4.5 (0.9)/2.8 (0.8), $n = 25$ Arm 2: 4.4 (0.8)/2.1 (0.6), $n = 23$ Arm 3: 4.2 (1.0)/3.6 (1.0), $n = 25$ MPH > BT ($t = 3.08$, $p = 0.01$); comb > MPH ($t = 3.42$, $p = 0.003$); comb > BT (6.27, $p = 0.0001$)			
Hillside Behaviour Scale: gross motor activity (teachers). Adjusted mean (SD) factor scores before/after treatment (12 weeks) Arm 1: 5.1 (1.2)/2.2 (1.2), $n = 25$ Arm 2: 4.8 (1.3)/1.6 (0.8), $n = 23$ Arm 3: 4.8 (1.4)/3.4 (1.7), $n = 25$ MPH > BT ($t = 3.08$, $p = 0.01$); comb > BT ($t = 4.69$, $p = 0.0001$), MPH vs comb (not significant)			
Home Hyperactivity Scale (parents). Adjusted mean (SD) scale scores before/after treatment (12 weeks) Arm 1: 3.7 (0.87)/2.1 (0.46), $n = 29$ Arm 2: 3.6 (0.87)/1.8 (0.51), $n = 28$ Arm 3: 3.4 (0.75)/2.4 (0.86), $n = 28$ No significant differences			
Overall Severity Index (blinded observers). Adjusted mean (SD) ratings before/after treatment (12 weeks) Arm 1: 1.9 (0.6)/1.0 (0.8), $n = 28$ Arm 2: 2.0 (0.5)/0.7 (0.7), $n = 29$ Arm 3: 2.0 (0.6)/1.9 (0.8), $n = 28$ MPH > BT ($t = 4.42$, $p = 0.0001$); comb > BT ($t = 5.59$, $p = 0.0001$); MPH vs comb (not significant)			
Hillside Behaviour Scale: concentration, interest in tasks, impulse control and gross motor activity (parents, psychologists, blinded observers)			
Children's Psychiatric Rating Scale: fidgetiness, hyperactivity and distractibility			

continued

Core symptoms	Educational performance	Quality of life	Adverse events
Classroom Code: off-task, minor and gross motor activity, out of chair (blinded observers)			
Conclusions	**Authors' conclusions:** BT delivered in school and home is not nearly as effective as MPH for ADHD, but may be a useful adjunct to MPH **Reviewer's comments:** No comments noted		

Study	Intervention	Participants	Outcomes
Reference Klorman *et al.*, 1987[66,304] **Source** AHRQ Report **Setting** USA **Design** Crossover trial **Duration** Total treatment period: 6 weeks (3 weeks per treatment arm) **Purpose** To determine whether MPH has a similar beneficial impact on ADD adolescents as previously found for prepubertal ADD patients	**Arm 1** MPH Week 1: 10 mg at breakfast and lunch; 5 mg at 4 p.m. Weeks 2 and 3: 15 mg at breakfast and lunch; 10 mg at 4 p.m. (Individual administering medication not reported) **Arm 2** Placebo (PLA) Lactose capsules administered 3 times daily (breakfast, lunch, 4 p.m.) (Individual administering medication not reported)	**Inclusion criteria** 1. ⩾2 SDs above mean on Abbreviated Conners' Hyperactivity Questionnaire 2. ⩾2 SDs above mean on Home Activity Scale 3. No evidence of organic brain disorder, psychosis or uncorrected sensory impairment 4. IQ score =74 on WAIS-R or WISC-R 5. No MPH treatment for 2 weeks or MPH/thioridazine treatment for 4 weeks preceding trial **Diagnostic criteria** See inclusion criteria **Number** Total randomised = 19 (male = 16) Arm 1 = 19 Arm 2 = 19 No withdrawals reported **Age** 14.80 years (mean); 1.91 years (SD); 12–19 years (range) **IQ** 100.58 (mean) **Co-morbid disorders** Not reported **Diagnostic subtypes** Not reported **Additional information** Previous medication: 13/19 had been treated with MPH, sometimes supplemented with thioridazine. 5/19 had never received medication. 1/19 had previously received PEM Participants were required not to receive MPH for 2 weeks or combined MPH/thiroridazine treatment for 4 weeks preceding the trial	**Core symptoms** Abbreviated Conners' Questionnaire (parents, teachers) Loney and Milich's Inattention/Overactivity and Aggression (non-compliance) scales (parents, teachers) **Co-existent problems** Not reported **Educational performance** Not reported **Psychological function** Not reported **Depression or anxiety** Mood ratings: dysphoria, euphoria, anxiety, differentness **Quality of life** Loney and Ordona Scale: response (patients, parents) **Adverse events** STESS (based on interviews with parent and patient) **Additional outcomes** EKG recordings

Core symptoms	Educational performance	Quality of life	Adverse events
Abbreviated Conners' Questionnaire (parents): Mean (SD) scores at week 3: PLA: 1.33 (0.76) MPH: 0.87 (0.60) Analyses including 3 weekly scores: $F(1,17) = 6.52$, $p < 0.03$ Abbreviated Conners' Questionnaire (teachers) PLA: 0.64 (0.52) MPH: 0.50 (0.46) No significant difference Loney and Milich's Inattention/Overactivity scale (parents) MPH: 1.26 (0.69) PLA: 0.88 (0.69) Analyses including 3 weekly scores: $F(1,17) = 4.88$, $p < 0.05$ Loney and Milich's Aggression (non-compliance) scale (parents) MPH: 1.34 (0.80) PLA: 0.92 (0.56) No significant difference: $F(1,17) = 3.36$, $p < 0.09$. Loney and Milich's Inattention/Overactivity scale (teachers) MPH: 0.82 (0.66) PLA: 0.64 (0.60) At week 3: $t(26) = 2.06$, $p < 0.02$ Loney and Milich's Aggression (non-compliance) scale (teachers) MPH: 0.29 (0.35) PLA: 0.16 (0.24) At week 3: $t(26) = 2.52$, $p < 0.02$	Not reported	Loney and Ordona Scale: response (patients, parents) End of trial (blinded) statement which phase yielded better results and outcomes rating in comparison with no medication [7 = dramatic response; 0 = no change at all; –3 = dramatically bad response (preferred placebo)] for parent/patient: 7 = Dramatic response 10.5/0.0 6 = Total improvement 10.5/10.5 5 = Good response 0.0/15.6 4 = General improvement 31.6/10.5 3 = Some consistent improvement 5.3/0.0 2 = Mixed or variable response 10.5/15.6 1 = Unimpressive response 0.0/15.6 0 = No change at all 15.6/31.6 –1 = No change except side-effects 5.3/0/0 –2 = Bad response 0.0/0.0 –3 = Dramatically bad response 10.5/0.0 No significant difference between parent and child ratings; average of parents' and children's ratings compared with expected value of 0 = no change: $F(1,17) = 20.89$, $p < 0.0003$	STESS (investigator) % of parents and patients reporting side-effects for MPH/PLA: Parents / Patients Eat less 10.5/10.5 / 10.5/ 31.6 Eat more 5.3/10.5 / 0.0/5.3 Drink more 11.8/5.9 / 11.1/16.7 Drink less 0.0/0.0 / 0.0/5.3 Dry mouth 0.0/0.0 / 10.5/5.3 Wet mouth 0.0/0.0 / 0.0/0.0 Stomach ache 0.0/0.0 / 5.3/5.3 Nausea 5.3/0.0 / 0.0/0.0 Rashes 0.0/0.0 / 0.0/0.0 Headaches 0.0/15.8 / 0.0/0.0 Dizziness 0.0/0.0 / 0.0/0.0 Shakiness 5.3/0.0 / 0.0/0.0 Pronunciation 0.0/0.0 / 0.0/0.0 Clumsiness 5.3/0.0 / 0.0/0.0 Restlessness 62.5/62.5 / 17.6/23.5 Fatigue 11.1/16.7 / 15.8/26.3 Sleepiness 11.8/11.8 / 10.5/26.3 Sleep problem 26.3/15.8 / 15.8/21.1 Crying 5.3/0.0 / 0.0/5.3 Irritability 47.4/42.1 / 5.6/16.7 Unhappiness 15.8/26.3 / 10.5/15.8 Sadness 10.5/ 15.8 / 0.0/21.1 Patient: $t(18) = 2.19$, $p < 0.05$ Inattention 26.7/26.7 / 5.6/5.6

Conclusions	
	Authors' conclusions: The authors conclude that stimulant therapy is a useful approach in the management of ADD in adolescents
	Reviewer's comments: No comments noted

Study	Intervention	Participants	Outcomes
Reference Klorman, R *et al.*, 1990[67] **Source** AHRQ Report **Setting** USA **Design** Crossover trial **Duration** Treatment periods: 3 weeks per treatment arm **Purpose** To investigate whether unselected, previously untreated ADD adolescents benefit from stimulant therapy	**Arm 1** MPH <37.5 kg: Week 1: 7.5 mg (a.m., noon) Week 2: 10 mg (a.m., noon) Week 3: 10 mg (a.m., noon), 5 mg (afternoon) 37.5–54.5 kg: Week 1: 10 mg (a.m., noon) Week 2: 12.5 mg (a.m., noon) Week 3: 12.5 mg (a.m., noon), 7.5 mg (afternoon) >54.5 kg: Week 1: 12.5 mg (a.m., noon) Week 2: 15 mg (a.m., noon) Week 3: 15 mg (a.m., noon), 10 mg (afternoon) Mean dose in 3rd week: 35.21 (5.94) mg/day (Administered by parent and school nurse) **Arm 2** Placebo Lactose with yellow dye and quinine (Administered by parent and school nurse)	**Inclusion criteria** 1. No CNS involvement, childhood autism, psychosis, physical handicaps, and uncorrected visual or auditory problems 2. No mental deficiency – full scale IQ >80 **Diagnostic criteria** DSM-III **Number** Total = 48 (male = 42) Arm 1 = 48 Arm 2 = 48 No withdrawals reported **Age** 14.12 years (mean); 12–18 years (range); 1.69 years (SD) **IQ** 108.62 (mean) **Co-morbid disorders** ODD: *n* = 36/48; CD: *n* = 12/48; major depression (past): *n* = 1/48; adjustment order with depressive mood (past or present): *n* = 17/48; overanxious disorder: *n* = 5/48; phobia: *n* = 5/48; enuresis (past or present): *n* = 16/48; encopresis (past): *n* = 3/48 **Diagnostic subtypes** Not reported **Additional information** Previous medication: 2/48 had received brief (2–4 months) trials of stimulants in childhood 46/48 had not previously received stimulant therapy 0/48 had previously been treated with other psychotropics	**Core symptoms** Abbreviated Conners' Hyperactivity Questionnaire (parents, teachers) IOWA Inattention/Overactivity Scale (parents, teachers) TOTS: hyperactivity and attention scales (parents, teachers) Open-ended questions: ability to concentrate, general deportment (parents) Open-ended questions: behaviour in class (teachers) Nowlis Mood Scale: concentration (patients) Child Psychiatric Scale: overall behaviour (examiners) **Co-existent problems** IOWA Aggression Scale (parents, teachers) TOTS: aggression scale (parents, teachers) Open-ended questions: relations with others (parents) **Educational performance** Open-ended questions: involvement in school work (parents) Open-ended questions: academic work, attitude towards school (teachers) **Psychological function** Not reported **Depression or anxiety** Nowlis Mood Scale: vigour, elation, surgency (patients) **Quality of life** Global improvement (parents, patients) **Adverse events** STESS (patients, parents) Nowlis Mood Scale: fatigue (patients) **Additional outcomes** Weight

Core symptoms	Educational performance	Quality of life	Adverse events
Results presented in figures for majority of outcomes Child Psychiatric Scale mean ± SD ratings: Pretrial = 0.10 ± 0.15, Placebo = 0.12 ± 0.16, MPH = 0.06 ± 0.06 MPH was significantly superior to placebo: $F(1,44) = 8.66$, $p < 0.006$	Not reported	% ratings of global outcome: parent's/patient's reports Dramatic response (score 7): 0.0/4.4% Total improvement (score 6): 4.2/2.2% Good response (score 5): 22.9/19.6% General improvement (score 4): 22.9/10.9% Some consistent improvement (score 3): 2.1/0.0% Mixed or variable response (score 2): 10.4/13.0% Unimpressive response (score 1): 4.2/ 4.4% No change at all (score 0): 10.4/30.4% Dramatically bad response: (score –3): 22.9/15.2% Ratings by parents and patients were similar: $F(1,44)<1$, $p = 0.69$. Judgements indicated improved outcome: $F(1,44)=27.84$, $p < 0.0001$	% side-effects: parent report Appetite loss: placebo = 10.4%, MPH = 27.1%; $\chi^2 = 4.00$, $p < 0.05$ Increased thirst: placebo = 4.3%, MPH = 2.1% Dry mouth: placebo = 2.1%, MPH = 8.3% Stomach aches: placebo = 6.2%, MPH = 6.2% Nausea: placebo = 2.1%, MPH = 0.0% Headaches: placebo = 6.4%, MPH = 12.8% Sleep problem: placebo: 14.6%, MPH = 16.7% Shakiness: placebo = 0.0%, MPH = 0.0% Crying: placebo = 8.5%, MPH = 4.3% Anger: placebo = 34.8%, MPH = 23.9% Unhappiness: placebo = 22.9%, MPH = 20.8% Sadness: placebo = 4.2%, MPH = 4.2% % side-effects: patient report Appetite loss: placebo =6.4%, MPH = 29.8%; $\chi^2 = 8.07$, $p < 0.01$ Increased thirst: placebo = 8.7%, MPH = 13.0% Dry mouth: placebo = 8.5%, MPH = 19.1%, $\chi^2 = 3.57$, $p < 0.10$ Stomach aches: placebo = 4.3%, MPH = 8.5% Nausea: placebo = 2.1%, MPH = 2.1% Headaches: placebo = 4.3%, MPH = 6.4% Sleep problem: placebo = 12.8%, MPH = 17.0% Shakiness: placebo = 2.1%, MPH = 8.5%, $\chi^2 = 3.00$, $p < 0.10$ Crying: placebo = 0.0%, MPH = 6.4% Anger: placebo = 17.4%, MPH = 10.9% Unhappiness: placebo = 12.8%, MPH = 10.6% Sadness: placebo = 0.0%, MPH = 4.3% Overall significant elevation in side-effects for MPH vs placebo according to patient reports ($p < 0.01$), but not according to parent reports
Conclusions	**Authors' conclusions:** These results support the continued effectiveness of stimulant therapy for ADD in adolescence **Reviewer's comments:** No comments noted		

Study	Intervention	Participants	Outcomes
Reference Klorman *et al.*, 1994[68] **Source** CCOHTA Report **Setting** USA **Design** Crossover trial **Duration** Referral period: 5 years; Treatment period: 21 days per treatment arm **Purpose** To investigate the impact of stimulant therapy on ADD children's clinical response and specific aspects of cognitive processing during memory search	**Arm 1** MPH MPH plus placebo assigned on the basis of body weight; increased each week to a maximum average dose of 22.3 mg/day or 0.76 mg/kg/day; administered three times daily (a.m., noon, 4 p.m.) (Administered by school staff and parent) **Arm 2** Placebo Administered three times daily (a.m., noon, 4 p.m.) (Administered by school staff and parent)	**Inclusion criteria** (Unclear whether the following were inclusion criteria or a description of the sample) 1. 5.6–11.9 years old 2. Scheduled by their physicians for a trial of stimulants for problems related to ADD 3. No organic brain disease, psychosis or uncorrected sensory deficits 4. No current medication except treatment for allergies 5. IQ score >80 on WISC-R within preceding year 6. No previous psychotropic treatment **Diagnostic criteria** Parent and teacher rating scales were employed: Home Activity Scale, IOWA Conners' Scale and Conners' Hyperactivity Questionnaire **Number** Total randomised = 114 (male = 85% of 107) Total withdrawals = 7 Reasons for withdrawals: Withdrawn from trial: $n = 2$; consistently uncooperative in laboratory tasks: $n = 2$; experienced significant life events (remarriage or separation by parents) during trial: $n = 2$; incorrect dosage: $n = 1$ In addition, some outcomes were only reported for part of the sample, owing to incomplete returns or late introduction of some measures **Age** 8.51 years (NC mean); 8.63 years (ADD mean); 8.62 years (ADD/O mean); 1.48 years (NC SD); 1.56 years (ADD SD); 1.64 years (ADD/O SD) **IQ** 109 (NC mean); 108.84 (ADD mean); 108.97 (ADD/O mean) **Co-morbid disorders** "… highly unlikely that any subject would have met DSM-III or DSM-III-R criteria for Conduct Disorder"; 1 subject met dual criteria for learning disorder **Diagnostic subtypes** 44/107 designated as ADD; 34/107 designated as ADD and oppositional disturbance (not CD) (ADD/O); 29/107 classified as meeting neither criterion (NC) **Additional information** Previous medication: None of the participants had received previous psychotropic treatment. This was a requirement for entry into the trial Concurrent medication: All of the participants were drug free, except for occasional use of anti-allergy medication	**Core symptoms** Abbreviated Conners' Hyperactivity Questionnaire (parents, teachers) IOWA Conners' Scales: inattention/overactivity (parents, teachers) TOTS: hyperactivity, attention (parents, teachers) **Co-existent problems** IOWA Conners' Scales: aggression/compositionality (parents, teachers) TOTS: aggression (parents, teachers) Child Psychiatric Scale: global disruptiveness (experimenter) **Educational performance** Not reported **Psychological function** Sternberg task: performance **Depression or anxiety** Not reported **Quality of life** Teacher ratings Parent ratings **Adverse events** Somatic complaints (parents) Mood problems (parents) **Additional outcomes** Weight EEG and EOG (electroculargraph) readings

Core symptoms	Educational performance	Quality of life	Adverse events
Abbreviated Conners' Hyperactivity Questionnaire (parents) Means (SD) for NC/ADD/ADD-O populations at 3 weeks: MPH: 0.84 (0.47)/0.99 (0.60)/1.13 (0.60) PLA: 1.29 (0.63)/1.41 (0.60)/1.80 (0.57) MPH > placebo, $F(1,101) = 46,72$, $p < 0.01$ Abbreviated Conners' Hyperactivity Questionnaire (teachers) Means (SD) for NC/ADD/ADD-O populations at 3 weeks: MPH: 0.43 (0.34)/0.56 (0.42)/0.77 (0.45) PLA: 0.69 (0.43)/1.09 (0.52)/1.80 (0.67) MPH > placebo, $F(1,98) = 122.18$, $p < 0.01$ IOWA Conners' Scales: inattention/overactivity (parents) Means (SD) for NC/ADD/ADD-O populations at 3 weeks: MPH: 0.90 (0.51)/1.02 (0.73)/1.14 (0.63) PLA: 1.29 (0.55)/1.54 (0.68)/1.81 (0.59) MPH > placebo, $F(1,101) = 47.74$, $p < 0.01$ IOWA Conners' Scales: inattention/overactivity (teachers) Means (SD) for NC/ADD/ADD-O populations at 3 weeks: MPH: 0.61 (0.48)/0.71 (0.51)/0.87 (0.48) PLA: 0.94 (0.57)/1.44 (0.66)/2.02 (0.69) MPH > placebo, $F(1,98)=116.52$, $p < 0.01$ Time on Task Scales (TOTS): hyperactivity (parents) Means (SD) for NC/ADD/ADD-O populations at 3 weeks: MPH: –0.46 (0.37)/–0.44 (0.51)/–0.39 (0.42) PLA: –0.22 (0.41)/–0.11 (0.48)/0.04 (0.41) MPH > placebo, $F(1,93)=42.73$, $p < 0.01$ TOTS: hyperactivity (teachers) Means (SD) for NC/ADD/ADD-O populations at 3 weeks: MPH: –1.26 (0.37)/–1.04 (0.43)/–0.89 (0.47) PLA: –0.97 (0.44)/–0.61 (0.45)/–0.14 (0.53) MPH > placebo, $F(1,92)=85.57$, $p < .01$ TOTS: attention (parents) Means (SD) for NC/ADD/ADD-O populations at 3 weeks: MPH: 0.11 (0.38)/0.08 (0.49)/0.01 (0.40) PLA: –0.12 (0.34)/–0.09 (0.38)/–0.25 (0.50) MPH > placebo, $F(1,93) = 25.73$, $p < 0.01$	Not reported	Valence of weekly comments, parents ratings: Means (SD) for NC/ADD/ADD-O populations at 3 weeks: MPH: 0.24 (0.54)/0.19 (0.56)/0.15 (0.57) PLA: –0.04(0.53)/–0.39(0.38)/–0.29 (0.45) MPH > placebo, $F(1,38)=16,09$, $p < 0.01$ Valence of weekly comments, teacher ratings: Means (SD) for NC/ADD/ADD-O populations at 3 weeks: MPH: 0.27 (0.46)/0.42(0.43)/0.45 (0.32) PLA: 0.09(0.49)/–0.11(0.63)/–0.61 (0.33) MPH > placebo, $F(1,38)=52.61$, $p < 0.01$	Total somatic complaints (parents) MPH: 0.85 (1.08) PLA: 0.49 (0.80); $F(1,101) = 10.49$, $p < 0.01$ Proportion of parents reporting: Poor appetite: MPH: 23.4% PLA: 6.5%; $\chi^2(1, N = 107) = 13.5$, $p < 0.01$ Sleep difficulties: MPH: 36.4% PLA: 18.7%; $\chi^2(1, N = 107) = 13.37$, $p < 0.01$ Total counts of negative moods: MPH: 0.64 (0.99) PLA: 1.16 (1.19); $F(1,101) = 15.60$, $p < 0.01$ Proportion of parents reporting: Crying: MPH: 19.6% PLA: 37.4%; $\chi^2(1, N = 107) = 9.26$, $p < 0.01$ Anger: MPH: 28.0% PLA: 50.5% ; $\chi^2(1, N = 107) = 7.50$, $p < 0.01$ Unhappiness: MPH: 12.1% PLA: 22.4% ; $\chi^2(1, N = 107) = 5.26$, $p < 0.05$ Weight (kg): Baseline: NC: 29.78 (7.75)/ADD: 28.87 (6.42)/ADD-O: 31.34 (9.39) MPH: total group: –0.498 kg PLA: total group: +0.567 kg Total group: $F(1,64) = 59.15$, $p < 0.01$

continued

Core symptoms	Educational performance	Quality of life	Adverse events
TOTS: attention (teachers) Means (SD) for NC/ADD/ADD-O populations at 3 weeks: MPH: 0.48 (0.44)/0.30 (0.49)/0.22 (0.52) PLA: 0.24 (0.38)/–0.08 (0.43)/–0.30 (0.41) MPH > placebo, $F(1,92) = 65.00$, $p < 0.01$			
Conclusions	**Authors' conclusions:** The authors concluded that stimulant treatment improved ADD-spectrum children's behaviour at both home and school not only with regard to inattention and hyperactivity but also aggression/compositionality. MPH increased accuracy on the Sternberg test over levels found in the placebo and baseline sessions, but did not differentially reduce errors to targets **Reviewer's comments:** No comments noted		

Study	Intervention	Participants	Outcomes
Reference Kolko *et al.*, 1999[69] **Source** Updated search **Setting** USA (Partial hospitalisation – STP) **Design** Crossover trial **Duration** 6 weeks **Purpose** To evaluate the separate and incremental effects of two doses of MPH and behaviour modification in children with ADHD and co-morbid disorders across multiple settings	**Arm 1** MPH plus non-drug intervention Low-dose MPH (0.3 mg/kg) and high dose MPH (0.6 mg/kg). Each MPH condition was administered twice daily (8 and 11.30 a.m.) one day per week for six weeks (a total of 6 days). Behaviour modification (BM) consisted of the STEP programme: a 5 days/week, 8 hours/day programme consisting of hourly, structured therapeutic, educational and recreational activities (e.g. skills group, classroom enrichment, gym). BM was alternated with no behaviour modification on a weekly basis for a total of 3 weeks each (Administered by medical personnel) **Arm 2** MPH Doses as above with no BM (Administered by medical personnel) **Arm 3** Placebo plus non-drug intervention Placebo with BM (Administered by medical personnel) **Arm 4** Placebo Placebo only (Administered by medical personnel)	**Inclusion criteria** 1. 7–13 years of age 2. No concurrent medication **Diagnostic criteria** DSM-III-R **Number** Total randomised = 22 (male = 22) Total withdrawals = 6 Reasons for withdrawals: 2 were hospitalised for aggressive and unmanageable behaviour, 2 had serious side-effects in the first week and 2 later declined to take MPH Randomisation procedure: Note that each drug treatment was administered for 6 days over the 6-week trial (randomly administered on a daily basis, each once per week, across a 3-day period) **Age** 9.6 years (mean); 1.9 years (SD) **IQ** Not reported **Co-morbid disorders** CD: *n* = 7/16 (44%); ODD: *n* = 9/16 (56%); three children also had an anxiety disorder, 2 had major depressive disorder, 1 had dysthymia and 1 had intermittent explosive disorder **Diagnostic subtypes** Not reported **Additional information** Previous medication: Before the trial began, there was a 2-week baseline during which no MPH was given. All patients had failed to respond to less intensive outpatient treatment Concurrent medication: Individuals receiving other medication were excluded from the trial	**Core symptom** Abbreviated IOWA/Conners' Rating Scale: inattentive/overactive (evaluated in the classroom and enrichment room) **Co-existent problems** Abbreviated IOWA/Conners' Rating Scale: oppositional/defiant Overt Aggression Scale (verbal aggression, physical aggression against objects, physical aggression against people) Peer conflicts Positive mood/behaviour (social skills group, gym and field) **Educational performance** Not reported **Psychological function** Not reported **Depression or anxiety** Not reported **Quality of life** Not reported **Adverse events** Stimulant Drug Side Effects Rating Scale **Additional outcomes** Not reported

Core symptoms	Educational performance	Quality of life	Adverse events
Abbreviated IOWA/Conners' Rating Scale: inattentive/overactive (results from classroom) Low-dose MPH + BM: 1.8 (3.5) High-dose MPH + BM: 3.2 (2.8) Placebo + BM: 3.3 (3.9) Low-dose MPH + no BM: 4.1 (4.4) High-dose MPH + no BM: 3.3 (2.9) Placebo + no BM: 9.9 (3.8) (Low/high MPH > placebo, $p < 0.0001$). The two MPH conditions did not differ from each other. Behaviour modification was associated with reductions in inattentive/overactive Abbreviated IOWA/Conners' Rating Scale: inattentive/overactive Effect sizes: MPH (low and high dose): 1.63 (1.24) BM: 1.29 (0.80) MPH (low and high dose) + BM: 1.88 (0.83) (MPH + BM > BM, $p < 0.01$); MPH alone and BM alone were not significantly different from each other Data also presented for enrichment room, but not extracted	Not reported	Not reported	No specific effects were reported. The authors state that MPH was associated with more side-effects than placebo. Serious side-effects were found in 2/22 of children (who were omitted from the analysis)

Conclusions	
	Authors' conclusions: The authors state that core symptoms of ADHD and positive behaviour showed significant improvements with high- and low-dose MPH
	Reviewer's comments: No comments noted

Study	Intervention	Participants	Outcomes
Reference Kratochvil *et al.*, 2002;[70] Dittmann *et al.*, 2001[305] **Source** Updated search **Setting** USA/Canada **Design** Parallel trial **Duration** 10 weeks **Purpose** This study was designed to select treatment responders to enter a relapse prevention study and incorporated a comparison of ATX and MPH for ADHD	**Arm 1** ATX For CYP 2D6 extensive metabolisers, ATX was titrated to a max. of 2 mg/kg per day; administered twice daily (a.m. and late afternoon) [final mean dose = 1.40 (0.48) mg/kg per day]. For CYP 2D6 poor metabolisers, ATX was initiated at 0.2 mg/kg day and titrated to 1.0 mg/kg day [final mean dose = 0.48 (0.29) mg/kg day] (Individuals administering medication not reported) **Arm 2** MPH Doses beginning at 5 mg from one to three times daily. Total daily dose did not exceed 60 mg [final mean dose = 0.85 (0.53) mg/kg/day (31.3 mg/day)] (Individuals administering medication not reported)	**Inclusion criteria** 1. Boys aged 7–15 years and girls aged 7–9 years 2. No history of bipolar or psychotic disorders, motor tics or a family history of Tourette syndrome, substance abuse 3. Participants had to have a response to a previous trial of MPH 4. Participants with other concurrent psychiatric diagnoses were included in the trial 5. No concomitant use of other psychoactive medications **Diagnostic criteria** DSM-IV **Number** Total = 228 (male = 211) Arm 1 = 184 Arm 2 = 44 Total withdrawals = 85 Arm 1 = 66 Arm 2 = 19 **Age** 10.4 years (mean); 2.1 years (SD) **IQ** Not reported **Co-morbid disorders** ODD: *n* = 122, major depressive disorder: *n* = 15; elimination disorders, primarily enuresis: *n* = 38 **Diagnostic subtypes** The majority of children met criteria for the combined ADHD subtype; 139/184 and 34/44 **Additional information** Previous medication: There was a drug washout period before the trial began (length not stated). Participants were required to have previously responded to a trial of MPH Concurrent medication: No concomitant use of other psychoactive medications was allowed by participants in the trial	**Core symptoms** ADHD Rating Scale IV – Parent Version (investigator administered and scored): total score; hyperactivity/impulsivity subscale scores; inattention subscale score CPRS-R: ADHD Index; hyperactive ADHD Rating Scale IV – Parent Version (parent scored): total *T* score **Co-existent problems** CPRS-R: cognitive **Educational performance** Not reported **Psychological function** Not reported **Depression or anxiety** Not reported **Quality of life** CGI of Severity of ADHD Symptoms **Adverse events** Assessed through open-ended questions and collection of ECG and laboratory data. 27 adverse events (including weight) plus blood pressure and heart rate **Additional outcomes** Not reported

Core symptoms	Educational performance	Quality of life	Adverse events
ADHD Rating Scale IV – Parent Version (investigator administered and scored): total score baseline/end-point/mean change ATX (n = 178): 39.43 (8.51)/19.99 (13.86)/–19.44 (13.31) MPH (n = 40): 37.6 (9.67)/19.83 (16.65)/–17.78 (14.69) (NS, p = 0.658, 95% CI: –3.6 to 5.6) ADHD Rating Scale IV – Parent Version (investigator administered and scored): hyperactivity/impulsivity subscale scores – baseline/end-point/mean change ATX (n = 178): 17.77 (6.31)/8.26 (7.44)/–9.50 (6.99) MPH (n = 40): 16.95 (7.07)/8.48 (8.24)/–8.48 (7.08) (NS, p = 0.540, 95% CI: –1.6 to 3.0) ADHD Rating Scale IV – Parent Version (investigator administered and scored): inattention subscale score baseline/end-point/mean change ATX (n = 178): 21.66 (4.23)/11.72 (7.65)/–9.94 (7.73) MPH (n = 40): 20.65 (4.77)/11.35 (9.18)/–9.30 (8.89) (NS, p = 0.924, 95% CI –2.5 to 2.8) CPRS-R: ADHD Index baseline/end-point/mean change ATX (n = 178): 27.37 (6.3)/16.01 (9.93)/–11.36 (10.23) MPH (n = 40): 25.92 (6.94)/13.95 (10.83)/–11.97 (10.64) (NS, p = 0.411, 95% CI: –4.8 to 2.0) CPRS-R: hyperactive baseline/endpoint/mean change ATX (n = 149): 10.25 (4.39)/4.69 (4.55)/–5.56 (4.74) MPH (n = 39): 10.05 (5.35)/5.18 (5.33)/–4.78 (4.49) (NS, p = 0.427, 95% CI: –0.9 to 2.0) ADHD Rating Scale IV – Parent Version (parent scored): total T score baseline/end-point/mean change ATX (n = 161): 77.22 (10.33)/58.38 (13.59)/–18.83 (14.54) MPH (n = 36): 74.28 (10.01)/55.90 (14.53)/–18.38 (13.07) (NS, p = 0.615, 95% CI: –6.0 to 3.6)	Not reported	CGI of Severity of ADHD Symptoms baseline/end-point/mean change ATX (n = 178): 4.83 (0.79)/3.16 (1.26)/–1.67 (1.30) MPH (n = 40): 4.70 (0.88)/3.00 (1.55)/–1.70 (1.51) (NS, p = 0.663, 95% CI: –0.5 to 0.3)	Withdrawals: 15 children discontinued owing to adverse events (ATX 10/184; MPH 5/44) Treatment-emergent adverse events occurring in >5% of either group: ATX (n = 184) / MPH (n = 40) Headache 57 (31%) / 13 (33%) Abdominal pain 43 (23%) / 7 (18%) Anorexia 35 (19%) / 6 (15%) Rhinitis 33 (18%) / 8 (20%) Nervousness 29 (16%) / 4 (10%) Vomiting 22 (12%) / 0 p = 0.017, 95% CI: 7.3 to 16.6 Fever 20 (11%) / 4 (10%) Somnolence 20 (11%) / 0 p = 0.029, 95% CI: 6.4 to 15.4 Nausea 19 (10%) / 2 (5%) Insomnia 17 (9%) / 7 (18%) Asthenia 14 (8%) / 1 (3%) Diarrhoea 13 (7%) / 1 (3%) Emotional lability 11 (6%) / 2 (5%) Pharyngitis 11 (6%) / 3 (8%) Tachycardia 11 (6%) / 2 (5%) Accidental injury 10 (5%) / 5 (13%) Cough increased 10 (5%) / 2 (5%) Dyspepsia 10 (5%) / 2 (5%) Pain 10 (5%) / 1 (3%) Flu syndrome 9 (5%) / 4 (10%) Infection 8 (4%) / 3 (8%) Rash 7 (4%) / 3 (8%) Depression 5 (3%) / 2 (5%) Weight loss 5 (3%) / 2 (5%) Hyperkinesia 3 (2%) / 2 (5%) Palpitation 3 (2%) / 2 (5%) Thinking abnormal 0 (%) / 2 (5%) p = 0.031, 95% CI: –11.8 to 1.8

continued

Core symptoms	Educational performance	Quality of life	Adverse events
			Weight (kg) baseline/end-point/mean change ATX (n = 179): 41.36 (16.05)/40.72 (16.05)/–0.63 (1.64) MPH (n = 40): 40.74 (17.2)/40.60 (18.14)/–0.13 (1.89) (NS, p = 0.089, 95% CI: –0.1 to 1.1)
Conclusions	**Authors' conclusions:** Similar reductions in ADHD symptoms were seen in both the ATX and MPH treatment groups. Both drugs were generally well tolerated, with few discontinuations due to adverse events. Vomiting and somnolence were more frequently reported among participants randomised to ATX **Reviewer's comments:** Participants were randomised to open-label treatment		

Study	Intervention	Participants	Outcomes
Reference Kupietz *et al.*, 1988[71] **Source** AHRQ Report **Setting** USA **Design** Parallel trial **Duration** Study length: 8 weeks; total treatment period: 6 months **Purpose** To investigate the effects of 6-month MPH treatment on home and school behaviour and on cognitive performance in hyperactive, reading-disabled children	**Arm 1** Placebo plus non-drug intervention Placebo administered once daily One-to-one reading therapy programme during weeks 3–14 and 16–27: weekly with reading therapist and 5 days/week at home with parent (Administered by parent) **Arm 2** MPH plus non-drug intervention 0.3 mg/kg/day administered in one dose for weeks 1–14 and 16–27; placebo during week 15. One-to-one reading therapy programme during weeks 3–14 and 16–27: weekly with reading therapist and 5 days/week at home with parent (Administered by parent) **Arm 3** MPH plus non-drug intervention 0.5 mg/kg/day administered in one dose for weeks 1–14 and 16–27; placebo during week 15. One-to-one reading therapy programme during weeks 3–14 and 16–27: weekly with reading therapist and 5 days/week at home with parent (Administered by parent) **Arm 4** MPH plus non-drug intervention 0.7 mg/kg/day administered in one dose for weeks 1–14 and 16–27; placebo during week 15. One-to-one reading therapy programme during weeks 3–14 and 16–27: weekly with reading therapist and 5 days/week at home with parent (Administered by parent)	**Inclusion criteria** 1. 7–13 years old 2. IQ $\geq$ 80 3. Diagnosis of both ADDH and Developmental Reading Disorder according to DSM-III criteria 4. No additional Axis I psychiatric diagnosis 5. No uncorrected hearing or visual deficits **Diagnostic criteria** DSM-III **Number** Total randomised = 58 (male/female split not reported) Arm 1 = 16 Arm 2 = 19 Arm 3 = 12 Arm 4 = 11 Total withdrawals = 11 Arm 1 = 4 Arm 2 = 5 Arm 3 = 1 Arm 4 = 1 **Age** 116.9 months (mean); 20.1 months (SD) **IQ** 93.8 (mean) **Co-morbid disorders** All children received a dual diagnosis of ADDH and Developmental Reading Disorder (Reading Grade Level: mean = 2.3, SD = 1.0) **Diagnostic subtypes** Not reported **Additional information** No relevant information reported	**Core symptoms** CTRS: inattentiveness and hyperactivity Devereux Elementary School Behaviour Rating Scale Conners' Abbreviated Rating Scale (parents) Devereux Child Behaviour Rating Scale (parents) Werry–Weiss–Peters Activity Scale **Co-existent problems** CTRS: aggressiveness **Educational performance** Not reported **Psychological function** Paired-Associated Learning task Short-term Memory task **Depression or anxiety** Not reported **Quality of life** Not reported **Adverse events** Not reported **Additional outcomes** Plasma assay using gas chromatography

Core symptoms	Educational performance	Quality of life	Adverse events
CTRS: hyperactivity [unadjusted; baseline/week 2/14/27: *N*, mean (SD)]: Placebo: 11, 3.23 (0.40)/11, 2.94 (0.58)/11, 2.80 (0.50)/11, 2.89 (0.69) 0.3: 8, 3.02 (0.63)/8, 2.04 (0.46)/8, 2.15 (0.64)/8, 2.21 (0.53) 0.5: 11, 3.14 (0.53)/11, 2.12 (0.59)/11, 2.07 (0.52)/11, 2.04 (0.43) 0.7: 10, 3.01 (0.43)/10, 1.63 (0.47)/10, 1.65 (0.42)/10, 2.03 (0.64) CTRS: inattentiveness [unadjusted; week 2/14/27: *N*, mean (SD)]: Placebo: 11, 2.74 (0.81)/11, 2.59 (0.65)/11, 2.29 (0.62)/11, 2.60 (0.91) 0.3: 8, 2.99 (0.69)/8, 2.00 (0.60)/8, 2.06 (0.50)/8, 2.32 (0.76) 0.5: 11, 2.83 (0.35)/11, 2.21 (0.58)/11, 1.91 (0.48)/11, 2.15 (0.49) 0.7: 10, 2.46 (0.50)/10, 1.61 (0.40)/10, 1.64 (0.41)/10, 1.51 (0.42) Devereux Elementary School Behaviour Rating Scale Not reported; "only the main effect of dose group was significant ($F3,33 = 4.65$, $p < 0.01$)". Adjusted mean ratings for the placebo, 0.3, 0.5, and 0.7 groups were 140.3, 128.0, 112.6 and 104.9, respectively Conners' Abbreviated Rating Scale (parents) [unadjusted; baseline/week 2/14/27: *N*, mean (SD)]: Placebo: 11, 2.98 (0.48)/11, 2.44 (0.93)/11, 2.59 (0.55)/11, 2.49 (0.64) 0.3: 14, 2.89 (0.58)/14, 2.18 (0.54)/14, 2.51 (0.72)/14, 2.30 (0.68) 0.5: 10, 3.18 (0.65)/10, 2.50 (0.80)/10, 2.42 (0.90)/10, 2.54 (0.80) 0.7: 10, 2.92 (0.49)/10, 1.95 (0.36)/10, 1.54 (0.36)/10, 1.79 (0.59) Devereux Child Behaviour Rating Scale (parents) Not reported; "the main effect of dose group was not significant" Werry–Weiss–Peters Activity Scale Not reported; "No dose group effects were obtained …"	Not reported	Not reported	Not reported

Conclusions	**Authors' conclusions:** No support was obtained for the hypothesis that behaviourally optimal MPH doses are not effective in improving learning performance. The unexpected finding of a significant increase in the severity of hyperactive behaviours with chronic MPH therapy underscores the need for further studies **Reviewer's comments:** No comments noted

Study	Intervention	Participants	Outcomes
Reference Manos *et al.*, 1999;[72] Findling *et al.*, 2001;[306] Findling *et al.*2001;[307] Faraone *et al.* 2001;[308] and Faraone *et al.*, 2002[309] **Source** NICE Report **Setting** USA **Design** Crossover trial **Duration** Trial length: 4 weeks **Purpose** To compare the effectiveness of a single dose of Adderall with two daily doses of MPH given in children with ADHD	**Arm 1** MPH 5 mg/dose administered at 8 a.m. and 12 p.m.; six dose orders such that 15 mg was always preceded by 10 mg dose (Administered by parent and school staff) **Arm 2** MPH 10 mg/dose administered at 8 a.m. and 12 p.m.; six dose orders such that 15-mg was always preceded by 10-mg dose (Administered by parent and school staff) **Arm 3** MPH 15 mg/dose administered at 8 a.m. and 12 p.m.; six dose orders such that 15-mg was always preceded by 10-mg dose (Administered by parent and school staff) **Arm 4** Placebo administered at 8 a.m. and 12 p.m.; six dose orders such that 15 mg was always preceded by 10 mg dose (Administered by parent and school staff)	**Inclusion criteria** Diagnosis of ADHD **Diagnostic criteria** DSM-IV **Number** Total = 42 (male = 33) No withdrawals reported Randomisation procedure: Participants were assigned to MPH or Adderall based on physician discretion and familiarity with medication. Participants were consequently randomised to dose orders. This paper reports on 42 participants assigned to Adderall and a matched set of 42 participants assigned to MPH. Only data on those assigned to MPH have been extracted **Age** 10.1 years (mean); 5–17 years (range) **IQ** Not reported **Co-morbid disorders** Anxiety disorder: *n* = 2; learning disability: *n* = 11; ODD: *n* = 5. **Diagnostic subtypes** Inattentive type = 19; Combined type = 23 **Additional information** Previous medication: None of the participants who were prescribed MPH had previously been prescribed Adderall	**Core symptoms** ADHD Rating Scale (parent) ASQ (parents, teachers) School Situations Questionnaire – Revised (teachers) **Co-existent problems** Not reported **Educational performance** Not reported **Psychological function** Not reported **Depression or anxiety** Not reported **Quality of life** Composite ratings (clinician) **Adverse events** Side Effects Behaviour Monitoring Scale (parents) **Additional outcomes** Not reported

Core symptoms	Educational performance	Quality of life	Adverse events
ASQ (parents) MPH, best dose: 50.64 (10.64) PLA: 67.00 (17.32) Best dose better than placebo but statistical results for direct comparisons not reported ASQ (teachers) MPH, best dose: 56.12 (11.81) PLA: 64.38 (15.41) Best dose better than placebo but statistical results for direct comparisons not reported ADHD Rating Scale (parent) MPH, best dose: 10.10 (6.71) PLA: 18.61 (11.86) Best dose better than placebo but statistical results for direct comparisons not reported School Situations Questionnaire – Revised (teachers) MPH, best dose: 1.92 (2.11) PLA: 2.62 (2.86) Best dose better than placebo but statistical results for direct comparisons not reported	Not reported	Composite ratings (clinician): MPH, best dose: 3.31 (0.52) PLA: 0.50 (1.27)	Side Effects Behaviour Monitoring Scale (parents, $n = 42$) No placebo data reported Insomnia: 2/42 Nightmares: 0/42 Stares a lot: 4/42 Decreased appetite: 1/42; Irritability: 2/42 Stomach ache: 0/42 Headache: 1/42 Drowsiness: 3/42 Sad/unhappy: 4/42 Prone to cry: 3/42 Anxious: 7/42 Perseverative: 5/42 Bites nails: 3/42 Euphoric: 2/42 Dizziness: 0/42 Tics/nervousness: 0/42 Overfocused: 0/42 Rebound: 1/42

Conclusions	
	Authors' conclusions: Note reviewer's comment
	Reviewer's comments: Conclusions should only be drawn within each medication arm rather than across treatments

Study	Intervention	Participants	Outcomes
References Michelson *et al.*, 2001[73] Newcorn *et al.*, 2004[310] and Matza *et al.*, 2004[311] **Source** Updated search **Setting** USA **Design** Parallel trial **Duration** Treatment period: 8 weeks; washout period: 12–18 days **Purpose** To assess the efficacy of 3 doses of atomoxetine compared with placebo in children and adolescents with ADHD	**Arm 1** ATX 0.5 mg/kg/day administered in equally divided doses (morning and late afternoon) (Individuals administering medication not reported) **Arm 2** ATX 0.5 mg/kg/day for first week 0.8 mg/kg/day for second week 1.2 mg/kg/day subsequently administered in equally divided doses (morning and late afternoon) (Individuals administering medication not reported) **Arm 3** ATX 0.5 mg/kg/day for first week 0.8 mg/kg/day for second week 1.2 mg/kg/day for third week 1.8 mg/kg/day subsequently administered in equally divided doses (morning and late afternoon) (Individuals administering medication not reported) **Arm 4** Placebo Administered morning and late afternoon (Individuals administering medication not reported)	**Inclusion criteria** 1. IQ $\geq$ 80 (WISC-III) 2. No serious medical illness, co-morbid psychosis or bipolar disorder 3. No history of seizure disorder 4. No ongoing use of psychoactive medications other than study drug 5. No treatment for a co-existing disorder that took precedence over or otherwise mitigated child's treatment for ADHD 6. Participants with learning disorders were not excluded **Diagnostic criteria** DSM-IV **Number** Total randomised = 297 (male = 212) Arm 1 = 44 Arm 2 = 84 Arm 3 = 85 Arm 4 = 84 Total withdrawals = 49 Arm 1 = 10 Arm 2 = 15 Arm 3 = 12 Arm 4 = 12 Reasons for withdrawals: Lack of efficacy (n = 10): Arm 1: n = 3; Arm 2: n = 2; Arm 3: n = 1; Arm 4: n = 4 Lost to follow up: n = 10; Arm 1: n = 3; Arm 2: n = 1; Arm 3: n = 2; Arm 4: n = 4 Conflict (n = 17): Arm 1: n = 3; Arm 2: n = 6; Arm 3: n = 4; Arm 4: n = 4 Adverse events (n = 7): Arm 1: n = 1; Arm 2: n = 2; Arm 3: n = 4; Arm 4: n = 0 Moved: n = 1 (Arm 2) Physician decision: n = 1 (Arm 2) Protocol violation: n = 2 (Arm 2) Entry criteria: n = 1 (Arm 3)	**Core symptoms** Attention Deficit/Hyperactivity Disorder Rating Scale IV–Parent Version: investigator administered and scored: total, hyperactivity/impulsivity and inattention CPRS-Short Form: total, hyperactive **Co-existent problems** CRPS-R: Short Form: oppositional **Educational performance** Not reported **Psychological function** CPRS-R: cognitive **Depression or anxiety** Children's Depression Rating Scale – Revised **Quality of life** CGI Severity CHQ (parents): physical, psychosocial summary score, behaviour, family activity, parent impact – emotional, parent impact – time, child emotional, child mental health, child self-esteem **Adverse events** Open-ended questioning **Additional outcomes** Blood pressure Weight Pulse

continued

Study	Intervention	Participants	Outcomes
		Age Arm 1: 11.3; Arm 2: 11.5; Arm 3: 11.1; Arm 4: 10.9 years (mean); 8–18 years (range); Arm 1: 2.1; Arm 2: 2.5; Arm 3: 2.4; Arm 4:2.1 (SD) **IQ** Not reported **Co-morbid disorders** ODD: $n = 113$; depression: $n = 1$, generalised anxiety disorder: $n = 1$ **Diagnostic subtypes** Mixed: $n = 199$; hyperactive/impulsive: $n = 5$; inattentive: $n = 92$; unspecified: $n = 1$ **Additional information** Concurrent medication: Participants in the trial were not to be in receipt of ongoing psychoactive medications other than study drug. In addition, they were not to be in receipt of any treatment for a co-existing disorder that took precedence over or otherwise mitigated child's treatment for ADHD	

Core symptoms	Educational performance	Quality of life	Adverse events
ADHD Rating Scale total: Change from baseline to end-point – mean (SD; 95% CI for difference from placebo) for ATX0.5/ATX1.2/ATX1.8 –9.9 (14.6; –8.9 to 0.9)/–13.6*(14.0; –12.1 to –4.0)/–13.5* (14.5; –11.9 to –3.7 Placebo: –5.8 (10.9) *$p < 0.05$ compared with placebo ADHD Rating Scale Inattention subscale Change from baseline to end-point – mean (SD; 95% CI for difference from placebo) for ATX0.5/ATX1.2/ATX1.8 –5.1(7.5; –5.2 to 0.3)/–7.0* (8.1; –6.8 to –2.2)/–6.8* (7.9; –6.6 to –2.0) Placebo: –2.5 (6.6) *$p = <0.05$ compared with placebo ADHD Rating Scale Hyperactivity/Impulsiveness subscale Change from baseline to end-point – mean (SD; 95% CI for difference from placebo) for ATX0.5/ATX1.2/ATX1.8 –4.8(7.9; –4.1 to 1.0)/-6.6* (7.1; –5.6 to –1.4)/-6.7* (7.5; –5.7 to –1.4) Placebo: –3.2 (5.6) *$p = < 0.05$ compared with placebo CPRS-R ADHD Index Change from baseline to end-point – mean (SD; 95% CI for difference from placebo) for ATX0.5/ATX1.2/ATX1.8 –7.2*(8.9; –9.2 to -2.1)/–8.9* (9.7; –10.3 to –4.5)/–8.8* (9.7; –10.0 to –4.2) Placebo: –1.5 (8.5) *$p = <0.05$ compared with placebo CPRS-R Hyperactive scale Change from baseline to end-point – mean (SD; 95% CI for difference from placebo) for ATX0.5/ATX1.2/ATX1.8 –4.1* (4.4; –4.5 to 1.2)/–4.1* (4.9; –4.4 to –1.6)/–4.3* (4.6; –4.5 to –1.8) Placebo: –1.1 (3.9) *$p = < 0.05$ compared with placebo	Not reported	CGI-ADHD-S scores for ODD group: mean (SD) Arm 1 ($n = 21$): baseline: 5.1 (0.9); change: –1.0 (1.5); Arm 1 vs placebo: $p = 0.149$ Arm 2 ($n = 27$): baseline: 5.1 (0.7); change: –0.9 (1.4); Arm 2 vs placebo: $n = 0.207$ Arm 3 ($n = 34$): baseline: 5.0 (0.7); change: –1.2 (1.2); Arm 3 vs placebo: $p = 0.040$ Arm 4 ($n = 31$): baseline: 5.0 (0.9); change: –0.4 (1.2) CGI-ADHD-S: scores for non-ODD group: mean (SD) Arm 1 ($n = 22$): baseline: 4.5 (0.7); change: –0.6 (1.4); Arm 1 vs placebo: $p = 0.930$ Arm 2 ($n = 56$): baseline: 4.7 (0.9); change: –1.5 (1.4); Arm 2 vs placebo: $p = 0.002$ Arm 3 ($n = 48$): baseline: 4.8 (0.8); change: –1.3 (1.4); Arm 3 vs placebo: $p = 0.038$ Arm 4 ($n = 49$): baseline: 4.4 (0.6); change: –0.6 (1.1) CHQ: psychosocial summary score: mean (SD) Arm 1 ($n = 44$): baseline: 32.9 (9.6); change: 4.4 (10.3); Arm 1 vs placebo: $p < 0.05$ Arm 2 ($n = 84$): baseline: 35.4 (10.4); change: 6.0 (9.0); Arm 2 vs placebo: $p < 0.05$ Arm 3 ($n = 85$): baseline: 31.3 (10.6); change: 9.1 (11.1); Arm 3 vs placebo: $p < 0.05$ Arm 4 ($n = 84$): baseline: 35.2 (11.4); change: –0.9 (11.8)	Analyses of safety are restricted to those patients who took at least 1 dose of the study drug ($n = 294$) Treatment-emergent adverse events reported by at least 5% of patients in any treatment group *N* (%) placebo/ATX 0.5/ATX 1.2/ATX 1.8 Headache 19 (22.9)/11 (25)/20 (23.8)/20 (24.1) Rhinitis 19 (21.7)/7(15.9)/10 (11.9)/12(14.5) Abdominal pain 9(10.8)/5(11.4)/12(14.3)/12(14.5) Pharyngitis 12(14.5)/4(9.1)/9(10.7)/9(10.8) Anorexia 4(4.8)/3(6.8)/10(11.9)10(12.0) Vomiting 5(6.0)/3(6.8)/6(7.1)/9(10.8) Cough increased 4(4.8)/3(6.8)/10(11.9)/10(12.0) Somnolence 3(3.6)/2(4.5)/6(7.1)/9(10.8) Insomnia 5(6.0)/4(9.1)/5(6.0)/4(4.8) Rash 3(3.6)/3(6.8)/5(6.0)/7(8.4) Nausea 5(6.0)/2(4.5)/6(7.1)/4(4.8) Nervousness 4(4.8)/3(6.8)/5(6.0)/5(6.0) Fever 5(6.0)/1(2.3)/7(8.3)/3(3.6) Pain 5(6.0)/4(9.1)/2(2.4)/5(6.0) Accidental injury 7(8.4)/1(2.3)/3(3.6)/3(3.6) Asthenia 4(4.9)/3(6.8)/2(2.4)/4(4.8) Infection 1(1.2)/–/5(6.0)/6(7.2)

continued

Core symptoms	Educational performance	Quality of life	Adverse events
			Dizziness 1(1.2)/4(9.1)[a]/2(2.4)/4(4.8) Diarrhoea 5(6.0)/0/4(4.8)/0 Depression 5(6.0)/1(2.3)/0/2(2.4) Pruritus 0/0/1(1.2)/5(6.0) No adverse event was statistically significantly more frequent among the 1.2 or 1.8 mg/kg/day ATX dose groups compared with placebo; however, in the 0.5mg/kg/day group dizziness[a] occurred significantly more frequently compared with placebo Withdrawals: adverse events Arm 1: $n = 1$ Arm 2: $n = 2$ Arm 3: $n = 4$ Arm 4: $n = 0$
Conclusions	**Authors' conclusions:** Among children and adolescents aged 8–18 years, atomoxetine was superior to placebo in reducing ADHD symptoms. ATX was associated with a graded dose–response, and 1.2 mg/kg/day seems to be as effective as 1.8 mg/kg/day and is likely to be the most appropriate initial target dose for most patients. Treatment with ATX was safe and well tolerated **Reviewer's comments:** No comments noted		

Study	Intervention	Participants	Outcomes
Reference Michelson *et al.*, 2002;[74] Dunn *et al.*, 2002;[312] Bukstein, 2003[313] and Michelson, 2002[314] **Source** Updated search **Setting** USA **Design** Parallel trial **Duration** 6 weeks **Purpose** To assess the efficacy of one-daily ATX in the treatment of children and adolescents with ADHD This trial is also reported in several abstracts[312–314]	**Arm 1** ATX 0.5 mg/kg/day for 3 days, followed by 0.75 mg/kg/day for the remainder of the first week. The dose was then increased to 1.0 or 1.5 mg/kg/day; administered once daily (a.m.) (Individual administering medication not reported) **Arm 2** Placebo No details reported (Individual administering medication not reported)	**Inclusion criteria** 1. 6–16 years of age 2. Had to meet symptom severity threshold 3. No serious medical illness 4. No history of psychosis or bipolar disorder, alcohol or drug abuse within the past 3 months 5. No ongoing use of psychoactive medications other than the study drug **Diagnostic criteria** DSM-IV **Number** Total randomised = 171 (male = 120) Arm 1 = 85 Arm 2 = 86 Total withdrawals = 23 Arm 1 = 12 Arm 2 = 11 One assigned patient did not receive any medication, and analyses excluded this patient **Age** 10 years (mean); 2 years (SD) **IQ** Not reported **Co-morbid disorders** ODD: *n* = 34; depression: *n* = 3; generalised anxiety disorder: *n* = 1; specific phobia: *n* = 5 **Diagnostic subtypes** ADHD subtype: 58% mixed; 2% hyperactive/impulsive; 41% inattentive **Additional information** Previous medication: All patients followed a minimum 5-day medication-free evaluation period before randomisation. 94 of the children reported having been previously treated with a stimulant **Concurrent medication:** Participants in the trial were not to receive ongoing psychoactive medications other than the study drug	**Core symptoms** ADHD Rating Scale IV: total score; inattention symptoms; hyperactivity/impulsive symptoms CPRS CTRS **Co-existent problems** Not reported **Educational performance** Not reported **Psychological function** Not reported **Depression or anxiety** Not reported **Quality of life** CGI severity score **Adverse events** 16 types of adverse effects reported assessed by open-ended questioning; blood pressure; pulse; weight; height **Additional outcomes** Parent rating of behaviour in evening: problems with homework/tasks; sitting through dinner; difficulty playing quietly; inattentive and distractible; arguing or struggling; irritability; difficulty with transitions; difficulty settling at bedtime; difficulty falling asleep. Parent rating of behaviour in morning: difficulty getting out of bed; difficulty getting ready; arguing or struggling; irritability

Core symptoms	Educational performance	Quality of life	Adverse events
ADHD Rating Scale IV: total score (baseline/change from baseline) ATX: 37.6 (9.4)/–12.8 (12.4) Placebo 36.7 (8.8)/–5.0 (10.4) (ATX > placebo, $p < 0.001$) ADHD Rating Scale IV: inattention symptoms ATX: 21.9 (3.5)/–7.1 (6.9) Placebo: 21.4 (4.0)/–2.9 (5.7) (ATX > placebo, $p < 0.001$) ADHD Rating Scale IV: hyperactivity/impulsive symptoms ATX: 15.7 (8.0)/–5.7 (6.8) Placebo: 15.3 (7.1)/–2.1 (5.7) (ATX > placebo, $p < 0.001$) CPRS (ATX: $n = 80$, placebo: $n = 77$) ATX: 27.0 (5.5)/–7.6 (8.2) Placebo: 26.5 (5.8)/–2.4 (7.0) (ATX > placebo, $p < 0.001$) CTRS ATX: 21.5 (8.7)/–5.1 (8.0) Placebo: 21.6 (9.0)/–1.6 (8.3) (ATX > placebo, $p = 0.02$)	Not reported	CGI severity score (baseline/change from baseline) ATX: 4.7 (0.6)/–1.2 (1.3) Placebo: 4.6 (0.6)/–0.5 (1.0) (ATX > placebo, $p < 0.001$)	ATX ($n = 85$) / Placebo ($n = 85$) Headache 17 (20%) / 15 (18%) Rhinitis 14 (17%) / 18 (21%) Decreased appetite 17 (20%) / 5 (6%) Abdominal pain 14 (17%) / 7 (8%) Pharyngitis 6 (7%) / 13 (15%) Increased coughing 6 (7%) / 11 (13%) Somnolence 9 (11%) / 6 (7%) Vomiting 13 (15%) / 1 (1%) Nausea 10 (12%) / 2 (2%) Asthenia 9 (11%) / 1 (1%) Emotional lability 6 (7%) / 4 (5%) Rash 6 (7%) / 4 (5%) Accidental injury 5 (6%) / 4 (5%) Fever 6 (7%) / 3 (4%) Dyspepsia 8 (9%) / 0 (%) Dizziness 5 (6%) / 0 (%) Change in height from baseline to end-point was similar for the two groups [mean change = 0.9 cm (SD 1.3) and 0.8 cm (SD 1.0), $p < 0.65$)]
Conclusions	**Authors' conclusions:** The authors state that once-daily administration of atomoxetine is an effective treatment for children with ADHD **Reviewer's comments:** No comments noted		

Study	Intervention	Participants	Outcomes
References Michelson *et al.*, 2004;[75] Michelson *et al.*, 2003[315] **Source** Updated search **Setting** International **Design** Parallel trial **Duration** 9 months **Purpose** To assess the efficacy of ATX in preventing relapse in paediatric patients with ADHD during 9 months after an initial 12-week treatment period	**Arm 1** ATX Mean dose: 1.56 mg/kg day; administered twice daily (Individuals administering medication not reported) **Arm 2** Placebo (Individuals administering medication not reported)	**Inclusion criteria** 1. 6–15 years of age 2. Symptom severity above 1.5 SD for age and gender 3. No bipolar disorder or psychotic illness 4. No unstable medical illness or condition that requires ongoing psychoactive medication (other than ATX) **Diagnostic criteria** DSM-IV **Number** Total randomised = 416 (male = 373) Arm 1 = 292 Arm 2 = 124 Total withdrawals = 10 Arm 1 = 9 Arm 2 = 1 Reasons for withdrawals: All discontinuations were due to adverse events (9 in ATX group and 1 in placebo group) **Age** 10 years (mean); 2.3 years (SD) **IQ** Not reported **Co-morbid disorders** ODD: 43%, depression: 2%, generalised anxiety disorder: 3% **Diagnostic subtypes** Combined: 73%; hyperactive/impulsive: 5%; inattentive: 22% **Additional information** Previous medication: The participants in this trial were children who responded to an initial 12-week open-label period of treatment with ATX. Patients who relapsed during the 9-month period were removed from the study and offered the option of entering an open-label extension of the study Concurrent medication: No participants were to be in receipt of ongoing psychoactive medication (other than ATX) for an unstable medical illness or condition	**Core symptoms** ADHD Rating Scale IV: total score; inattentive symptoms; hyperactive/impulsive symptoms CPRS: hyperactivity CTRS: hyperactivity **Co-existent problems** CPRS: oppositional; cognitive problems CTRS: oppositional; cognitive problems **Educational performance** Not reported **Psychological function** Not reported **Depression or anxiety** Not reported **Quality of life** CGI Severity of Illness scale Child Health Questionnaire psychosocial summary score **Adverse events** Some adverse events reported **Additional outcomes** Relapse prevention (symptom return to ≥ 90% baseline ADHD Rating Scale IV total score and increase in CGI Severity of Illness scale of at least 2 points)

Core symptoms	Educational performance	Quality of life	Adverse events
ADHD Rating Scale IV: total score (baseline/change from baseline) ATX: 15.8 (9.6)/6.8 (13.6) Placebo: 15.7 (10.0)/12.3 (14.3) (ATX > placebo, $F = 15.58$, $p < 0.001$) ADHD Rating Scale IV : inattentive symptoms (baseline/change from baseline) ATX: 8.6 (5.1)/3.7 (7.4) Placebo: 8.6 (5.4)/6.4 (7.7) (ATX > placebo, $F = 14.17$, $p < 0.001$) ADHD Rating Scale IV: hyperactive/impulsive symptoms (baseline/change from baseline) ATX: 7.2 (5.5)/3.1 (7.0) Placebo: 7.1 (5.5)/5.9 (7.4) (ATX > placebo, $F = 13.37$, $p < 0.001$) CPRS: hyperactivity (baseline/change from baseline) ATX: 4.5 (3.8)/1.5 (4.7) Placebo: 4.6 (4.2)/3.1 (4.9) (ATX > placebo, $F = 10.25$, $p = 0.001$) CTRS: hyperactivity (baseline/change from baseline) ATX ($n = 228$): 7.7 (5.1)/0.4 (5.2) Placebo ($n = 93$): 8.1 (5.5)/1.4 (4.6) (NS, $F = 3.1$, $p = 0.079$)	Not reported	CGI Severity of Illness scale (baseline/change from baseline) ATX: 2.3 (1.0)/0.9 (1.6) Placebo: 2.2 (0.9)/1.4 (1.6) (ATX > placebo, $F = 9.13$, $p = 0.003$) Child Health Questionnaire psychosocial summary score (baseline/change from baseline) ATX ($n = 235$): 43.4 (10.0)/–5.6 (13.2) Placebo ($n = 96$): 44.0 (8.6)/–9.5 (12.0) (ATX > placebo, $F = 5.83$, $p = 0.016$)	Withdrawals: All discontinuations were due to adverse events (9 in ATX group and 1 in placebo group) The authors state that gastroenteritis and pharyngitis were more common on ATX, whereas increased appetite was more common on placebo (reported by ≥ 5% in either group). Patients on ATX gained weight more slowly than on placebo: absolute increase in kilograms for ATX 1.2 (2.4) and placebo 3.3 (3.6), $p < 0.001$
Conclusions	**Authors' conclusions:** In patients who responded favourably to 12 weeks of initial treatment, ATX was superior to placebo in maintaining response for the ensuing 9 months **Reviewer's comments:** No comments noted		

Study	Intervention	Participants	Outcomes
Reference Pelham *et al.*, 1987[77] **Source** AHRQ Report **Setting** USA (STP) **Design** Crossover trial **Duration** Treatment programme: 7 weeks; drug period: 5 weeks; baseline/adaptation period: 2 weeks **Purpose** To investigate the relative effects of sustained release MPH and standard MPH	**Arm 1** MPH plus non-drug intervention Standard 10 mg/dose administered twice daily (a.m., noon); behaviour modification programme; condition varied daily on a random basis (Administered by parents/programme staff) **Arm 2** MPH plus non-drug intervention Sustained-release 20 mg (a.m.) plus placebo capsule (noon); behaviour modification programme; condition varied daily on a random basis (Administered by parents/programme staff) **Arm 3** Placebo plus non-drug intervention Administered twice daily (a.m., noon); behaviour modification programme; condition varied daily on a random basis (Administered by parents/programme staff)	**Inclusion criteria** Inclusion criteria are not explicitly reported **Diagnostic criteria** DSM-III **Number** Total randomised = 13 (male = 13) Total withdrawals = 0 **Age** 8.8 years (mean); 1.5 years (SD); 6 years 7 months–11 years (range) **IQ** 95.3 (mean) **Co-morbid disorders** 4/13 were diagnosed with CD; 6/13 were diagnosed with ODD; 3/13 were diagnosed with a learning disability **Diagnostic subtypes** 11/13 diagnosed with ADD with hyperactivity; 2/13 diagnosed with ADD without hyperactivity **Additional information** No relevant information reported	**Core symptoms** Abbreviated Conners' Rating Scale Revised Behaviour Problem Checklist (counsellors) **Co-existent problems** Appropriate and inappropriate behaviours: following rules, positive peer behaviours, non-compliance, conduct problems, negative verbalisations (counsellors) Number of time-outs (used as a consequence for aggression, destruction of property, stealing and repeated non-compliance) RECESS Code: percentages of time child engaged in positive, negative or no interaction with peers **Educational performance** Arithmetic drill: number of problems attempted, percentage completed correctly Reading task: number of problems attempted, percentage completed correctly Individualised academic tasks: accuracy, productivity **Psychological function** Not reported **Depression or anxiety** Not reported **Quality of life** Not reported **Adverse events** Side-effects checklists (parents, teachers, counsellors) **Additional outcomes** Daily report cards: percentage of days child reached academic and behavioural goals

Core symptoms	Educational performance	Quality of life	Adverse events
Abbreviated Conners' Rating Scale (teacher rating), mean (SD): Baseline: 19.0 (3.63) MPH: 3.4 (4.87) MPH-SR: 1.9 (2.00) Placebo: 4.6 (3.75) *t*-Test: placebo versus average of 2 drugs: $t = 1.6$, $p < 0.10$; MPH versus MPH-SR: $t = -1.3$, NS Revised Behaviour Problem Checklist (counsellors), mean (SD) MPH: 106.4 (27.76) MPH-SR: 105.9 (29.88) Placebo: 114.2 (39.10) *t*-Test: placebo versus average of 2 drugs: $t = 1.5$, $p < 0.10$; MPH versus MPH-SR: $t = 0.1$, NS	Arithmetic drill: number of problems attempted, mean (SD): MPH: 21.0 (7.68) MPH-SR: 21.7 (9.93) Placebo: 18.7 (6.71) *t*-Test: placebo versus average of 2 drugs: $t = -2.7$, $p < 0.01$; MPH versus MPH-SR: $t = -0.5$, NS Arithmetic drill: percentage completed correctly, mean (SD): MPH: 93.4 (5.75) MPH-SR: 94.4 (7.53) Placebo: 88.8 (11.88) *t*-Test: Placebo versus average of 2 drugs: $t = -2.2$, $p < 0.05$; MPH versus MPH-SR: $t = -0.5$, NS Reading task: number of problems attempted, mean (SD): MPH: 19.8 (8.20) MPH-SR: 18.2 (7.02) Placebo: 16.2 (5.99) *t*-Test: placebo versus average of 2 drugs: $t = -3.0$, $p < 0.01$; MPH versus MPH-SR: $t = 1.4$, NS Reading task: percentage completed correctly, mean (SD): MPH: 79.8 (11.59) MPH-SR: 77.9 (19.94) Placebo: 74.3 (17.16) *t*-Test: placebo versus average of 2 drugs: $t = -1.1$, NS; MPH versus MPH-SR: $t = 0.4$, NS Individualised academic tasks: % completion, mean (SD): MPH: 86.1 (8.41) MPH-SR: 89.1 (9.43) Placebo: 73.7 (13.39) *t*-Test: placebo versus average of 2 drugs: $t = -4.3$, $p < 0.001$; MPH versus MPH-SR: $t = -0.9$, NS	Not reported	The drugs caused similar side-effects MPH-SR: 5/13 boys showed evidence of anorexia MPH: 4/13 boys showed evidence of anorexia No boys showed insomnious effects. Irritability, dullness, and stomach aches were reported infrequently, inconsistently and not differentially across drugs

continued

Core symptoms	Educational performance	Quality of life	Adverse events
	Individualised academic tasks: % correct, Mean (SD): MPH: 83.7 (8.22) MPH-SR: 82.9 (7.44) Placebo: 79.0 (7.78) *t*-Test: placebo versus average of 2 drugs: $t = -1.7$, $p < 0.10$; MPH versus MPH-SR: $t = 0.3$, NS		
Conclusions	**Authors' conclusions:** The authors concluded that sustained-release MPH was significantly less effective than the standard MPH regimen on several critical measures of disruptive behaviour, with only a minority of children responding equally positively to both preparations **Reviewer's comments:** No comments noted		

Study	Intervention	Participants	Outcomes
Reference Pelham *et al.*, 1990[78] **Source** AHRQ Report **Setting** USA (STP) **Design** Crossover trial **Duration** STP: 8 weeks; drug treatment period: $6\frac{1}{2}$ weeks; baseline assessment period: $1\frac{1}{2}$ weeks **Purpose** To evaluate the relative efficacy of comparable doses of the three long-acting forms of stimulant – PEM, dextroamphetamine and MPH – with the standard MPH preparation	**Arm 1** MPH plus non-drug intervention Standard; 10 mg administered twice daily (a.m., noon); broad spectrum behaviour modification intervention (Administered by parent and programme staff) **Arm 2** MPH plus non-drug intervention Sustained release 20 mg administered once daily with midday placebo; broad spectrum behaviour modification intervention (Administered by parent and programme staff) **Arm 3** DEX plus non-drug intervention Sustained release 10 mg administered once daily (a.m.) with midday placebo; broad spectrum behaviour modification intervention (Administered by parent and programme staff) **Arm 4** PEM plus non-drug intervention 56.25 mg administered once daily (a.m.) with midday placebo; broad spectrum behaviour modification intervention (Administered by parent and programme staff)	**Inclusion criteria** Inclusion criteria are not explicitly reported **Diagnostic criteria** DSM-III **Number** Total randomised = 22 (male = 22) No withdrawals reported Randomisation procedure: Note that placebo, standard MPH, sustained-release MPH and DEX were randomised over single days whereas PEM was randomised in triplets of days, with only the last two days of the three being used to record data **Age** 10.39 years (mean); 8.08–13.17 years (range); 1.38 years (SD) **IQ** 105.68 (mean) **Co-morbid disorders** ODD: $n = 9/22$; CD: $n = 4/22$; learning disability suggested: $n = 13/22$; Concurrent seizure disorder: $n = 1/22$. **Diagnostic subtypes** Not reported **Additional information** No relevant information reported	**Core symptoms** Abbreviated ACTRS (teachers, counsellors) **Co-existent problems** Appropriate/inappropriate behaviour ratings: following rules, positive peer behaviours, non-compliance, conduct problems, negative verbalisations (counsellors) Rule-following behaviour (teachers) **Educational performance** Arithmetic drill: number of questions attempted, percentage completed correctly Timed reading task: number of questions attempted, percentage completed correctly **Psychological function** Continous Performance Task: errors of commission, errors of omission **Depression or anxiety** Not reported **Quality of life** Not reported. **Adverse events** Side-effects checklists (parents, teachers, counsellors) **Additional outcomes** Daily report cards: percentage of days child reached academic and behavioural criteria

Core symptoms	Educational performance	Quality of life	Adverse events
Abbreviated CTRS (teachers): mean (SD) Baseline: 15.5 (6.52) Placebo: 3.8 (4.6) MPH 10 mg: 2.3 (2.0) MPH SR-20: 2.3 (2.1) DEX: 1.7 (1.4) *Post hoc* analyses: DEX > placebo, $p < 0.05$ Abbreviated CTRS (counsellors) Baseline: Not reported Placebo: 6.3 (4.8) MPH, 10 mg: 4.8 (3.2) MPH, SR-20: 5.0 (3.6) DEX: 4.5 (3.0) *Post hoc* analyses: MPH 10 mg > placebo, $p < 0.05$; MPH, SR-20 > placebo, $p < 0.05$; DEX > placebo, $p < 0.05$	Timed reading task: number of questions attempted Placebo: 14.3 (8.0) MPH 10mg: 18.0 (8.3) MPH SR-20: 16.4 (7.3) DEX: 17.5 (8.9) *Post hoc* analyses: MPH 10 mg > placebo, $p < 0.01$; DEX > placebo, $p < 0.005$ Timed reading task: percentage completed correctly Placebo: 69 (18) MPH 10 mg: 73 (18) MPH SR-20: 73 (13) DEX: 74 (16) No significant differences compared with placebo Arithmetic drill (seatwork): percentage completed Placebo: 70 (24) MPH 10 mg: 78 (17) MPH SR-20: 77 (18) DEX: 76 (16) *Post hoc* analyses: MPH, 10 mg > placebo, $p < 0.05$; MPH, SR-20 > placebo, $p < 0.05$ Arithmetic drill (seatwork): percentage completed correctly Placebo: 84 (8) MPH 10 mg: 84 (10) MPH SR-20: 87 (9) DEX: 86 (8) *Post hoc* analyses: MPH SR-20 > placebo, $p < 0.10$	Not reported	Side-effects checklists (staff rating): % of children rated as showing side-effects or placebo/MPH/MPH-SR/DEX: Crabby, touchy: 22.7/0.0/9.1/0.0 Whiny: 22.7/ 4.8/9.1/18.2 Worried, anxious: 4.5/0.0/0.0/0.0 Withdrawn: 0.0/10.0/0.0/13.6 Dull, not alert: 4.5/14.3/4.3/9.0 Drowsy, tired: 4.5/ 9.5/4.5/13.6 Tearful, cries a lot: 13.6/ 4.8/4.5/ 0.0 Jittery: 0.0/0.0/0.0/4.5 Sad, depressed: 4.5/0.0/0.0/4.5 Stomach aches, nausea: 13.6/14.3/9.1/22.7 Headaches: 9.1/0.0/0.0/22.7 Muscle aches: 4.5/9.5/4.5/0.0 Rash: 0.0/0.0/0.0/0.0 Weakness: 4.5/0.0/4.5/0.0 Dry mouth: 4.5/4.8/4.5/0.0 Loss of appetite: 45.0/61.9/76.2/77.3 Vomiting: 0.0/0.0/0.0/4.5 Fainting, dizziness: 0.0/0.0/0.0/4.5 Eye/muscle twitches: 4.5/4.8/9.1/4.5 Fingernail biting: 9.1/4.8/4.5/4.5 Repetitive tongue movements: 9.1/4.8/0.0/4.5 Picking: 0.0/0.0/0.0/4.5 Distortion of vision: 0.0/0.0/0.0/0.0 Side-effects checklists (parents rating): % of children rated as showing side effects or placebo/MPH/MPH-SR/DEX Difficulty falling asleep: 5.3/5.9/18.8/20.0 Awake during the night: 5.3/12.5/13.3/14.3 Nightmares: 0.0/0.0/0.0/0.0 Bed wetting: 0.0/5.6/0.0/6.3
Conclusions	**Authors' conclusions:** The authors noted generally equivalent and beneficial effects of all four medications **Reviewer's comments:** No comments noted		

Study	Intervention	Participants	Outcomes
Reference Pelham *et al.*, 1993[79] **Source** AHRQ Report **Setting** USA (STP) **Design** Crossover trial **Duration** Treatment programme: 8 weeks; Total treatment period: 6 weeks (2 weeks per treatment arm) **Purpose** To evaluate the separate and combined effects of BM and two doses of MPH compared with baseline (no BM and a placebo) on classroom behaviour and academic performance	**Arm 1** MPH alone and with non-drug intervention 0.3 mg/kg/dose (n = 27) or 0.15 mg/kg/dose (n = 4) administered twice daily (a.m., noon); mean 8.1 mg/dose; range 5–15 mg/dose; 1/2 weeks with BM intervention (Individual administering medication not reported) **Arm 2** MPH alone and with non-drug intervention 0.6 mg/kg/dose (n = 27) or 0.3 mg/kg/dose (n = 4) administered twice daily (a.m., noon); mean 16.0 mg/dose; range 10–22.5 mg/dose; 1/2 weeks with BM intervention (Individual administering medication not reported) **Arm 3** Placebo alone and with non-drug intervention Administered twice daily (a.m. noon); 1/2 weeks with BM intervention (Individual administering medication not reported)	**Inclusion criteria** No explicit inclusion criteria except DSM-III-R diagnosis **Diagnostic criteria** DSM-III-R **Number** Total = 31 (male = 31) No withdrawals reported **Age** 8.23 years (mean); 5.42–9.92 years (range) **IQ** 110.7 (mean) **Co-morbid disorders** ODD: n = 10/31; CD: n = 15/31; learning achievement score discrepancies: n = 17/31; receiving help for learning or behavioural problems: n = 12/31 **Diagnostic subtypes** Not reported **Additional information** Co-interventions: 12/31 were receiving part- or full-time services for learning or behaviour problems	**Core symptoms** IOWA CTRS: inattention/overactivity **Co-existent problems** Rule-following behaviour (teachers) CO-CADD Observation Scheme: on-task behaviour, disruptive behaviour (trained observers) IOWA CTRS: oppositional/defiant Social validity ratings: normality, pleasantness (teachers) **Educational performance** Individualised academic tasks: accuracy, productivity **Psychological function** Not reported **Depression or anxiety** Not reported **Quality of life** Not reported **Adverse events** Not reported **Additional outcomes** Not reported

Core symptoms	Educational performance	Quality of life	Adverse events
IOWA CTRS: inattention/overactivity With/without BM, mean (SD): MPH 0.3: 2.1 (2.1)/2.0 (2.1) MPH 0.6: 1.5 (1.8)/1.7 (2.1) Placebo: 4.9 (3.3)/6.0 (4.3) Effect BM: $F(1,29) = 3.36$, NS Effect MPH: $F(2,58) = 36.19$, $p < 0.0001$	Individualised academic tasks: % accuracy With/without BM, mean (SD): MPH, 0.3: 92.1 (6.5)/90.7 (9.6) MPH, 0.6: 91.6 (7.2)/90.1 (8.0) Placebo: 87.0 (12.4)/88.4 (13.6) Effect BM: $F(1,29) = 0.38$, NS Effect MPH: $F(2,58) = 0.63$, NS Individualised academic tasks: % productivity With/without BM, mean (SD): MPH, 0.3: 77.4 (21.0)/79.6 (19.7) MPH, 0.6: 81.2 (17.1)/81.1 (18.4) Placebo: 62.2 (26.3)/62.2 (28.8) Effect BM: $F(1,29) = 0.00$, NS Effect MPH: $F(2,58) = 10.31$, $p < 0.001$	Not reported	Not reported
Conclusions	**Authors' conclusions:** The authors concluded that BM and MPH separately improved the classroom behaviour of ADHD boys, although only MPH had a beneficial effect on the children's academic performance. Further, the combination of the two treatments was more effective than BM alone but yielded limited improvement beyond that afforded by MPH alone **Reviewer's comments:** No comments noted		

Study	Intervention	Participants	Outcomes
Reference Pelham *et al.*, 1999[80] **Source** NICE Report **Setting** USA (STP) **Design** Crossover trial **Duration** Treatment period: 6 weeks **Purpose** To compare two doses of Ritalin and Adderall in the treatment of ADHD in children in an acute study and assess the medications' time courses	**Arm 1** MPH plus non-drug intervention 10 mg/dose administered at 7.45 a.m. and 12.15 p.m. Monday to Thursday for 6 weeks in random order with conditions changing daily for 24 days; comprehensive behavioural programme incorporating parental training and a BM system (Individual administering medication not reported) **Arm 2** MPH plus non-drug intervention 17.5 mg/dose administered at 7.45 a.m. and 12.15 p.m. Monday to Thursday for 6 weeks in random order with conditions changing daily for 24 days; comprehensive behavioural programme incorporating parental training and a BM system (Individual administering medication not reported) **Arm 3** Adderall plus non-drug intervention 7.25 mg/dose administered at 7.45 a.m. and 12.15 p.m. Monday to Thursday for 6 weeks in random order with conditions changing daily for 24 days; comprehensive behavioural programme incorporating parental training and a BM system (Individual administering medication not reported) **Arm 4** Adderall plus non-drug intervention 12.5 mg/dose administered at 7.45 a.m. and 12.15 p.m. Monday to Thursday for 6 weeks in random order with conditions changing daily for 24 days; comprehensive behavioural programme incorporating parental training and a BM system (Individual administering medication not reported)	**Inclusion criteria** Informed consent of parents and participants **Diagnostic criteria** DSM-IV **Number** Total randomised = 26 (male = 22) Total withdrawals = 1 Reasons for withdrawals: Child removed owing to uncontrollable behaviour not ameliorated by medication **Age** 9.6 years (mean); range 5.8–12.7 years; 1.6 years (SD) **IQ** Not reported **Co-morbid disorders** ODD: *n* = 13; CD: *n* = 8 **Diagnostic subtypes** Not reported **Additional information** No relevant information reported	**Core symptoms** Classroom measures: on-task behaviour Individual target measures (Daily Report Cards) IOWA Conners' Rating Scale: inattention–overactivity (counsellors, teachers, parents) **Co-existent problems** Point system measures: following activity rules, non-compliance, interrupting, complaining, positive peer behaviours, conduct problems and negative verbalisations Classroom measures: rule-following behaviour and disruptive behaviour IOWA Conners' Rating Scale: oppositional/defiance (counsellors, teachers, parents) Recess rule violations **Educational performance** Classroom measures: accuracy and productivity of seatwork tasks Point system measures: attention questions answered correctly **Psychological function** Not reported **Depression or anxiety** Not reported **Quality of life** Not reported **Adverse events** Side-effects checklist (teachers, counsellors, parents) **Additional outcomes** Global impression of effectiveness of medication (counsellors, teachers, parents)

Core symptoms	Educational performance	Quality of life	Adverse events
Post-treatment means (SD) for: placebo/MPH (10 mg)/MPH (17.5 mg) Baseline (teachers only): 11.8 (2.3) IOWA Conners' Rating Scale: inattention–overactivity (teachers): 3.7 (2.6)/1.8 (1.4)/1.1 (1.2) IOWA Conners' Rating Scale: inattention–overactivity (parents, 5-6 p.m.) 3.0 (2.9)/1.9 (1.4)/1.0 (1.1) IOWA Conners Rating Scale: inattention–overactivity (counsellors) 5.6 (2.9)/3.4 (1.8)/2.6 (1.4) Individual target measures (daily report cards) 50.5 (20.7)/76.4 (9.7)/81.7 (12.3) Classroom measures: on-task behaviour 78.9 (15.4)/89.2 (10.5)/89.6 (8.6)	Seatwork completion: mean (SD) Placebo: 58.0 (25.8) MPH 10 mg: 69.5 (15.4) MPH 17.5 mg: 69.2 (19.5) Seatwork accuracy: mean (SD) Placebo: 89.0 (9.6) MPH 10 mg: 87.9 (9.8) MPH 17.5 mg: 87.1 (12.4) Point system measures: attention: mean (SD) Placebo: 62.9 (14.9) MPH 10 mg: 64.0 (15.7) MPH 17.5 mg: 64.3 (15.4)	Not reported	Side-effects checklist (teachers, counsellors, parents): teachers not reported % of children with moderate or severe side-effects 'on at least 1-day': 'on average', for placebo/MPH (10 mg)/MPH (17.5 mg), rated by parents: Motor tics: 8:0/4:0/0:0 Buccal–lingual movement.: 4:0/0:0/4:0 Picking, nail-biting: 4:0/0:0/0:0 Worried/anxious: 4:0/4:4/4:0 Dull, tired, listless: 28:0/8:0/12:0 Headaches: 4:0/12:0/16:0 Stomach ache: 0:0/4:0/8:0 Crabby, irritable: 32:4/24:4/16:0 Tearful, sad, depressed: 8:4/20:0/16:0 Socially withdrawn: 12:0/0:0/8:0 Hallucinations: 0:0/0:0/0:0 Trouble sleeping: 12:4/32:8/24:4 Loss of appetite: 8:0/8:0/20:4 % of children with moderate or severe side-effects 'on at least 1day': 'on average', for: placebo/MPH (10 mg)/MPH (17.5 mg), rated by counsellors: Motor tics: 0:0/8:0/4:0 Buccal–lingual movement: 0:0/12:0/4:4 Picking, nail-biting: 4:0/4:0/8:0 Worried/anxious: 8:0/8:0/8:0 Dull, tired, listless: 8:0/0:0/20:0 Headaches: 4:0/8:0/8:0 Stomach ache: 12:0/8:0/28:0 Crabby, irritable: 32:4/4:0/8:0 Tearful, sad, depressed: 8:0/16:0/24:0 Socially withdrawn: 0:0/8:0/16:0 Hallucinations: 0:0/0:0/0:0 Trouble sleeping: –:–/-:–/–:– Loss of appetite: 60:4/60:4/68:12
Conclusions	**Authors' conclusions:** The authors conclude that Adderall is at least as effective as Ritalin in improving acutely the behaviour and academic productivity of children with ADHD **Reviewer's comments:** No comments noted		

Study	Intervention	Participants	Outcomes
Reference Pelham *et al.*, 1999[81] **Source** NICE Report **Setting** USA (STP) **Design** Crossover trial **Duration** Treatment period: 6 weeks **Purpose** 1. To compare standard twice-daily PH dosing with a single morning dose of MPH and of Adderall during a typical school-day period 2. To conduct a dose–response study of the effects of a late-afternoon dose of MPH and Adderall on evening behaviour and side-effects	**Arm 1** MPH plus non-drug intervention 0.3 mg/kg/dose administered a.m., noon and p.m. Monday to Thursday; comprehensive behavioural programme incorporating parental training and a BM system (Individual administering medication not reported) **Arm 2** MPH plus non-drug intervention 0.3 mg/kg/dose administered in the morning and placebo at noon and p.m. Monday to Thursday; comprehensive behavioural programme incorporating parental training and a BM system (Individual administering medication not reported) **Arm 3** MPH plus non-drug intervention 0.3 mg/kg/dose administered a.m. and noon and 0.15 mg/kg/dose administered in the afternoon Monday to Thursday; comprehensive behavioural programme incorporating parental training and a BM system (Individual administering medication not reported) **Arm 4** Adderall plus non-drug intervention 0.3 mg/kg/dose administered a.m. and p.m. and placebo at noon, administered Monday to Thursday; comprehensive behavioural programme incorporating parental training and a BM system (Individual administering medication not reported) **Arm 5** Adderall plus non-drug intervention 0.3 mg/kg/dose administered in the morning and placebo at noon and p.m., administered Monday to Thursday; comprehensive behavioural programme incorporating parental training and a BM system (Individual administering medication not reported) **Arm 6** Adderall plus non-drug intervention	**Inclusion criteria** 1. Diagnosis of ADHD 2. No medical history prohibiting psychostimulant medication or participation in STP activities. **Diagnostic criteria** DSM-IV **Number** Total randomised = 21 (male = 19) No withdrawals reported Randomisation procedure: Each participant was randomised daily to one of seven drug conditions **Age** 10.26 years (mean); 6–12 years (range) **IQ** 109.9 (mean) **Co-morbid disorders** Learning problems: n = 9/21; ODD: n = 14/21; CD: n = 5/21 **Diagnostic subtypes** Not reported **Additional information** Previous medication: 88% of participants were on MPH, 6% were on *d*-amphetamine and 6% were on clonidine before the STP	**Core symptoms** Classroom measures: on-task behaviour Individual target measures (Daily Report Cards) IOWA Conners' Rating Scale: inattention–overactivity (counsellors, teachers, parents) **Co-existent problems** Point system measures: following activity rules, non-compliance, interrupting, complaining, positive peer behaviours, conduct problems and negative verbalisations Classroom measures: rule-following behaviour and disruptive behaviour IOWA Conners' Rating Scale: oppositional/defiant (counsellors, teachers, parents) **Educational performance** Classroom measures: accuracy and productivity of seatwork tasks **Psychological function** Not reported **Depression or anxiety** Not reported **Quality of life** Not reported **Adverse events** Pittsburgh Side Effect Rating Scale (counsellors, teachers, parents) **Additional outcomes** Not reported

continued

Study	Intervention	Participants	Outcomes
	0.3 mg/kg/dose in the morning, placebo at noon and 0.15 mg/kg/dose in the afternoon Administered Monday to Thursday; comprehensive behavioural programme incorporating parental training and a BM system (Individual administering medication not reported) **Arm 7** Placebo plus non-drug intervention Administered am, noon and pm Monday to Thursday; comprehensive behavioural programme incorporating parental training and a BM system (Individual administering medication not reported)		

Core symptoms	Educational performance	Quality of life	Adverse events
IOWA Conners' Rating Scale: inattention–overactivity (teachers) MPH, qAM: 2.0 (2.0); MPH, qAM > placebo, $p < 0.05$ MPH, b.d.: 0.9 (0.8); MPH, b.d. > MPH, qAM, $p < 0.05$, MPH b.d. > placebo, $p < 0.05$ Placebo: 3.9 (2.8) IOWA Conners' Rating Scale: inattention–overactivity (parents) MPH, qAM: 2.6 (2.0) MPH, tid (0.3/0.3/0.15): 2.9 (2.0) MPH, tid (0.3/0.3/0.3): 1.8 (1.5); MPH, tid (0.3/0.3/0.3) > Placebo, $p < 0.05$ Placebo: 3.1 (1.9) IOWA Conners' Rating Scale: inattention–overactivity (counsellor) MPH, qAM: 4.3 (2.2); MPH, qAM > placebo, $p < 0.05$ MPH, bid: 3.3 (1.7); MPH, b.d. > placebo, $p < 0.05$, MPH, b.d. > MPH, qAM, $p < 0.05$ Placebo: 5.8 (3.3) Classroom measures: on-task behaviour (teacher): MPH, qAM: 94.9 (6.6); MPH, qAM > placebo, $p < 0.05$ MPH, b.d.: 96.1 (5.3); MPH, b.d. > placebo, $p < 0.05$ Placebo: 88.3 (10.2) Individual target measures (Daily Report Card, parents): MPH, qAM: 69.0 (17.5); MPH, qAM > placebo, $p < 0.05$ MPH, b.d.: 80.5 (11.0); MPH, b.d. > placebo, $p < 0.05$ Placebo: 55.3 (22.9)	Seatwork complete: MPH, qAM: 86.9 (9.7); MPH, qAM > placebo, $p < 0.05$ MPH, b.d.: 86.1 (11.6); MPH, b.d. > placebo, $p < 0.05$ Placebo: 73.2 (16.3) Seatwork correct: MPH, qAM: 87.5 (11.2) MPH, b.d.: 89.8 (6.2) Placebo: 87.8 (8.1) No significant differences	Not reported	Pittsburgh Side Effect Rating Scale (parents) % of children with moderate to severe side-effects on at least 1/day. (tics/buccal/picking at skin/worried/dull/headache/stomach ache/crabby/tearful/withdrawn/hallucinations/appetite loss/sleep trouble) MPH, qAM: 10/5/10/0/0/5/0/10/0/0/0/20/15 MPH, t.d.s. (0.3/0.3/0.15): 10/0/15/15/15/10/10/25/5/15/0/33/20 MPH, t.d.s. (0.3/0.3/0.3): 5/0/5/5/5/0/15/15/5/5/0/33/20 Placebo: 10/0/15/10/20/20/20/33/10/10/0/25/25 Pittsburgh Side Effect Rating Scale (teachers): % of children with moderate to severe side-effects on at least 1/day (tics/buccal/picking at skin/worried/dull/headache/stomach ache/crabby/tearful/withdrawn/hallucinations/appetite loss/sleep trouble) MPH, qAM: 0/0/5/0/5/5/0/5/0/0/0/–/– MPH, t.d.s. (0.3/0.3/0.15): 5/5/0/0/0/0/5/0/0/0/5/–/– MPH, t.d.s. (0.3/0.3/0.3): 0/0/0/0/0/5/0/0/0/0/0/–/– Placebo: 5/0/5/0/5/5/10/10/5/0/0/–/–

Conclusions	
	Authors' conclusions: The authors conclude that a single morning dose of Adderall had behavioural effects throughout an entire school-day period that were equivalent to standard twice-daily MPH dosing. Hence Adderall may be used as a long-acting stimulant for children for whom midday dosing is a problem
	Reviewer's comments: No comments noted

Study	Intervention	Participants	Outcomes
References Pelham *et al.*, 2001;[82] Pelham *et al.*, 2000;[316] Pelham *et al.*, 2000[317] and Connor, 2002[318] **Source** Updated search **Setting** USA (Saturday school) **Design** Crossover trial **Duration** Treatment period: 7 days **Purpose** To test the efficacy and duration of action, in natural and laboratory settings, of an extended-release MPH preparation designed to last 12 hours and therefore be equivalent to 3 times daily dosing	**Arm 1** Placebo plus non-drug intervention Administered 3 times daily (7.30 a.m., 11.30 a.m., 3.30 p.m.); behavioural programme incorporating parent training, teacher consultation and point systems (Administered by parent, school personnel and study staff) **Arm 2** MPH plus non-drug intervention Immediate release; 5, 10, or 15 mg/dose administered three times (7.30 a.m., 1130 a.m., 3.30 p.m.) depending on child's MPH dosing before the study; average dose: 29 mg/day or 0.88 mg/kg/day; behavioural programme incorporating parent training, teacher consultation and point systems (Administered by parent, school personnel and study staff) **Arm 3** MPH plus non-drug intervention Concerta; 18, 36 or 54 mg once per day (7.30 a.m.) depending on child's MPH dosing before the study, placebo twice per day (11.30 a.m., 3.30 p.m.); average dose: 35 mg/day or 1.05 mg/kg/day; behavioural programme incorporating parent training, teacher consultation and point systems (Administered by parent, school personnel and study staff)	**Inclusion criteria** 1. Age 6–12 years 2. Diagnosis of DSM-IV criteria ADHD (any subtype) 3. Required to be medicated with MPH on entry to the study and must have been receiving stable dose for at least 4 weeks before the beginning of the study 4. No presence of medical condition that would contraindicate the use of stimulant medication 5. No presence of any physical condition or severe learning difficulty that would interfere with participation in the laboratory classroom assessment (e.g. IQ <80 as determined by WISC at screening) 6. Not receiving additional medication (beyond MPH) for ADHD 7. Not receiving any medication having CNS effects, anticonvulsants, or investigational medications 8. Not having reached menarche 9. Not having blood pressure at or above the 95th percentile for age and height 10. Parent's attendance at premedication behavioural parent training (at least 4 sessions) **Diagnostic criteria** DSM-IV **Number** Total randomised = 70 (male = 89%) Total withdrawals = 2 Reasons for withdrawals: Administration of non-study immediate release MPH (n = 2) Five participants missed 1 laboratory session day because of illness or inclement weather 1 participant missed 2 days of school because of suspension; another missed 1 full week of school and a laboratory session because of illness **Age** 9.1 (mean); 6–12 years (range), 1.6 years (SD) **IQ** 104.8 (mean)	**Core symptoms** IOWA Conners' Rating Scale: inattention, impulsivity and overactivity (teacher, parent, counsellor) Abbreviated Conners' Rating Scale (teacher, parent) SKAMP rating scale: attention (teacher) **Co-existent problems** IOWA Conners' Rating Scale: oppositional–defiant behaviour (teacher, parent, counsellor) SNAP Rating Scale: Peer Relations (teacher) Classroom Observation Code for Attention Deficit Disorders: observed on-task behaviour, observed disruptive behaviour (independent observers) Rule violations (teacher) Negative behaviours: teasing, interrupting, complaining (counsellors) SKAMP rating scale: deportment (teacher) **Educational performance** Timed Maths Task: problems completed, percentage correct Daily Individualised Report Cards (teacher) **Psychological function** Not reported **Depression or anxiety** Not reported **Quality of life** Global effectiveness ratings (teacher, parent) **Adverse events** Questions regarding adverse events, sleep quality, appetite, and tics (parents) Spontaneous reports of adverse events **Additional outcomes** Blood pressure Pulse rate

continued

Study	Intervention	Participants	Outcomes
		Co-morbid disorders ODD: 43% CD: 37% **Diagnostic subtypes** Not reported **Additional information** Previous medication: Participants were required to be medicated with MPH on entry to the study: they should have received a stable dose for at least 4 weeks before study commencement Concurrent medication: In addition, they were required not to be receiving additional medication (beyond MPH) for ADHD or any medication having CNS effects, anticonvulsants or investigational medications	

Core symptoms	Educational performance	Quality of life	Adverse events
Natural setting: IOWA Conners' Rating Scale (inattention–overactivity), teacher rated: mean (SD) Placebo:10.34 (4.21) t.d.s. IR-MPH: 5.00* (3.69) *significantly different from placebo ($p < 0.001$) Concerta 4.69* (3.31) *significantly different from placebo ($p < 0.001$) Natural setting: IOWA Conners' rating scale (inattention–overactivity), parent rated: mean (SD) Placebo: 10.59 (3.28) t.d.s. IR-MPH: 5.93* (3.09) *significantly different from placebo ($p < 0.001$) Concerta: 4.78** (2.86) **significantly different from placebo ($p < 0.001$) and tid MPH ($p < 0.05$; effect size = 0.4) Laboratory session: IOWA Conners' Rating scale (inattention–overactivity), teacher rated: mean (SD) Placebo: 5.01 (4.48) t.d.s. IR-MPH: 2.75* (3.73) *significantly different from placebo Concerta: 2.59* (3.91) *significantly different from placebo Laboratory session: IOWA Conners' Rating scale (inattention–overactivity) counsellor rating: mean (SD) Placebo: 7.95 (3.85) t.d.s. IR-MPH: 6.31* (3.24) *significantly different from placebo Concerta: 6.10* (3.10) *significantly different from placebo	Timed Maths Task: graphical presentation only Daily Individualised Report Cards: % positive: Arm 1: 61.17 (24.22); Arm 2: 84.36 (15.76); Arm 3: 86.06 (13.52) Significant differences between Arms 1 and 2 and between Arms 1 and 3 ($p < 0.001$)	Global effectiveness (parent): Arm 1: poor: 73.5%; fair: 22.1%; good: 2.9%; excellent: 1.5% Arm 2: poor: 8.8%; fair: 26.5%; good: 50.0%; excellent: 14.7% Arm 3: poor: 5.9%; fair: 27.9%; good: 39.7%; excellent: 26.5% Significant differences between Arms 1 and 2 and between Arms 1 and 3 ($p < 0.001$) Global effectiveness (teacher): Arm 1: poor: 69.1%; fair: 14.7%; good: 14.7%; excellent: 1.5% Arm 2: poor: 10.3%; fair: 32.4%; good: 36.8%; excellent: 20.6% Arm 3: poor: 10.4%; fair: 22.4%; good: 44.8%; excellent: 22.4% Significant differences between Arms 1 and 2 and between Arms 1 and 3 ($p < 0.001$)	Adverse events seen in at least 2% of children in any treatment group: n (%) in placebo/ t.d.s. IR-MPH/Concerta/total Headache 16 (23.2%)/11 (15.9%)/8 (11.8%)/22 (31.4%) Abdominal pain 8 (11.6%)/12 (17.4%)/9 (13.2%)/20 (28.6%) Upper respiratory tract infection 3 (4.3%)/3 (4.3%)/2 (2.9%)/8 (11.4%) Accidental injury 2 (2.9%)/3 (4.3%)/1 (1.5%)/6 (8.6%) Vomiting 2 (2.9%)/2 (2.9%)/2 (2.9%)/5 (7.1%) Twitching 0 (0.0%)/4 (5.8%)/0 (0.0%)/4 (5.7%) Diarrhoea 1 (1.4%)/2 (2.9%)/0 (0.0%)/3 (4.3%) Pharyngitis 0(0.0%)/ 2(2.9%)/1 (1.5%)/3 (4.3%) Rhinitis 0 (0.0%)/2 (2.9%)/1 (1.5%)/3 (4.3%) Dizziness 0 (0.0%)/1 (1.4%)/2 (2.9%)/2 (2.9%) Urinary Incontinence 2 (2.9%)/1 (1.4%)/0 (0.0%) 2 (2.9%) Occurrences of adverse events were similar across conditions Withdrawals: None due to adverse events Tics: 3 reported moderate motor tics during study, 1 reported a mild vocal tic. Two of these were new or worsened cases Sleep: Arm 1: poor: 10%; fair: 21%; good: 57%; excellent:12% Arm 2: poor: 7%; fair: 21%; good: 65%; excellent: 7% Arm 3: poor: 16%; fair: 24%; good: 47%; excellent: 13% No significant differences between treatment arms Appetite: Arm 1: usual: 59%; increased: 37%; decreased: 4% Arm 2: usual: 66%; increased: 6%; decreased: 24% Arm 3: usual: 77%; increased: 10%; decreased: 18%

continued

Core symptoms	Educational performance	Quality of life	Adverse events
Natural setting: Abbreviated Conners' Scale (teacher): mean (SD) Arm 1: 16.40 (7.74); Arm 2: 7.94 (5.83); Arm 3: 7.82 (5.92) Significant differences between Arms 1 and 2, and between Arms 1 and 3 ($p < 0.001$)			The proportion of participants reporting appetite loss differed significantly between Arms 1 and 2, $p = 0.001$, and between Arms 1 and 3, $p = 0.13$, but not between Arms 2 and 3
Natural setting: Abbreviated Conners' Scale (parent): mean (SD) Arm 1: 19.91 (6.02); Arm 2: 11.41 (6.23); Arm 3: 9.49 (6.50) Significant differences between Arms 1 and 2 ($p < 0.001$), Arms 1 and 3 ($p < 0.001$), Arms 2 and 3 ($p < 0.05$)			
Laboratory setting: Abbreviated Conners' Scale (teacher): mean (SD) Arm 1: 7.03 (7.07); Arm 2: 4.03 (6.31); Arm 3: 3.75 (6.66) Significant differences between Arms 1 and 2, and between Arms 1 and 3 ($p < 0.001$)			
Laboratory setting: Abbreviated Conners' Scale (counsellor): mean (SD) Arm 1: 12.70 (7.15); Arm 2: 9.91 (6.15); Arm 3: 9.26 (5.73) Significant differences between Arms 1 and 2 and between Arms 1 and 3 ($p < 0.001$)			
SKAMP Teacher ratings: graphical presentation only			

Conclusions	
	Authors' conclusions: This investigation supports the efficacy of Concerta long-acting formulation of MPH for parents who desire to have medication benefits for their child throughout the day and early evening
	Reviewer's comments: No comments noted

Study	Intervention	Participants	Outcomes
References Pliszka *et al.*, 1999;[319] Pliszka *et al.*, 2000;[83] Faraone *et al.*, 2001[320] and Pliszka, 2003[100] **Source** NICE Report **Setting** USA **Design** Parallel trial **Duration** Treatment period: 3 weeks **Purpose** To compare Adderall with MPH for the treatment of ADHD	**Arm 1** MPH Dosage and number of administrations were adjusted at the end of weeks 1 and 2 via an algorithm based on teacher and parent ratings. Final dose: 25.2 ± 13.6 mg/day; (0.39 mg/kg per dose); administered one to three times daily (morning, noon or after school) (Individual administering medication not reported) **Arm 2** Adderall Dosage and number of administrations were adjusted at the end of weeks 1 and 2 via an algorithm based on teacher and parent ratings. Final dose: 12.5 ± 4.1 mg/day (0.31 mg/kg per dose); administered once or twice daily (morning or after school) (Individual administering medication not reported) **Arm 3** Placebo One to three times daily (Individual administering medication not reported)	**Inclusion criteria** 1. Diagnosis of ADHD 2. School grades 1–5 3. No other medical illness 4. No current treatment with other non-stimulant psychotropic medication 5. No major depression episode, manic episode, or tic disorder. (Children with other co-morbid conditions, e.g. CD, ODD or mild anxiety were included) 6. No history of psychosis or signs of psychosis or significantly depressed mood 7. At least 1.5 SD above the mean for age and sex on the IOWA CTRS inattention–overactivity factor and elevated Conners' Global Index 8. IQ not lower than 75 (KBIT composite) **Diagnostic criteria** Diagnostic Interview Schedule for Children **Number** Total randomised = 58 (male/female split not reported) Arm 1 = 20 Arm 2 = 20 Arm 3 = 18 58 participants are reported on in this paper, but is ambiguous whether more were initially randomised (up to 62?) Total withdrawals = 5 Arm 1 = 1 Arm 2 = 2 Arm 3 = 2 Reasons for withdrawals: Arm 1: No response and adverse effects (n = 11) Arm 2: Adverse events (n = 2) Arm 3: No response (n = 2) **Age** 8.1 years (mean); 1.4 years (SD)	**Core symptoms** IOWA CTRS Inattention–overactivity **Co-existent problems** IOWA CTRS Aggression/defiance factor **Educational performance** Not reported **Psychological function** Not reported **Depression or anxiety** Not reported **Quality of life** Conners' Global Index (parents) CGI-I (psychiatrist) **Adverse events** Multi-Modality Treatment of ADHD Side Effects Scale **Additional outcomes** Weight

continued

Study	Intervention	Participants	Outcomes
		IQ Not reported **Co-morbid disorders** ODD, CD and anxiety disorder **Diagnostic subtypes** Not reported **Additional information** Previous medication: 46 (79.3%) of the sample had no prior history of treatment with any psychotropic medication. 12 (20.6%) had been treated in the past with stimulants: Arm 1: *n* = 5 (25%); Arm 2: *n* = 6 (20%); Arm 3; *n* = 1 (6%) Concurrent medication: Individuals receiving treatment with other non-stimulant psychotropic medication were not included in the trial	

Core symptoms	Educational performance	Quality of life	Adverse events
IOWA CTRS Inattention–overactivity, mean and SD at baseline/3 weeks: MPH: 2.2 (0.5) (n = 20)/0.81 (0.62) (n = 14) Placebo: 2.2 (0.5) (n = 18)/1.49 (0.87) (n = 12) MPH > placebo, $p < 0.05$	Not reported	Conners' Global Index (parents), mean and SD at baseline/3 weeks: MPH: 2.1 (0.5) (n = 20)/1.28 (0.72) (n = 14) Placebo:2.2 (0.5) (n = 18)/1.54 (0.88) (n = 12) No significant difference CGI-I, mean and SD at 3 weeks (no baseline data): MPH: 2.35 (0.81) (n = 14) Placebo: 3.22 (1.44) (n = 12) MPH > placebo, $p < 0.05$ CGI-I: % responders (defined as score = 2) MPH 65% Adderall 90% Placebo 27%	Percentage (n) of parents reporting moderate or severe intensity of side-effects at end of study for MPH/placebo: Facial tics 0% (0), 6% (1) Tongue movements 0% (0), 0% (0) Picking at skin 0% (0), 0% (0) Anxious 10% (2), 6% (1) Tired 20% (4), 11% (2) Headache 0% (0), 6% (1) Stomach ache 5% (1), 0% (0) Irritable 15% (3), 11% (2) Sad/tearful 5% (1), 0% (0) Appetite loss 15% (3), 0% (0) Gets wild when medication wears off 40% (8), 44% (8) No significant differences Withdrawals (due to adverse events): MPH: 1 subject withdrew owing to side-effects and non-response Placebo: 0
Conclusions	**Authors' conclusions:** Both medications were superior to placebo at reducing inattentive and oppositional symptoms in the classroom and on the CGI. Adderall produced significantly more improvements on teacher ratings and the CGI than MPH, although the algorithm may have limited dosing in the MPH group **Reviewer's comments:** No comments noted		

Study	Intervention	Participants	Outcomes
Reference Quinn, 2003[84]		**[Confidential information removed]**	

Core symptoms	Educational performance	Quality of life	Adverse events
[Confidential information removed]			
Conclusions	**Authors' conclusions: [Confidential information removed]**		
	Reviewer's comments: [Confidential information removed]		

Study	Intervention	Participants	Outcomes
Reference Rapport *et al.*, 1989[85] **Source** CCOHTA Report **Setting** USA **Design** Crossover trial **Duration** Treatment periods: 6 consecutive days; washout period: 1 day **Purpose** To examine directly the dose–response relationship between MPH and gross body weight in a large sample of children with ADHD	**Arm 1** MPH 5 mg (range: 0.14–0.22 mg/kg); once daily (breakfast) (Individual administering medication not reported) **Arm 2** MPH 10 mg (range: 0.28–0.44 mg/kg); once daily (breakfast) (Individual administering medication not reported) **Arm 3** MPH 15 mg (range: 0.42–0.66 mg/kg); once daily (breakfast) (Individual administering medication not reported) **Arm 4** MPH 20 mg (range: 0.56–0.88 mg/kg); once daily (breakfast) (Individual administering medication not reported)	**Inclusion criteria** 1. ADHD using DSM-III-R criteria 2. Maternal report of a developmental history consistent with ADHD 3. 2 SD above mean on the Werry–Weiss–Peters Activity Scale (maternal rating) 4. ACTRS > 15 (teacher rating) 5. No gross neurological, sensory or motor impairment 6. No current medication **Diagnostic criteria** DSM-III-R **Number** Total randomised = 45 (male = 45) No withdrawals reported **Age** 7.8 years (mean); 5–15 years (range), 1.5 years (SD) **IQ** 100 (mean) **Co-morbid disorders** Not reported **Diagnostic subtypes** Not reported **Additional information** Randomisation method: Three groups of 15 children were each randomised: low-weight group (22–26 kg), mid-weight group (27–31 kg), high-weight group (32–36 kg) Concurrent medication: Participants were required not to be receiving concurrent medication	**Core symptoms** Abbreviated CTRS: total score On-task behaviour **Co-existent problems** Not reported **Educational performance** Academic efficiency score **Psychological function** Not reported **Depression or anxiety** Not reported **Quality of life** Not reported **Adverse events** Not reported **Additional outcomes** Not reported

Core symptoms	Educational performance	Quality of life	Adverse events
Abbreviated CTRS: total score, mean (SD) Low-weight group: Arm 1: 10.2 (5.2); Arm 2: 7.4 (4.0); Arm 3: 5.8 (4.1); Arm 4: 5.0 (4.6); placebo: 15.7 (5.8) Mid-weight group: Arm 1: 13.9 (6.8); Arm 2: 8.4 (6.4); Arm 3: 8.2 (4.7); Arm 4: 7.5 (4.4); placebo: 15.9 (5.9) High-weight group: Arm 1: 10.1 (6.2); Arm 2: 9.1 (6.4); Arm 3: 7.5 (5.0); Arm 4: 7.1 (5.4); placebo: 13.8 (6.1) The authors state that each of the MPH doses results in statistically significant improvement ($p < 0.01$) relative to placebo. In addition, the 10, 15 and 20-mg doses led to greater improvement ($p < 0.01$) than the 5-mg dose On-task behaviour, mean (SD) Low-weight group: Arm 1: 72.4 (16.7); Arm 2: 78.1 (11.0); Arm 3: 79.6 (14.2); Arm 4: 81.7 (12.1); placebo: 60.9 (19.5) Mid-weight group: Arm 1: 65.6 (20.9); Arm 2: 81.0 (9.1); Arm 3: 76.5 (13.6); Arm 4: 81.7 (8.5); placebo: 59.9 (19.2) High-weight group: Arm 1: 68.0 (24.1); Arm 2: 75.3 (20.1); Arm 3: 76.3 (19.4); Arm 4: 84.8 (9.8); placebo: 62.0 (22.1) Each MPH dose > placebo, $p < 0.01$	Academic efficiency score, mean (SD) Low-weight group: Arm 1: 69.8 (19.1); Arm 2: 78.6 (16.3); Arm 3: 82.6 (17.2); Arm 4: 79.0 (13.2); placebo: 54.0 (19.2) Mid-weight group: Arm 1: 63.9 (24.2); Arm 2: 78.4 (12.3); Arm 3: 74.3 (21.4); Arm 4: 87.4 (9.3); placebo: 56.9 (25.7) High-weight group: Arm 1: 57.9 (30.4); Arm 2: 69.2 (21.2); Arm 3: 65.7 (20.6); Arm 4: 70.0 (20.7); placebo: 48.7 (18.4) Each MPH dose > placebo, $p < 0.01$	Not reported	Not reported
Conclusions	**Authors' conclusions:** There were significant improvements in the classroom performance of children with ADHD as a result of treatment with MPH. At a group level, the relationship between dose and behavioural response was primarily linear and unrelated to factors such as gross body weight, body surface area or age **Reviewer's comments:** No comments noted		

Study	Intervention	Participants	Outcomes
References Schachar *et al.*, 1997;[86] Law and Schachar; 1999[321] Diamond *et al.*[87] **Source** AHRQ Report **Setting** Canada **Design** Parallel trial **Duration** Titration phase: 3–4 weeks: Follow-up period: 4 months **Purpose** To determine the behavioural, situational, and temporal effects of 4 months of MPH treatment for ADHD	**Arm 1** MPH plus non-drug intervention Titration to target of 0.7 mg/kg/dose administered twice per day (breakfast, lunch); parent training or parent support; Final mean dose was 31.4 mg/day (Administered by parent) **Arm 2** Placebo plus parent training or support Twice per day (breakfast, lunch); parent training or parent support (Administered by parent) At 4-month point, children not taking any medication were grouped with those taking placebo	**Inclusion criteria** 1. 6–12 years of age 2. Pervasive ADHD 3. History of ADHD symptoms of at least 6 months duration before the age of 7 years 4. IQ > 80 (full scale) 5. No primary anxiety or affective disorder 6. No prior treatment for ADHD or tics 7. No severe motor or vocal tic disorder or Tourette's disorder 8. No regular medication for a medical problem 9. No chronic medical condition 10. No current attendance at a full-time residential or day treatment programme 11. Willingness to participate in a study involving random assignment to treatment 12. One parent able to communicate in English **Diagnostic criteria** DSM-III-R Number (randomised/analysed) Total randomised = 91 (male = 74) Arm 1 = 46 Arm 2 = 45 Total withdrawals = 25 Arm 1 = 9 Arm 2 = 16 Reasons for withdrawals: Lack of effectiveness: Arm 1: 3/46; Arm 2: 14/45 Side-effects: Arm 1: 5/46, Arm 2: 1/45 Parents changed mind about need for medication: Arm 1: 1/46; Arm 2: 1/45 A further 11 participants in Arm 2 were no longer taking pills regularly at 4 months follow-up. Diamond *et al.*[87] reported an additional 9 withdrawals, 3 from Arm 1 and 6 from Arm 2 Randomisation procedure: Subjects were randomly assigned after stratification based on the presence of co-morbid conduct or oppositional disorder	**Core symptoms** Telephone Interview Probe, parent and teacher ratings: inattention; hyperactivity-impulsiveness IOWA-C, parent and teacher ratings: hyperactivity–inattentiveness **Co-existent problems** Telephone Interview Probe, parent and teacher ratings: oppositional behaviour IOWA-C, parent and teacher ratings: aggression **Educational performance** Not reported **Psychological function** Not reported **Depression or anxiety** Not reported **Quality of life** Not reported **Adverse events** Barkley 10-point scale: physiological, affective, overfocus, tics (parents, teachers) **Additional outcomes** Telephone Interview Probe, parent and teacher ratings: difficulty experienced in the course of typical daily problem situations Height Weight

continued

Study	Intervention	Participants	Outcomes
		Age Arm 1: 8.4 years; Arm 2: 8.3 years (mean) Arm 1: 1.6 years; Arm 2: 1.5 years (SD) **IQ** Arm 1: 108.4 (mean); Arm 2: 108.3 (mean) **Co-morbid disorders** ODD: Arm 1: 56.5%; Arm 2: 44.4% CD: Arm 1: 6.5%; Arm 2: 20.0% Anxiety: Arm 1: 21.7%; Arm 2: 24.4% Pre-existing tics: Arm 1: 11/46 (23.9%); Arm 2: 16/45 (35.6%); overall, 16/91 had mild tics and 11/91 had moderate tics Children with ADHD and co-morbid anxiety were significantly heavier and had significantly higher levels of conduct disorder at baseline **Diagnostic subtypes** Not reported **Additional Information** Previous medication: Only participants who had not previously received medication for ADHD were included in the trial Concurrent medication: Individuals who received medication for a medical condition were not included in the trial Co-interventions: Families were encouraged to continue with other treatments or seek other assessments or treatments as necessary. However, individuals attending a full-time residential or day treatment programme were excluded from the trial	

Core symptoms	Educational performance	Quality of life	Adverse events
IOWA-C, parent ratings: hyperactivity: mean (SD) MPH: baseline 1.8 (0.6); 4 months 1.2 (0.7) Placebo: baseline 1.8 (0.7); 4 months 1.3 (0.7) No significant difference between groups, *p* not reported IOWA-C, teacher ratings: hyperactivity–inattentiveness: mean (SD) MPH: baseline 2.0 (0.8); 4 months 0.9 (0.7) Placebo: baseline 2.0 (0.6); 4 months 1.7 (0.7) MPH > placebo, F (2,120) = 9.1, $p < 0.001$ Telephone Interview Probe, teacher ratings: hyperactivity–impulsiveness: mean (SD) MPH: baseline 2.1 (1.2); 4 months 0.8 (0.7) Placebo: baseline 1.7 (1.0); 4 months 1.3 (1.1) MPH > placebo, $F(1,62) = 12.9$, $p < 0.001$ Telephone Interview Probe, teacher ratings: inattention: mean (SD) MPH: baseline 2.6 (1.1); 4 months 1.0 (0.8) Placebo: baseline 2.2 (1.1); 4 months 1.7 (1.0) MPH > placebo, $F(1,62) = 15.4$, $p < 0.001$ Telephone Interview Probe, parent ratings: hyperactivity–impulsiveness: mean (SD) MPH: baseline 1.6 (1.3); 4 months 1.2 (1.1) Placebo: baseline 1.5 (1.1); 4 months 0.9 (0.9) No significant difference between groups Telephone Interview Probe, parent ratings: inattention: mean (SD) MPH: baseline 2.0 (1.1); 4 months 1.5 (1.1) Placebo: baseline 1.6 (1.0); 4 months 1.2 (0.9) No significant difference between groups IOWA-C hyperactivity (parent rating): [(Baseline, end-titration, 4 months means (SD)] MPH in ADHD without anxiety: 1.78 (0.7), 0.85 (0.6), 1.01 (0.6) Placebo in ADHD without anxiety: 1.77 (0.7), 1.15 (0.7), 1.27 (0.6) MPH in ADHD with anxiety: 1.91 (0.6), 0.77 (0.6), 1.23 (0.7)	Not reported	Not reported	Withdrawals: MPH: $n = 5$; 3 during titration (sadness and behavioural deterioration, irritability, withdrawal, lethargy, violent behaviour or rash), 1 in 2nd month (withdrawal and mild mania) and 1 in 3rd month (withdrawal and dysphoria). Placebo: $n = 1$; stuttering Physiological side-effects (teacher): mean (SD) MPH: baseline 0.5 (0.6); 4 months 0.3 (0.6) Placebo: baseline 0.3 (0.5); 4 months 0.4 (0.7) No significant differences between treatment arms Physiological side-effects (parent): mean (SD) MPH: baseline: 0.5 (0.7); 4 months: 1.1 (0.9) Placebo: baseline: 0.9 (0.8); 4 months: 0.7 (0.8) MPH > placebo, $F(1,63) = 9.2$, $p < 0.005$ Most common with MPH: anorexia and stomach aches Affective side-effects (teacher rating): mean (SD) MPH: baseline 1.2 (1.3); 4 months 0.6 (1.1) Placebo: baseline 1.1 (1.2); 4 months 0.9 (1.2) No significant differences between treatment arms Affective side-effects (parent rating): mean (SD) MPH: baseline: 1.1 (1.3); 4 months: 1.5 (1.6) Placebo: baseline: 1.5 (1.7); 4 months: 0.5 (1.0) MPH > placebo, $F(1,63) = 6.8$, $p < 0.01$ Most common with MPH: withdrawal, sadness and crying Tics (teacher): mean (SD) MPH: baseline 0.2 (0.8); 4 months 0.2 (0.7) Placebo: baseline 0.2 (0.5); 4 months 0.5 (1.5) No significant difference between treatment arms Tics (parent): mean (SD) MPH: baseline: 0.3 (0.8); 4 months: 0.4 (0.8) Placebo: baseline: 0.5 (1.0); 4 months: 0.2 (0.5) No significant differences between treatment arms Overfocus (teacher): mean (SD) MPH: baseline 2.6 (2.3); 4 months 1.0 (1.6) Placebo: baseline 2.0 (1.7); 4 months 1.6 (1.5) No significant difference between treatment groups

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Core symptoms	Educational performance	Quality of life	Adverse events
Placebo in ADHD with anxiety: 1.87 (0.4), 1.24 (0.7), 1.24 (0.7) *F* (end titration/4 months) = 0.36/ 0.63 No direct comparisons were made between MPH and placebo groups for ADHD children only IOWA-C hyperactivity (teacher rating): [baseline, end-titration, 4 month mean (SD)] MPH in ADHD without anxiety: 2.04 (0.7), 0.82 (0.6), 0.86 (0.6) Placebo in ADHD without anxiety: 1.97 (0.4), 1.42 (0.8), 1.40 (0.7) MPH in ADHD with anxiety: 1.84 (0.8), 0.71 (0.6), 1.07 (0.6) Placebo in ADHD with anxiety: 1.97 (0.6), 1.62 (0.7), 1.43 (0.9) *F* (end titration/4 months) = 1.47/0.82 Telephone Interview Probe, inattention (parent rating): [baseline, end-titration, 4 month mean (SD)] MPH in ADHD without anxiety: 1.89 (1.2), NA, 1.45 (1.1) Placebo in ADHD without anxiety: 1.66 (1.0), NA, 1.13 (0.8) MPH in ADHD with anxiety: 2.01 (1.0), NA, 1.51 (1.0) Placebo in ADHD with anxiety: 1.82 (1.0), NA, 1.24 (1.1) *F* (4 months) = 0.03 Telephone Interview Probe, inattention (teacher rating): [baseline, end-titration, 4 month mean (SD)] MPH in ADHD without anxiety: 2.66 (1.2), NA, 0.93 (0.7) Placebo in ADHD without anxiety: 2.57 (1.1), NA, 1.55 (1.1) MPH in ADHD with anxiety: 2.33 (1.0), NA, 1.29 (0.9) Placebo in ADHD with anxiety: 2.51 (1.0), NA, 1.21 (0.9) *F* (4 months) = 0.75 Telephone Interview Probe, hyperactive/impulsive (parent rating): [baseline, end-titration, 4 month means (SD)] MPH in ADHD without anxiety: 1.48 (1.3), NA, 1.20 (1.1)			Overfocus (parent): mean (SD) MPH: baseline: 1.3 (2.1); 4 months: 0.8 (1.6) Placebo: baseline: 1.8 (1.9); 4 months: 0.6 (1.1) No significant differences between treatment arms Tics: Subjects without pre-existing tics: (occurrence) MPH: 10/51 (19.6%) (note that 1 of these developed Tourette-like symptoms) Placebo: 2/12 (16.7%) Fisher's exact test, $p = 0.59$; relative risk = 1.17; 95% CI, 0.31 to 4.40 Those who developed tics were managed by maintenance of MPH at level before emergence of tics ($n = 8$), reduction of MPH dose ($n = 3$) or addition of clonidine ($n = 1$) Subjects with pre-existing tics (worsening): MPH: 7/21 (33.3%) (note that 1 of these developed Tourette-like symptoms) Placebo: 2/6 (33.3%) Fisher's exact test, $p = 0.70$; relative risk = 1.0; 95% CI, 0.40 to 1.85 Those whose tics worsened were predominantly managed with the reduction of medications; one child's medication was discontinued. The remainder experienced improvement or no change in their tics. Presence and severity of common physical side-effects on 10-point parent scale (affective)): mean (SD) in MPH without anxiety/MPH with anxiety/placebo without anxiety/placebo with anxiety Baseline: 0.89 (1.3)/1.04 (1.1)/1.13 (1.4)/1.88 (1.8) End-titration: 0.56 (0.7)/1.26 (1.5)/0.88 (1.2)/0.06 (1.3) 4 months: 1.72 (1.8)/1.52 (1.6)/0.48 (1.1)/0.57 (0.8) p = NS Presence and severity of common physical side-effects on 10-point teacher scale (affective)): mean (SD) in MPH without anxiety/MPH with anxiety/placebo without anxiety/placebo with anxiety Baseline: 1.15 (1.3)/1.05 (1.1)/0.71 (0.8)/1.42 (1.2)

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Core symptoms	Educational performance	Quality of life	Adverse events
Placebo in ADHD without anxiety: 1.53 (1.1), NA, 0.79 (0.7) MPH in ADHD with anxiety: 1.52 (1.2), NA, 1.09 (0.9) Placebo in ADHD with anxiety: 1.74 (1.0), NA, 0.96 (0.9) *F* (4 months) = 0.22 Telephone Interview Probe, hyperactive/impulsive (teacher rating): [Baseline, end-titration, 4 month mean (SD)] MPH in ADHD without anxiety: 2.16 (1.4), NA, 0.85 (0.9) Placebo in ADHD without anxiety: 1.89 (1.1), NA, 1.25 (1.2) MPH in ADHD with anxiety: 2.02 (1.0), NA, 0.82 (0.6) Placebo in ADHD with anxiety: 2.25 (1.0), NA, 1.01 (0.7) *F* (4 months) = 0.05			End-titration: 0.37 (0.8)/0.46 (0.9)/0.47 (0.8)/1.01 (1.8) 4 months: 0.56 (0.9)/0.83 (1.3)/0.57 (0.9)/1.23 (1.4) *p* = NS Presence and severity of common physical side-effects on 10-point parents scale (overfocusing): mean (SD) in MPH without anxiety/MPH with anxiety/placebo without anxiety/placebo with anxiety Baseline: 0.76 (1.6)/1.61 (2.2)/1.37 (1.9)/1.5 (1.5) End-titration: 0.21 (0.6)/0.33 (0.7)/0.25 (0.8)/1.00 (1.6) 4 months: 0.35 (0.8)/1.14 (2.0)/0.80 (1.4)/0.67 (1.1) *p* = NS Presence and severity of common physical side-effects on 10-point teacher scale (overfocusing): mean (SD) in MPH without anxiety/MPH with anxiety/placebo without anxiety/placebo with anxiety Baseline: 2.09 (2.1)/2.45 (2.6)/1.96 (2.1)/1.92 (1.7) End-titration: 0.41 (0.5)/0.58 (1.4)/0.40 (1.1)/1.22 (1.6) 4 months: 0.85 (1.2)/1.30 (1.9)/1.11 (1.4)/1.89 (1.6) *p* = NS Presence and severity of common physical side-effects on 10-point parents scale (physiological): mean (SD) in MPH without anxiety/MPH with anxiety/placebo without anxiety/placebo with anxiety Baseline: 0.41 (0.7)/0.6 (0.5)/0.51 (0.6)/0.74 (0.7) End-titration: 1.07 (0.9)/1.36 (1.3)/0.56 (0.9)/0.56 (0.8) 4 months: 0.94 (0.8)/1.18 (0.9)/0.57 (0.8)/0.54 (0.8) *p* = NS Presence and severity of common physical side-effects on 10-point teacher scale (physiological): mean (SD) in MPH without anxiety/MPH with anxiety/placebo without anxiety/placebo with anxiety Baseline: 0.30 (0.5)/ 0.52 (0.7)/0.39 (0.8)/0.27 (0.4) End-titration: 0.17 (0.5)/0.15 (0.3)/0.01 (0.00)/0.14 (0.6) 4 months: 0.36 (0.5)/0.43 (0.7)/0.26 (0.6)/0.46 (0.8) **$p < 0.05$ for occasion × anxiety × medication status interaction at the end of titration

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Core symptoms	Educational performance	Quality of life	Adverse events
			Presence and severity of common physical side-effects on 10-point parents scale (tics): mean (SD) in MPH without anxiety/MPH with anxiety/placebo without anxiety/placebo with anxiety Baseline: 0.26 (0.8)/0.34 (0.8)/0.80 (0.7)/0.47 (1.0) End-titration: 0.58 (1.5)/0.11 (0.3)/0.06 (0.3)/0.65 (1.2) 4 months: 0.50 (1.1)/0.14 (0.5)/0.13 (0.4)/0.14 (0.5) p = NS Presence and severity of common physical side-effects on 10-point teacher scale (tic): mean (SD) in MPH without anxiety/MPH with anxiety/placebo without anxiety/placebo with anxiety Baseline: 0.26 (0.9)/0.05 (0.2)/0.48 (1.3)/0.42 (0.9) End-titration: 0.19 (0.5)/0.13 (0.6)/0.26 (0.9)/0.43 (1.0) 4 months: 0.35 (1.0)/0.16 (0.6)/0.19 (0.7)/0.75 (2.0) p = NS
Conclusions	**Authors' conclusions:** Positive effects of MPH on behaviour are evident in the classroom, but with MPH given twice daily, parents do not report that MPH improves behaviour at home Note that additional data included on tics are taken from a separate paper: doses of MPH based on the typical clinical titration procedure did not produce significantly more tics than the placebo in children with or without pre-existing (mild to moderate) tics No differential response to MPH between ADHD + ANX and ADHD – ANX was noted at end-titration or at 4 months on any side-effect or behavioural measure. Co-morbid anxiety does not appear to influence development of side-effects or behavioural response to MPH when dose is titrated as in standard clinical practice **Reviewer's comments:** No comments noted		

Study	Intervention	Participants	Outcomes
Smith *et al.*, 1998;[88] Evans *et al.*, 2001;[322], Smith *et al.*, 2000[323] **Source** Updated search **Setting** USA (STP) **Design** Crossover trial **Duration** 8 weeks **Purpose** To describe the shape of the dose–response curves across multiple measures of social functioning. To determine the percentage of adolescents whose social behaviour improved in response to MPH and to assess the incremental gains that result from increases in dose Smith[323]: To assess the effects of MPH on academic performance and classroom behaviour	**Arm 1** MPH plus non-drug treatment 10 mg twice per day (7.45 and 11.45 a.m.) plus 5 mg at 3.45 p.m. for 6 days. Behavioural treatment programme involved daily activities 5 days/week for 8 weeks including classroom, study hall, therapeutic recreation, social skills and problem-solving groups (Individual administering medication not reported) **Arm 2** MPH plus non-drug treatment 20 mg twice per day (7.45 and 11.45 a.m.) plus 10 mg at 3.45 p.m for 6 days. Behavioural therapy as above (Individual administering medication not reported) **Arm 3** MPH plus non-drug treatment 30 mg twice per day (7.45 and 11.45 a.m.) plus 15 mg at 3.45 p.m. for 6 days. Behavioural therapy as above (Individual administering medication not reported) **Arm 4** Placebo plus non-drug treatment 3 times per day at 7.45 and 11.45 a.m. and 3.45 p.m. for 6 days Behavioural therapy as above (Individual administering medication not reported)	**Inclusion criteria** 1. DSM-III-R criteria for ADHD 2. Participants to have 12th birthday before the protocol began 3. Verbal IQ >80 4. No conditions that precluded a trial of stimulant medication or full participation in the STP academic and athletic activities **Diagnostic criteria** DSM-III-R **Number** Total = 49 (male = 41/46) Total withdrawals = 3 Reasons for withdrawals: Two participants were discharged from the programme owing to poor attendance. Another participant withdrew against medical advice Randomisation procedure: Medication conditions were randomised daily with condition occurring once per week **Age** 13.8 years (mean); 12–17 years (range); 1.2 years (SD) **IQ** 101 (mean) **Co-morbid disorders** ODD: *n* = 23 (50%) CD: *n* = 7 (15%) **Diagnostic subtypes** Not reported **Additional information** Previous medication: 33 (72%) were taking stimulant medication, 2 (4%) were taking tricyclic antidepressants, 11 (24%) were not taking any psychoactive medication. All psychoactive medications were discontinued for at least 2 weeks before the beginning of the trial of stimulant medication	**Core symptoms** IOWA-C (inattention/overactivity) **Co-existent problems** Frequency of negative behaviours IOWA-C (oppositional/defiant) **Educational performance** History worksheet correct History quiz correct History notes (main ideas recorded) History notes (details recorded) Written language (words written) Written language (sequence length) Written language (story idea) Homework completed **Psychological function** Not reported **Depression or anxiety** Not reported **Quality of life** Not reported **Adverse events** Side-effects rating from 0 (not troubling) to 3 (severe) (counsellor and parent rated) **Additional outcomes** Not reported

Core symptoms	Educational performance	Quality of life	Adverse events
IOWA-C (inattention/overactivity), mean (SD) Placebo 4.2 (0.4) 10 mg 3.2 (0.3) 20 mg 2.7 (0.3) 30 mg 2.2 (0.2) The authors state that a significant difference was observed between all comparisons at the $p < 0.05$ level; no further detail is given Evans *et al.*:[322] IOWA-C (inattention/overactivity), mean (SD) Placebo 4.4 (3.5) 10 mg 2.7 (2.7) > placebo 20 mg 1.7 (2.2) > placebo and 10 mg 30 mg 1.2 (1.5) > placebo and 20 mg No *p*-values reported	Evans *et al.*:[322] mean (SD) History worksheet correct Placebo: 53.2 (31.1) 10 mg: 70.2 (25.8) > placebo (no *p*-values reported) 20 mg: 79.8 (19.8) > placebo and 10 mg 30 mg: 78.5 (20.9) > placebo $F(3,132) = 38.52$, $p < 0.0001$ History quiz correct Placebo: 46.6 (29.6) 10 mg: 63.8 (22.2) > placebo 20 mg: 71.0 (18.5) > placebo and 10 mg 30 mg: 72.1 (20.1) > placebo $F(3,132) = 51.08$, $p < 0.0001$ History notes (main ideas recorded) Placebo: 69.8 (28.8) 10 mg: 77.3 (23.5) > placebo 20 mg: 85.1 (17.7) > placebo and 10 mg 30 mg: 83.2 (18.8) > placebo $F(3,132) = 12.42$, $p < 0.0001$ History notes (details recorded) Placebo: 41.1 (26.5) 10 mg: 52.8 (24.7) > placebo 20 mg: 58.9 (21.3) > placebo and 10 mg 30 mg: 60.0 (24.6) > placebo $F(3,132) = 35.82$, $p < 0.0001$ Written language (words written) Placebo: 58.8 (47.6) 10 mg: 82.6 (53.4) > placebo 20 mg: 96.9 (49.4) > placebo and 10 mg 30 mg: 102.0 (54.5) > placebo $F(3,132) = 32.76$, $p < 0.0001$ Written language (sequence length) Placebo: 7.4 (7.6) 10 mg: 9.8 (8.5) > placebo 20 mg: 10.7 (7.9) > placebo 30 mg: 11.7 (10.6) > placebo $F(3,132) = 11.25$, $p < 0.0001$	Not reported	% participants reporting moderate or severe side-effects: Motor tics: placebo/10 mg/20 mg/30 mg Counsellor: 0/0.3/0/0.4 [$F(3,135) = 0.48$, $p = 0.693$] Parent: 0/0.4/0/0.4 [$F(3,135) = 0.53$, $p = 0.660$] Tearful: placebo/10 mg/20 mg/30 mg Counsellor: 6.4/3.0/3.3/3.0 [$F(3,135) = 0.48$, $p = 0.695$] Parent: 2.0/2.2/2.7/2.3 [$F(3,135) = 0.13$, $p = 0.943$) Worried: placebo/10 mg/20 mg/30 mg Counsellor: 5.5/6.3/4.9/3.8 [$F(3,135) = 1.29$, $p = 0.281$] Parent: 3.3/1.8/0.4/2.7 [$F(3,135) = 0.7$, $p = 0.556$] Headache: placebo/10 mg/20 mg/30 mg Counsellor: 3.8/3.3/3.4/5.7 [$F(3,135) = 0.93$, $p = 0.429$] Parent: 0.8/1.6/4.2/3.0 [$F(3,135) = 2.18$, $p = 0.093$] Picking at skin, fingers etc: placebo/10 mg/20 mg/30 mg Counsellor: 7.2/13.4/12.6/13.4* [$F(3,135) = 2.14$, $p = 0.099$] Parent: 6.6/5.4/4.0/5.9 [$F(3,135) = 0.75$, $p = 0.526$] *Rate of side-effects is significantly different from placebo Buccal lingual movement: placebo/10 mg/20 mg/30 mg Counsellor: 7.9/4.0/4.3/2.7 [$F(3,135) = 3.7$, $p = 0.030$] Parent: 0.4/1.1/0.4/1.1 [$F(3,135) = 0.27$, $p = 0.848$] Crabby: placebo/10 mg/20 mg/30 mg Counsellor: 24.2/13.4*/10.5*/9.4* [$F(3,135) = 11.0$, $p = 0.000$] Parent: 8.4/6.3/5.0/4.3 [$F(3,135) = 0.46$, $p = 0.710$] *Rate of side-effects is significantly different from placebo Dull/tired/listless: placebo/10 mg/20 mg/30 mg Counsellor: 4.2/6.5/8.2/12.4** [$F(3,135) = 6.03$, $p = 0.001$] Parent: 1.8/4.0/4.4/5.0* [$F(3,135) = 2.0$, $p = 0.118$] **Rate of side-effects is significantly different from placebo and 10 mg condition *Rate of side-effects is significantly different from placebo

continued

Core symptoms	Educational performance	Quality of life	Adverse events
	Written language (story idea) Placebo: 2.2 (1.1) 10 mg: 2.6 (1.1) > placebo 20 mg: 2.9 (1.0) > placebo and 10 mg 30 mg: 3.0 (1.1) > placebo $F(3,132)=20.74$, $p < 0.0001$ Homework completed Placebo: 33.0 (26.1) 10 mg: 37.7 (26.5) 20 mg: 39.3 (29.3) 30 mg: 42.5 (27.5) > placebo $F(3,132) = 3.07$ $p < 0.05$		Withdrawn: placebo/10 mg/20 mg/30 mg Counsellor: 0.7/4.1/4.1*/7.8* [$F(3,135) = 6.33$, $p = 0.001$] Parent: 1.6/2.2/1.1/1.2 [$F(3,135) = 0.18$, $p = 0.909$] *Rate of side-effects is significantly different from placebo Stomach ache: placebo/10 mg/20 mg/30 mg Counsellor: 4.6/3.0/4.2/4.3 [$F(3,135) = 0.33$, $p = 0.804$] Parent: 1.5/1.5/3.1/3.8 [$F(3,135) = 4.42$, $p = 0.005$] Ate less than half of lunch: placebo/10 mg/20 mg/30 mg Counsellor: 12.4/19.9/30.4**/35.5** [$F(3,135) = 16.2$, $p = 0.000$] **Rate of side-effects is significantly different from placebo and 10 mg condition Loss of appetite: placebo/10 mg/20 mg/30 mg Parent: 1.8/3.8/8.6**/3.9** [$F(3,135) = 12.6$, $p = 0.000$) **Rate of side-effects is significantly different from placebo and 10 mg condition Difficulty falling asleep: placebo/10 mg/20 mg/30 mg Parent: 2.1/3.3/3.0/3.9* [$F(3,135) = 1.33$, $p = 0.269$] *Rate of side-effect is significantly different from placebo
Conclusions	**Authors' conclusions:** MPH is an effective treatment for negative social behaviour exhibited by adolescents with ADHD. Group data showed positive effects of MPH on academic measures; however, the greatest benefit came with the lowest dose. Although additional benefit did occur for some participants with higher doses, the largest increment of change usually occurred between the placebo and 10-mg dose. Many adolescents did not experience added benefit with increased dosages and in some cases they experienced deterioration **Reviewer's comments:** No comments noted		

Study	Intervention	Participants	Outcomes
References Spencer *et al.*, 2002;[89] Biederman *et al.*, 2002[142] **Source** Updated search **Setting** USA **Design** Parallel trial **Duration** 12 weeks (2-week washout, 9 weeks of treatment and 1-week drug discontinuation phase) **Purpose** To assess the safety and efficacy of ATX compared with placebo in school-aged children with ADHD	**Arm 1** ATX Maximum dose 2 mg/kg/day (90 mg/day) in two or three daily doses depending on prior psychostimulant exposure (Individuals administering medication not reported) **Arm 2** Placebo (Individuals administering medication not reported)	**Inclusion criteria** 1. ADHD DSM-IV criteria 2. Score on ADHD Rating Scale of >1.5 SD above age and gender norms for their diagnostic subtype (primarily inattentive or primarily hyperactive/impulsive) or the total score for the combined subtype 3. No poor metabolisers of CYP2D6 4. Weight >25 kg at study entry 5. Normal intelligence on WISC 6. Aged 7–13 years 7. No documented history of bipolar I or II disorder or any history of psychosis 8. No history of organic brain disease or history of seizure disorder 9. No psychotropic medication 10. No history of alcohol or drug abuse within past 3 months and no significant prior or current medical conditions **Diagnostic criteria** DSM-IV **Number** Total = 147 Arm 1 = 65 Arm 2 = 62 Total withdrawals = 25 Arm 1 = 16 Arm 2 = 9 (For both trials:[89] ATX n = 129, placebo n = 124) Males: ATX n = 98, placebo n = 103 Females: ATX n = 31, placebo n = 21 Reasons for withdrawals: The most common reason for discontinuation was lack of efficacy Randomisation procedure: Patients were stratified according to prior exposure to psychostimulants. 20 patients with no prior exposure to psychostimulants were randomised to MPH. MPH treatment was included to validate study design in the event that ATX failed to separate from placebo. MPH results not reported	**Core symptoms** ADHD Rating Scale total score CPRS-S (short form) ADHD Rating Scale subscales (inattentive; hyperactive/impulsive) **Co-existent problems** Not reported **Educational performance** Not reported **Psychological function** Not reported **Depression or anxiety** Not reported **Quality of life** CGI–ADHD, Severity **Adverse events** Unsolicited adverse events **Additional outcomes** Not reported

continued

Study	Intervention	Participants	Outcomes
		Age (For both trials:[89] ATX $n = 129$, placebo $n = 124$) ATX: 9.7 years (mean), 1.6 years (SD) Placebo: 10.0 years (mean), 1.5 years (SD) **IQ** (For both trials:[89] ATX $n = 129$, placebo $n = 124$) ATX: 103 (mean) Placebo: 106.9 (mean) **Co-morbid disorders** (For both trials:[89] ATX $n = 129$, placebo $n = 124$) ODD: ATX: $n = 53$ (41.1%); placebo: $n = 45$ (36.3%) Elimination disorders: ATX: $n = 10$ (7.8%); placebo: $n = 15$ (12.1%) Phobias: ATX: $n = 16$ (12.4%); placebo: $n = 13$(10.5%) Dysthymia: ATX: $n = 7$ (5.4%); placebo: $n = 5$ (4.0%) Generalised anxiety disorder: ATX: $n = 4$ (3.1%); placebo: $n = 3$ (2.4%) Major depressive disorder: ATX: $n = 4$(3.1%); placebo: $n = 4$ (3.2%) **Diagnostic subtypes** (For both trials:[89] ATX $n = 129$, placebo $n = 124$) Inattentive: ATX: $n = 24$ (18.6%); placebo: $n = 24$ (19.4%) Hyperactive/impulsive: ATX: $n = 1$ (0.8%); placebo: $n = 2$ (1.6%) Combined: ATX: $n = 104$ (80.6%); placebo: $n = 98$ (79%) **Additional information** Previous/concurrent medication: To be admitted into the trial, individuals were required not to be in receipt of psychotropic medication	

Core symptoms	Educational performance	Quality of life	Adverse events
ADHD Rating Scale, total ATX baseline (n = 64), mean (SD) 41.2 (8.9), change mean (SD) –15.6 (13.7) Placebo baseline (n = 61), mean (SD) 41.4 (7.9), change mean (SD) –5.5 (11.6) F = 19.0, p < 0.001 CPRS–ADHD Index ATX baseline (n = 59), mean (SD) 27.4 (6.2), change mean (SD) –5.7 (10.4) Placebo baseline (n = 54), mean (SD) 28.7 (5.8), change mean (SD) –2.6 (8.4) F = 5.3, p = 0.023 ADHD Rating Scale, inattentive subscales ATX baseline (n = 64), mean (SD) 22.0 (3.9), change mean (SD) –7.5 (7.2) Placebo baseline (n = 61), mean (SD) 22.2 (4.0), change mean (SD) –3.0 (6.6) F = 15.2, p < 0.001 ADHD Rating Scale, hyperactive/impulsive subscale ATX baseline (n = 64), mean (SD) 19.3 (6.1), change mean (SD) –8.0 (7.4) Placebo baseline (n = 61), mean (SD) 19.2 (5.5), change mean (SD) –2.5 (5.9) F = 20.0, p < 0.001	Not reported	CGI–ADHD, Severity ATX baseline (n = 64), mean (SD) 4.9 (0.8), change mean (SD) –1.2 (1.4) Placebo baseline (n = 61) mean (SD) 4.8 (0.8), change mean (SD) –0.5 (1.0) F = 9.5, p = 0.003	NB: combined results Adverse events occurring in >10% of any treatment group [% of ATX (n = 129)/placebo group (n = 124)] Headache 30.2/28.2% Abdominal pain 31/21.8% Rhinitis 25.6/32.3% Decreased appetite *21.7/7.3% Pharyngitis 16.3/15.3% Vomiting 14.7/12.1% Cough increased 13.2/11.3% Nervousness 13.2/6.5% Somnolence 9.3/8.1% Nausea 10.1/10.5% *p < 0.05 vs placebo Weight (kg): mean (SD) ATX (n = 127): baseline 37.0 (12.1); change –0.5 (1.4) Placebo: (n = 122): baseline 37.8 (10.7); change 1.4 (1.4) Placebo > ATX, p < 0.001
Conclusions	**Authors' conclusions:** ATX significantly reduced ADHD Rating Scale total scores compared with placebo (p < 0.001). Changes in the CGI–ADHD-S (p = 0.003) and CPRS–ADHD Index (p = 0.023) also showed ATX to be statistically superior to placebo in reducing ADHD symptoms. ATX was effective for the treatment of children with ADHD. In addition, ATX was found to be well tolerated **Reviewer's comments:** No comments noted		

Study	Intervention	Participants	Outcomes
Reference Spencer *et al.*, 2002[89] **Source** Updated search **Setting** USA **Design** Parallel trial **Duration** 12 weeks **Purpose** To assess the safety and efficacy of ATX compared with placebo in school-aged children with ADHD	**Arm 1** ATX Maximum dose 2 mg/kg/day (90 mg/day) in two or three daily doses depending on prior psychostimulant exposure (Individual administering medication not reported) **Arm 2** Placebo (Individual administering medication not reported)	**Inclusion criteria** 1. Diagnosis of ADHD 2. Score on ADHD Rating Scale of >1.5 SD above age and gender norms for their diagnostic subtype (primarily inattentive or primarily hyperactive/impulsive) or the total score for the combined subtype 3. No poor metabolisers of CYP2D6 4. Weight >2 kg at study entry 5. No documented history of bipolar I or II disorder or any history of psychosis 6. No history of organic brain disease or history of seizure disorder 7. No psychotropic medication 8. No history of alcohol or drug abuse within past 3 months and on significant prior or current medical conditions 9. Age 7–13 years 10. Normal intelligence on WISC **Diagnostic criteria** DSM-IV **Number** Total randomised = 144 Arm 1 = 64 Arm 2 = 62 Total withdrawals = 34 Arm 1 = 17 Arm 2 = 17 (For both trials: ATX *n* = 129, placebo *n* = 124) Males: ATX *n* = 98, placebo *n* = 103 Females: ATX *n* = 31, placebo *n* = 21 Reasons for withdrawals: The most common reason for discontinuation was lack of efficacy Randomisation procedure: Patients were stratified according to prior exposure to psychostimulants. 20 patients with no prior exposure to psychostimulants were randomised to MPH. MPH treatment was included to validate study design in the event that ATX failed to separate from placebo. MPH results not reported	**Core symptoms** ADHD Rating Scale total score CPRS-S (short form) ADHD Rating Scale subscales (inattentive; hyperactive/impulsive) **Co-existent problems** Not reported **Educational performance** Not reported **Psychological function** Not reported **Depression or anxiety** Not reported **Quality of life** CGI–ADHD, severity **Adverse events** Unsolicited adverse events **Additional outcomes** Not reported

continued

Study	Intervention	Participants	Outcomes
		Age (For both trials: ATX *n* = 129, placebo *n* = 124) ATX: 9.7 years (mean); 1.6 years (SD) Placebo: 10.0 years (mean); 1.5 years (SD) **IQ** (For both trials: ATX *n* = 129, placebo *n* = 124) ATX: 103 (mean) Placebo:106.9 (mean) **Co-morbid disorders** (For both trials: ATX *n* = 129, placebo *n* = 124) ODD: ATX: *n* = 53 (41.1%); placebo: *n* = 45 (36.3%) Elimination disorders: ATX: *n* = 10 (7.8%); placebo: *n* = 15 (12.1%) Phobias: ATX: *n* = 16 (12.4%); placebo: *n* = 13(10.5%) Dysthymia: ATX: *n* = 7 (5.4%); placebo: *n* = 5 (4.0%) Generalised anxiety disorder: ATX: *n* = 4 (3.1%); placebo: *n* = 3 (2.4%) Major depressive disorder: ATX: *n* = 4 (3.1%); placebo: *n* = 4 (3.2%) **Diagnostic subtypes** (For both trials: ATX *n* = 129, placebo *n* = 124) Inattentive: ATX: *n* = 24 (18.6%); placebo: *n* = 24 (19.4%) Hyperactive/impulsive: ATX: *n* = 1 (0.8%); placebo: *n* = 2 (1.6%) Combined: ATX: *n* = 104 (80.6%); placebo: *n* = 98 (79%) **Additional information** Previous/concurrent medication: To be admitted into the trial, individuals were required not to be in receipt of psychotropic medication	

Core symptoms	Educational performance	Quality of life	Adverse events
ADHD Rating Scale, total ATX baseline (n = 63): mean (SD) 37.8 (7.9); change: mean (SD) –14.4 (13.0) Placebo baseline (n = 60): mean (SD) 37.6 (8.0); change: mean (SD) –5.9 (13.0) F = 12.7, p < 0.001 CPRS ADHD Index ATX baseline (n = 61): mean (SD) 26.5 (6.6); change: mean (SD) –8.8 (9.8) Placebo baseline (n = 60): mean (SD) 26.3 (5.7); change: mean (SD) –2.1 (9.6) F = 15.3, p < 0.001 ADHD Rating Scale, Inattentive subscale ATX baseline (n = 63): mean (SD) 21.0 (4.0); change: mean (SD) –7.6 (7.6) Placebo baseline (n = 60): mean (SD) 21.1 (3.8); change: mean (SD) –3.0 (6.8) F = 12.0, p < 0.001 ADHD Rating Scale, Hyperactive/impulsive subscale ATX baseline (n = 63): mean (SD) 16.8 (6.5); change: mean (SD) –6.9 (6.6) Placebo baseline (n = 60): mean (SD) 16.5 (6.1); change: mean (SD) –2.9 (7.1) F = 9.7, p = 0.002	Not reported	CGI–ADHD, Severity ATX-baseline (n = 63): mean (SD) 4.9 (0.8); change: mean (SD) –1.5 (1.4) Placebo: baseline (n = 61): mean (SD) 4.9 (0.8); change: mean (SD) –0.7 (1.2) F = 11.8, p = 0.001	NB: combined results from both trials Adverse events occurring in >10% of any treatment group (% of ATX/placebo group) Headache 30.2/28.2% Abdominal pain 31/21.8% Rhinitis 25.6/32.3% Decreased appetite *21.7/7.3% Pharyngitis 16.3/15.3% Vomiting 14.7/12.1% Cough increased 13.2/11.3% Nervousness 13.2/6.5% Somnolence 9.3/8.1% Nausea 10.1/10.5% *p < 0.05 vs placebo Weight (kg): mean (SD) ATX (n = 127): baseline 37.0 (12.1); change –0.5 (1.4) Placebo: (n = 122): baseline 37.8 (10.7); change 1.4 (1.4) Placebo > ATX, p < 0.001
Conclusions	**Authors' conclusions:** ATX significantly reduced ADHD Rating Scale total scores compared with placebo (p < 0.001). Changes in the CGI–ADHD-S (p = 0.003) and CPRS–ADHD Index (p = 0.023) also showed ATX to be statistically superior to placebo in reducing ADHD symptoms. ATX was effective for the treatment of children with ADHD. In addition, ATX was found to be well tolerated **Reviewer's comments:** No comments noted		

Study	Intervention	Participants	Outcomes
Reference Steele *et al.*, 2004[90]		**[Confidential information removed]**	

Core symptoms	Educational performance	Quality of life	Adverse events
[Confidential information removed]			

Conclusions	**Authors' conclusions: [Confidential information removed]** **Reviewer's comments: [Confidential information removed]**

Study	Intervention	Participants	Outcomes
Reference Stein *et al.*, 1996[91] **Source** AHRQ Report **Setting** USA **Design** Crossover trial **Duration** Study period: 5 weeks; baseline assessment period: 1 week; treatment period: 4 weeks (1 week per treatment arm) **Purpose** To evaluate the short-term efficacy and side-effects associated with two MPH dosing patterns	**Arm 1** MPH 2 × MPH capsules, 1 × lactose capsule daily; 4 hours apart (8 a.m., 12 p.m., 4 p.m.); mean dose 8.8 ± 0.5 mg/dose (0.30 ± 0.1 mg/kg/dose), range 5–20 mg (Administered by parent) **Arm 2** MPH 3 × MPH capsules daily; 4 hours apart (8 a.m., 12 p.m., 4 p.m.); mean dose same as above (Administered by parent) **Arm 3** MPH 1 × MPH capsule with half test dose and 2 × lactose capsules on first day; 4 hours apart (8 a.m., 12 p.m., 4 p.m.); increased dosage until target dose reached on day 6 (Administered by parent) **Arm 4** Placebo 3 × lactose capsules daily; 4 hours apart (8 a.m., 12 p.m., 4 p.m.) (Administered by parent)	**Inclusion criteria** 1. Scores >65 on the impulsivity/hyperactivity factor of the CPRS 2. Scores >65 on the attention factor of the CBCL 3. Ratings below 20th percentile for attention or hyperactivity problems on the ACTeRS 4. No history of significant developmental delay 5. No diagnosis of pervasive developmental disorder 6. Willingness of parents and school personnel to meet study requirements **Diagnostic criteria** DSM-III **Number** Total randomised = 25 (male = 25) Total withdrawals = 1 Reasons for withdrawals: Withdrawal from trial due to increased anxiety and negative mood symptoms together with obsessive–compulsive behaviours. The authors suggest that in retrospect, he appears to have had a primary anxiety disorder **Age** 8.0 years (mean); 6–12 years (range); 1.8 years (SD) **IQ** Not reported **Co-morbid disorders** ODD: *n* = 7/25; CD: *n* = 2/25. **Diagnostic subtypes** ADHD–Combined Type: *n* = 22/25; ADHD–Predominantly Inattentive Type: *n* = 3/25 **Additional information** Previous medication: 14/25 (56%) had previously received MPH treatment. There was a 5-day washout period before the beginning of the study Co-interventions: No additional psychoactive medications, including oral asthma or allergy medications, were administered during the study	**Core symptoms** CPRS: impulsivity/hyperactivity ACTeRS: hyperactivity, attention **Co-existent problems** CPRS: conduct problem ACTeRS: social skills, oppositional behaviour Child Conflict Index (research assistants): specific conflict behaviours, negativity, social withdrawal **Educational performance** CPRS: learning problem **Psychological function** Test of Variables of Attention: omission errors, commission errors, response time, variability **Depression or anxiety** CPRS: anxiety Child Depression Inventory **Quality of life** Not reported **Adverse events** SSERS (parents) **Additional outcomes** Sleep log (parents): time child sent to bed, time child fell asleep, total sleep duration Actigraph measurements: activity level, latency to sleep onset, duration of sleep, number and duration of awakenings Weight Heart rate Blood pressure

Core symptoms	Educational performance	Quality of life	Adverse events
CPRS: hyperactivity index; mean (SD) Placebo: 11.7 (6.4) MPH, titration: 11.4 (4.0) MPH, b.d.: 9.7 (5.8) MPH, t.d.s.: 9.2 (7.5) B.d. = t.d.s.: NS CPRS: impulsivity/hyperactivity Placebo: 6.3 (3.5) MPH, titration: 5.6 (3.2) MPH, b.d.: 5.5 (3.1) MPH, t.d.s.: 4.2 (2.9) B.d. < t.d.s.: $t = 2.73$, $p < 0.01$ ACTeRS: hyperactivity Placebo: 16.3 (5.7) MPH, titration: 16.3 (4.6) MPH, b.d.: 15.5 (4.8) MPH, t.d.s.: 13.5 (4.8) B.d. = t.d.s.: NS ($t = 1.86$, $p < 0.08$). ACTeRS: attention Placebo: 16.0 (6.0) MPH, titration: 16.1 (6.3) MPH, b.d.: 18.1 (5.2) MPH, t.d.s.: 19.1 (5.8) B.d. = t.d.s.: NS	CPRS: learning problem Placebo: 4.6 (2.8) MPH, titration: 5.0 (3.0) MPH, b.d.: 4.0 (2.9) MPH, t.d.s.: 3.7 (3.2) B.d. = t.d.s.: NS	Not reported	SSERS (parents). % present and severe side-effects in baseline/placebo/MPH (titration)/MPH (b.d)/MPH (t.d.s.). present / severe Insomnia: 44/50/56/61/60 / 12/4/4/0/4 Nightmares: 20/17/16/9/4 / 0/4/0/0/0 Staring: 52/33/40/35/36 / 12/4/0/0/4 Talks less: 24/38/20/17/8 / 0/4/0/0/0 Disinterested in others: 24/29/28/29/8 / 4/4/0/0/0 Decrease in appetite: 32/33/64/62/72 / 0/0/12//4/16 Irritable: 92/21/68/79/68 / 28/21/12/17/16 Stomach aches: 24/17/36/38/20 / 0/0/8/4/4 Headaches: 24/8/20/21/16 / 0/0/4/0/4 Drowsiness: 24/17/28/21/20 / 8/8/4/0/4 Sad/unhappy: 48/48/36/38/36 / 12/4/4/0/4 Prone to crying: 72/72/64/63/56 / 12/8/8/8/12 Anxious: 56/56/56/46/40 / 24/13/8/4/12 Nail biting: 24/24/32/29/16 / 8/0/0/4/4 Euphoric: 28/28/28/8/12 / 8/0/8/4/4 Dizziness: 4/4/0/8/4 / 0/0/0/0/0 Tics/nervous movements: 20/20/16/8/12 / 4/8/4/0/4 B.d. = t.d.s.: no significant differences

Conclusions	
	Authors' conclusions: For many children with ADHD, t.d.s dosing may be optimal. There are few differences in acute side effects between b.i.d. and t.d.s MPH dosing. The dosing schedule should be selected according to the severity and time course of ADHD symptoms rather than in anticipation of dosing schedule-related side-effects **Reviewer's comments:** No comments noted

Study	Intervention	Participants	Outcomes
References Stein *et al.*, 2003;[92] Stein *et al.*, 2003[324] **Source** Updated search **Setting** USA **Design** Crossover trial **Duration** 4 weeks (plus 2-week washout for those on prior psychostimulants) **Purpose** To examine dosage effects on ADHD symptoms and stimulant side-effects and to explore potential moderating effects of ADHD subtypes	**Arm 1** Placebo 1 week (Individual administering medication not reported) **Arm 2** MPH OROS 18 mg; 1 week (Individual administering medication not reported) **Arm 3** MPH OROS 36 mg; 1 week (Individual administering medication not reported) **Arm 4** MPH OROS 54 mg; 1 week (Individual administering medication not reported)	**Inclusion criteria** 1. DSM-IV criteria for ADHD 2. No mental retardation, severe mood disorders (requiring antidepressant or concurrent psychotropic medications), Tourette syndrome, seizure disorders or other medical disorders associated with symptoms that may mimic ADHA (e.g. thyroid disorder) **Diagnostic criteria** DSM-IV **Number** Total randomised = 47 (male = 33) No withdrawals reported **Age** 9.0 years (mean); 5 years 11 months to 16 years, 2.5 (SD) **IQ** 106.8 (mean) **Co-morbid disorders** ODD: 17% Encopresis/enuresis: 10.6% Tic disorders: 2.1% **Diagnostic subtypes** ADHD–Combined type: *n* = 32 (68%), ADHD–Inattentive type: *n* = 15 (32%) **Additional information** Previous medication: 33 (70%) were stimulant-naive, 14 (30%) had taken stimulant medications in the past	**Core symptoms** ADHD Rating Scale IV: Home version (parents) ACTeRS **Co-existent problems** Not reported **Educational performance** Not reported **Psychological function** Not reported **Depression or anxiety** Not reported **Quality of life** CGI-S (assessed weekly) – to determine global changes in severity **Adverse events** Side-effect rating scale (parents) – severity on 10-point scale ranging from absent to serious **Additional outcomes** Reliable change index to calculate clinically significant change (defined as when the post-treatment level of functioning results in a subject rated closer to the mean of the functional population than to the mean of the dysfunctional population)

Core symptoms	Educational performance	Quality of life	Adverse events
ADHD Rating Scale IV (data presented as dose–response curves) As OROS MPH dose increased from 0 to 54 mg, parent-rated ADHD symptoms decreased in a linear manner [$F(1,38) = 96.71$, $p < 0.001$], similarly for inattentive and hyperactive-impulsive symptoms [$F(1,38) = 89.55$, $p < 0.001$ and $F(1,38) = 81.28$, $p = 0.001$, respectively] ADHD Parent Rating Scale IV (attention subscale) No significant difference between ADHD-CT and ADHD-PI ($p = 0.085$) Inattentive subtype ($n = 15$): baseline score/% improved (attaining threshold score 62.49) 18 mg 76.1/57% 36 mg 76.1/60% 54 mg 76.1/57% ADHD Parent Rating Scale IV (attention subscale) Combined subtype ($n = 32$): baseline score/% improved (attaining threshold score 62.49) 18 mg 75.6/45% 36 mg 75.6/61% 54 mg 75.6/76% ADHD Parent Rating Scale IV (hyperactivity subscale). No significant difference between ADHD-CT and ADHD-PI ($p = 0.09$) Combined subtype ($n = 32$): baseline score/% improved (attaining threshold score 60.71) 18 mg 72.5/52% 36 mg 72.5/55% 54 mg 72.5/76% Inattentive subtype: data not presented	Not reported	CGI severity scores – Overall impairment decreased with increasing dose of MPH $F(1,38) = 57.49$, $p < 0.001$ CGI severity scores – n (%) improvement using CGI in ADHD children (inattentive subtype, $n = 15$): CGI < 2: baseline/placebo/18 mg/36 mg/54 mg 0/2 (14%)/3 (21%)/6 (43%)/7 (58%) CGI < 3: baseline/placebo/18 mg/36 mg/54 mg 4 (31%)/5 (36%)/9 (64%)/10 (71%)/9 (75%) CGI severity scores – n (%) improvement using CGI in ADHD children (combined subtype, $n = 32$): CGI < 2: baseline/placebo/18 mg/36 mg/54 mg 0/2 (7%)/8 (25%)/14 (45%)/15 (52%) CGI < 3: baseline/placebo/18 mg/36 mg/54 mg 4 (13%)/4 (14%)/14 (44%)/20 (65%)/21 (72%)	MPH dose did not have a significant effect on SERS total score Parents reported more problems with sleep on all doses of MPH relative to placebo ($p < 0.001$) There was significantly greater appetite suppression with increasing doses of MPH ($p < 0.001$) Frequency of presence of any side-effect at each dose of MPH (% present in placebo/18 mg/36 mg/54 mg): Insomnia or trouble sleeping 45.5/66/65.2/72.7 Nightmares 20.5/17/15.2/15.9 Stares a lot or daydreams 50/51.1/47.8/54.5 Talks less with others 22.7/23.4/32.6/29.5 Uninterested in others 22.7/23.4/34.8/25 Decreased appetite 34.1/63.8/73.9/79.5 Irritable 56.8/59.6/71.7/65.9 Stomach aches 22.7/40.4/47.8/38.6 Headaches 34.1/29.8/37/31.8 Drowsiness 27.3/25.5/28.3/40.9 Sad/unhappy 38.6/34/47.8/34.1 Prone to crying 38.6/48.9/54.3/34.1 Anxious 52.3/55.3/47.8/43.2 Bites fingernails15.9/17/21.7/22.7 Euphoric/unusually happy 25/10.6/13/15.9 Dizziness 6.8/4.3/4.3/11.4 Tics or nervous movements 18.2/14.9/17.4/18.2 Frequency of severe (rating ≥ 7) side-effects at each dose of MPH (% severe in placebo/18 mg/36 mg/54 mg): Insomnia or trouble sleeping 9.1/8.5/10.9/25 Nightmares 0/0/2.2/0 Stares a lot or daydreams 4.5/2.1/2.2/0 Talks less with others 2.3/2.1/0/6.8 Uninterested in others 2.3/2.1/4.3/6.8 Decreased appetite 4.5/10.6/13/27.3 Irritable 4.5/12.8/17.4/9.1 Stomach aches 0/2.1/6.5/9.1 Headaches 0/0/6.5/6.8 Drowsiness 0/2.1/2.2/2.3 Sad/unhappy 2.3/8.5/8.7/9.1

continued

Core symptoms	Educational performance	Quality of life	Adverse events
			Prone to crying 4.5/8.5/13/13.6 Anxious 11.4/4.3/10.9/4.5 Bites fingernails 4.5/4.3/13/6.8 Euphoric/unusually happy 0/2.1/4.3/0 Dizziness 0/0/0/0 Tics or nervous movements 0/0/4.3/4.5
Conclusions	**Authors' conclusions:** In children with ADHD–Combined type, the most common subtype of ADHD, increasing doses of stimulant medication were associated with increased improvement of inattention and hyperactivity symptoms. In children with ADHD–Inattentive subtype, symptom improvement occurred at lower doses and less benefit was derived from higher doses. In both ADHD subtypes, higher doses were associated with parent ratings of increased insomnia and decreased appetite **Reviewer's comments:** The authors report that it was not possible to ensure identical appearance of placebo and active drug		

Study	Intervention	Participants	Outcomes
Reference Swanson *et al.*, 2004[32] **Source** Updated search **Setting** USA (laboratory school) **Design** Crossover trial **Duration** Each treatment for 7 days; no washout period **Purpose** To evaluate differences in the pharmacodynamic profile of Metadate CD	**Arm 1** MPH Metadate CD (MCD) – Participants were assigned to a dose level according to their pre-existing dosing requirement for MPH: 20, 40 or 60 mg/day (Individual administering medication not reported) **Arm 2** MPH Concerta (CON) – Participants were assigned to a dose level according to their pre-existing dosing requirement for MPH: 18, 36 or 54 mg/day (Individual administering medication not reported)	**Inclusion criteria** 1. 6–12 years of age 2. Children with a clinical diagnosis being treated with MPH in doses of 10–60 mg/day 3. IQ >80 (had to follow and understand study instructions) 4. Not pregnant 5. No history of seizure or tic disorder 6. No family history of seizure or Tourette's syndrome 7. No congenital cardiac abnormality, history of cardiac disease including myocardial infarction within 3 months of study entry, glaucoma or hyperthyroidism 8. No history of substance abuse 9. No concurrent chronic or acute illness or other condition that might confound the study rating measures 10. No documented allergy or intolerance to MPH 11. No use of concomitant medication that could interfere with the assessment of efficacy and safety of study treatments **Diagnostic criteria** DSM-IV	**Core symptoms** SKAMP: deportment; attention (measured by two trained observers) **Co-existent problems** Not reported **Educational performance** Not reported **Psychological function** Not reported **Depression or anxiety** Not reported **Quality of life** Not reported **Adverse events** Side-effects on the Barkley Scale

continued

Study	Intervention	Participants	Outcomes
and Concerta. The authors assessed the various treatments at different hours post-dose	**Arm 3** Placebo (Individual administering medication not reported)	**Number** Total randomised = 184 (male = 74%) Total withdrawals = 27 Randomisation procedure: Patients were stratified by previous MPH dose, creating the following comparisons: MCD 20 mg vs CON 18 mg vs placebo, MCD 40 mg vs CON 36 mg vs placebo, MCD 60 mg vs CON 54 mg vs placebo **Age** 9.7 years (mean); 1.8 years (SD) **IQ** Not reported **Co-morbid disorders** 25% had a co-morbid condition including anxiety and ODD (other conditions not reported) **Diagnostic subtypes** Inattentive: 13%; hyperactive/impulsive: 5%; combined: 82% **Additional information** Previous medication: All participants were taking MPH before the study – this was part of the inclusion criteria. 1% of the participants were taking Focalin Concurrent medication: Individuals taking additional medication that could interfere with the assessment of efficacy and safety of study treatments were excluded from the trial	**Additional outcomes** SKAMP – 10-minute math test to provide an objective measure from its permanent product, defined as the number of problems answered correctly Blood pressure and pulse rate

Core symptoms	Educational performance	Quality of life	Adverse events
SKAMP: deportment MCD vs CON: mean difference = 1.62, $p < 0.001$; MCD > CON SKAMP: attention MCD vs CON: mean difference = 0.86, $p = 0.0003$; CON > MCD MCD and CON vs placebo not reported. Results not reported by dose	Not reported	Not reported	Adverse events occurring in >2% of patients: ITT population (results not reported by dose)

	MCD (n = 174)	CON (n = 181)	Placebo (n = 183)
Gastrointestinal disorders	8 (4.6%)	11 (6.1%)	13 (7.1%)
Abdominal pain upper	6 (3.4%)	8 (4.4%)	6 (3.3%)
Vomiting	1 (0.6%)	1 (0.6%)	4 (2.2%)
Infections and infestations	1 (0.6%)	5 (2.8%)	2 (1.1%)
Injury, poisoning and procedural complications	6 (3.4%)	3 (1.7%)	5 (2.7%)
Metabolism and nutrition disorders	8 (4.6%)	11 (6.1%)	4 (2.2%)
Anorexia	5 (2.9%)	5 (2.8%)	2 (1.1%)
Appetite decreased	3 (1.7%)	6 (3.3%)	1 (0.5%)
Nervous system disorders	6 (3.4%)	10 (5.5%)	10 (5.5%)
Headache	3 (1.7%)	7 (3.9%)	6 (3.3%)
Psychiatric disorders	12 (6.9%)	13 (7.2%)	17 (9.3%)
Insomnia	3 (1.7%)	3 (1.7%)	6 (3.3%)
Irritability	3 (1.7%)	2 (1.1%)	5 (2.7%)

Conclusions	**Authors' conclusions:** The authors state that once-daily doses of MCD and CON produced statistically significantly different pharmacodynamic effects on surrogate measures of behaviour and performance among children with ADHD in the laboratory school setting **Reviewer's comments:** No comments noted

Study	Intervention	Participants	Outcomes
Reference Tervo *et al*., 2002[93] **Source** Updated search **Setting** USA **Design** Crossover trial **Duration** Total treatment period: 3 weeks (6 days per treatment arm followed by a 1-day washout period) **Purpose** To evaluate the medication responsiveness of children with ADHD (with or without motor dysfunction). Only data for children without motor dysfunction (ADHD-MD) have been extracted	**Arm 1** Placebo Twice daily for 6 days (Individual administering medication not reported) **Arm 2** MPH 0.05 mg/kg twice daily for 6 days (Individual administering medication not reported) **Arm 3** MPH 0.3 mg/kg twice daily for 6 days (Individual administering medication not reported)	**Inclusion criteria** Diagnosis of ADHD **Diagnostic criteria** DSM-IV **Number** Total randomised = 41 (male/female split not reported) Total withdrawals unclear The authors described withdrawals, but did not present them separately for children with and without ADHD-MD **Age** 10 years (mean); 2.86 years (SD) **IQ** Not reported **Co-morbid disorders** Children with ADHD-MD were also included in the review, but data are not extracted here **Diagnostic subtypes** Not reported **Additional information** No relevant information reported	**Core symptoms** CBCL parent rated Teacher report form **Co-existent problems** Not reported **Educational performance** Not reported **Psychological function** Not reported **Depression or anxiety** Not reported **Quality of life** Not reported **Adverse events** Not reported **Additional outcomes** Not reported

Core symptoms	Educational performance	Quality of life	Adverse events
CBCL parent rated: mean (SE) ADHD (placebo/low dose/high dose) 68.76 (3.2)/61.6 (2.9)/56.37 (2.7) Teacher report form: mean (SE) ADHD (placebo/low dose/high dose) 65.03 (2.8)/50.21 (1.9)/51.34 (1.9) The authors state that the children had a significant linear response to medication [$F(2,46)$, $p = 0.001$]	Not reported	Not reported	Not reported
Conclusions	**Authors' conclusions:** Both ADHD and ADHD-MD are psychostimulant responders whose hyperactive/impulsive behaviour responds well to low-dose medication. Both groups of children had a linear dose–response to medication (placebo, low, high) and there was no evidence of a group by dose interaction or an overall group effect at home or school **Reviewer's comments:** Publication results focus on difference in behavioural outcomes in ADHD and ADHD-MD. Treatment outcomes are a very small part of this publication		

Study	Intervention	Participants	Outcomes
Reference Weiss *et al.*, 2004[94]	**[Confidential information removed]**		

Core symptoms	Educational performance	Quality of life	Adverse events
[Confidential information removed]			
Conclusions	**Authors' conclusions: [Confidential information removed]** **Reviewer's comments: [Confidential information removed]**		

Study	Intervention	Participants	Outcomes
Reference Wernicke *et al.*, 2004[95] **Source** Updated search **Setting** USA **Design** Parallel trial **Duration** Wash-out period: 2 weeks; treatment period: 9 weeks; discontinuation phase: 1 week placebo **Purpose** To assess the effect of discontinuing ATX in children with ADHD	**Arm 1** ATX Titrated to maximum of 2.0 mg/kg/day; administered twice daily in evenly divided doses (Individuals administering medication not reported) **Arm 2** Placebo (Individuals administering medication not reported)	**Inclusion criteria** 1. School-aged children, aged 7–12 years 2. ADHD diagnosis **Diagnostic criteria** DSM-IV **Number** Total = 194 (male/female split not reported) Arm 1 = 102 Arm 2 = 92 Two studies are reported on in this paper. 194 children completed the discontinuation phase of either study and are reported on here **Age** Mean not reported; 7–12 years (range) **IQ** Not reported **Co-morbid disorders** Not reported **Diagnostic subtypes** Not reported **Additional information** No relevant information reported	**Core symptoms** ADHD Rating Scale IV, Parent Version: total score **Co-existent problems** Not reported **Educational performance** Not reported **Psychological function** Not reported **Depression or anxiety** Not reported **Quality of life** Not reported **Adverse events** Barkley Behaviour and Adverse Events Questionnaire – Modified Open-ended questions **Additional outcomes** Vital signs Laboratory measures including hepatic function, full blood count, ECG

Core symptoms	Educational performance	Quality of life	Adverse events
ADHD Rating Scale IV, Parent Version: mean (SD) Arm 1: pre-treatment to end of treatment phase: –17.2 (12.6) Arm 2: pre-treatment to end of treatment phase: –6.4 (12.4) Arm 1 had significantly lower mean values at end of treatment phase	Not reported	Not reported	Only reported for the discontinuation phase – not relevant to our review

Conclusions	
	Authors' conclusions: It appears that ATX can be stopped without the risk of symptom rebound or discontinuation emergent adverse events **Reviewer's comments:** No comments reported

Study	Intervention	Participants	Outcomes
Reference Werry *et al.*, 1980[96] **Source** AHRQ Report **Setting** New Zealand **Design** Crossover trial **Duration** Treatment periods: 3–4 weeks **Purpose** To compare imipramine with MPH (Ritalin) and placebo as control, with particular attention given to physiological effects, cognitive function, self-image and dosage	**Arm 1** MPH 0.40 mg/kg/dose (once daily?, unclear) (Administered by parent) **Arm 2** Imipramine 1.00 mg/kg/dose (14 subjects) or 2.00 mg/kg/dose (16 subjects) (once daily?, unclear) (Administered by parent) **Arm 3** Placebo (Administered by parent)	**Inclusion criteria** (Inclusion criteria not reported explicitly) 1. Normal IQ 2. Without pronounced physical or neurological disability 3. Prolonged history of inattention and hyperactivity at home and school (as predominant clinical issue) **Diagnostic criteria** American NIMH diagnostic measures used, but final decision was clinical **Number** Total randomised = 30 (male = 26) Arm 1 = 30 Arm 2 = 30 Arm 3 = 30 No withdrawals reported Randomisation procedure: Note that placebo was always the second drug condition assigned to avoid possible toxic interactions **Age** 8 years 5 months (mean); 5 years 6 months–12 years 7 months (range) **IQ** Not reported **Co-morbid disorders** Not reported **Diagnostic subtypes** Not reported **Additional information** Co-interventions: No other treatment was given to the children during the study	**Core symptoms** Conners' Parent Questionnaire: hyperactivity Conners' Teacher Questionnaire: inattention and hyperactivity Short Term Memory Task: seat movement Continuous Performance Task: seat movement **Co-existent problems** Conners' Parent Questionnaire: conduct, antisocial Conners' Teacher Questionnaire: conduct **Educational performance** Short Term Memory Task: accuracy, speed Conners' Parent Questionnaire: learning **Psychological function** Not reported **Depression or anxiety** Conners' Parent Questionnaire: anxiety Conners' Teacher Questionnaire: anxiety **Quality of life** CGI **Adverse events** Conners' Parent Questionnaire: psychosomatic **Additional outcomes** Height Weight Cardiovascular function: heart rate, systolic and diastolic blood pressure Motor Coordination Tests: Maze Test and Graduated Holes Test Children's Self-Concept Scale Conners' Parent Questionnaire: perfectionism, muscular tension

Core symptoms	Educational performance	Quality of life	Adverse events
Conners' Teacher Questionnare: hyperactivity MPH: 2.22 (no variance reported) PLA: 2.56 No significant difference Conners' Teacher Questionnare: inattention MPH: 1.95 (no variance reported) PLA: 2.14 No significant difference Conners' Parent Questionnaire: hyperactivity, MPH: 1.29 (no variance reported) PLA: 1.17 No significant differences between MPH and placebo Short Term Memory Task (STM): seat movement MPH: 86.19 (no variance reported) PLA: 148.37 MPH > placebo, $p < 0.001$ (Newman–Keuls test) Continuous Performance Task: seat movement MPH: 13.03 (no variance reported) PLA: 32.77 MPH > placebo, $p < 0.005$ (Newman–Keuls test)	Short Term Memory Task (STM): accuracy/speed MPH: 86.82/0.548 (no variance reported) PLA: 85.17/0.526 No significant differences for both Conners' Parent Questionnaire: learning MPH: 0.55 (no variance reported) PLA: 0.43 No significant differences	CGI (physician) MPH: 3.52 (no variance reported) PLA: 4.04 No significant difference between MPH and placebo	Not reported
Conclusions	**Authors' conclusions:** In the short term, imipramine was found to be clinically more effective than MPH, but side-effects were greater **Reviewer's comments:** No comments noted		

Study	Intervention	Participants	Outcomes
References Wolraich *et al.*, 2001[97]; Wolraich, 2000[325]; Wolraich *et al.*, 2002[326] **Source** Updated search **Setting** USA **Design** Parallel trial **Duration** Treatment period: 4 weeks **Purpose** To compare the efficacy and safety of once-a-day investigational OROS extended-release MPH (Concerta) with conventional MPH three times a day (MPH t.d.s.) and placebo in children with ADHD	**Arm 1** Placebo Administered three times daily (7.30 a.m., 11.30 a.m., 3.30 p.m.) (Individual administering medication not reported) **Arm 2** MPH Participants were assigned to a dose level according to dose titration or pre-existing dose requirement for MPH: 15, 30, 45 mg/day given in 3 capsules (7.30 a.m., 11.30 a.m., 3.30 p.m.); mean daily dose: 0.9 ± 0.4 mg/kg/day (Individual administering medication not reported) **Arm 3** MPH Participants were assigned to a dose level according to dose titration or pre-existing dose requirement for MPH: 18, 36, 54 mg/day in one extended-release capsule (7.30 a.m.) plus placebo (11.30 a.m., 3.30 p.m.); 1.1 ± 0.5 mg/kg/day (Individual administering medication not reported)	**Inclusion criteria** 1. Clinical diagnosis of ADHD (any subtype) 2. Aged 6–12 years 3. Patients who were taking MPH or had taken it in the past had to have been on a total daily MPH dose of at least 10 mg but not more than 60 mg (immediate or sustained release) 4. No acute or serious chronic disease 5. No hypersensitivity to MPH or previous significant adverse experiences from MPH 6. No medication that would interfere with safe administration of MPH 7. No glaucoma, Tourette's syndrome, ongoing seizure disorder or psychotic disorder 8. No girls who had reached menarche 9. Consent to take study drug as only medication during 4-week trial **Diagnostic criteria** Confirmed by Diagnostic Interview Schedule for Children (version 4). Severity of ADHD symptoms rated both at school and at home using SNAP-IV, IOWA-C and C-GAS **Number** Total randomised = 312 (male = 233/282) Arm 1 = 99 Arm 2 = 107 Arm 3 = 106 Total withdrawals = 106 Arm 1 = 53 Arm 2 = 26 Arm 3 = 27 Reasons for withdrawals: Site excluded: $n = 30$ Never received medication: $n = 5$ Adverse effects: $n = 3$; Arm 1: $n = 1$; Arm 2: $n = 1$, Arm 3: $n = 1$ Noncompliance: $n = 3$; Arm 1: $n = 1$; Arm 2: $n = 1$; Arm 3: $n = 1$ Lost to follow-up: $n = 1$; Arm 1: $n = 0$; Arm 2: $n = 0$; Arm 3: $n = 1$ Lack of efficacy: $n = 59$; Arm 1: $n = 38$; Arm 2: $n = 10$; Arm 3: $n = 11$ Could not swallow pills: $n = 1$; Arm 1: $n = 0$; Arm 2: $n = 0$; Arm 3: $n = 1$ Protocol violation: $n = 2$; Arm 1: $n = 1$; Arm 2: $n = 1$; Arm 3: $n = 0$ Did not return: $n = 1$; Arm 1: $n = 1$; Arm 2: $n = 0$; Arm 3: $n = 0$	**Core symptoms** IOWA Conners' Rating Scale: inattention/overactivity subscale (teacher, parent) SNAP-IV: inattention, hyperactivity/impulsivity (parent, teacher) **Co-existent problems** IOWA Conners' Rating Scale: oppositional subscale (teacher, parent) SNAP-IV: oppositional, peer interaction (parent, teacher) **Educational performance** Not reported **Psychological function** Not reported **Depression or anxiety** Not reported **Quality of life** Clinical Global Impression: improvement (investigators) Global efficacy (parent, teacher) **Adverse events** Solicited and spontaneous reports: focus on sleep quality, tics and appetite (parent) **Additional outcomes** Blood pressure Pulse rate Parent Satisfaction Questionnaire

continued

Study	Intervention	Participants	Outcomes
		Mother gave child IR-MPH; *n* = 1; Arm 1: *n* = 1; Arm 2: *n* = 0; Arm 3: *n* = 0 **Age** 9.0 years (mean); 6–12 years (range); 1.8 years (SD) **IQ** Not reported **Co-morbid disorders** ODD: *n* = 118/282 (41.8%) CD: *n* = 32/282 (11.3%) Tic disorder: *n* = 15/282 (5.3%) Anxiety disorder: *n* = 4/282 (1.4%) Depression: *n* = 2/282 (0.7%) Total: *n* = 131/282 (46.5%) **Diagnostic subtypes** Combined: *n* = 207/282 (73.4%) Inattentive: *n* = 55/282 (19.5%) Hyperactive/impulsive: *n* = 20/282 (7.1%) **Additional information** Previous medication: No previous MPH treatment: 102/312 (these were enrolled in a dose titration study immediately prior to the randomisation phase of this trial) Previous MPH treatment: 210/312 Concurrent medication: Individuals in receipt of any medication that would interfere with the safe administration of MPH were excluded from the trial No previous stimulant therapy: 57/282 (20.2%); Arm 1: 19/90 (21.1%); Arm 2: 18/97 (18.6%); Arm 3: 20/95 (21.1%) No stimulant therapy in previous 4 weeks: 18/282 (6.4%); Arm 1: 6/90 (6.7%); Arm 2: 9/97 (9.3%); Arm 3: 3/95 (3.2%) Previous non-MPH therapy: 16/282 (5.7%); Arm 1: 5/90 (5.6%); Arm 2: 8/97 (8.2%); Arm 3: 3/95 (3.2%) Previous MPH therapy: 191/282 (67.7%); Arm 1: 60/90 (66.7%); Arm 2: 62/97 (63.9%); Arm 3: 69/95 (72.6%) Co-interventions: Patients were allowed to receive behavioural interventions during the trial provided that they had been initiated before the beginning of the study and did not change during the course of the study	

Core symptoms	Educational performance	Quality of life	Adverse events
IOWA-C mean scores: Inattention/overactivity (teacher rated) Mean (SD), OROS MPH/IR-MPH/placebo Baseline (n = 276): 9.74 (4.1)/9.94 (3.7)/10.28 (3.8) Week 1 (n = 238): 5.58* (3.64)/5.70* (3.84)/9.87 (4.09) *p < 0.05 compared with placebo; no significant differences between OROS and IR-MPH (p = 0.838) End of study (n = 271): 5.98* (3.91)/6.35* (4.31)/9.77 (4.02) *p < 0.05 compared with placebo; no significant differences between OROS and IR-MPH (p = 0.539) Overall treatment effect (week 1): $F(2,235)$ = 30.59, p < 0.001 Overall treatment effect (end of study): $F(2,258)$ = 21.95, p < 0.001 IOWA-C mean scores: Inattention/overactivity (parent rated) Mean (SD), OROS MPH/IR-MPH/placebo Baseline (n = 281): 11.08* (2.6)/9.90 (3.2)/10.44 (3.0) *p < 0.01 compared with IR-MPH Week 1 (n = 243): 5.38* (3.38)/5.44* (3.22)/9.48 (3.78) *p < 0.05 compared with placebo End of study (n = 265): 6.29* (3.54)/6.17* (3.19)/10.11 (3.92) *p < 0.05 compared with placebo Overall treatment effect (week 1): $F(2,240)$ = 36.49, p < 0.001 Overall treatment effect (end of study): $F(2,262)$ = 34.22, p < 0.001 SNAP-IV Inattention (teacher rated) Mean (SD), OROS MPH/IR-MPH/placebo Baseline (n = 274): 2.03 (0.7)/2.06 (0.6)/2.04 (0.7) End of study (n = 236): 1.34* (0.84)/1.26* (0.79)/1.97 (0.79)	Not reported	Mean CGI (investigator rated) Mean (SD), OROS MPH/IR-MPH/placebo End of study (n = 263): 4.24* (1.34)/4.19* (1.45)/2.48 (1.67) Overall treatment effect: $F(2,260)$ = 39.35, *p < 0.001 compared with placebo CGI: % much or very much improved at end of study (n = 192) OROS MPH: 46.7%; IR-MPH: 47.2%; placebo: 16.7% Global Efficacy (parent) end of study: mean (SD) (n = 247) OROS: 1.47 (1.07); significantly different from placebo (p < 0.05) IR-MPH: 1.28 (0.93); significantly different from placebo (p < 0.05) Placebo: 0.61 (0.93) Overall treatment effect: $F(2,244)$ = 16.71 (p < 0.001) Global Efficacy (teacher) end of study: mean (SD) (n = 233) OROS: 1.42 (0.97); significantly different from placebo (p < 0.05) IR-MPH: 1.43 (1.01); significantly different from placebo (p < 0.05) Placebo: 0.62 (0.81) Overall treatment effect: $F(2,230)$ = 17.64, p < 0.001 Global efficacy (teacher): % rated good or excellent OROS: 42.9% IR: 46.9% Placebo: 17.7%	306 participants were included in analyses of safety Any adverse event: occurrence Total: n = 126 (41.2%) OROS: 42.3% IR-MPH: 46.2% Placebo: 34.7% Withdrawals: OROS: n = 1, depression IR-MPH: n = 1, emotional lability Placebo: n = 1, tics Headache: occurrence OROS: 14.4% IR-MPH: 5.8% Placebo: 10.2% Abdominal pain: occurrence OROS: 6.7% IR: 5.8% Placebo: 1.0% Sleep: At baseline, most were assessed as having good or excellent sleep: 70.5, 72.8 and 76.6% in OROS, IR and placebo groups. On days 14 and 28, >65% continued to have good or excellent sleep quality. There appeared to be no significant differences between groups Appetite: At day 14, 22.5, 18.8 and 12.0% in the OROS, IR-MPH and placebo groups, respectively had eaten less than usual in the preceding 2 weeks. There were significant differences between the active and placebo arms (p < 0.001). Percentages were similar on day 28 Tics: New onset or clinically significant increase IR-MPH: n = 1 Placebo: n = 4

continued

Core symptoms	Educational performance	Quality of life	Adverse events
$p < 0.05$ compared with placebo; no significant differences between OROS and IR-MPH Overall treatment effect $F(2,233) = 16.40$, $p < 0.001$ SNAP-IV Hyperactivity/Impulsivity (teacher rated) Mean (SD), OROS MPH/IR-MPH/placebo Baseline ($n = 274$): 1.60 (0.9)/1.62 (0.8)/1.00 (0.8) End of study ($n = 236$): 0.96 (0.79)/0.93* (0.79)/1.57 (0.89) *$p < 0.05$ compared with placebo; no significant differences between OROS and IR-MPH Overall treatment effect $F(2,233) = 4.23$, $p < 0.001$ SNAP-IV Inattention (parent rated) Mean (SD), OROS MPH/IR-MPH/placebo Baseline ($n = 276$): 2.29 (0.5)/2.16 (0.6)/2.18 (0.5) End of study ($n = 250$): 1.38* (0.68)/1.39* (0.73)/2.00 (0.78) *$p < 0.05$ compared with placebo; no significant differences between OROS and IR-MPH Overall treatment effect $F(2,247) = 19.15$, $p < 0.001$ SNAP-IV Hyperactive/impulsivity (parent rated) Mean (SD), OROS MPH/IR-MPH/placebo Baseline ($n = 276$): 2.02 (0.6)/1.84 (0.7)/1.99 (0.7) End of study ($n = 250$): 1.11* (0.65)/1.10* (0.69)/1.83 (0.89) *$p < 0.05$ compared with placebo; no significant differences between OROS and IR-MPH Overall treatment effect $F(2,248) = 24.79$, $p < 0.001$		Global efficacy (parent): % rated good or excellent OROS: 54.0% IR: 46.5% Placebo: 20.3%	

Conclusions	**Authors' conclusions:** For the treatment of core ADHD symptoms, OROS MPH dose once daily and IR-MPH dose t.d.s. were superior to placebo and were not significantly different from each other
	Reviewer's comments: No comments noted

Study	Intervention	Participants	Outcomes
References Zeiner, 1999;[101] Zeiner *et al.*, 1999[98] **Source** NICE Report **Setting** Norway **Design** Crossover trial **Duration** Two treatment periods of 3 weeks plus 1-week washout in between **Purpose** To analyse changes in behaviour and test performances during treatment with MPH and placebo in ADHD children and to identify predictors of clinically significant responses to methylphenidate[101] To examine changes in behaviour and test performances during a 3-week period of placebo treatment in ADHD boys who were receiving extended MPH treatment[98]	**Arm 1** MPH Total daily dose of 0.5 mg/kg (8 and 11:30 a.m.)[101] Same dose as on pretrial. Mean daily dose 22.4 mg (SD 7.4 mg). Range 15–35 mg; administered 2 or 3 times daily[98] (Individual administering medication not reported) **Arm 2** Placebo (Individual administering medication not reported)	**Inclusion criteria** 1. Male 7–12-year-olds fulfilling diagnostic criteria for ADHD 2. IQ of ≥ 70 3. No pervasive developmental disorder, psychosis or mood disorder 4. No acute or chronic medical or neurological disease 5. Never used stimulants or other psychotropic drug **Diagnostic criteria** DSM-III-R **Number** Total randomised = 36 (male = 36/21) Total withdrawals = 0 Two crossover trials were conducted: the second trial[98] only included responders to MPH who subsequently completed an extended treatment phase (n = 21) **Age** 8.8 years (mean at admission); 1.1 years (SD) **IQ** 102 (mean) **Co-morbid disorders** ODD: n = 23/36; developmental reading disorder: n = 4/36; delayed development of motor function: n = 5/36 **Diagnostic subtypes** ADHD Combined Type: >75%. All children in sample would fulfil ICD-10 for HKD **Additional information** Previous medication: Participants in the trial were required not to have previously used stimulants or other psychotropic drugs	**Core symptoms** PACS: hyperactivity scale CTRS: hyperactivity **Co-existent problems** PACS: defiance scale CTRS: defiance scale; conduct problems **Educational performance** Not reported **Psychological function** Children's Checking Task (CCT) Continuous Performance Test (CPT) Paced Auditory Serial-Addition Task (PASAT-A and PASAR-R) Maze Coordination Test Grooved Pegboard Test **Depression or anxiety** PACS: emotional problems **Quality of life** Not reported **Adverse events** The authors briefly state that no serious physical side-effects were reported **Additional outcomes** Neurodevelopmental examination: total score

Core symptoms	Educational performance	Quality of life	Adverse events
CTRS: hyperactivity (data from Zeiner *et al.*:[98] $n = 21$/from Zeiner:[101] $n = 36$) MPH: 11.2 (4.8)/8.83 (6.49) Placebo: 16.8 (5.7/14.69 (6.17) Zeiner *et al*[98] and Zeiner:[101] MPH > placebo, $p < 0.0001$); $t = 5.2$ (Zeiner *et al.*); $t = 6.76$ (Zeiner)[101] PACS: hyperactivity (data from Zeiner *et al.*, 1999:[98] $n = 21$/from Zeiner, 1999:[101] $n = 36$) MPH: 3.8 (3.9)/3.08 (3.70) Placebo: 4.5 (4.0)/5.25 (5.01) Zeiner *et al.*:[98] NS; Zeiner:[101] MPH > placebo, $p < 0.05$; $t = 0.61$ (Zeiner *et al.*,[98] $t = 2.37$ (Zeiner)[101]	Not reported	Not reported	PACS: side-effects (data from Zeiner *et al.*:[98] $n = 21$/ from Zeiner:[101] $n = 36$) No results reported
Conclusions	**Authors' conclusions:** Zeiner *et al.*[98] concluded that in most ADHD children the beneficial effects of MPH treatment dissipate rapidly when the drug treatment is stopped Zeiner[101] concluded that most ADHD children treated with stimulants show clinically significant improvements in their behaviour in at least one setting; response may vary depending on both the setting and the tasks that the child completes **Reviewer's comments:** No comments noted		

Study	Intervention	Participants	Outcomes
Reference MTA Cooperative Group, 1999[76] **Source** Updated search **Setting** USA **Design** Parallel trial **Duration** Enrolment period: 1994–8; treatment period: 14 months; Follow-up period: 24 months **Purpose** The authors addressed the following questions: 1. How do long-term medication and behavioural treatments compare with one another? 2. Are there additional benefits when they are used together? 3. What is the effectiveness of systematic, carefully delivered treatments vs routine community care?	**Arm 1** Medication management 28-day daily switch titration of placebo, 5 mg MPH, 10 mg MPH, 15 mg MPH or 20 mg MPH; full dose with breakfast and lunch, half dose in afternoon; best dose became subject's initial maintenance dose; for non-responders to MPH, DEX, PEM, imipramine and approved other drugs subsequently titrated (in stated order); monthly maintenance visits with algorithmic dose adjustments; supplementary general advice and bibliotherapy; case management by pharmacotherapist; emergency services as needed (Individuals administering medication not reported) **Arm 2** Behavioural treatment Parent training (27 group sessions, 8 individual sessions per family), child-focused treatment (8-week summer treatment programme), and school-based treatment (10–16 teacher consultation sessions and 12 weeks part-time aide working directly with child); supplementary general advice; case management by therapist–consultant; emergency services as needed (Administered by therapist–consultant, counsellor-aides)	**Inclusion criteria** Inclusion criteria: 1. 7–9.9 years old 2. In grades 1–4 3. In residence with same primary caretaker(s) for last 6 months or longer 4. Score above 90th percentile on standardised teacher rating scales **Exclusion criteria** (Limited to situations that would prevent families' full participation in study, or might require additional treatment incompatible with study treatments) 1. Child currently in hospital 2. Child currently in another study 3. <80 on all WISC-III scales and on Scales of Independent Behaviour 4. Bipolar disorder, psychosis, or personality disorder 5. Chronic serious tics or Tourette syndrome 6. ODD serious enough to require separate treatment 7. Neuroleptic medication in previous 6 months 8. Major neurological or medical illness 9. History of intolerance to MTA medications 10. Ongoing or previously unreported abuse 11. Missed one quarter of school days in previous 2 months 12. Same classroom as child already in MTA study 13. Parental stimulant abuse in previous 2 years 14. Non-English speaking primary caretaker 15. Another child in same household in MTA study 16. No telephone 17. Suicidal or homicidal **Diagnostic criteria** DSM-IV **Number** Total = 579 (male = 465) Arm 1 = 144 Arm 2 = 144 Arm 3 = 145 Arm 4 = 146	**Core symptoms** SNAP scale: inattention, hyperactivity and impulsivity subscales (parents, teachers) Abikoff Classroom Observational System: school-based core symptoms **Co-existent problems** SNAP scale: ODD subscale (parents, teachers) Social Skills Rating System: social skills subscale (parents, teachers) Parent–child Relationship Questionnaire: 2 composite scales Abikoff Classroom Observational System: oppositional/aggressive symptoms Peer sociometric procedures: social skills, peer relations Videotaped parent–child interactions 'negative/ineffective discipline' factor **Educational performance** Wechsler Individual Achievement Test: reading, maths and spelling subscales **Psychological function** Not reported **Depression or anxiety** Social Skills Rating System: internalising subscale (parents, teachers) Multidimensional Anxiety Scale for Children: children's self-ratings **Quality of life** Not reported **Adverse events** Pittsburgh Side Effects Rating Scale

continued

Study	Intervention	Participants	Outcomes
	Arm 3 Medication management plus Behavioural treatment Integration of all treatment components in Arms 1 and 2 (except bibliotherapy), such that information is shared amongst all involved in decision-making (Administered by therapist–consultant, counsellor-aides) **Arm 4** Standard community care List of community mental health resources given to those without treatment provider; otherwise referred back for treatment (Individuals administering medication not reported)	Total withdrawals = 20 (at 14 months) Arm 1 = 8 Arm 2 = 3 Arm 3 = 3 Arm 4 = 6 Total withdrawals = 39 (93%) (24 months) **Age** 8.5 years (mean); 0.8 years (SD) **IQ** 100.9 (mean) **Co-morbid disorders** Anxiety disorder: *n* = 194 (33.5%) CD: *n* = 83 (14.3%) ODD: *n* = 231 (39.9%) Affective disorder: *n* = 22 (3.8%) Tic disorder: Total: *n* = 63 (10.9%) Mania/hypomania: *n* = 13 (2.2%) Other co-morbid conditions (e.g. bulimia, enuresis): *n* = 1 (0.2%) **Diagnostic subtypes** All children met criteria for ADHD Combined Type **Additional information** Previous medication: Total: *n* = 178 (31%): Arm 1: *n* = 46 (32%), Arm 2: *n* = 38 (26%), Arm 3: *n* = 44 (30%), Arm 4: *n* = 50 (34%) No significant differences were found across sites ($p = 0.0001$). Participants in the trial were not to have been in receipt of any neuroleptic medication in previous 6 months	**Additional outcomes** Services Use by Children and Adolescents–Parent Interview: use and dose of medication, use of specialty mental health services, use of special education services

Core symptoms	Educational performance	Quality of life	Adverse events
(Results for whole sample, i.e. including co-morbid patients) Inattention: teacher rating: mean (SD) (no. of subjects) Arm 1: Baseline: 2.27 (0.61) (135); 14-month follow-up: 1.11 (0.77) (120) Arm 2: Baseline: 2.28 (0.64) (136); 14-month follow-up: 1.47 (0.81) (119) Arm 3: Baseline: 2.16 (0.67) (137); 14-month follow-up: 1.12 (0.75) (134) Arm 4: Baseline: 2.19 (0.69) (135); 14-month follow-up: 1.48 (0.82) (128) Inattention: parent rating: mean (SD) (no. of subjects) Arm 1: Baseline: 2.03 (0.64) (140); 14-month follow-up: 1.12 (0.70) (121) Arm 2: Baseline: 1.99 (0.63) (139); 14-month follow-up: 1.40 (0.68) (129) Arm 3: Baseline: 2.07 (0.61) (140); 14-month follow-up: 1.02 (0.66) (133) Arm 4: Baseline: 2.05 (0.65) (142); 14-month follow-up: 1.49 (0.67) (130) Hyperactive/impulsive: teacher rating: mean (SD) (no. of subjects) Arm 1: Baseline: 2.08 (0.71) (135); 14-month follow-up: 0.82 (0.69) (120) Arm 2: Baseline: 2.05 (0.75) (136); 14-month follow-up: 1.10 (0.77) (119) Arm 3: Baseline: 1.89 (0.77) (137); 14-month follow-up: 0.75 (0.71) (134) Arm 4: Baseline: 1.93 (0.81) (135); 14-month follow-up: 1.25 (0.84) (128) Hyperactive/impulsive: parent rating: mean (SD) (no. of subjects) Arm 1: Baseline: 1.89 (0.62) (140); 14-month follow-up: 0.91 (0.65) (121) Arm 2: Baseline: 1.89 (0.64) (140); 14-month follow-up: 1.24 (0.72) (129) Arm 3: Baseline: 1.91 (0.69) (140); 14-month follow-up: 1.85 (0.63) (133) Arm 4: Baseline: 1.95 (0.67) (142); 14-month follow-up: 1.35 (0.72) (130) Hyperactive/impulsive: classroom observer rating: mean (SD) (no. of subjects) Arm 1: Baseline: 0.31 (0.21) (119); 14-month follow-up: 0.16 (0.15) (110) Arm 2: Baseline: 0.37 (0.26) (120); 14-month follow-up: 0.29 (0.26) (107) Arm 3: Baseline: 0.33 (0.22) (122); 14-month follow-up: 0.21 (0.20) (114) Arm 4: Baseline: 0.38 (0.27) (118); 14-month follow-up: 0.18 (0.15) (109)	(Results for whole sample, i.e. including co-morbid patients) Reading scores: mean (SD) (no. of subjects) Arm 1: Baseline: 96.1 (13.7) (144); 14-month follow-up: 97.9 (14.1) (124) Arm 2: Baseline: 96.2 (14.9) (134); 14-month follow-up: 96.2 (14.9) (134) Arm 3: Baseline: 96.5 (14.6) (145); 14-month follow-up: 99.4 (15.2) (136) Arm 4: Baseline: 95.5 (14.3) (146); 14-month follow-up: 95.4 (14.2) (131) Mathematics scores: mean (SD) (no. of subjects) Arm 1: Baseline: 97.2 (12.6) (144); 14-month follow-up: 99.7 (13.0) (124) Arm 2: Baseline: 97.7 (13.2) (144); 14-month follow-up: 100.3 (13.7) (134) Arm 3: Baseline: 97.9 (15.1) (145); 14-month follow-up: 100.5 (16.4) (136) Arm 4: Baseline: 98.6 (14.1) (146); 14-month follow-up: 100.4 (14.2) (131) Spelling scores: mean (SD) (no. of subjects) Arm 1: Baseline: 95.2 (13.1) (144); 14-month follow-up: 96.0 (14.8) (124) Arm 2: Baseline: 92.8 (12.5) (144); 14-month follow-up: 93.7 (13.9) (134) Arm 3: Baseline: 95.1 (14.8) (144); 14-month follow-up: 97.0 (14.4) (136) Arm 4: Baseline: 93.7 (13.1) (146); 14-month follow-up: 94.2 (14.1) (131)	Not reported	Not adequately presented data by drug

Conclusions	
	Authors' conclusions: For ADHD symptoms, medication management was superior to behavioural treatment and to routine community care that included medication. Combined treatment did not yield significantly greater benefits than medication management for core ADHD symptoms, but may have provided modest advantages for non-ADHD symptoms and positive functioning outcomes **Reviewer's comments:** No comments noted

Appendix 13

Data extraction table of the systematic review of adverse events

Study characteristics	Results	Validity
Reference Rapport and Moffitt, 2002[114] **Objective** To review three classes (height/weight, cardiovascular and somatic complaints) of treatment-emergent symptoms (side-effects) associated with MPH therapy for children with ADHD **Intervention** Studies assessing MPH treatment **Population** Studies examining children described as hyperactive (pre-1980) or meeting DSM criteria for ADHD (post-1980) **Included studies** 10 longitudinal studies 22 RCTs 2 CCTs	**Adverse events** Weight: 8/11 studies investigating effects on weight found significant differences in expected levels of weight gain, less comparable weight gain between treated and untreated children, between placebo and active medication conditions or between baseline and active medication. However, one of these studies consequently found no difference between groups at 2-year follow-up Height: 4/10 studies reported significant reductions in expected levels of height gain, less comparable height gain relative to control children, lower height percentile under active medication contrasted with baseline and greater expected gains in height percentiles at 2-year follow-up in children discontinued from medication during summer months. In two of these studies, initial differences were no longer significant at longer term follow-up assessments Cardiovascular effects: 7/14 studies detected significant effects of MPH on heart rate between placebo and active drug conditions or between high- vs low-dose conditions. One further study found that initial differences were not sustained over time 5/10 studies reported elevated systolic blood pressure compared with placebo or baseline. 6/10 studies reported elevated diastolic blood pressure compared with placebo or baseline Somatic complaints: 8/12 studies reported significantly more complaints under MPH conditions. Loss of appetite, sleep disturbances, dizziness, headaches and stomach aches were the most common complaints reported. 4/12 studies reported a greater number of complaints under placebo conditions, whereas 2/12 detected no differences between treatment arms **Authors' conclusions** The more easily quantifiable side-effects (e.g. blood pressure, heart rate, height/weight) are mostly transient, dose dependent, easily rectified with dosage adjustments and considered minor from a clinical perspective considering the breadth and level of improvement in behaviour and cognitive functioning observed in most children. Previously reported somatic complaints associated with psychostimulant therapy may reflect symptoms occurring prior to initiation of treatment and require additional study	**Inclusion criteria** Fair **Search strategy** Fair **Validity assessment** Poor **Study details** Good **Reviewers' comments** A 'vote counting' method of synthesis is used in this review; degree of effect is not given

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.hta.ac.uk) 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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